

The Dictionary of Substances and their Effects

Second Edition

Editor

Sharat Gangolli

DOSE



Volume 2

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**The Dictionary
of Substances
and their Effects**
Second Edition

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Volume 2 ISBN 0-85404-813-8
Seven-volume set ISBN 0-85404-803-0

A catalogue record for this book is available from the British Library.

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Published by The Royal Society of Chemistry, Thomas Graham House, Science Park, Milton Road, Cambridge, CB4 0WF, UK

Typeset by Land & Unwin (Data Sciences) Ltd, Bugbrooke, UK

Printed and bound by Bookcraft (Bath) Ltd., UK

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Guide to Content

The data for each chemical in DOSE are organised as follows:

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Carcinogenicity and chronic effects
Teratogenicity and reproductive effects
Metabolism and toxicokinetics
Irritancy
Sensitisation

Genotoxicity

Other effects

Other adverse effects (human)
Any other adverse effects

Legislation

Other comments

References

These headings only appear in an item when data have been identified for that heading. The user can, therefore, assume that the absence of a heading means that no relevant data were retrieved from the sources examined.

Dose No.

Each of the 4123 compounds in DOSE is identified by a unique, sequential alphanumeric DOSE No. For example, the first compound in DOSE, *A- α -C*, has DOSE No. *A1*; the last entry, *zoxazolamine*, has DOSE No. *Z25*.

Chemical name

In general, the chemical name is the common name of the substance, for example *nitrobenzene*. If it is not possible to allocate a precise chemical name (i.e. if the substance is of unknown or variable composition, or consists of biological materials), a short phrase appears instead, for example *chlorinated paraffins (C12, 60%)*.

Molecular formula

This is the elemental composition of the compound. The elements appear alphabetically for inorganic compounds, i.e. Ag_2CO_3 , Cl_2Cr , etc, but for organic compounds, carbon and hydrogen content are shown first followed by the other elements in alphabetical order, i.e. $\text{C}_6\text{H}_5\text{Br}$.

Molecular weight

This is directly calculated from the molecular formula. No molecular weights are given for polymers.

CAS Registry No.

The CAS Registry No. is a number sequence adopted by the Chemical Abstracts Service (American Chemical Society, Columbus, Ohio, USA) to uniquely identify specific chemical substances. The number contains no information relating to the chemical structure of a substance and is, in effect, a catalogue number relating to one of the millions of unique chemical substances recorded in the CAS Registry. New numbers are assigned sequentially to each new compound identified by Chemical Abstracts Service. This information is also provided in the full index of CAS Registry Numbers available at the end of Volume 7.

Synonyms

For common chemicals, several chemical names and numerous trade names may be applied to describe the chemical in question. Many of these names are identified to aid users on the range of names which have been used to describe each substance.

EINECS No.

This number is assigned by the European Commission to each record in the EINECS (European Inventory of Existing Commercial Chemical Substances) inventory. The numbers are in the format XXX-XXX-X, for example, *202-716-0* for *nitrobenzene*.

RTECS No.

The RTECS (Registry of Toxic Effects of Chemical Substances) number is a unique identifier assigned by NIOSH (National Institute of Occupational Safety and Health in the US) to every substance in the RTECS database. The number is in the format of two alphabetic characters followed by seven numeric characters, for example, *DA 6475000* for *nitrobenzene*.

Uses

Principal uses of the substances are given, with information on other significant uses in industrial processes.

Occurrence

Natural occurrences, whether in plants, animals or fungi are reported.

Physical properties

Melting/Boiling point

These data are derived from various sources.

Flash point

The flash point is the lowest temperature at which the vapours of a volatile combustible substance will sustain combustion in air when exposed to a flame. The flash point information is derived from various sources. Where possible the method of determination of the flash point is given.

Specific gravity (density)

The specific gravity of each substance has been derived from a variety of sources. Where possible the data have been standardised.

Partition coefficient

Partition coefficients, important for structure-activity relationship considerations, particularly in the aquatic environment, are indicated. Ideally the *n*-octanol/water partition coefficient is quoted. The major data source for this measurement is:

Sangster, J J. *Phys. Chem. Ref. Data* 1989, **18**(3), 1111-1229

Where no reference is quoted, it can be assumed that the information was derived from this source.

Volatility

The vapour pressure and vapour density are quoted where available. Where possible, the data have been standardised.

Solubility

Solubility data derived from several sources are quoted for both water and organic solvents where available.

Occupational exposure

Limit values

This field contains the occupational exposure limit values (or threshold limit values) from France, Germany, Japan, Sweden, UK and USA.

The airborne limits of permitted concentrations of hazardous chemicals represent conditions under which it is believed that nearly all workers may be repeatedly exposed day after day without adverse effect. These limits are subject to periodic revision and vary between different countries. The term *threshold limit* relates primarily to the USA, but equivalent terms are available in most industrialised countries. The data relates to concentrations of substances expressed in *parts per million (ppm)* and *milligrams per cubic meter (mg m⁻³)*.

French exposure limits are published by the French Ministry in Charge of Labour and presented in the report *Valeurs limites d'exposition professionnelle aux agents chimiques en France* (ND 1945-153-93). The values in DOSE have been taken from the 1998 edition. The FR-VLE values are short-term limits (15 minutes), and FR-VME values are long-term limits (8 hours).

German data currently include the national MAK values where available. The MAK value (Maximale Arbeitsplatz-Konzentration) is defined as the maximum permissible concentration of a chemical compound present in the air within a working area which, according to current knowledge, does not impair the health of the employee or cause undue annoyance. Under those conditions, exposure can be repeated and of long duration over a daily period of eight hours, constituting an average working week of 40 hours. MAK values are published by the Geschäftsstelle der Deutschen Forschungsgemeinschaft, Bonn, in "Maximum Concentrations at the Workplace and Biological Tolerance Values for Working Materials." The values in DOSE have been taken from the 1998 edition.

Japanese exposure limits are those recommended by the Japanese Society of Occupational Health. Unless otherwise indicated, these values are long-term exposure limits (the mean exposure concentration at or below which adverse health effects caused by the substance do not appear in most workers, working 8 hours a day, 40 hours a week under a moderate workload). The values in DOSE were published in 1997.

Swedish data can include short-term exposure limit, a level limit, or a ceiling limit. The values in DOSE were adopted in 1996.

In the UK occupational limits relating to airborne substances hazardous to health are published by the Health and Safety Executive annually in Guidance Note EH40. The values in the DOSE items have been taken from the 1999 edition.

There are Maximum Exposure Limits (MEL) in the UK which are subject to regulation and which should not normally be exceeded. They derive from Regulations, Approved Codes of Practice, European Community Directives, or from the Health and Safety Commission. In addition, there are Occupational Exposure Standards (OES) which are considered to represent good practice and realistic criteria for the control of exposure. In an analogous fashion to the USA Threshold Limits, there are long-term limits, expressed as time-weighted average concentrations over an 8-hour working day, designed to protect workers against the effects of long-term exposure. The short-term exposure limit is for a time-weighted average of 15 minutes. For those substances for which no short-term limit is listed, it is recommended that a figure of three times the long-term exposure limit averaged over a 15-minute period be used as a guideline for controlling exposure to short-term excursions.

The threshold limit values for the USA have been taken from the *Threshold Limit Values and Biological Exposure Indices, 1999* produced by the American Conference of Governmental Industrial Hygienists, Cincinnati, USA. The limits relate to *Threshold Limit – Time Weighted Average*, *Threshold Limit – Short Term Exposure Limit* and *Threshold Limit – Ceiling Limit*. The Threshold Limit Value – Time Weighted Average (TLV-TWA) allows a time-weighted average concentration for a normal 8-hour working day and a 40-hour working week, to which nearly all workers may be repeatedly exposed day after day, without adverse effect. The Threshold Limit Value – Short Term Exposure Limit (TLV-STEL) is defined as a 15-minute, time-weighted average which should not be exceeded at any time during a work day, even if the 8-hour time-weighted average is within the TLV. It is designed to protect workers from chemicals which may cause irritancy, chronic or irreversible tissue damage, or narcosis of sufficient degree to cause the likelihood of accidental injury. Many STELs have been deleted pending further toxicological assessment. With Threshold Limit – Ceiling Values (TLV-C) the concentration should not be exceeded during any part of the working day.

UN number

The United Nations Number is a four-figure code used to identify hazardous chemicals and is used for identification of chemicals transported internationally by road, rail, sea and air. In the UK this number is also called the “Substance Identification Number” or “SI Number”.

HAZCHEM code

The Hazchem Code is used to instruct United Kingdom emergency services on equipment, evacuation and other methods of dealing with transportation incidents. It is administered by the Chemical Industries Association.

Conveyance classification

The information presented for the transportation of substances dangerous for conveyance by road is derived from the UK’s Approved Carriage List, Health and Safety Commission, UK.

Supply classification

The information presented for the supply of substances is derived from the UK’s Approved Supply List: information approved for the classification and labelling of substances and preparations dangerous for supply [Chemicals (Hazard Information and Packaging) Regulations 1999 (CHIP 99)*] Health and Safety Commission, UK.

Risk and safety phrases

Risk and safety phrases used in connection with DOSE items are approved phrases for describing the risks involved in the use of hazardous chemicals and have validity in the United Kingdom and throughout the countries of the European Community. The approved texts have designated R (Risk) and S (Safety) numbers from which it is possible to provide translations for all approved languages adopted by the European Community. The risk and safety phrases quoted in DOSE relate to the UK’s Approved Supply List: information

*At the time of going to press the Health and Safety Commission, UK announced that an amendment (Amendment No. 2) to the CHIP 99 regulations is intended to come into force on 1 January 2000. The supply classifications and the risk and safety phrases reported in this edition of DOSE do not include any changes which are proposed in Amendment No. 2 to CHIP 99. These changes are incorporated in the updates to the electronic versions of DOSE released after 1 January 2000.

approved for the classification and labelling of substances and preparations dangerous for supply [Chemicals (Hazard Information and Packaging) Regulations, 1999 (CHIP 99)] Health and Safety Commission, UK. The risk and safety phrases should be used to describe the hazards of chemicals on data sheets for use and supply; for labelling of containers, storage drums, tanks etc., and for labelling of articles specified as dangerous for conveyance by road. (See also footnote on page xi.)

Ecotoxicity

Information is presented on the effects of chemicals on various ecosystems. Results of studies carried out on aquatic species, primarily fish and invertebrates, but also fresh water and marine microorganisms and plants are reported. Persistence and potential for accumulation in the environment and any available information on the harmful effects to non-target species, i.e. the unintentional exposure of terrestrial and/or aquatic species to a toxic substance is given. Ecotoxicology can be defined as that science involved in the study of the production of harmful effects by substances entering the natural environment, especially effects on populations, communities and ecosystems; or as the study of the effects of chemicals on ecosystems and their non-human components. An essential part of the ecotoxicology is the assessment of movement of potentially toxic imbalance through environmental compartments and through food webs.

Ecotoxicology, unlike human toxicology, is more concerned with the effects to populations than to individuals. Human toxicology is based on the extrapolation of data from many species to one species man, whereas ecotoxicology necessitates the extrapolation from a few species to many, or from limited field data to entire ecosystems.

Ecotoxicology must not be confused with environmental toxicology which is the direct effects of environmental chemicals to humans. The term environmental toxicology should only be applied to the study of direct effects of environmental chemicals on human beings. Although the main thrust of preventative toxicology is in the area of human health, it is becoming increasingly evident that human health is intimately connected with conditions in the natural environment. Chemicals released into the environment far from human habitation may become a health hazard for humans through food chain accumulation. Other chemicals may adversely affect crop growth or kill economically important fish stocks or bird life.

Fish toxicity

LC₅₀ values, with duration of exposure, are quoted for two species of freshwater and one marine species if available. Any additional information on bioassay type (static or flow through) and water condition (pH, temperature, hardness or oxygen content) is reported.

Invertebrate toxicity

LC₅₀ values with duration of exposure, are quoted for molluscs and crustaceans. EC₅₀ values, i.e. concentrations which will immobilise 50% of an exposed population, are given for microbes, algae and bacteria. Values which will inhibit microbial or algal growth are reported. Duration of exposure is given when available.

Toxicity to other species

Toxicity to species other than mammals, birds, invertebrates and fish (e.g. reptiles, amphibians, plants, seaweeds), is reported here. LD₅₀, LC₅₀ and EC₅₀ values are given with duration of exposure, concentration and as much supplementary information as possible.

Bioaccumulation

Bioaccumulation, biomagnification and bioconcentration data are quoted primarily for fish, invertebrates, bacteria and algae. Bioaccumulation is the progressive increase in the amount of a chemical in an organism or part of an organism which occurs because the rate of intake exceeds the organism's ability to remove the substance from its body. Bioconcentration is a process leading to a higher concentration of a chemical in an organism than in its environment. Lastly, biomagnification is a sequence of processes in an ecosystem by which higher concentrations are attained in organisms at higher trophic levels, i.e. at higher levels in the food chain.

Environmental Fate

Degradation data are used to assess the persistence of a chemical substance in the environment, in water, soil and air. If the substance does not persist, information on the degradation products is also desirable. Intermediates may be either harmless or toxic substances which will themselves persist. Degradation occurs via two major routes, microbial degradation utilising microorganisms from a variety of habitats and decomposition by chemical methods. Microbial degradation is associated with the production of elemental carbon, nitrogen and sulfur from complex molecules. Standard biodegradation tests estimate the importance of microbial biodegradation as a persistence factor. Most tests use relatively dense microbial populations adapted to the compound being studied. Rapid degradation results in these tests implies that the compound will degrade under most environmental conditions, although specialised environments where degradation would not occur can exist. Compounds which are not readily degradable are likely to persist over a wide range of environmental situations.

Chemical degradation processes include photolysis, hydrolysis, oxidation and removal by reversible/irreversible binding to sediment. Factors which influence degradation rates, such as duration of exposure, temperature, pH, salinity, concentrations of test substance, microbial populations, and other nutrients, must also be taken into account.

Due care must also be given when metabolism results in the production of substances that are more toxic than their parents.

Nitrification inhibition

The nitrogen cycle is the major biogeochemical process in the production of nitrogen, an essential element contained in amino acids and proteins. Nitrogen is an essential element in microorganisms, higher plants and animals. Interference in the production of nitrogen from more complex molecules can be determined by standard tests using nitrogen-fixing bacteria. The degree of inhibition can be used to estimate the environmental impact of the test chemical.

Carbonaceous inhibition

Another major biogeochemical process is the recycling of carbon via the decomposition of complex organic matter by bacteria and fungi. In nature the process is important in the cycling of elements and nutrients in ecosystems. The degradation sequence occurs in stages, cellulose → cellobiose → glucose → organic acids and carbon dioxide. Chemical inhibition of microbial processes at all or any of these stages is reported here.

Anaerobic effects

Anaerobic microbial degradation of organic compounds occurs in the absence of oxygen and is an important degradation process in both the natural environment and in waste treatment plants. Data on the effects of chemicals on anaerobic systems are reported here. An important method uses anaerobic digestion tests which compare the production of methane and carbon dioxide by anaerobic microbes in a sludge sample with and without added test material. Methane production is at the end of the food chain process used by a wide range of anaerobic microorganisms.

Degradation studies

This section focuses on microbial degradation in both soil and water under anaerobic and aerobic conditions. The half-life of the chemical substance in the environment is reported with its degradation products where possible, giving an indication of the degree of its persistence. Water pollution factors: BOD (biochemical/biological oxygen demand), COD (chemical oxygen demand) and ThOD (theoretical oxygen demand) are stated, where available. BOD estimates the extent of natural purification which would occur if a substance were discharged into rivers, lakes or the sea. COD is a quicker chemical method for this determination which uses potassium dichromate or permanganate to establish the extent of oxidation likely to occur. ThOD measures the amount of oxygen needed to oxidise hydrocarbons to carbon dioxide and water. When organic molecules contain other elements nitrogen, sulfur or phosphorus, the ThOD depends on the final oxidation stage of these elements.

Abiotic removal

Information on chemical decomposition processes is contained in this section. The energy from the sun is able to break carbon-carbon, and carbon-hydrogen bonds, cause photodissociation of nitrogen dioxide to nitric oxide and atomic oxygen and photolytically produce significant amounts of hydroxyl radicals. Hydrolysis occurs when a substance present in water is able to react with the hydrogen or hydroxyl ions of the water. Therefore the extent of photolytic and oxidative reactions occurring in the atmosphere and hydrolysis in water can be used as a measure of environmental pollution likely to arise from exposure to a substance. Removal by activated carbon is also reported.

Adsorption and retention

The environmental impact of a chemical substance is determined by its ability to move through the environment. This movement depends on the affinity of the chemical toward particulate matter: soil and sediment. Chemicals which have a high affinity for adsorption are less readily transported in the gaseous phase or in solution, and therefore can accumulate in a particular medium. Chemical substances which are not readily adsorbed are transported through soil, air and aquatic systems.

Mammalian and avian toxicity

Studies on mammalian species are carried out to determine the potential toxicity of substances to humans. Avian species are studied primarily to assess the environmental impact on the ecosystem, however data from avian studies are also used for assessing human toxicity. This is specifically applied to pesticides, with neurotoxicology studies.

Procedures involve undertaking a series of established exposure studies on a particular substance using specific routes, oral, inhalation, dermal or injection for variable durations. Exposure durations include acute or single exposure to a given concentration of substance. Sub-acute or sub-chronic exposure, i.e. repeat doses over an intermediate time period, up to 4 weeks for sub-acute and 90 day/13 week (in rodents) or 1 year (in dogs) for sub-chronic studies. Chronic/long-term studies involve exposure to specific concentrations of chemical for a duration of 18 month-2 years. A variety of species are used in toxicity testing, most commonly rodents (rats, mice, hamsters) and rabbits, but tests can also be carried out on monkeys, domestic animals and birds.

Acute data

Single exposure studies quoting LD₅₀, LC_{LO}, LD_{LO}, TC_{LO} and TD_{LO} data.

Sub-acute and sub-chronic data

Results of repeat doses, intermediate duration studies are quoted. Priority is given to reporting the adverse effects on the gastro-intestinal, hepatic, circulatory, cardiopulmonary, immune, renal and central nervous systems.

Carcinogenicity and chronic effects

Information on the carcinogenicity of substances unequivocally proven to cause cancer in humans and laboratory animals, together with equivocal data from carcinogenicity assays in laboratory animals are reported. Additionally, treatment-related chronic adverse effects are reported. Criteria for inclusion required the study to report the species, duration of exposure, concentration and target organ(s); sex is also given where available.

Teratogenicity and reproductive effects

The results of studies carried out in intact animal and *in vitro* systems to determine the potential for teratogenic, foetotoxic and reproductive damage are reported here. Criteria for inclusion required the species, duration of exposure, concentration and details of the effect in relation to fertility to be stated. Adverse effects reported in this section include sexual organ dysfunction, developmental changes (to embryos and foetuses), malformations, increases in spontaneous abortions or stillbirths, impotence, menstrual disorders and neurotoxic effects on offspring.

Metabolism and toxicokinetics

Data are quoted on the metabolic fate of the substance in mammals, and includes adsorption, distribution, storage and excretion. Mechanisms of anabolic or catabolic metabolism, enzyme activation and half-lives within the body are reported when available. Additionally findings from *in vitro* studies are reported.

Irritancy

Chemical substances which cause irritation (itching, inflammation) to skin, eye and mucous membranes on immediate contact in either humans or experimental animals are reported here. Exposure can be intentional in human or animal experiments, or unintentional via exposure at work or accident to humans.

Sensitisation

Sensitisation occurs where an initial accidental or intentional exposure to a large or small concentration of substance causes no reaction or irritant effects. However, repeat or prolonged exposure to even minute amounts of a sensitising chemical causes increasingly acute allergic reactions.

Genotoxicity

Genotoxicity testing is carried out to determine the mutagenic and/or carcinogenic potential of a chemical substance. A standard series of tests are carried out under controlled laboratory conditions on an established set of test organisms. A hierarchical system using bacteria, yeasts, cultured human and mammalian cells, *in vivo* cytogenetic tests in mammals and plant genetics is used to assess the genotoxic potential of the substance under study. Bacteria, unlike mammals, lack the necessary oxidative enzyme systems for metabolising foreign compounds to the electrophilic metabolites capable of reacting with DNA. Therefore, bacteria are treated with the substance under study in the presence of a post-mitochondrial supernatant (S9) prepared from the livers of mammals (usually rats). This fraction is supplemented with essential co-factors to form the S9 mix necessary for activation. DOSE reports published studies: giving the test organisms, whether metabolic activation (S9) was required, and the result, positive or negative.

Other effects

Other adverse effects (human)

Adverse effects to humans from single or repeat exposures to a substance are given. The section includes results of epidemiological studies, smaller less comprehensive studies of people exposed through their work environment and accidental exposure of a single, few or many individuals.

Any other adverse effects

Adverse effects to organisms or animals other than man are reported here.

Legislation

Any form of legislation, medical (food and drugs) or environmental from European, American and worldwide sources is reported.

Other comments

All other relevant information, including chemical instability and incompatibility, reviews, phytotoxicity and toxic effects associated with impurities, is contained in this section.

References

Contains references to data from above sections.

Indexes

The most convenient means of accessing a chemical in DOSE is via one of the indexes at the back of Volume 7. DOSE contains three indexes: chemical name and synonyms, CAS Registry Numbers and molecular formulae.

Index of chemical names and synonyms

Contains the name of the chemical used in DOSE together with a number of synonyms for that chemical. All names are arranged alphabetically.

Index of CAS Registry Numbers

Contains a list of the CAS Registry Numbers of the chemicals in DOSE in ascending order. This number is linked to the preferred DOSE name for that chemical and its DOSE number.

Index of molecular formulae

Contains a list of the molecular formulae of the chemicals in DOSE in alphabetical order for inorganic compounds, i.e. Ag_2CO_3 , Cl_2Cr , etc., but for organic compounds, carbon and hydrogen content are shown first followed by the other elements in alphabetical order, i.e. $\text{C}_6\text{H}_5\text{Br}$. This number is linked to the preferred DOSE name for that chemical and its DOSE number.

Note

The Royal Society of Chemistry (RSC) has only assessed published information in compiling The Dictionary of Substances and their Effects. However, the RSC would welcome any relevant information on the chemicals that is not readily accessible, but in the public domain, for inclusion when the items in DOSE are updated.

If you have any relevant information, please contact:

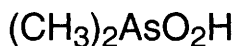
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c1 cacodylic acid



$\text{C}_2\text{H}_7\text{AsO}_2$

Mol. Wt. 138.00

CAS Registry No. 75-60-5

Synonyms dimethylarsinic acid; hydroxydimethylarsine oxide; dimethylarsenic acid; Weed Ender; Bolls-Eye; Phytar

EINECS No. 200-883-4

RTECS No. CH 7525000

Uses Catalyst. Herbicide. Has been used in the treatment of chronic eczema and anaemia.

Physical properties

M. Pt. 195-196°C

Solubility Water: 829 g l⁻¹ at 22°C. Organic solvents: acetic acid, ethanol

Ecotoxicity

Fish toxicity

LC₅₀ (48 hr) bluegill sunfish >1000 mg l⁻¹. The addition of surfactants increases toxicity (1).

Juvenile rainbow trout (8 wk) 1479 µg l⁻¹ no signs of toxicity induced (2).

Bioaccumulation

Bioconcentration factor in algae 1635, snails 420, dolphin 1660 and fish 21 (species unspecified) (3).

Environmental fate

Degradation studies

Converted into trimethylarsinic oxide by sedimentary microorganisms under aerobic conditions in laboratory tests. At a concentration of 0.084% As, conversion began after 14-day incubation and was complete after 35 days at 25°C (4).

Abiotic removal

Undergoes photochemical demethylation in distilled water and seawater (5).

Mammalian & avian toxicity

Acute data

LD₅₀ oral rat, mouse 640, 1200 mg kg⁻¹, respectively (6,7).

LD₅₀ intraperitoneal rat, mouse 520, 720 mg kg⁻¹, respectively (8).

♀ Rats were administered dimethylarsinic acid orally at 21 and 4 hr before sacrifice. 387 mg kg⁻¹ caused a decrease in serum alanine transferase activity and hepatic glutathione content and increased hepatic haem oxygenase activity. Ornithine decarboxylase activity in the lung was decreased by 387 and 129 mg kg⁻¹ dosages and DNA damage in lung tissue was significantly higher at 387 mg kg⁻¹ (demonstrating organ-specific DNA damage) (9).

Sub-acute and sub-chronic data

Oral ♂, ♀ F344/DuCrj rat (4 wk) 57, 85 and 113 mg kg⁻¹ caused dose-related decreases in body weight and survival in both sexes. Mortality was higher and appeared faster in ♀. Histopathological findings in the kidney were proximal tubular degeneration and necrosis, as well as papillary necrosis, and hyperplasia of the epithelium covering the papillae. Extensive proximal tubular necrosis was observed only in dead animals not in survivors or controls. It was concluded that the main cause of death was nephrotoxicity attributed to dimethylarsinic acid (10).

Carcinogenicity and chronic effects

Oral mouse (19 month) 46 mg kg⁻¹ day⁻¹ for 3 wk, followed by 121 mg kg⁻¹ diet for 18 months. There was no increase in the incidence of tumours compared with controls (11).

Subcutaneous mouse (18 month) single injection of 464 mg kg⁻¹ at 28 days of age. There was no increase in the incidence of tumours compared with controls (12).

Metabolism and toxicokinetics

Following single oral administration to humans (0.1 mg As kg⁻¹), mice and hamsters (40 mg As kg⁻¹). In mice and hamsters 3.5-6.4% of the dose was excreted in the urine as trimethylarsine oxide and 80-85% was eliminated as unmetabolised dimethylarsinic acid in the urine and faeces. 13-15% was also eliminated in the urine and faeces as an unidentified dimethylarsinic acid complex. No demethylation to inorganic As was observed in humans. ~4% was excreted in the urine as trimethylarsine oxide and ~80% unchanged (13).

Irritancy

Whole body exposure of rat and mouse (2 hr) 2600 mg m⁻³ caused skin and eye irritation (14).

Genotoxicity

Salmonella typhimurium TA98, TA100, TA1537, with and without metabolic activation negative (15).

Escherichia coli SOS Chromotest, without metabolic activation positive (16).

Saccharomyces cerevisiae D3 mitotic recombination, positive (15).

Saccharomyces cerevisiae D7, gene conversion and crossing over positive (15).

In vitro Chinese hamster ovary cells, sister chromatid exchanges negative (15).

In vitro L5178Y tk⁺/tk⁻ mouse lymphoma cells, forward mutation assay positive (15).

Mice administered a single intraperitoneal injection showed significantly increased bone-marrow cell mitotic cell indexes at 16, 24 and 48 hr. Average generation time was increased by 1.5 hr at 24 hr, but the activity of mitotic arrest was much weaker than that induced by colchicine. Induction of aneuploids was significant. The authors suggest that aneuploidy induced by dimethylarsinic acid might be associated with the carcinogenicity of arsenic (17).

Other effects

Other adverse effects (human)

An organotypic culture of a human keratinocyte cell line over a human fibroblast-embedded collagen gel was used to model human epidermis in arsenicism. Acute or chronic exposure of keratinocytes to individual arsenic compounds [0.5 µM arsenate, 0.6 µM monomethylarsonic acid (MMA) 1.5 µM dimethylarsinic acid (DMA)] demonstrated that all arsenic mixture-induced changes could be duplicated by exposure to arsenate alone. In contrast, MMA and DMA were inactive, implicating inorganic arsenic as the ultimate carcinogen (18).

Any other adverse effects

Oral mouse, single dose of 1500 mg kg⁻¹ as the sodium salt caused a significant increase in the activities of mitochondrial superoxide dismutase, glutathione peroxidase and glucose-6-phosphate dehydrogenase of the lung. Cytosolic superoxide dismutase and catalase activities were not affected. With regard to cellular sulfhydryls, levels of reduced glutathione and non-protein sulfhydryl decreased, while mixed disulfides increased significantly. The concentration of NADPH was also markedly increased. These cellular variations indicated that the mouse pulmonary cell produced superoxide anion radicals, hydrogen peroxide and subsequent reactive oxygen radicals in the metabolism of dimethylarsinic acid and that these were responsible for pulmonary DNA damage (19).

In vitro mouse spleen cells. High doses of dimethylarsinic acid suppressed the plaque-forming cell response to sheep erythrocytes and the proliferative response to mitogens, whereas low doses enhanced both responses (dose levels not stated) (20).

Legislation

Included in Schedule 6 (Release into Land: Prescribed Substances) of Statutory Instrument No. 472, 1991 (21).

Limited under EC Directive on Drinking Water Quality 80/778/EEC. Pesticides: maximum admissible concentration 0.1 µg l⁻¹ (22).

WHO Toxicity Class III (23).

Other comments

Major metabolite of inorganic arsenic in mammals.

Physical properties, occurrence, analysis, carcinogenicity, mammalian toxicity, metabolism and mutagenicity of arsenic and arsenic compounds reviewed (24).

Human health effects reviewed (25).

Carcinogenic potential of dimethylarsinic acid as assessed in rat *in vivo* models reviewed. (The conclusion was that dimethylarsinic acid is a carcinogen or promoter in the urinary bladder, liver, kidneys and thyroid gland.) (26).

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c2 cadmium

Cd

Cd

Mol. Wt. 112.41

CAS Registry No. 7440-43-9

Synonyms CI 77180

EINECS No. 231-152-8

RTECS No. EU 9800000

Uses Used in electroplating and smelting operations. Manufacture of pigments and insecticides. Cadmium is used as the negative electrode in nickel-cadmium batteries. Minor uses in the nuclear industry. Manufacture of stabilisers for PVC.

Occurrence Found in zinc ores, also as greenockite (CdS) and otavite (CdCO₃).

Volcanic activity is also a major natural source of cadmium release.

Cadmium is depleted in the surface of the Pacific Ocean relative to deeper waters indicating uptake by organisms at the surface and regeneration from sinking biological detritus. Concentrations ranged from 0.1±0.1 to 1.1±0.1 nmol kg⁻¹. The cadmium concentration at the mouth of the Amazon river (Macapa, Brazil, May 1974) was 0.6 nmol kg⁻¹ (1).

Physical properties

M. Pt. 321°C B. Pt. 769°C Specific gravity 8.65 at 25°C Volatility v.p. 1 mmHg at 394°C

Occupational exposure

FR-VME 0.05 mg m⁻³

JP-OEL 0.05 mg m⁻³

SE-LEVL 0.05 mg m⁻³ (total dust); 0.01 mg m⁻³ (respirable dust)

UK-LTEL MEL 0.025 mg m⁻³

US-TWA 0.01 mg m⁻³ (inhalable fraction); 0.002 mg m⁻³ (respirable fraction)

UN No. 2570

Supply classification harmful

Ecotoxicity

Fish toxicity

Lowest-observed-effect concentration (LOEC) and no-observed-effect concentration (NOEC) for fathead minnow were 57 and 37 µg l⁻¹ and for bluegill sunfish 80 and 31 µg l⁻¹, respectively, for exposures of 30 to 60-day post-natal duration (2).

In scorpion fish exposed to sublethal doses of cadmium, 10 and 20 mg l⁻¹ for 4 wk, inhibition of Cu-Zn superoxide dismutase enzyme activity in the intestine was observed (3).

LC₅₀ (96 hr) Japanese marine species, girella and goby 5.5-30.5 mg l⁻¹ (4).

Rainbow trout were exposed to Cd in waters of low alkalinity (30 mg l⁻¹) and hardnesses of 400, 200, and 50 mg l⁻¹ adjusted with MgSO₄. LC₅₀ (96 h) were 3.02, 6.12, and 5.70 µg Cd l⁻¹ at Mg hardnesses of 50, 200, and 400 mg l⁻¹. LC₅₀ (100 day) were 1.47, 3.57, and 3.64 µg l⁻¹ for the same range of hardness. These tests did not show a strong antagonistic influence of Mg hardness on Cd toxicity. Antagonistic properties of hardness are primarily controlled by Ca, with Mg playing a minor role (5).

Invertebrate toxicity

Acute exposure to cadmium (concentration unspecified) in *Daphnia magna* affected the body size of the young and brood sensitivity (6).

The acute lethality of Cd towards *Daphnia magna* was increased in humic lake water compared with humus-free control water (7).

Dunaliella salina 3-5 mg l⁻¹ caused chlorosis and inhibition of cell division (8).

Dunaliella tertiolecta and *Isochrysis galbana* were exposed to cadmium concentrations of 13.8 and 0.2 mg l⁻¹ for 8 days. Cadmium significantly reduced population growth (9).

The presence of zinc increases the toxic effect of cadmium on invertebrates (10).

EC₅₀ values for the reproduction of the springtail *Folsomia candida* Willem were determined after 6-wk exposure to cadmium in an artificial soil. EC₅₀ (6 wk) 51 µg Cd g⁻¹ dry soil for total cadmium in soil, corresponding to an internal concentration of 44 µg Cd g⁻¹ dry body weight. EC₅₀ (6-wk) 0.13 µg Cd g⁻¹ dry soil for water-soluble cadmium. The effects of a mixture of cadmium and zinc on growth were antagonistic, whilst the effects on reproduction were additive (11).

EC₇₅ (14 day) growth of the snail *Helix aspersa maxima* 370 µg Cd g⁻¹ dry food (12).

EC₇₅ (28 day) growth of the snail *Helix aspersa aspersa* 290 µg Cd g⁻¹ dry food (12).

Sea urchin eggs exposed to 0.1 mg l⁻¹ and 0.5 mg l⁻¹ cadmium at fertilisation and development. Sea urchin development was normal to gastrulation stage but all plutei were abnormal (13).

LC₅₀ (96 hr) *Palaemonetes vulgaris* 0.76 mg l⁻¹ (14).

LC₅₀ (96 hr) *Penaeus duorarum* 3.5 mg l⁻¹ (14).

Midge (96 hr) exposed to 0.1-1.0 mg l⁻¹ cadmium showed deviations from the normal feeding patterns of unexposed larvae. Nodemonstrable effects on survival of larvae, but development was retarded as indicated by the lower biomass values observed. At concentrations of 2.5-10 mg l⁻¹ a large variability in behavioural responses was observed (15).

Bioaccumulation

In aquatic systems, cadmium (Cd²⁺ ion) is most commonly taken up directly from the water, but may also be ingested with contaminated feed. Water hardness affects the uptake from water; high concentrations of calcium and magnesium salts reduce cadmium uptake (16).

Inorganic cadmium complexes appear not to be taken up by fish (17).

The chemical properties of organic cadmium complexes are important with respect to their bioavailability.

Complexes with EDTA, nitrilotriacetic acid and diethylenetriaminepentaacetic acid are unavailable to water organisms. Cadmium complexed with fulvic acids of low relative molecular mass molecules are available but less so than the free ion. Hydrophobic cadmium complexes, for example xanthates and dithiocarbamates, are readily available (16).

Increased temperature increases the uptake of cadmium from water (18).

Bioconcentration factor 35 reported in *Chlorella vulgaris* (19).

Minnows pre-exposed for 0, 30, 91 days to 0.33 µg l⁻¹ cadmium were then exposed for 24 hr to 0.33 µg l⁻¹ followed by a 64-day post-exposure period at 0.33 µg l⁻¹. Cadmium accumulated in liver, kidney, muscle and bone but was eliminated from gills, head and skin during the 64-day post-exposure period (20).

Cadmium accumulates in marine, freshwater and terrestrial organisms. Average accumulation in freshwater fish 85 µg kg⁻¹ (21).

Xenopus laevis embryos at seven developmental stages were exposed to solutions containing cadmium concentrations ranging from 0.1 to 2.0 mg Cd²⁺ l⁻¹ for 72 hr. Bioaccumulation factors ranged from 5 to 460 with the general pattern being that at all developmental stages the bioaccumulation factor was higher in embryos exposed to the lower cadmium concentration, and that as development of the embryo advanced so the bioaccumulation factor increased (22).

Platichthys flesus mean cadmium concentration 3.4-7.3 mg kg⁻¹ (dry weight) (23).

White-beaked dolphins: accumulation in kidney 13.6 mg kg⁻¹ (dry weight). Pilot whales: accumulation in kidney 108 mg kg⁻¹ (dry weight) (24).

Freshwater crayfish (10 wk) 2 µg l⁻¹ at 10°C cadmium accumulated initially in digestive gland and gills (4).

Cadmium uptake by *Ostrea sinuata* from water containing 50 mg l⁻¹ radiolabelled ¹¹⁵Cd. The soft parts of the oyster contained 100 mg cadmium kg⁻¹ after 100 hr (25).

Field studies have shown that cadmium is bioconcentrated by earthworms (*Allolobophora tuberculata* Eisen and *Lumbricus rubellus* Hoffmeister), the bioconcentration being greater at lower soil concentrations. The elimination rate for worms from a highly contaminated soil is 0.028 day⁻¹ which is greater by a factor of 4 than the elimination rate of 0.0076 day⁻¹ estimated for worms from a less contaminated soil (26).

Certain species of macrofungi bioaccumulate cadmium. The following levels, ppm (dry wt), were determined in higher mushrooms from Hungary: *Agaricus augustus* 15.1, *A. arvensis* 17.3, *A. abruptibulbus* 45.0, *A. purpurellus* 86.3, *A. silvestris* 49.4, *Russula foetens* 16.5, *R. vesca* 12.4, *Amanita muscaria* 22.2 (27).

Bioconcentration and uptake of cadmium by carp is reduced by EDTA and histidine (28).

Environmental fate

Nitrification inhibition

Inhibition of denitrification, rotating disc threshold inhibition concentration 1 mg l⁻¹ (29).

Nitrosomonas europaea exposed to cadmium concentrations of 0.05, 0.1 and 0.4 mg l⁻¹ and to a range of ammonia concentrations (1 to 100 mg l⁻¹ as nitrogen). Growth was inhibited at the highest cadmium concentration especially when combined with ammonia concentrations >10 mg l⁻¹ (30).

Carbonaceous inhibition

Forest soil and litter was incubated with cadmium salts at concentrations of 0.1-10 mg kg⁻¹ cadmium. Oxygen consumption, carbon dioxide evolution and bacterial and fungal populations were measured. High concentrations of cadmium caused initial stimulation of oxygen consumption, suggesting that it affected uncoupling of respiratory phosphorylation. Both oxygen consumption and carbon dioxide evolution were reduced at later stages. No effect on microorganisms was noted (31).

Anaerobic effects

The effect of cadmium on 96-hr anaerobiosis in acrid clam caused an increase in plasma glucose concentration of 10-25 mg l⁻¹ (32).

Degradation studies

Soil samples which were undisturbed for 30 yr had average Cd²⁺ levels in soil of 0.35 mg kg⁻¹ dry weight and in earthworms 5.7 mg kg⁻¹ dry weight (33).

Adsorption and retention

Cd²⁺ binds strongly to soil, sediment and organic matter (13).

Mammalian & avian toxicity

Acute data

LD₅₀ oral rat 225 mg kg⁻¹ (34).

LD₅₀ oral rat, mouse 890 mg kg⁻¹. Adverse effects included epithelial desquamation and necrosis of the gastric and intestinal mucosa with dystrophic changes of the liver, heart and kidneys (35).

LC₅₀ (30 min) inhalation rat 25 mg m⁻³ (36).

LD₅₀ intraperitoneal rat 4 mg kg⁻¹ (34).

Sub-acute and sub-chronic data

Oral rabbit (6 month) 160 mg l⁻¹ Cd²⁺ in drinking water. Kidney function was not investigated but histopathological examination revealed pronounced morphological changes in the proximal tubules (37).

Groups of ♀ rabbits were administered 1.5 mg kg⁻¹ intraperitoneally (group A) and 1.0 mg kg⁻¹ orally for a five-month period (group B), and also 1.0 mg kg⁻¹ orally for five months followed by a seven-month cessation of application (group C). After the experimental period the percentage of glandular epithelium in the endometrium was significantly lower in group A compared with group C. The amount of stroma was significantly higher in the group receiving intraperitoneal injection compared with those receiving oral administration. Oedematisation of the uterus with disintegrations in the blood vessel wall and subsequent diapedesis were evident (38).

Rats (14 wk) 80 ppm Cd²⁺ in drinking water and fed a modified AIN-76 diet displayed smaller body weight gains and larger relative kidney and testis weights than controls. Vitamins A and D were synergistic in ameliorating these symptoms. Vitamin C had no protective action on the kidneys or testes but caused an increase in the dry weight of the femurs of Cd-exposed rats. Exposure to Cd²⁺ depressed the haemocrits and erythrocyte counts significantly and altered the ratio of granuloid to mononuclear peripheral leukocytes. Treatment with either vitamin A and 1, 25-dihydroxyvitamin D3 or vitamins A and 1,25-dihydroxyvitamin D3 and fluoride (F⁻) appeared to lessen this haemotoxicity (39).

♂ Guinea pigs (12 wk) 2 or 100 mg animal⁻¹ day⁻¹ vitamin C and 1 mg Cd animal⁻¹ day⁻¹ in drinking water. The results showed that high vitamin C intake can be effective in the protection of Cd-induced nephrotoxicity (i.e. against dilation of intestinal veins with apparent paravenous lymphatic infiltrates and increased serum creatinine and urea levels) (40).

Carcinogenicity and chronic effects

Sufficient evidence for carcinogenicity of cadmium and cadmium compounds to humans, sufficient evidence for carcinogenicity of cadmium compounds to animals, limited evidence for carcinogenicity of cadmium metal to animals, IARC classification group 1 (41).

Oral rabbit (54 wk) 300 mg kg⁻¹ diet caused aminoaciduria and enzymuria which were observed at 16 wk. Proteinuria and glycosuria were observed at 37-42 wk (42).

Oral ♂ rats (52 wk) 10 mg Cd l⁻¹ in drinking water. At 56 wk all cadmium-treated rats showed pathological testicular alterations and liver and kidney damage. At the end of 52 wk 40% of the cadmium-treated rats had lost their reproductive capacity. Cadmium levels were highest in the kidney (1.009 µg g⁻¹ wet tissue in the infertile group) (43).

Long-term human exposure (duration and doses unspecified) to large amounts of cadmium by inhalation or ingestion causes renal tubular dysfunction. Disturbances in mineral metabolism may eventually result in osteomalacia (15).

Single intramuscular injection of metallic cadmium to rats (dose unspecified) induced sarcomata at injection site (44).

Teratogenicity and reproductive effects

Cadmium (as unspecified salt) injected into the air sacs of chicken eggs on day-2 of incubation caused reduced body size, micromelia, hoisted neck, haemorrhage, everted viscera and microphthalmia (44).

Irrespective of route of administration in pregnant rats and hamster, cadmium crossed the placental barrier. Single injections of cadmium salts to experimental animals (species unspecified) caused testicular necrosis (45).

Oral mice (2 yr) 10 mg l⁻¹ in drinking water induced foetal mortality, runting, malformations including sharp angulation of the distal third of the tail, and early death (46).

Investigations on rat blastocytes show that cadmium has the potential to exert a clear toxic effect on early embryonic development in rats in dose-dependent fashion (47).

Metabolism and toxicokinetics

During the early, fast elimination phase, cadmium in mouse plasma is mainly bound to plasma proteins with molecular weights of 40,000 – 60,000 (probably albumin), whereas in the slower phase (more than 24 hr after injection), it is partly bound to a low molecular weight protein (similar to metallothionein) (48).

Movement of cadmium through the placenta is limited; <0.02% of the total dose of cadmium injected intravenously into rat dams reached the foetus (49).

Oral rat (1 yr) 1 ppm Cd²⁺ in calcium-deficient diet, accumulated 0.33-0.48% liver and kidney (50).

Inhalation of cadmium salts leads to the retention of large amounts of cadmium, particularly in the kidneys, liver, pancreas and thyroid (species unspecified) (51).

In humans, cadmium is transported in the body by binding to a low-weight plasma protein, metallothionein.

After distribution, concentrations unspecified, 50% of total body burden is detected in the liver and kidneys, t_{1/2} is estimated at 16-33 yr (52,53).

Plasma concentrations decrease rapidly during the first hr after injection, reaching a level that is <1% of the initial value at 24 hr. This level then decreases much more slowly (48).

After single administration of cadmium by oral or parenteral routes (concentration unspecified) the highest levels of cadmium were found initially in the liver. However, kidney levels of cadmium increased for up to eight months after exposure and could then exceed liver levels. The pancreas and spleen also showed relatively high concentrations (54,55).

The critical organ in long-term exposure to low concentrations of cadmium is the kidney. Initially cadmium-induced effects occur mainly in the proximal tubes, situated in the cortex of the kidney (56).

It has been shown that smoking cigarettes may significantly increase the body burden of cadmium (57).

After exposure to cadmium, high concentrations accumulate in the liver and kidney. After kidney damage has occurred excretion of cadmium increases considerably, therefore cadmium levels in the kidney are low compared with the liver (58).

~5% of cadmium ingested by humans is absorbed, but calcium and iron deficiency can increase this amount. The proportion of inhaled cadmium absorbed is dependent on particle size and solubility (58).

In five ♂ humans retention of ingested cadmium varied between 4% and 8%, normal human excretion via faeces is 30-50 µg day⁻¹ and via urine 102 µg day⁻¹ (16).

50 pregnant women were studied for placental transfer of cadmium following environmental exposure. Cadmium was detected in maternal erythrocytes and plasma, in placenta, and in erythrocytes and plasma of umbilical cord blood (59).

The main routes of exposure for humans are inhalation and ingestion; absorption through the skin is negligible. In individuals with iron deficiency, a gastrointestinal absorption rate of ≥20% is reported (60). Women with low

body-iron stores, as reflected by low serum ferritin levels, had on average, a gastrointestinal absorption rate twice as high (10%) as a control group of women. The highest individual absorption rate was 20% (61). Experimental and epidemiological evidence indicates that the biological $t_{1/2}$ in the body is extremely long (yrs). One subject given radioactive cadmium and examined periodically for the next 2 yr, showed a biological $t_{1/2}$ of 26 yr (62). In a study of the $t_{1/2}$ of cadmium in blood of five smelter workers who had previously experienced high cadmium exposure, repeated blood analysis carried out over a 10-13 yr period revealed short-term (75-128 days) and long-term (7-16 yr) $t_{1/2}$ components (63). The age-dependent increase in testicular Cd did not become apparent until after the 4th decade which appears not to implicate Cd in the aetiology of male infertility and in the genesis of glandular neoplasms. (64). Cadmium ions were detected in the liver, brain and digestive tract of the newborn (65).

Genotoxicity

In vitro human peripheral blood lymphocytes, dose-dependent inhibition of DNA synthesis, decreases in γ -interferon and tumour necrosis factor α reported (66). Murine sarcoma virus (MuSV) frameshift mutation positive (67). *In vivo* mouse bone cells 0.6-2.8 mg cadmium kg^{-1} induced increased frequency of chromatid breaks after 6 hr (68).

Other effects

Other adverse effects (human)

Workers in a cadmium plant exposed to high (unspecified doses) of cadmium and lead were found to have a high number of severe chromosome anomalies including sister chromatid exchanges, disturbance of spiralsation, chromosome translocations and ring and dicentric chromosomes (69).

Reports of workers exposed to fumes of cadmium metal or cadmium-containing materials indicate that the principal symptom of poisoning is respiratory distress pneumonitis, and oedema (both fatal and non-fatal) (70).

A case is reported of a 53-year-old man who was exposed to cadmium fumes while cutting an alloy containing about 10% cadmium with a butane torch for a period of 60-75 min. Four hours after finishing work he was admitted to hospital with progressive dyspnoea. He developed hypoxaemia and died of pneumonitis 19 days after exposure. He had elevated levels of cadmium in the blood and urine 15 days after exposure, and autopsy revealed accumulations in the kidney, liver and lung (71).

Exposure to lower cadmium concentrations for longer periods are likely to result in renal dysfunction and emphysema (72).

32 workers exposed to cadmium compounds 0.1-5.5 mg m^{-3} for 4-20 yr complained of bone pains.

Pseudofractures suggestive of osteomalacia were seen in two workers exposed for 16 and 19 yr but no histological confirmation of osteomalacia was obtained (73).

An inhibitory effect on blastogenesis in cultured human lymphocytes has been detected at Cd doses found in occupationally exposed subjects (74).

Low doses of Cd may have immunosuppressive effects (75).

Investigation of Cd-induced renal effects in 16 workers who had been shown five years earlier to have had tubular damage confirmed that damage was irreversible and that glomerular dysfunction after Cd exposure is irreversible and also progressive after exposure ceases (76).

Examination of 37 σ workers exposed to airborne cadmium showed their blood and urine cadmium concentrations to be higher than those of unexposed controls. No differences in the serum IgG, IgM, and IgA levels between the two groups were found. Monocyte counts in the exposed group were significantly increased compared with controls, but lymphocyte, neutrophil, and eosinophil counts were unchanged (77).

The Cd contents of liver, kidney, and various reproductive organs removed at necropsy from 41 men who had died suddenly were determined. Tissue concentrations of Cd increased with increasing age in all reproductive organs examined, with the epididymides and seminal vesicles containing the highest concentrations.

Investigations on 1987 participants (σ and f aged 20-80 years old) suggested that Ca metabolism is gradually affected as Cd accumulates in the body. The morbidity associated with this phenomenon in industrialised countries remains presently unknown (78).

Quantitative estimates of risk based on epidemiological data provide lower and more plausible estimates of lifetime risks than do estimates from a rodent bioassay. Epidemiological data suggest that the 8-hour permissible exposure limit should not exceed $5 \mu\text{g m}^{-3}$ to protect workers from kidney dysfunction and lung cancer over a working lifetime (79).

Any other adverse effects

Subcutaneous injection to rat, $2 \text{ mg Cd}^{2+} \text{ kg}^{-1} \text{ day}^{-1}$ for 2 wk resulted in kidney damage, including polyuria, glycosuria, phosphaturia and aminoaciduria, as observed in chronic cadmium intoxicated humans and experimental animals (65).

Legislation

Included in Schedule 5 (Release into Water: Prescribed Substances) Statutory Instruments No. 472, 1991 (80). Limited under EC Directive on Drinking Water Quality 80/778/EEC. Cadmium: maximum admissible concentration $5 \mu\text{g l}^{-1}$ (81).

HMIP Approved Codes of Practice and other Guidelines: Environmental Hygiene Guidance Notes: Cadmium – health and safety precautions (82).

Other comments

The toxicity of cadmium is dependent on the ability of the organism to absorb it. Therefore toxicity data refer to bioavailable forms such as the ion in solution or particulate matter.

Cytotoxicity, experimental toxicology, metabolic and environmental fate and human exposure to cadmium is extensively reviewed (83-89).

The main source of cadmium intake in non-occupationally exposed persons is in food, including sea-foods, grains and vegetables (90).

Toxicity and hazards reviewed (91).

Cadmium and its compounds are comprehensively reviewed (15).

Critical reviews on cadmium listed (92).

Cadmium bioaccumulation in pelagic seabirds reviewed (93).

Review of exposure data and body burdens of cadmium (94).

Studies on the effects of cadmium on the testes and reproductive organs reviewed (95,96).

Effects of cadmium on the cardiovascular system reviewed (97).

Cadmium in the human environment, toxicity and carcinogenicity reviewed (98).

Cadmium vapour is oxidised in air to form cadmium oxide. When reactive gas or vapour, such as carbon dioxide, water vapour, sulfur dioxide, sulfur trioxide or hydrogen chloride is present, cadmium vapour reacts to produce cadmium carbonate, hydroxide, sulfite, sulfate or chloride, respectively.

Genotoxic studies of Cd compounds published after 1985 reviewed (99).

Chronic effects of occupational exposure to kidney and the immune system reviewed (100).

Experiments were conducted in soilless culture to determine the absorption and accumulation of Cd in different parts of the tomato plant (*Lycopersicon esculentum* Mill) and fruits. Cd was transported to stems and branches, leaves and fruits. The concentration in the fruits was dependent on the Cd treatment applied (101).

Two-week-old *Pinus pinea* L., *Pinus pinaster* Ait., and *Fraxinus angustifolia* Vahl. seedlings grown for 4 wk in complete culture solution and a range of Cu and Cd concentrations, CuSO_4 ($0.012\text{--}5 \mu\text{M}$) and CdSO_4 ($0.0\text{--}5 \mu\text{M}$), suffered decreasing chlorophyll content with increasing metals content. *F. angustifolia* leaves of Cd-treated seedlings were chlorotic. Mn and Zn content of roots of all species decreased with increasing Cu and Cd concentrations; Ca and Mg uptake and distribution differed with species (102).

Biomagnification of metals in terrestrial ecosystems reviewed (103).

Cadmium toxicity and tolerance in vascular plants reviewed (104).

Cadmium can be discharged into the environment from manufacturing facilities for cadmium or zinc, because zinc contains a cadmium impurity, and from electroplating operations (105). Cadmium (1 and 2 mg l^{-1}) caused ultrastructural changes in plastids and heavy staining of the cell walls and mucilage of vegetative cells of *Ceramium ciliatum*. Carpospores remained unmodified (106).

Occurs as sludge from zinc sulfate purification. Occurs in incinerator emissions.

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C3 cadmium acetate



$\text{C}_4\text{H}_6\text{CdO}_4$

Mol. Wt. 230.50

CAS Registry No. 543-90-8

Synonyms acetic acid, cadmium salt; bis(acetoxy)cadmium; cadmium diacetate; C.I. 77185

EINECS No. 208-853-2

RTECS No. AF 7505000

Uses Colorant in glass, ceramics and textiles. Electroplating. Laboratory reagent. Separation of mercaptans from crude oils and gasolines.

Physical properties

M. Pt. 256°C B. Pt. decomp. Specific gravity 2.341

Solubility Water: freely soluble. Organic solvents: ethanol, methanol

Occupational exposure

FR-VME 0.05 mg m⁻³ (as Cd)

JP-OEL 0.05 mg m⁻³ (as Cd)

UK-LTEL MEL 0.025 mg m⁻³ (as Cd)

US-TWA 0.01 mg m⁻³ (inhalable fraction as Cd); 0.002 mg m⁻³ (respirable fraction as Cd)

UN No. 2570 Conveyance classification toxic substance

Supply classification harmful

Risk phrases Harmful by inhalation, in contact with skin and if swallowed (R20/21/22)

Safety phrases Keep out of reach of children (if sold to general public) – Do not breathe dust (S2, S22)

Ecotoxicity

Fish toxicity

Threespine stickleback exposed to 10 mg l⁻¹ died within 8-12 hr, steelhead trout exposed to 10 mg l⁻¹ died within 12-16 hr. Fish were acclimated for at least 60 hr. Test conditions: temperature 15°C; total hardness 67-120 mg l⁻¹; alkalinity 151-183 mg l⁻¹ (methyl orange); total dissolved solids 160-175 mg l⁻¹; pH 7.1 (1).

Bioaccumulation

Zebra fish were fed food contaminated with cadmium acetate at 10 mg kg⁻¹ over a 6 month period. Maximum residues in ♂ and ♀ were 5 and 13, respectively, on a dry weight basis (2).

Mammalian & avian toxicity

Acute data

LD₅₀ intraperitoneal mouse 14 mg kg⁻¹ (3).

After single intravenous injection (species unspecified) 2.5-25 mg kg⁻¹ caused severe endothelial damage in the small vessels of the peripheral nervous system and testis. Most pronounced changes were found in the liver (4-6).

Carcinogenicity and chronic effects

Sufficient evidence for carcinogenicity of cadmium and cadmium compounds to humans, sufficient evidence for carcinogenicity of cadmium compounds to animals, limited evidence for carcinogenicity of cadmium metal to animals, IARC classification group 1 (7).

Long-Evans rats (sex distribution unspecified) 5 mg l⁻¹ cadmium acetate in drinking water for life. Tumour incidence in cadmium-treated animals was similar to that in controls (8).

Cadmium acetate was not carcinogenic in a mouse-lung adenoma assay (9).

Teratogenicity and reproductive effects

A single subcutaneous injection to Wistar rats (17-21 days pregnant) 4.5 mg cadmium kg⁻¹ (administered as cadmium acetate) caused rapid development of severe placental damage and foetal death (10).

Genotoxicity

In vitro human lymphocytes in whole blood treated for 3 hr showed increased incidence of chromatid breaks, exchanges and fragments (11).

Legislation

Limited under EC Directive on Drinking Water Quality 80/778/EEC. Cadmium: maximum admissible concentration $5 \mu\text{g l}^{-1}$ (12).

Included in Schedule 5 (Release into Water: Prescribed Substances) Statutory Instrument No. 472, 1991 (13).

Other comments

Cadmium and its compounds have been extensively reviewed (7,14,15).

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c4 cadmium bromide



CdBr_2

Mol. Wt. 272.22

CAS Registry No. 7789-42-6

Synonyms cadmium dibromide

EINECS No. 232-165-1

RTECS No. EU 9935000

Uses Veterinary applications for control of roundworm. Photography. Lithography and engraving.

Physical properties

M. Pt. 568°C B. Pt. 963°C

Solubility Water: 570 g l^{-1} . Organic solvents: acetone, diethyl ether

Occupational exposure

FR-VME 0.05 mg m^{-3} (as Cd)

JP-OEL 0.05 mg m^{-3} (as Cd)

SE-LEVL 0.05 mg m⁻³ (as Cd) (total dust); 0.01 mg m⁻³ (as Cd) (respirable dust)
UK-LETL MEL 0.025 mg m⁻³ (as Cd)
US-TWA 0.01 mg m⁻³ (inhalable fraction as Cd); 0.002 mg m⁻³ (respirable fraction as Cd)
UN No. 2570 **Conveyance classification** toxic substance
Supply classification harmful
Risk phrases Harmful by inhalation, in contact with skin and if swallowed (R20/21/22)
Safety phrases Keep out of reach of children (if sold to general public) – Do not breathe dust (S2, S22)

Ecotoxicity

Fish toxicity

Threespine stickleback exposed to 10 mg l⁻¹ died within 16-24 hr; steelhead trout exposed to 10 mg l⁻¹ died within 6-8 hr. Fish were acclimated for at least 60 hr. Test conditions: temperature 15°C; total hardness 67-120 mg l⁻¹; alkalinity 151-183 mg l⁻¹ (methyl orange); total dissolved 160-175 mg l⁻¹; pH 7.1 (1).

Mammalian & avian toxicity

Carcinogenicity and chronic effects

Sufficient evidence for carcinogenicity of cadmium and cadmium compounds to humans, sufficient evidence for carcinogenicity of cadmium compounds to animals, limited evidence for carcinogenicity of cadmium metal to animals, IARC classification group 1 (2).

Legislation

Limited under EC Directive on Drinking Water Quality 80/778/EEC. Cadmium: maximum admissible concentration 5 µg l⁻¹ (3).
Included in Schedule 5 (Release into Water: Prescribed Substances) Statutory Instrument No. 472, 1991 (4).

Other comments

Cadmium and its compounds have been extensively reviewed (2,5,6).
Mutagenic potential of cadmium bromide assessed (7).

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C5 cadmium chloride



CdCl_2

Mol. Wt. 183.32

CAS Registry No. 10108-64-2

Synonyms caddy; cadmium dichloride; Vi-Cad

EINECS No. 233-296-7

RTECS No. EV 0175000

Uses Photography. Dyeing textiles. Special mirrors. Fungicide. Manufacture of cadmium yellow. In sulfide analysis to absorb hydrogen sulfide. Vacuum tube industry. Lubricant.

Physical properties

M. Pt. 568°C B. Pt. 960°C Specific gravity 4.047 at 25°C Volatility v.p. 10 mmHg at 656°C

Solubility Water: 1400 g l⁻¹ at 20°C. Organic solvents: acetone, slightly soluble in ethanol and methanol

Occupational exposure

FR-VME 0.05 mg m⁻³ (as Cd)

JP-OEL 0.05 mg m⁻³ (as Cd)

SE-LEVL 0.05 mg m⁻³ (as Cd) (total dust); 0.01 mg m⁻³ (as Cd) (respirable dust)

UK-LTEL MEL 0.025 mg m⁻³ (as Cd)

US-TWA 0.01 mg m⁻³ (inhalable fraction as Cd); 0.002 mg m⁻³ (respirable fraction as Cd)

UN No. 2570 Conveyance classification toxic substance

Supply classification toxic

Risk phrases May cause cancer – Toxic: danger of serious damage to health by prolonged exposure through inhalation and if swallowed (R45, R48/23/25)

Safety phrases Restricted to professional users – Avoid exposure – obtain special instruction before use – In case of accident or if you feel unwell, seek medical advice immediately (show label where possible) (S53, S45)

Ecotoxicity

Fish toxicity

Steelhead trout exposed to 10 mg l⁻¹ died within 6-8 hr. Fish were acclimated for at least 60 hr. Test conditions: temperature 15°C; total hardness 67-120 mg l⁻¹; alkalinity 151-183 mg l⁻¹ (methyl orange); total dissolved solids 160-175 mg l⁻¹; pH 7.1 (1).

Juvenile striped bass exposed to 0.5, 2.5 or 5 µg Cd l⁻¹ (as cadmium chloride) for 30-90 days. Recovery period 30 days in running seawater. Inhibition of gill tissue respiration observed, which recovered 60 days after exposure period. Enzyme activity was not affected (2).

White sucker larvae and young common shiners were exposed to cadmium chloride 6-200 µg Cd l⁻¹ (duration unspecified), relative growth rates were significantly reduced except at lowest concentration levels (3).

Rainbow trout (30 days) adults 10 and 25 µg l⁻¹, juveniles 1 and 5 µg l⁻¹. A significant reduction was seen in liver size, glycogen content, and body mass gain in both juvenile and adult fish. Plasma cortisol levels increased after exposure to the lower dose but decreased at the higher dose. In the adults, plasma T3 and T4 tended to increase. No significant differences in plasma glucose or cholesterol levels were detected between controls and exposed fish; plasma calcium levels were lower in exposed fish. The authors considered that long-term exposure to Cd at sub-lethal doses have adverse effects on the physiological status of the fish, mediated partly through alterations of endocrine function (4).

Invertebrate toxicity

EC₅₀ (96 hr) *Chlorella vulgaris* 3.7 mg l⁻¹. No-toxic-effect level 1.5 mg l⁻¹ (5).

LC₅₀ (96 hr) *Callinectes sapidus* 0.32, 4.7 and 11 mg Cd l⁻¹ at salinity 1, 15 and 35‰, respectively (6).

Aelosomas headlyi (10-14 day) no-observed-effect level for population growth 32 and 53.6 µg l⁻¹ (hard water 17.2 µg l⁻¹).

LC₅₀ (48 hr) *Aeolosomas headlyi* 4.98 and 1.2 mg l⁻¹ in hard and soft water, respectively (7).
 LC₅₀ (96 hr) *Gammarus pulex* 50 µg Cd l⁻¹ (administered as chloride) (8).
 EC₅₀ (60 min) sea urchin sperm 12-26 mg l⁻¹ (9).
 LC₅₀ (14, 21 day) *Daphnia magna* 24 and 14 µg Cd l⁻¹, respectively; completely inhibited at concentrations >3.2 µg l⁻¹ and time-dependent survival and reproduction were significantly reduced at 1.8 µg l⁻¹ (10).
Stichococcus bacillaris (96 hr) 8.2 and 16.5 mg l⁻¹ inhibited growth rate by 28% and 45%, respectively (11).
Zoogloea ramigera (sewage treatment bacteria) 30 hr exposure to 1, 3, 5 and 10 mg cadmium l⁻¹ (administered as the chloride). Prolonged lag phase and decrease in growth resulted (12).

Toxicity to other species

Low levels (1.0-100.0 µM) of cadmium chloride caused significant structural damage to isolated bullfrog corneas, including focal disruption and denuding of the apical endothelial membrane (13).

Bioaccumulation

Bay scallops were exposed for 96 hr to cadmium chloride at 2 mg l⁻¹, bioconcentration factor 50 (14).
 In laboratory experiments with gastropod molluscs, bioaccumulation rate occurred in a dose-dependent manner. The rate of Cd uptake for *Dorax serra* was 0.01 mg kg⁻¹ day⁻¹ and for *Bullio rhodostoma* was 0.16 mg kg⁻¹ day⁻¹ after exposure to cadmium at 20 µg l⁻¹ (administered as cadmium chloride). Most of the cadmium accumulated in the gill (15).
 Brook trout were exposed to cadmium chloride via water or by injection. Exposure in water at 1 µg l⁻¹ showed greatest uptake in gills, kidney and liver (16).
Uca pugilator (24 hr) 1 mg Cd l⁻¹ (as cadmium chloride) accumulated in hepatopancreas and gill (17).
 Adult frogs (*Rana ridibunda*) were exposed to 200 ppm cadmium chloride for 10 days and subsequently transferred to clean water for 30 days. Investigations showed that (a) cadmium is mainly accumulated in the liver and kidneys, (b) during the detoxification period cadmium was most probably mobilised from the peripheral tissues to the liver and kidneys, (c) the striated muscle of this frog contained cadmium below the detection limits, (d) exposure of cadmium resulted in a significant increase of hepatic metallothioneins and GSH content even during the detoxification period (18).

Environmental fate

Nitrification inhibition

Soil composition 0.8% organic carbon and 55% clay was incubated with concentrations of between 50 and 500 mg cadmium kg⁻¹ (administered as the chloride) for 8 wk. Ammonia nitrogen concentration increased for 7 days at all treatment levels then decreased for the low concentrations. Nitrate levels increased. Significant accumulation of nitrate nitrogen was observed. Fungal and bacterial soil populations were significantly decreased (19).

Mammalian & avian toxicity

Acute data

LD₅₀ oral mouse, rat 60, 88 mg kg⁻¹, respectively (20,21).
 LD₅₀ oral mouse 93.7 mg kg⁻¹ (22).
 LC₉₀ (30 min) inhalation dog 420 mg m⁻³ (23).
 LD₅₀ intravenous mouse 3.5 mg kg⁻¹ (24).

Sub-acute and sub-chronic data

Oral adult mallard ducks fed on a diet of 2, 20 or 200 mg kg⁻¹ cadmium chloride were sacrificed at 30-day intervals. Cadmium accumulation was dose and time-dependent, highest concentration found in liver and kidney (25).
 LC₅₀ (14 day) Japanese quail 2440 mg kg⁻¹ (26).
 Oral ♂ rat (6 month) 1-4 µg kg⁻¹ cadmium chloride in drinking water caused changes in calcium metabolism and bone structure characteristic of osteomalacia (27).
 Oral ♂ Sprague-Dawley rats. Group 1, oral saline controls. Group 2, single dose CdCl₂ 80 mg kg⁻¹. Group 3, four repeated doses 20 mg kg⁻¹ every 24 h. Group 4, as for group 3 followed by a single acute dose after 24 h. Serum thyroxine and triiodothyronine levels fell gradually in treated rats over the duration of the experiment, whilst

cholesterol content gradually increased, demonstrating that oral administration of cadmium chloride enhances the risk of disturbances that might occur in the thyroid function as well as cholesterol metabolism (28). Subcutaneous ♂ mice (30 days) decreased serum thyroxine and triiodothyronine concentrations and weights of testis, vas deferens, Cowper's gland, and prostate gland. The effects were dose-dependent. Cadmium appears primarily to inhibit the synthesis and (or) release of thyroxine at the glandular level and in higher doses it inhibits peripheral conversion of thyroxine into triiodothyronine (29).

♀ Rats administered 0.25, 0.5 or 1.0 mg kg⁻¹ wk⁻¹ CdCl₂ for 14, 18 or 22 wk. Cd treatment caused a slight decrease in body weight but failed to alter the weight of the endocrine organs. The pituitary gland accumulated more Cd than the adrenals, and the lowest levels were found in the ovary. Even the highest dose of 1.0 mg kg⁻¹ wk⁻¹ failed to alter the ovarian cycle and production of progesterone and estradiol-17β (30).

Oral rabbit (6 wk) 1 mg CdCl₂ wk⁻¹ either with or without 1 ml Liv-52 orally daily. Liv-52 treatment reduced significantly the histological and biochemical abnormalities resulting from Cd treatment. The results confirm the protective role of this drug during Cd toxicity (31).

Oral hamster (10 wk) 10 mg Cd l⁻¹ as (CdCl₂) in drinking water with or without the simultaneous administration of vitamin C (1 g l⁻¹) in drinking water. Cytosolic glutathione S-transferase and serum alanine aminotransferase levels were significantly changed by cadmium administration but these changes were effectively eliminated by administration of vitamin C. Long-term supplementation with vitamin C may be effective in the protection of hepatic enzymes against cadmium toxicity (32).

Carcinogenicity and chronic effects

Sufficient evidence for carcinogenicity of cadmium and cadmium compounds to humans, sufficient evidence for carcinogenicity of cadmium compounds to animals, limited evidence for carcinogenicity of cadmium metal to animals, IARC classification group 1 (33).

Inhalation rat (18 month) 12.5, 25 and 50 µg m⁻³ induced 15, 53 and 71% incidence of lung cancers, respectively. Tumours included adenocarcinomas, epidermoid carcinomas, mucoepidermoid carcinomas and combined epidermoid and adenocarcinomas (34).

Subcutaneous rat (12 month) 1 mg kg⁻¹ daily caused osteoporosis and osteosclerosis (35).

Oral rat (91 wk) 200 mg cadmium chloride l⁻¹ in drinking water. Morphological changes to kidney included degenerative changes in the proximal convoluted tubules, proliferation of smooth endoplasmic reticulum, vacuolisation and coagulative necrosis of the tubular cells (36).

Inhalation mouse, golden hamster (14 month) 30 and 90 µg m⁻³ cadmium chloride significantly increased incidence of alveolar hyperplasia and interstitial fibrosis (37).

Teratogenicity and reproductive effects

Subcutaneous ♂ Fischer (F344) and Wistar (WF) rats 10 or 30 µmol CdCl₂ kg⁻¹ caused the typical spectrum of testicular lesions. Pretreatment of F344 rats with progesterone (100 mg kg⁻¹ s.c.) at -48, -24 and 0 h followed by 20 µmol CdCl₂ unexpectedly caused 53% mortality. In contrast to previously reported data the results indicate that progesterone pretreatment increases the lethality of cadmium in ♂ F344 rats and had no effect on cadmium-induced testicular toxicity in F344 and WF rats (38).

Single subcutaneous injection Wistar rats (17-21 day pregnant) 4.5 mg cadmium kg⁻¹ (administered as chloride) caused rapid development of severe placental damage and foetal death (39).

Metabolism and toxicokinetics

Inhalation Syrian hamster (concentration unspecified), 25-35% of the initial exposure was present in liver, kidney and skull and 50% in lung after 3 wk (40).

Dermal rabbit painted with an unspecified concentration 5 times in 3 wk accumulated 0.4-0.6% cadmium, while mice skin painted 1 to 4 times in 7 days accumulated 0.2-0.8% of applied dose (41).

Genotoxicity

In vivo rat oocytes, cadmium accumulation in ovary and aneuploidy reported (42).

HeLa DNA synthesis inhibition test without metabolic activation positive at 45 mg l⁻¹. However, in 2/4 tests carried out cadmium chloride gave negative results (43).

Other effects

Other adverse effects (human)

Cadmium-induced changes to progesterone production in cultured human ovarian granulosa cells after exposure to 8-64 μM CdCl_2 for 2-48 hr were investigated. Cadmium caused a decrease in progesterone production in unstimulated and FSH-supported cells, depending on its concentration and exposure time. FSH (100 ng ml^{-1}) protected against Cd-induced suppression of progesterone production. The lowest Cd concentration that was able to reduce progesterone production (16 μM) was around 3.5 \times higher than levels reported in the ovary of a women smoker (44).

Legislation

Limited under EC Directive on Drinking Water Quality 80/778/EEC. Cadmium: maximum admissible concentration 5 $\mu\text{g l}^{-1}$ (45).

Included in Schedule 5 (Release into Water: Prescribed Substances) Statutory Instrument No. 472, 1991 (46).

Covered in the UK by the Control of Carcinogenic Substances, Control of substances Hazardous to Health Regulations 1988 (47).

Other comments

In marine water, cadmium is present predominantly as soluble chloride complexes which are not available to fish (48).

Oral σ Wistar albino rats (2-months-old) were exposed during 30 days to 200 ppm Cd (as CdCl_2), 0.1 ppm Se (as Na-selenite), or to the same dosages of Cd+Se, simultaneously. The results indicated that Se only partially improved the antioxidant defense system that is insufficient to prevent Cd-induced nephrotoxicity (49).

Cadmium and its compounds have been extensively reviewed (36,50,51).

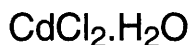
Experimental toxicology and human health effects reviewed (52,53).

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c6 cadmium chloride monohydrate



$\text{CdCl}_2 \cdot \text{H}_2\text{O}$

Mol. Wt. 201.33

CAS Registry No. 35658-65-2

RTECS No. EV 0190000

Occupational exposure

FR-VME 0.05 mg m⁻³ (as Cd)

JP-OEL 0.05 mg m⁻³ (as Cd)

SE-LEVL 0.05 mg m⁻³ (as Cd) (total dust); 0.01 mg m⁻³ (as Cd) (respirable dust)

UK-LTEL MEL 0.025 mg m⁻³ (as Cd)

US-TWA 0.01 mg m⁻³ (inhalable fraction as Cd); 0.002 mg m⁻³ (respirable fraction as Cd)

UN No. 2570 **Conveyance classification** toxic substance

Supply classification toxic

Risk phrases May cause cancer – Toxic: danger of serious damage to health by prolonged exposure through inhalation and if swallowed (R45, R48/23/25)

Safety phrases Restricted to professional users – Avoid exposure – obtain special instruction before use – In case of accident or if you feel unwell, seek medical advice immediately (show label where possible) (S53, S45)

Mammalian & avian toxicity

Carcinogenicity and chronic effects

Sufficient evidence for carcinogenicity of cadmium and cadmium compounds to humans, sufficient evidence for carcinogenicity of cadmium compounds to animals, limited evidence for carcinogenicity of cadmium metal to animals, IARC classification group 1 (1).

Teratogenicity and reproductive effects

TD_{Lo} oral rat 179 mg kg⁻¹ caused reproductive paternal effects to testes, epididymis and sperm duct (2).

Legislation

Limited under EC Directive on Drinking Water Quality 80/778/EEC. Cadmium: maximum admissible concentration 5 µg l⁻¹ (3).

Included in Schedule 5 (Release into Water: Prescribed Substances) Statutory Instrument No. 472, 1991 (4).

Other comments

Cadmium and its compounds are comprehensively reviewed (1,5,6).

References

1. *IARC Monograph* 1993, **58**, 119-237.
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c7 cadmium fluoride



CdF₂

Mol. Wt. 150.41

CAS Registry No. 7790-79-6

Synonyms cadmium fluorure (French)

EINECS No. 232-222-0

RTECS No. EV 0700000

Uses Catalyst. Coating metals. Manufacture of glass. Nuclear reactor control.

Physical properties

M. Pt. 1049°C B. Pt. 1748°C Specific gravity 6.64 Volatility v.p. 1 mmHg at 1112°C

Solubility Water: 43 g l⁻¹ at 25°C

Occupational exposure

DE-MAK 2.5 mg m⁻³ (as F) (inhalable dust fraction)

FR-VME 0.05 mg m⁻³ (as Cd)

JP-OEL 0.05 mg m⁻³ (as Cd)

SE-LEVL 0.05 mg m⁻³ (as Cd) (total dust); 0.01 mg m⁻³ (as Cd) (respirable dust)
UK-LTEL MEL 0.025 mg m⁻³ (as Cd)
US-TWA 0.01 mg m⁻³ (inhalable fraction as Cd); 0.002 mg m⁻³ (respirable fraction as Cd)
UN No. 2570 **Conveyance classification** toxic substance
Supply classification toxic
Risk phrases Toxic by inhalation and if swallowed – Danger of cumulative effects – Possible risk of irreversible effects (R23/25, R33, R40)
Safety phrases Keep locked up and out of the reach of children (if sold to general public) – Do not breathe dust – In case of accident or if you feel unwell, seek medical advice immediately (show label where possible) (S1/2, S22, S45)

Mammalian & avian toxicity

Carcinogenicity and chronic effects

Sufficient evidence for carcinogenicity of cadmium and cadmium compounds to humans, sufficient evidence for carcinogenicity of cadmium compounds to animals, limited evidence for carcinogenicity of cadmium metal to animals, IARC classification group 1 (1).

Legislation

Limited under EC Directive on Drinking Water Quality 80/778/EEC. Cadmium: maximum admissible concentration 5 µg l⁻¹ (2).
Included in Schedule 5 (Release into Water: Prescribed Substances) Statutory Instrument No. 472, 1991 (3).

Other comments

Cadmium and its compounds have been extensively reviewed (4,5).
Reviews on experimental toxicology and human health effects listed (6).

References

1. IARC Monograph 1993, 58, 119-237.
2. EC Directive Relating to the Quality of Water Intended for Human Consumption 1982, 80/778/EEC, Office for Official Publications of the European Communities, 2 rue Mercier, L-2985 Luxembourg.
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6. ECETOC Technical Report No. 71 1996, European Centre for Ecotoxicology and Toxicology of Chemicals, 4 Avenue E. Van Nieuwenhuyse (Bte 6), B-1160 Brussels, Belgium

c8 cadmium fluorosilicate



CdF₆Si

Mol. Wt. 254.49

CAS Registry No. 17010-21-8

Synonyms TL1070; cadmium hexafluorosilicate

EINECS No. 241-084-0

RTECS No. EV 0875000

Occupational exposure

FR-VME 0.05 mg m⁻³ (as Cd)

JP-OEL 0.05 mg m⁻³ (as Cd)

SE-LEVL 0.05 mg m⁻³ (as Cd) (total dust); 0.01 mg m⁻³ (as Cd) (respirable dust)

UK-LETL MEL 0.025 mg m⁻³ (as Cd)

US-TWA 0.01 mg m⁻³ (inhalable fraction as Cd); 0.002 mg m⁻³ (respirable fraction as Cd)

UN No. 2570 **Conveyance classification** toxic substance

Supply classification toxic

Risk phrases Toxic by inhalation and if swallowed – Danger of cumulative effects – Possible risk of irreversible effects (R23/25, R33, R40)

Safety phrases Keep locked up and out of the reach of children (if sold to general public) – Do not breathe dust – In case of accident or if you feel unwell, seek medical advice immediately (show label where possible) (S1/2, S22, S45)

Mammalian & avian toxicity

Carcinogenicity and chronic effects

Sufficient evidence for carcinogenicity of cadmium and cadmium compounds to humans, sufficient evidence for carcinogenicity of cadmium compounds to animals, limited evidence for carcinogenicity of cadmium metal to animals, IARC classification group 1 (1).

Legislation

Limited under EC Directive on Drinking Water Quality 80/778/EEC. Cadmium: maximum admissible concentration 5 µg l⁻¹ (2).

Included in Schedule 5 (Release into Water: Prescribed Substances) Statutory Instrument No. 472, 1991 (3).

Other comments

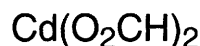
Cadmium and its compounds have been extensively reviewed (1,4,5).

Reviews on experimental toxicology and human health effects listed (6).

References

1. IARC Monograph 1993, **58**, 119-237.
2. EC Directive Relating to the Quality of Water Intended for Human Consumption 1982, 80/778/EEC, Office for Official Publications of the European Communities, 2 rue Mercier, L-2985 Luxembourg.
3. S. I. 1991 No. 472 *The Environmental Protection (Prescribed Process and Substances) Regulations* 1991, HMSO, London, UK.
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6. ECETOC Technical Report No. 71 1996, European Centre for Ecotoxicology and Toxicology of Chemicals, 4 Avenue E. Van Nieuwenhuyse (Bte 6), B-1160 Brussels, Belgium

c9 cadmium formate



C₂H₂CdO₄

Mol. Wt. 202.45

CAS Registry No. 4464-23-7

Synonyms formic acid, cadmium salt

EINECS No. 224-729-0

RTECS No. LQ 5550000

Physical properties

M. Pt. decomp. **Specific gravity** 2.44

Occupational exposure

FR-VME 0.05 mg m⁻³ (as Cd)

JP-OEL 0.05 mg m⁻³ (as Cd)

UK-LTEL MEL 0.025 mg m⁻³ (as Cd)

US-TWA 0.01 mg m⁻³ (inhalable fraction as Cd); 0.002 mg m⁻³ (respirable fraction as Cd)

UN No. 2570 **Conveyance classification** toxic substance

Supply classification toxic

Risk phrases Toxic by inhalation and if swallowed – Danger of cumulative effects – Possible risk of irreversible effects (R23/25, R33, R40)

Safety phrases Keep locked up and out of the reach of children (if sold to general public) – Do not breathe dust – In case of accident or if you feel unwell, seek medical advice immediately (show label where possible) (S1/2, S22, S45)

Mammalian & avian toxicity

Carcinogenicity and chronic effects

Sufficient evidence for carcinogenicity of cadmium and cadmium compounds to humans, sufficient evidence for carcinogenicity of cadmium compounds to animals, limited evidence for carcinogenicity of cadmium metal to animals, IARC classification group 1 (1).

Legislation

Limited under EC Directive on Drinking Water Quality 80/778/EEC. Cadmium: maximum admissible concentration 5 µg l⁻¹ (2).

Included in Schedule 5 (Release into Water: Prescribed Substances) Statutory Instrument No. 472, 1991 (3).

Other comments

Cadmium and its compounds are comprehensively reviewed (1,4,5).

Adsorption of cadmium from soils increased with increasing solubility of the cadmium compounds. Cadmium formate is very soluble, therefore if present would be expected to be easily adsorbed.

References

1. *IARC Monograph* 1993, **58**, 119-237.
2. *EC Directive Relating to the Quality of Water Intended for Human Consumption* 1982, 80/778/EEC, Office for Official Publications of the European Communities, 2 rue Mercier, L-2985 Luxembourg.
3. *S. I. 1991 No. 472 The Environmental Protection (Prescribed Processes and Substances) Regulations* 1991, HMSO, London, UK.
4. *Environmental Health Criteria 134: Cadmium* 1992, WHO, Geneva, Switzerland.
5. *Environmental Health Criteria 135: Cadmium – Environmental Aspects* 1992, WHO, Geneva, Switzerland

c10 cadmium iodide



CdI₂

Mol. Wt. 366.22

CAS Registry No. 7790-80-9

Synonyms cadmium diiodide

EINECS No. 232-223-6

RTECS No. EV 1290000

Uses Used in lithography, engraving, photography. In electrodeposition of cadmium. Manufacture of phosphors. In chemical analysis.

Physical properties

M. Pt. 388°C (α -form), 404°C (β -form) **B. Pt.** 787°C **Specific gravity** 5.67 (α -form), 5.30 (β -form)
Solubility Water: 862 g l⁻¹ at 25°C. Organic solvents: acetone, diethyl ether, ethanol

Occupational exposure

FR-VME 0.05 mg m⁻³ (as Cd)

JP-OEL 0.05 mg m⁻³ (as Cd)

SE-LEVL 0.05 mg m⁻³ (as Cd) (total dust); 0.01 mg m⁻³ (as Cd) (respirable dust)

UK-LTEL MEL 0.025 mg m⁻³ (as Cd)

US-TWA 0.01 mg m⁻³ (inhalable fraction as Cd); 0.002 mg m⁻³ (respirable fraction as Cd)

UN No. 2570 **Conveyance classification** toxic substance

Supply classification toxic

Risk phrases Toxic by inhalation and if swallowed – Danger of cumulative effects – Possible risk of irreversible effects (R23/25, R33, R40)

Safety phrases Keep locked up and out of the reach of children (if sold to general public) – Do not breathe dust – In case of accident or if you feel unwell, seek medical advice immediately (show label where possible) (S1/2, S22, S45)

Mammalian & avian toxicity

Acute data

LD₅₀ oral mouse, rat 166 mg kg⁻¹ (1).

Carcinogenicity and chronic effects

Sufficient evidence for carcinogenicity of cadmium and cadmium compounds to humans, sufficient evidence for carcinogenicity of cadmium compounds to animals, limited evidence for carcinogenicity of cadmium metal to animals, IARC classification group 1 (2).

Teratogenicity and reproductive effects

Oral pregnant rat (19 day) 1 mg cadmium kg⁻¹ (administered as the iodide) caused substantial foetal weight loss. ♀ reproduction, foetal organ weights and growth of rats in the first generation were also affected (3).

Legislation

Limited under EC Directive on Drinking Water Quality 80/778/EEC. Cadmium: maximum admissible concentration 5 µg l⁻¹ (4).

Included in Schedule 5 (Release into Water: Prescribed Substances) Statutory Instrument No. 472, 1991 (5).

Other comments

Cadmium and its compounds have been extensively reviewed (2,6,7).

References

1. Takasenko, N. Yu. *J. Hyg. Epidemiol. Microbiol. Immunol.* 1974, **18**, 144-153.
2. *IARC Monograph* 1993, **58**, 119-237.
3. Khalilou, S. Z. *Gig. Sanit.* 1985, **8**, 11-14 (Russ.) (*Chem. Abstr.* **103**, 117769u).
4. *EC Directive Relating to the Quality of Water Intended for Human Consumption* 1982, 80/778/EEC, Office for Official Publications of the European Communities, 2 rue Mercier, L-2985 Luxembourg.
5. *S. I.* 1991 No. 472 *The Environmental Protection (Prescribed Processes and Substances) Regulations* 1991, HMSO, London, UK.
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7. *Environmental Health Criteria 135: Cadmium – Environmental Aspects* 1992, WHO, Geneva, Switzerland

CdO

CdO

Mol. Wt. 128.41

CAS Registry No. 1306-19-0

Synonyms cadmium monoxide; cadmium oxide fume; cadmium fume; NCI-C02551

EINECS No. 215-146-2

RTECS No. EV 1925000

Uses Glass. Batteries. Catalyst for organic reactions. Semiconductors. Cadmium electroplating. Ceramic glazes. Acaricide in veterinary medicine.

Physical properties

M. Pt. amorphous <1426°C; cubic <1426°C B. Pt. amorphous 900-1000°C (decomp.); cubic 1559°C (sublimes)

Specific gravity amorphous 6.95; cubic 8.15 Volatility v.p. 1 mmHg at 1000°C

Occupational exposure

FR-VME 0.05 mg m⁻³ (as Cd)

JP-OEL 0.05 mg m⁻³ (as Cd)

SE-LEVL 0.05 mg m⁻³ (as Cd) (total dust); 0.01 mg m⁻³ (as Cd) (respirable dust)

UK-LTEL MEL 0.025 mg m⁻³ (fume) (as Cd) UK-STEL MEL 0.05 mg m⁻³ (fume) (as Cd)

US-TWA 0.01 mg m⁻³ (inhalable fraction as Cd); 0.002 mg m⁻³ (respirable fraction as Cd)

UN No. 2570 Conveyance classification toxic substance

Supply classification toxic

Risk phrases May cause cancer by inhalation – Harmful if swallowed – Toxic: danger of serious damage to health by prolonged exposure through inhalation and if swallowed (R49, R22, R48/23/25)

Safety phrases Restricted to professional users – Avoid exposure – obtain special instruction before use – In case of accident or if you feel unwell, seek medical advice immediately (show label where possible) (S53, S45)

Ecotoxicity

Bioaccumulation

Non-accumulative or low-accumulative (1).

Mammalian & avian toxicity

Acute data

LD₅₀ oral rat, mouse 72 mg kg⁻¹ (2).

LC₅₀ (10 min) inhalation mouse, rat 340, 780 mg m⁻³, respectively (3).

LC₅₀ (15 min) inhalation rabbit, guinea pig 3000 mg m⁻³ (3).

LD₅₀ intraperitoneal rat 12 mg kg⁻¹ (4).

Carcinogenicity and chronic effects

Limited evidence for carcinogenicity to humans, sufficient evidence for carcinogenicity to animals, IARC classification group 2A for cadmium and its compounds (5).

Inhalation rat (18 month) >30 µg Cd m⁻³ exposure to both fumes and dust, induced bronchoalveolar benign and malignant adenomas, squamous cell carcinomas. No primary tumour was found with cadmium oxide fumes at 10 µg Cd m⁻³ or cadmium oxide dust at 30 µg Cd m⁻³ when combined with a zinc oxide aerosol (6).

In a study of 458 workers exposed to high concentrations of cadmium oxide for at least one year, eight prostatic cancers were observed compared to two predicted (7).

Metabolism and toxicokinetics

Inhalation ♂ F344/N rats 0.0, 0.10, 0.25 or 1.0 mg m⁻³ 6 hr day⁻¹, 5 day wk⁻¹ for 13 wk. Accumulated lung burdens were not directly proportional to the exposure concentration, but became progressively less than

expected as exposure concentrations increased. Lung clearance half-lives did not alter significantly with exposure concentration. The concentration of cadmium in the blood was very low in all exposed animals, probably due to rapid clearance from the blood to the kidney and liver. The concentration of cadmium in the kidney was linearly proportional to the accumulated lung burden, and it was concluded that kidney cadmium concentrations should be well below the toxic threshold when lung burdens reach steady-state (8).

Irritancy

Irritating to the eyes and skin (species unspecified) (9).

Genotoxicity

Salmonella typhimurium TA98, TA100, TA1535, TA1537 with metabolic activation negative (10).

Other effects

Other adverse effects (human)

Vapour inhalation can lead to severe respiratory distress, cough, chest pain and dyspnoea, with the onset of symptoms 4-10 hr after exposure. Other symptoms include nausea, vomiting, chills and fever. The first symptoms following ingestion are nausea, vomiting, diarrhoea, muscular cramps and salivation (9).

A fatality occurred after 1 hr exposure to 50 mg m⁻³ cadmium oxide fumes from a furnace (11).

A study of 39 cadmium workers exposed to cadmium oxide dust for more than 15 yr found 44% had a history of renal stone formation (12).

Six workers exposed to cadmium oxide dust suffered from pains in the back and limbs and showed multiple pseudofractures when examined by X-ray and had osteomalacia (13).

72 ♀ and 20 ♂ workers at a battery factory exposed to cadmium oxide dust 0.04-0.5 mg m⁻³ showed increased prevalence of hypertension and absence from work due to hypertension and ischaemic heart disease (14).

Legislation

Limited under EC Directive on Drinking Water Quality 80/778/EEC. Cadmium: maximum admissible concentration 5 µg l⁻¹ (15).

Included in Schedule 5 (Release into Water: Prescribed Substances) Statutory Instrument No. 472, 1991 (16).

Other comments

Reviews on experimental toxicology, physico-chemical properties, environmental effects, exposure levels and human health effects listed (17).

Cadmium and its compounds have been extensively reviewed (18,19).

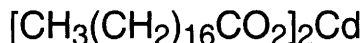
Cadmium oxide is insoluble in water, but there is a lack of information on the solubility of these compounds in biological fluids. Water-insoluble compounds can be converted into water-soluble salts under the influence of oxygen and acids.

References

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c12 cadmium stearate



$\text{C}_{36}\text{H}_{70}\text{CdO}_4$

Mol. Wt. 679.36

CAS Registry No. 2223-93-0

Synonyms octadecanoic acid, cadmium salt; stearic acid, cadmium salt; Synpro Cadmium Stearate

EINECS No. 218-743-6

RTECS No. RG 1050000

Uses Component of PVC heat and UV stabilisers.

Occupational exposure

FR-VME 0.05 mg m⁻³ (as Cd)

JP-OEL 0.05 mg m⁻³ (as Cd)

UK-LTEL MEL 0.025 mg m⁻³ (as Cd)

US-TWA 0.01 mg m⁻³ (inhalable fraction as Cd); 0.002 mg m⁻³ (respirable fraction as Cd)

UN No. 2570 **Conveyance classification** toxic substance

Supply classification harmful

Risk phrases Harmful by inhalation, in contact with skin and if swallowed (R20/21/22)

Safety phrases Keep out of reach of children (if sold to general public) – Do not breathe dust (S2, S22)

Mammalian & avian toxicity

Acute data

LD₅₀ oral rat 1125 mg kg⁻¹ (1).

LD₅₀ oral mouse 590 mg kg⁻¹ (2).

LC₅₀ (2 hr) inhalation rat 130 mg m⁻³ (3).

Carcinogenicity and chronic effects

Sufficient evidence for carcinogenicity of cadmium and cadmium compounds to humans, sufficient evidence for carcinogenicity of cadmium compounds to animals, limited evidence for carcinogenicity of cadmium metal to animals, IARC classification group 1 (4).

Other effects

Any other adverse effects

Single intratracheal administration of 10 mg to rats caused the development of chronic inflammatory changes, pneumonia, pneumosclerosis and lung emphysema. Oral mice 590 mg kg⁻¹ (LD₅₀ value) caused dystrophic changes in the heart, liver and kidneys and local necrosis of the gastrointestinal mucosa (5).

Legislation

Limited under EC Directive on Drinking Water Quality 80/778/EEC. Cadmium: maximum admissible concentration $5 \mu\text{g l}^{-1}$ (6).

Included in Schedule 5 (Release into Water: Prescribed Substances) Statutory Instrument No. 472, 1991 (7).

Other comments

Cadmium and its compounds have been extensively reviewed (8,9).

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c13 cadmium sulfate



CdO_4S

Mol. Wt. 208.47

CAS Registry No. 10124-36-4

Synonyms sulfuric acid, cadmium salt

EINECS No. 233-331-6

RTECS No. EV 2700000

Uses In electrodeposition of cadmium, copper and nickel; in phosphors. Manufacture of standard cadmium elements. Catalyst in the Marsh test for arsenic, determination of hydrogen sulfide and detection of fumaric acid. Used as a nematocide. Used in the manufacture of cadmium salts of long-chain fatty acids and as stabilisers for plastics.

Physical properties

M. Pt. 1000°C **Specific gravity** 4.691 at 20°C **Volatility** v.p. 1 mmHg at 394°C

Solubility Water: 755 g l^{-1} . Organic solvents: acetone, ethanol

Occupational exposure

FR-VME 0.05 mg m^{-3} (as Cd)

JP-OEL 0.05 mg m^{-3} (as Cd)

SE-LEVL 0.05 mg m^{-3} (as Cd) (total dust); 0.01 mg m^{-3} (as Cd) (respirable dust)

UK-LTEL MEL 0.025 mg m^{-3} (as Cd)

US-TWA 0.01 mg m^{-3} (inhalable fraction as Cd); 0.002 mg m^{-3} (respirable fraction as Cd)

UN No. 2570 **Conveyance classification** toxic substance

Supply classification toxic

Risk phrases May cause cancer by inhalation – Harmful if swallowed – Toxic: danger of serious damage to health by prolonged exposure through inhalation and if swallowed (R49, R22, R48/23/25)

Safety phrases Restricted to professional users – Avoid exposure – obtain special instruction before use – In case of accident or if you feel unwell, seek medical advice immediately (show label where possible) (S53, S45)

Ecotoxicity

Fish toxicity

Rainbow trout were exposed to $2 \mu\text{g l}^{-1}$ in constantly flowing hard water for 234 days. Statistically significant changes were not detectable (1).

LC₅₀ (270 day) bluegill sunfish $80 \mu\text{g Cd l}^{-1}$ (in hard water). Adult fish spawned at 239 and $2140 \mu\text{g Cd l}^{-1}$ but most larvae were severely crippled 6 days after hatching at these concentrations. Highest cadmium residues were found in liver, intestine and caecum and kidney. Cadmium concentrations increased with exposure concentration in gill, liver, intestine and caecum but not in kidney (2).

LC₅₀ (35 day) fathead minnow $37\text{--}57 \mu\text{g l}^{-1}$ continuous-flow bioassay. Highest concentration decreased survival of embryos (3).

Invertebrate toxicity

EC₅₀ (96 hr) *Daphnia magna* $5 \mu\text{g l}^{-1}$ (4).

LC₅₀ (96 hr) *Gammarus pulex* 0.68 mg l^{-1} (4).

Pseudomonas marina $1\text{--}25 \text{ mg Cd l}^{-1}$ (administered as sulfate for unspecified duration) caused lengthened lag-time, reduced growth-rate, reduced biomass and oxygen-uptake and a decrease in the activity of dehydrogenase and alkaline phosphatase. IC₅₀ for inhibition of biomass and growth rate were 11 and 11.5 mg l^{-1} , respectively (5).

LC₅₀ (14–21 day) *Daphnia magna* 24 and $14 \mu\text{g l}^{-1}$ cadmium, respectively. No effect on mortality was observed at $3.2 \mu\text{g l}^{-1}$ (6).

LC₅₀ (6 wk) *Hyalella azteca* $1 \mu\text{g l}^{-1}$ and *Gammarus fasciatus* $3.2 \mu\text{g l}^{-1}$ (7).

In a model ecosystem of *Daphnia* sp. phytoplankton were exposed to 1, 5 and $15 \mu\text{g Cd l}^{-1}$ (administered as cadmium sulfate). The *Daphnia* population collapsed after 9 wk of treatment with $5 \mu\text{g Cd l}^{-1}$ and chlorophyll levels increased. Exposure to $15 \mu\text{g Cd l}^{-1}$ caused the *Daphnia* population to collapse after 5 wk but chlorophyll levels remained at pre-exposure levels. No effects were observed at the $1 \mu\text{g Cd l}^{-1}$ level (8).

Environmental fate

Nitrification inhibition

Cadmium at $\geq 500 \text{ ppm}$ altered urea mineralisation in soil with ammonium, nitrate, and nitrite levels affected.

Both bacterial and fungal populations were lowered by all Cd concentrations. Cd at 100 and 500 ppm lowered actinomycetes populations, whereas lower Cd levels had no effect. The organisms showed some adaptation to Cd after 6 wk (9).

Adsorption and retention

Clay soils have a high capacity for adsorbing cadmium ions (10).

Mammalian & avian toxicity

Acute data

LD₅₀ oral mouse $46\text{--}47 \text{ mg kg}^{-1}$ (11).

LD_{Lo} oral dog 105 mg kg^{-1} (12).

LD₅₀ intraperitoneal mouse $12\text{--}76 \text{ mg kg}^{-1}$ (13).

LD_{Lo} subcutaneous dog 27 mg kg^{-1} (14).

Sub-acute and sub-chronic data

Subcutaneous rabbits (1–12 month) $0.65 \text{ mg Cd kg}^{-1}$ (administered as cadmium sulfate) 6 day wk⁻¹ caused proteinuria (15).

Inhalation ♂ rat (4 months) 0.3 and 3 mg m^{-3} 4 hr day⁻¹ showed decreased serum and urinary calcium concentrations compared with controls. Inhalation ♀ rats 2.8 mg m^{-3} , 3 hr wk⁻¹ during pregnancy showed radiological evidence of osteoporosis in addition to hypocalcaemia (16).

Carcinogenicity and chronic effects

Sufficient evidence for carcinogenicity of cadmium and cadmium compounds to humans, sufficient evidence for carcinogenicity of cadmium compounds to animals, limited evidence for carcinogenicity of cadmium metal to animals, IARC classification group 1 (17).

Wkly subcutaneous injections rat (2 yr) 0.022, 0.044, 0.087 mg Cd rat⁻¹ gave a liver cadmium level of 80 mg kg⁻¹ in highest dose-group but no malignant changes were found in prostate, the target organ; no malignant changes observed in other organs (18).

Inhalation rat (18 month) >30 µg Cd m⁻³ as fumes and dust induced bronchoalveolar benign and malignant adenomas and squamous cell carcinomas (19).

Inhalation ♂, ♀ Syrian golden hamsters and ♀ NMRT mice (50-70 wk) 10-270 µg Cd m⁻³ 19 hr day, 5 day wk⁻¹ and followed by 50 wk observation period. No increase in lung tumour incidence observed (20).

Teratogenicity and reproductive effects

TD_{Lo} (9-day pregnant) intraperitoneal mouse 2.57 mg kg⁻¹ caused musculoskeletal system abnormalities (21).

TD_{Lo} (8-day pregnant) intravenous hamster 2 mg kg⁻¹ caused development abnormalities of central nervous system, craniofacial structure, eyes and ears (22,23).

Intravenous pregnant ♀ hamster 88 mg kg⁻¹ induced unspecified teratogenic effects when administered during critical stages of embryogenesis (24).

Inhalation ♀ rat 2.8 mg m⁻³ 4 hr day⁻¹ during pregnancy caused reduced weight and increased mortality in offspring (25).

Genotoxicity

Bacillus subtilis H17, M45 1 g l⁻¹ induced DNA damage (26).

In vitro mouse lymphocytes 0.15 mg l⁻¹ gene mutation positive (27).

In vitro hamster fibroblasts 100 µg Cd l⁻¹ (administered as the sulfate) reduced mitotic index. Concentrations of 500 µg Cd l⁻¹ and above caused chromosome damage (28).

In vitro cultures *Physarum polycephalum* exposed to 5 × 0.1 g l⁻¹. Exposure immediately prior to early prophase of mitosis extended normal DNA replication from 3 to 4 hr. Two stages of cell cycle were particularly susceptible – the beginning and 80% of the way through the cycle (29).

Legislation

Limited under EC Directive on Drinking Water Quality 80/778/EEC. Cadmium: maximum admissible concentration 5 µg l⁻¹ (30).

Included in Schedule 5 (Release into Water: Prescribed Substances) Statutory Instrument No. 472, 1991 (31).

Other comments

Can be found in atmospheric emissions from thermal processes involving cadmium, e.g. incinerators. Can be detected in surface waters near Zn and Zn-Pb refineries that use sulfuric acid as an ore leachant.

Cadmium and its compounds are comprehensively reviewed (17,32,33).

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C14 cadmium sulfide

CdS

CdS

Mol. Wt. 144.48

CAS Registry No. 1306-23-6

Synonyms Aurora Yellow; Cadmium Orange; C.I. 77199; greenockite

EINECS No. 215-147-8

RTECS No. EV 3150000

Uses Pigment in textiles, glass, paper, rubber and printing inks.

Occurrence Occurs in nature as the mineral greenockite.

Physical properties

M. Pt. 1750°C at 100 atm. **Specific gravity** 4.820

Solubility Water: 1.3 g l⁻¹ at 18°C

Occupational exposure

FR-VME 0.05 mg m⁻³ (as Cd)

JP-OEL 0.05 mg m⁻³ (as Cd)

SE-LEVL 0.05 mg m⁻³ (as Cd) (total dust); 0.01 mg m⁻³ (as Cd) (respirable dust)

UK-LTEL MEL 0.03 mg m⁻³ (as Cd) (respirable dust)

US-TWA 0.01 mg m⁻³ (inhalable fraction as Cd); 0.002 mg m⁻³ (respirable fraction as Cd)

UN No. 2570 **Conveyance classification** toxic substance

Supply classification toxic

Risk phrases Harmful if swallowed – Possible risk of irreversible effects – Toxic: danger of serious damage to health by prolonged exposure through inhalation and if swallowed (R22, R40, R48/23/25)

Safety phrases Keep locked up and out of the reach of children (if sold to general public) – Do not breathe dust – Wear suitable protective clothing and gloves – In case of accident or if you feel unwell, seek medical advice immediately (show label where possible) (S1/2, S22, S36/37, S45)

Mammalian & avian toxicity

Acute data

LD₅₀ oral rat 7080 mg kg⁻¹ (1).

LD₅₀ oral mouse 1166 mg kg⁻¹ (1).

LC_{Lo} (duration not specified) inhalation mouse 1350 mg m⁻³ (2).

Sub-acute and sub-chronic data

Inhalation mouse (14 months, no further details given) hamster 90-100 µg m⁻³, increased incidence of alveolar hyperplasia and interstitial fibrosis (3).

Inhalation rat (22 hr day⁻¹, 7 days wk⁻¹ for 18 months) 90-2430 µg Cd m⁻³. Mortality was dose-dependent (4).

Oral rat (4 wk) 30 ppm Cd in diet. No toxic effects observed (5).

Carcinogenicity and chronic effects

Limited evidence for carcinogenicity to humans, sufficient evidence for carcinogenicity to animals, IARC classification group 2A (6).

Intramuscular ♂, ♀ rats 50 mg induced sarcomas in 5/14 rats 9-15 months after injection. Subcutaneous rat 25 mg produced sarcomas in 6/10 ♀ rats 6-10 months post-injection and in 6/26 ♂, ♀ rats 9-19 months post-injection (7).

Metabolism and toxicokinetics

Rats were exposed via inhalation for 6 hr day⁻¹ over 10 days to 0.2, 1.0 and 8.0 mg m⁻³ of CdS and killed over a three-month period for measurements of lung, renal and faecal Cd. High-dose animals showed a transient increase in lung weight. 41% of the lung burden was cleared rapidly (t_{1/2} 1.4 days) and 40% slowly (t_{1/2} 42 days), leaving a final residue of 19%. The renal accumulation of CdS was only 1% of the amount cleared from the lungs. The bioavailability of Cd from CdS appears to be poor, with the majority of CdS being cleared from the lungs and excreted in the faeces (8).

Legislation

Limited under EC Directive on Drinking Water Quality 80/778/EEC. Cadmium: maximum admissible concentration 5 µg l⁻¹ (9).

Included in Schedule 5 (Release into Water Prescribed Substances) of Statutory Instrument No. 472, 1991 (10).

Other comments

Reviews on human health effects, experimental toxicology, ecotoxicology, physico-chemical properties listed (11). Data on the carcinogenicity of cadmium sulfide presented (12).

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C₁₀H₂₃O₂PS₂

Mol. Wt. 270.40

CAS Registry No. 95465-99-9

Synonyms *S,S*-di-*sec*-butyl *O*-ethyl phosphorodithioate; *O*-ethyl *S,S*-bis(1-methylpropyl) phosphorodithioate; Apache; Rugby; Taredan

Uses Insecticide. Nematocide.

Physical properties

B. Pt. 112-14°C at 0.8 mmHg **Flash point** 129.4°C (closed cup) **Specific gravity** 1.054 at 20°C

Partition coefficient log *K*_{ow} 3.9 **Volatility** v.p. 9×10^{-4} mmHg

Solubility Water: 248 mg l⁻¹. Organic solvents: completely miscible with acetone, acetonitrile, dichloromethane, ethyl acetate, heptane, isotoluene, methanol and toluene

Ecotoxicity

Fish toxicity

LC₅₀ (96 hr) rainbow trout, bluegill sunfish 0.13, 0.17 mg l⁻¹, respectively (1).

Environmental fate

Degradation studies

Estimated t_{1/2} in silty clay, sandy loam soils 45 days (1).

Abiotic removal

Stable up to 50°C. t_{1/2} in light <115 days (1).

Mammalian & avian toxicity

Acute data

LD₅₀ oral mallard duck 230 mg kg⁻¹ (1).

LD₅₀ oral bobwhite quail 16 mg kg⁻¹ (1).

LD₅₀ oral mouse 71 mg kg⁻¹ (1).

LD₅₀ oral rat 37 mg kg⁻¹ (1).

LC₅₀ inhalation (4 hr) rat 0.026 mg l⁻¹ (1).

LD₅₀ dermal ♂ rabbit 24 mg kg⁻¹ (1).

LD₅₀ dermal ♀ rabbit 42 mg kg⁻¹ (1).

Carcinogenicity and chronic effects

In 2-yr dietary trials, no-effect level for rats 1 mg kg⁻¹ diet. In 1-yr dietary trials, no-effect level for dogs, ♂ 1 µg kg⁻¹ day⁻¹, ♀ 5 µg kg⁻¹ day⁻¹ (1).

In 2-yr dietary trial for cancer in mice, ♂ 0.5 mg kg⁻¹ diet, ♀ 1.0 mg kg⁻¹ diet, no adverse effects observed (1).

Irritancy

Non-irritating to skin and practically non-irritating to eyes of rabbits (1).

Other effects

Any other adverse effects

Mode of action is cholinesterase inhibition (1).

Legislation

Limited under EC Directive on Drinking Water Quality 80/778/EEC. Pesticides: maximum admissible concentration $0.1 \mu\text{g l}^{-1}$ (2).

Included in Schedule 6 (Release into Land: Prescribed Substances) Statutory Instrument No. 472, 1991 (3).

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C16 caesium

Cs

Cs

Mol. Wt. 132.91

CAS Registry No. 7440-46-2

Synonyms cesium; cesium-133

EINECS No. 231-155-4

RTECS No. FK 9225000

Uses Used in photoelectric cells, spectrographic instruments, scintillation counters, radio tubes, military infra-red signal lamps, and various optical and detecting devices. Glass and ceramic production. Adsorbent in carbon dioxide purification plants. The isotope ^{137}Cs used in the treatment of cancer.

Occurrence Caesium is not very abundant in the earth's crust; only 1 ppm is present (in the aluminosilicates pollucite and lepidolite, and in the borate rhodizite); $2 \mu\text{g l}^{-1}$ occurs in solution in sea water. Detectable amounts found in plant and animal organisms, mineral waters, and soils.

Physical properties

M. Pt. 28.5°C **B. Pt.** 705°C **Specific gravity** 1.873 at 20°C with respect to water at 4°C

Volatility v.p. 1 mmHg at 279°C

Solubility Water: decomp. to form hydroxide and hydrogen which ignites spontaneously. Organic solvents: dimethyl ether, ethylene glycol, polyethers, tetrahydrofuran

Occupational exposure

UN No. 1407 **HAZCHEM Code** 4WE **Conveyance classification** substance which in contact with water emits flammable gas

Mammalian & avian toxicity

Acute data

LD₅₀ intraperitoneal mouse caesium nitrate, iodide, bromide, chloride $1200\text{--}1500 \text{ mg kg}^{-1}$ (1).

LD₅₀ intraperitoneal mouse caesium hydroxide 100 mg kg^{-1} (1).

Metabolism and toxicokinetics

Analysis for ^{137}Cs after exposing rats to unspecified concentrations for an unspecified duration showed wide distribution in all tissues analysed at days 1, 3, 7, 14 and 28. Greatest accumulation and retention was in muscle. Rapid accumulation in liver, spleen and kidney. Blood always had lowest concentration (2).

Following single intramuscular injection (unspecified dose) to rats 71% was eliminated within 1 wk; at 4 wk 14%

of dose was still retained. Urinary excretion exceeded faecal in ratio of 10:1 at 7 and 28 days, respectively (2). $t_{1/2}$ in two patients was 50-60 days. Diuretics, corticosteroids and ion-exchange resins did not increase the excretion rate (3).

A correlation made from periodic, whole-body counting and excretion from 189 to 582 days post-exposure was performed on an individual who had incurred an estimated 4-7 μCi internal dose of ^{137}Cs . Estimated $t_{1/2}$ 80 days (4). In three subjects accidentally exposed to ^{137}Cs half-lives were 110, 115 and 119 days (5).

Other effects

Other adverse effects (human)

^{137}Cs in five human tissues, lung, liver, heart, bladder and ileum, was measured in the Boston area and other US locations in 1965 after nuclear detonations. Levels were highest in liver (20 pCi 100 g⁻¹ wet tissue) compared with 17, 14.4, 12 and 7 for heart, lung, bladder and ileum, respectively. These values had decreased to one-third of initial levels in liver, lung and heart after 2 yr (6).

A study of adult British subjects between 1958 and 1961 after nuclear test explosions found evidence for decreasing levels in 3 yr (7).

Legislation

Included in Schedule 6 (Release into Land: Prescribed Substances) Statutory Instrument No. 472, 1991 (8).

Other comments

^{137}Cs is a product of atomic fusion of uranium, a β -emitter with $t_{1/2}$ of 33 yr.

^{137}Cs was one of the major radioactive isotopes which contaminated the environment after the Chernobyl nuclear accident near Kiev in the Ukraine in 1986. High levels were recorded in many areas, including the UK. The sediment-associated transport of Chernobyl-derived radioactive Cs through the River Severn drainage basin and its redistribution by fluvial processes showed concentrations of ^{137}Cs in suspended sediment had increased by two orders of magnitude immediately after the accident; this declined rapidly, and remained almost an order of magnitude greater than pre-accident levels. Downstream redistribution of radioactive Cs occurred as a result of deposition of sediment-associated radioactive Cs in channel and floodplain sinks. An estimated 0.6% of the total fallout was transported out of the basin from 1986-1990. Work within the Wye basin, central Wales, demonstrated a complex distribution of Chernobyl-derived radio-caesium fallout. Fluvial transport and redistribution of this material was demonstrated by river sampling during the winter of 1988/89, when the radio-caesium content of suspended sediment transported by the River Wye (≈ 30 -50 mBq g⁻¹ of ^{137}Cs) remained 3-5 \times higher than pre-Chernobyl levels (9,10).

The distribution of radio-caesium in the sediments of Lake Hoesjoeen (The Netherlands) analysed 18 months after the Chernobyl fallout disaster showed the concentration in the sediment was similar to concentrations in surrounding terrestrial soils. Most of the radio-caesium was bound in the upper centimetres of sediment (11). Ignites on exposure to air. Reacts explosively with cold water. Reacts vigorously with oxygen to form Cs_2O , Cs_2O_2 and Cs_2O_3 . Keep immersed in mineral oil.

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C17 caesium hydroxide

CsOH

CsHO

Mol. Wt. 149.91

CAS Registry No. 21351-79-1

Synonyms cesium hydrate; cesium hydroxide

EINECS No. 244-344-1

RTECS No. FK 9800000

Uses Storage battery electrolytes. Catalyst in the polymerisation of cyclic siloxanes. Agent for the removal of sulfur from heavy oils.

Physical properties

M. Pt. 272.3°C **Specific gravity** 3.675 at 25°C

Solubility Water: 395 g ml⁻¹ at 15°C. Organic solvents: ethanol

Occupational exposure

FR-VME 2 mg m⁻³

UK-LTEL 2 mg m⁻³

US-TWA 2 mg m⁻³

UN No. 2682

UN No. 2681 (solution) **HAZCHEM Code** 2X **HAZCHEM Code** 2R (solution) **Conveyance classification** corrosive substance

Mammalian & avian toxicity

Acute data

LD₅₀ oral rat, mouse 570, 800 mg kg⁻¹, respectively (1,2).

LD₅₀ intraperitoneal rat 100 mg kg⁻¹ (3,4).

Irritancy

Dermal rabbit (24 hr) 5 mg caused mild irritation, and 5 mg instilled into rabbit eye for 5 min caused severe irritation (5).

Very irritating and corrosive to upper respiratory tract (6).

Other effects

Any other adverse effects

A powerful caustic agent. Inhalation may result in inflammation and oedema of the bronchi and larynx; pulmonary oedema, chemical pneumonitis and death may occur due to spasms (species unspecified) (6).

Other comments

Experimental toxicology and human health effects reviewed (7,8).

Deliquescent. Absorbs carbon dioxide from air.

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c18 caesium nitrate



CsNO₃

Mol. Wt. 194.91

CAS Registry No. 7789-18-6

Synonyms caesium nitrate (1:1); nitric acid, caesium salt; cesium nitrate

EINECS No. 232-146-8

RTECS No. FL 0700000

Physical properties

M. Pt. 414°C Specific gravity 3.685

Solubility Water: soluble in 5 parts cold and 0.5 parts boiling water. Organic solvents: acetone, methanol

Occupational exposure

UN No. 1451 HAZCHEM Code 1 $\frac{2}{+}$ Conveyance classification oxidising substance

Mammalian & avian toxicity

Acute data

LD₅₀ intraperitoneal rat 1200 mg kg⁻¹ (1).

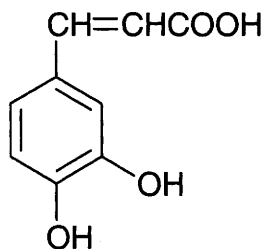
Genotoxicity

Bacillus subtilis H17, M45 potential to induce DNA damage negative (2).

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c19 caffeic acid



C₉H₈O₄

Mol. Wt. 180.16

CAS Registry No. 331-39-5

Synonyms 3-(3,4-dihydroxyphenyl)-2-propenoic acid; 3,4-dihydroxycinnamic acid; 3,4-dihydroxybenzeneacrylic acid

EINECS No. 206-361-2

RTECS No. GD 8950000

Occurrence Found in plants, mainly in conjugated forms. Exists in *cis* and *trans* forms. The *trans* form is the predominant naturally occurring form.

Physical properties

M. Pt. Decomp. 223-225°C (softens at 194°C)

Solubility Water: sparingly soluble in cold, freely soluble in hot. Organic solvents: ethanol

Environmental fate

Degradation studies

The hydrogenation and dehydroxylation of caffeic acid by a strain of *Pseudomonas* sp. isolated from rat faeces has been described. *p*-Hydroxyphenylacetic acid, dihydrocaffeic acid, and phloretic acid were identified as metabolites (1).

A mixed culture of anaerobic organisms obtained from enrichment cultures that grow on caffeic acid as the sole carbon and energy source utilised 43.5 mg of caffeic acid in 10 days and 79.8 mg in 20 days of anaerobic growth. The presence of low levels of O₂ prevented the metabolism of caffeic acid (2).

Caffeic acid is metabolised by the intestinal microbiota of both men and experimental animals. Of 12 species of bacteria isolated from human faeces, however, none had the ability to catalyse more than one reaction of the series leading from caffeic acid to hydroxyphenylpropionic acid or 4-ethylcatechol (3).

Mammalian & avian toxicity

Acute data

LD₅₀ 1500 mg/kg (4).

Carcinogenicity and chronic effects

Possibly carcinogenic to humans, sufficient evidence for carcinogenicity to animals, IARC classification Group 2B (5).

Oral rats (104 wk) 2% caffeic acid in diet caused retardation of body weight and elevated liver weights (6).

Oral rats (104 wk) 2% caffeic acid in diet induced forestomach squamous cell carcinoma in 57% of ♂ and 50% of ♀ mice (7).

Oral F344 rats (104 wk) C57BL/6N × C3H/HeN F1 mice 2% caffeic acid in diet induced forestomach squamous cell carcinoma in both sexes of rats and mice, renal tubular cell hyperplasias and adenomas in ♂ rats and ♀ mice, and alveolar type II cell tumours in ♂ mice (8).

Oral ♀ F344 rats (up to 104 wk) 0.4% caffeic acid, 0.4% butylated hydroxyanisole, 0.4% sesamol, 0.4%

4-methoxyphenol, and 0.16% catechol either alone or in combination in diet. Slightly increased incidences of forestomach papillomas were found in caffeic acid- (14.8%), sesamol- (15.8%), catechol- (3%), and 4-methoxyphenol- (11.5%) treated groups compared with the basal diet (0%). A significant increase was observed with the five antioxidants in combination (42.9%, $P < 0.001$) (9).

Metabolism and toxicokinetics

Following oral administration to human volunteers, *O*-methylated derivatives were excreted rapidly in the urine; *meta*-hydroxyphenyl derivatives were excreted later (10).

Genotoxicity

Investigations of chromosome aberrations in Chinese hamster ovary cells show that caffeic acid has clastogenic activity which cannot be entirely accounted for by the H_2O_2 generated by its autooxidation in solution (5).

Other effects

Any other adverse effects

♂ F344 rats were administered a single dose of 150 mg kg^{-1} *N*-methyl-*N'*-nitro-*N*-nitrosoguanidine intragastrically to initiate forestomach carcinogenicity and then 1 wk later were placed on a diet containing 1% caffeic acid for 51 wk and then killed. Caffeic acid treatment exerted a strong promotional activity for rat forestomach carcinogenicity – the incidences of forestomach papillomas and squamous cell carcinomas were significantly enhanced (95% and 100%) compared with control values. Glandular stomach carcinogenesis was not enhanced (11).

Other comments

The growth of rice rhizosphere *Azospirillum lipoferum* strain 4T was stimulated by caffeic acid under 5 kPa O_2 . The authors suggest that strain 4T can use polyphenolics such as caffeic acid as alternative terminal respiratory electron acceptors under low oxygen pressure and that such respiratory transformations could contribute to the fate of xenobiotics in the environment (12).

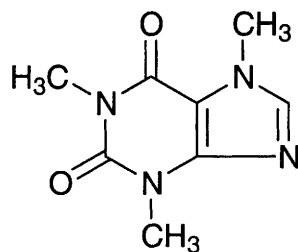
Caffeic acid caused a significant reduction in mung bean hypocotyl growth, but when incubated with isolated mung bean hypocotyl mitochondria did not inhibit respiration and coupling parameters (13).

It has been demonstrated by several investigators that lipid peroxidation induced by superoxide ion and the formation of hydroxyl radicals *in vitro* are inhibited by 10^{-4} M caffeic acid (14-16).

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c20 caffeine



$C_8H_{10}N_4O_2$

Mol. Wt. 194.19

CAS Registry No. 58-08-2

Synonyms methyltheobromine; 1,3,7-trimethylxanthine, 3,7-dihydro-1,3,7-trimethyl-1*H*-purine-2,6-dione; 1,3,7-trimethyl-2,6-dioxopurine; Organex

EINECS No. 200-362-1

RTECS No. EV 6475000

Uses A central nervous system stimulant and diuretic. Used in soft drinks and some foods as a flavouring ingredient.

Occurrence In tea, coffee, maté leaves, guarana paste and cola nuts.

Physical properties

M. Pt. 236-238°C (anhydrous) **B. Pt.** 178°C (sublimes) **Specific gravity** 1.23 at 18°C with respect to water at 4°C **Partition coefficient** log P_{ow} 0.07

Solubility Water: 181.8 g l⁻¹ at 80°C. Organic solvents: acetone, benzene, chloroform, ethanol

Occupational exposure

Supply classification harmful

Risk phrases Harmful if swallowed (R22)

Safety phrases Keep out of reach of children (if sold to general public) (S2)

Ecotoxicity

Invertebrate toxicity

EC₅₀ (24 hr) *Artemia salina* 4.24 µmol l⁻¹ Arttoxkit M test (1).

EC₅₀ (24 hr) *Streptocephalus proboscideus* 3.31 µmol l⁻¹ Streptoxkit F test (1).

EC₅₀ (24 hr) *Daphnia magna* 2.92 µmol l⁻¹ (1).

EC₅₀ (24 hr) *Brachionus calyciflorus* 4.38 µmol l⁻¹ (1).

EC₅₀ (15 min) *Photobacterium phosphoreum* 3.53 µmol l⁻¹ Microtox test (1).

Environmental fate

Degradation studies

Readily biodegradable (2).

Bacteria isolate metabolised caffeine as a nitrogen source rather than carbon source. The strains produced xanthine derivatives as degradation intermediates (3).

Pseudomonas sp. isolated from soil under coffee cultivation was able to utilise high concentrations of caffeine (50 g l⁻¹) as the sole source of carbon and nitrogen (4).

Mammalian & avian toxicity

Acute data

LD₅₀ oral redwing blackbird 316 mg kg⁻¹ (5).

LD₅₀ oral mouse, rat, guinea pig 127, 192, 230 mg kg⁻¹, respectively (6-8).

LD₅₀ intraperitoneal rat, rabbit 260, 305 mg kg⁻¹, respectively (9,10).

LD₅₀ intravenous mouse, rat 62, 105 mg kg⁻¹, respectively (11,12).

Sub-acute and sub-chronic data

♀ Albino rats given daily doses of 110 mg kg⁻¹ via intragastric cannula (total duration time unspecified) showed stress on reactions in the form of hypertrophy of the adrenal cortex and atrophy of the adrenal cortex and thymus gland (13).

Carcinogenicity and chronic effects

Inadequate evidence for carcinogenicity to humans, limited evidence for carcinogenicity in animals, IARC classification group 3 (14).

The effect of caffeine consumption on mortality from cancer of all sites among 10,064 participants in the Hypertension Detection and Follow-up Program was examined after 4 yr of follow-up in the mid-1980s. Exposure to caffeine was estimated from tea and coffee consumption and the use of caffeine-containing medications. No association was found between caffeine consumption and mortality from cancer or any other cause although the confidence limits for the study were very wide (15).

In a case-control study in Denmark of 371 (280 ♂, 91 ♀) bladder cancer cases, including papillomas and 771 controls, a weak association was found between cancer of the urinary bladder and intake from coffee and tea. The association was significant in men after adjustment for consumption of beer and soft drinks, in addition to age and smoking (16).

Teratogenicity and reproductive effects

Dilutions of fresh brewed coffee at 12.5, 25 and 50% resulting in caffeine intakes of 9, 19 and 38 mg kg⁻¹ day⁻¹ were consumed by ♀ rats as their sole beverage for 5 wk prior to mating, throughout gestation and in representative animals until day-27 after parturition. Other rats received 30 mg kg⁻¹ day⁻¹ in water. Results showed apparent delay in development, including calcification of foetal bones and focally irregular rib ossification but no dose-related teratological effects were found. In mature animals no gross anomalies were observed and no treatment-related difference in body weight gain, food or water consumption or reproductive performance could be detected (7).

Oral pregnant mice (5-18 day) 150 mg kg⁻¹ day⁻¹ (pellet) 250 mg kg⁻¹ day⁻¹ (in drinking water) reduction in foetal weight and low incidence of cleft palate noted in pellet group. Retarded ossification of supraoccipital bones in foetuses in drinking water group (17).

A/J pregnant mice (8-19 wk) 0.05% solution of caffeine or only tap water followed by subcutaneous injection with 150 or 250 mg kg⁻¹ caffeine on day-13 of gestation. Animals given 250 mg kg⁻¹ caffeine showed higher incidence of external malformations and subcutaneous haematomas but lower frequencies of foetal death than controls (18).

Oral CD-1 mice (8-12 day gestation) 200 mg kg⁻¹ in drinking water no effect (19).

Oral ♀ monkeys administered 0, 0.15 or 0.35 mg ml⁻¹ caffeine in drinking water, before, during and after pregnancy resulted in a dose-related increase in reproductive failure, still births, miscarriages and decreased maternal weight gain (20).

Caffeine intake from pharmaceutical sources has not been related to teratogenic effects in humans. High levels of either coffee or caffeine consumption were related to an increased frequency of low birthweight (14).

Metabolism and toxicokinetics

Caffeine (species unspecified) was metabolised almost completely via oxidation, demethylation and acetylation. The principal metabolites in the urine were 1-methyluric acid and 1-methylxanthine. Much smaller amounts of 1,3-dimethyluric acid, 7-methylxanthine, and 1,7-dimethylxanthine were detected (21).

The major metabolite in rats given ¹⁴C-labelled caffeine (route unspecified) was 6-amino-5-[N-formylmethylamine]-1,3 [Me¹⁴C]dimethyluracil (22).

Caffeine has a t_{1/2} in plasma of 3-7 hr which doubles in women during the later stages of pregnancy (23).

Caffeine is sequentially metabolised in humans by N-acetyltransferase, xanthine oxidase and cytochrome P501A2 (CYP1A2) (24).

Genotoxicity

Salmonella typhimurium TA98, TA100, TA1535, TA1537 with and without metabolic activation negative (25).

Escherichia coli PQ37 SOS chromotest with and without metabolic activation negative (25).

Escherichia coli inhibition of DNA repair systems positive (26).

Induced microbial mutation in *Klebsiella pneumoniae* without metabolic activation (27).

Saccharomyces cerevisiae induced sex chromosome loss and non-disjunction (28).

Drosophila melanogaster mutagenic and reduced oviposition, but had no effect on sex expression ratio or sterility (29).

Mouse lymphoma thymidine kinase-deficient tk⁺ tk⁻ mutants showed caffeine lacked structural groups for DNA reactivity. This implies a major class of non-DNA primary targets for mutagenicity in mammalian cells that interact secondarily with the chromosome (30).

Other effects

Other adverse effects (human)

The effects of terminating low dose levels of caffeine, 100 mg day⁻¹, in seven subjects was investigated. Over 21 days a range of symptoms, including headache, fatigue and other dysphoric mood changes, muscle pain, flu-like symptoms, nausea, vomiting and craving for caffeine, were seen in the subjects tested (31).

In a double-blind study in 28 patients with atopic dermatitis the application for 3 wk of a 30% caffeine cream produced significantly greater benefit in terms of erythema, scaling, lichenification, oozing and excoriation than a placebo. It was considered that caffeine increased the concentration of cyclic AMP in the skin (32).

In two separate epidemiological investigations an association was shown to exist between heavy coffee drinking and bladder cancer (33).

A Scottish Heart Health Study of 10,359 ♂ and ♀ subjects classified 2122 as having indications of coronary heart disease. ♂ and ♀ results were combined because they showed identical patterns in the prevalence of coronary heart disease. No positive relationship between coffee or tea consumption and coronary heart disease could be established in this British study where most coffee consumed is instant (34).

Any other adverse effects

Langendorff perfusion of rat hearts with 10 mM caffeine caused severe ultrastructural damage to the myofilaments and mitochondria (35).

Other comments

Reviews on human health effects, experimental toxicology, ecotoxicology and physio-chemical properties listed (36).

Metabolism and pharmacokinetics and genotoxicities of caffeine are reviewed (37-44).

Absorption rate of caffeine from human stomach increases as the pH is raised from pH 1 to pH 7 (45).

Possible relationship between caffeine consumption and breast disease in humans reviewed (46).

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c21 calcium

Ca

Ca

Mol. Wt. 40.08

CAS Registry No. 7440-70-2

Synonyms Calciat

EINECS No. 231-179-5

RTECS No. EV 8040000

Uses Therapeutically (as salts) in treatment of calcium deficiencies and as a dietary supplement. Metallurgy as deoxidiser for Cu, Be, steel. Hardening lead for bearings. Alloyed with cerium to make flints for cigarette and gas lighters. Manufacture of electronic vacuum tubes.

Occurrence The fifth element in order of abundance in the earth's crust. Sea water contains about 400 g tonne⁻¹. Never occurs naturally as elemental calcium, only as its combined forms. The principal commercial source is limestone (calcium carbonate). Essential constituent of bones, teeth, shells, corals and many soils.

Physical properties

M. Pt. 850°C B. Pt. 1440°C Specific gravity 1.54 at 20°C with respect to water at 4°C

Volatility v.p. 10 mmHg at 983°C

Solubility Water: decomp. to hydrogen and calcium hydroxide

Occupational exposure

UN No. 1401 HAZCHEM Code 4W Conveyance classification substance which in contact with water emits flammable gas

Supply classification highly flammable

Risk phrases Contact with water liberates extremely flammable gases (R15)

Safety phrases Keep out of reach of children (if sold to general public) – Keep container dry – Avoid contact with skin and eyes – In case of fire, use dry powder or sand never use water (S2, S8, S24/25, S43)

Ecotoxicity

Invertebrate toxicity

LC₅₀ (48 hr) *Daphnia magna* 330 mg l⁻¹ (1).

LC₅₀ (96 hr) *Nitocra spinipes* 580 mg l⁻¹ (2).

Mammalian & avian toxicity

Metabolism and toxicokinetics

Calcium is the most abundant mineral in the body, 14-20 g calcium kg⁻¹, ~99% is contained in the skeleton.

Calcium is an essential body electrolyte regulated by the parathyroid hormone, by calcitonin and by vitamin D.

Plasma concentration 88-104 mg l⁻¹. Major excretory route is via urine with small losses via faeces and sweat (3).

Irritancy

Eye irritant. Can cause lachrymation and burns. Severe exposure may result in adhesion between eyelids and corneas (4,5).

Other effects

Other adverse effects (human)

In humans increased absorption of soluble calcium salts from the gastrointestinal tract or increased mobilisation from the bone results in hypercalcaemia. Most common causes are neoplastic disease and primary hyperparathyroidism. Alternative causes are excessive intake of vitamin D, hyperparathyroidism, sarcoidosis and thiazide diuretics. Systemic effects include anorexia, nausea, vomiting, constipation, abdominal pain, muscle weakness, mental disturbances, polydipsia, polyuria, bone pain, nephrocalcinosis, renal calculi, cardiac arrhythmias and coma (3).

Decreased plasma-calcium concentration hypocalcaemia can result from impaired or reduced absorption from the gastrointestinal tract, increased deposition in bone or from excessive loss, for example, during lactation. Other causes are hypoalbuminaemia resulting from cirrhosis or nephrotic syndrome. Decreased parathyroid hormone activity, vitamin D deficiency and hypomagnesaemia may also cause hypocalcaemia. Systemic effects include paraesthesia, extra pyramidal signs, muscle cramps, increased muscle excitability, convulsions, mental changes, dermatitis and ECG changes (3).

Patients with low or low-normal levels of serum ionised calcium, when administered calcium chloride (7 mg kg⁻¹) and calcium gluconate (20 mg kg⁻¹) experienced rapid increase of serum ionised calcium levels, a decrease of serum-potassium levels and development of severe cardiac arrhythmias (4).

Legislation

Included in Schedule 6 (Release into Land: Prescribed Substances) of Statutory Instrument No. 472, 1991 (6).

Limited under EC Directive on Drinking Water Quality 80/778/EEC. Calcium: guide level 100 mg l⁻¹ (7).

Other comments

Experimental toxicology, hazards and human health effects, ecotoxicology and physico-chemical properties reviewed (8-10).

The importance of calcium in physiological and toxicological processes is reviewed (11).

Reacts with water, ethanol and dilute acids to evolve hydrogen. Insoluble and inert with benzene and kerosene. Explosion risk with alkali-metal hydrides and carbonates.

The toxicity of calcium is dependent on the ability of the organism to absorb it. Therefore toxicity data refers to bioavailable forms, such as the ion in solution or particulate matter.

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c22 calcium arsenate



$\text{As}_2\text{Ca}_3\text{O}_8$

Mol. Wt. 398.07

CAS Registry No. 7778-44-1

Synonyms arsenic acid, calcium salt; calcium orthoarsenate; tricalcium arsenate

EINECS No. 231-904-5

RTECS No. CG 0830000

Uses Insecticide. Fungicide. Molluscicide. Used against the cotton boll weevil.

Physical properties

M. Pt. 1455°C **Specific gravity** 3.62

Solubility Water: 130 mg l⁻¹ at 25°C

Occupational exposure

SE-LEVL 0.03 mg m⁻³ (as As)

UK-LTEL MEL 0.1 mg m⁻³ (as As)

US-TWA 0.01 mg m⁻³ (as As)

UN No. 1573 **HAZCHEM Code** 2X **Conveyance classification** toxic substance

Supply classification toxic

Risk phrases May cause cancer – Toxic by inhalation and if swallowed (R45, R23/25)

Safety phrases Restricted to professional users – Avoid exposure – obtain special instruction before use – In case of accident or if you feel unwell, seek medical advice immediately (show label where possible) (S53, S45)

Environmental fate

Nitrification inhibition

Nitrification of ammonium was significantly lower in soil underlying calcium arsenate treated turf (1).

Mammalian & avian toxicity

Acute data

LD₅₀ oral ♀ rat 298 mg kg⁻¹ (1).

LD_{Lo} oral rabbit 50 mg kg⁻¹ (2).

LD₅₀ dermal rat 2400 mg kg⁻¹ (3).

Carcinogenicity and chronic effects

Sufficient evidence for carcinogenicity to humans, limited evidence for carcinogenicity to animals, IARC classification group 1 for arsenic and its compounds (4).

A case of lung cancer was reported in an individual involved in the production of calcium arsenate (5).

In a study of 26 patients with liver angiosarcomas, two worked in arsenical pesticide production (6).

Single intratracheal instillation to rat of a pesticide mixture containing calcium arsenate (concentration unspecified) induced a high incidence of lung carcinomas (7).

Intratracheal instillation in hamster of calcium arsenate (duration and concentration unspecified) caused a borderline increase in the incidence of lung adenomas (7).

Other effects

Other adverse effects (human)

Epidemiological studies have implicated inorganic arsenic compounds as pulmonary carcinogens (8,9).

Three studies of two populations of workers in pesticide production showed an increased risk ratio for lung cancer and some excesses of malignant neoplasms of the lymphatic and haematopoietic tissue (6,10).

Legislation

Included in Schedule 6 (Release into Land: Prescribed Substances) of Statutory Instrument No. 472, 1991 (11).

Limited under EC Directive on Drinking Water Quality 80/778/EEC. Arsenic: maximum admissible concentration 50 µg l⁻¹. Calcium: guide level 100 mg l⁻¹. Pesticides and related products: maximum admissible concentration 0.1 µg l⁻¹ (12).

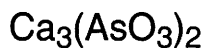
Other comments

Experimental toxicology and human health effects reviewed (13).

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c23 calcium arsenite



$\text{As}_2\text{Ca}_3\text{O}_6$

Mol. Wt. 366.07

CAS Registry No. 52740-16-6

Synonyms arsenious acid, calcium salt; monocalcium arsenite

EINECS No. 258-147-3

RTECS No. CH 9492050

Uses Insecticide. Germicide. Molluscicide.

Physical properties

M. Pt. decomp. Specific gravity 3.031

Occupational exposure

SE-LEVL 0.03 mg m⁻³ (as As)

UK-LTEL MEL 0.1 mg m⁻³ (as As)

US-TWA 0.01 mg m⁻³ (as As)

UN No. 1574 (in mixture with calcium arsenate) HAZCHEM Code 2X (in mixture with calcium arsenate)

Conveyance classification toxic substance (in mixture with calcium arsenate)

Mammalian & avian toxicity

Carcinogenicity and chronic effects

Sufficient evidence for carcinogenicity to humans, limited evidence for carcinogenicity to animals for arsenic and its compounds, IARC classification group 1 (1).

Metabolism and toxicokinetics

Absorbed arsenic excreted largely by the kidneys; but faeces, skin and hair sometimes contain appreciable amounts. After a single dose, excretion is essentially complete within 2 wk. Crosses the placental barrier and has been linked with neonatal death (species unspecified) (2).

Other effects

Other adverse effects (human)

Three studies of two populations of workers in pesticide production showed an increased risk ratio for lung cancer and some excess of malignant neoplasms of the lymphatic and haematopoietic tissues (3,4).

In a study of 26 patients with liver angiosarcomas, two of the 26 worked in the production of arsenical pesticides (3).

Legislation

Included in Schedule 6 (Release into Land: Prescribed Substances) of Statutory Instrument No. 472, 1991 (5).

Limited under EC Directive on Drinking Water Quality 80/778/EEC. Arsenic: maximum admissible concentration 50 µg l⁻¹. Calcium: guide level 100 mg l⁻¹. Pesticides and related products: maximum admissible concentration 0.1 µg l⁻¹ (6).

References

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c24 calcium carbide



CaC₂

Mol. Wt. 64.10

CAS Registry No. 75-20-7

Synonyms calcium acetylide; acetylenogen; calcium dicarbide; ethyne calcium derivate; Recozit Wuehlmaus-Gas; Delu Wuehlmaus-Gas; MCCI Carbide

EINECS No. 200-848-3

RTECS No. EV 9400000

Uses Acetylene generation. Preparation of cyanamide. Desulfurising and deoxidising agent in metallurgy.

Physical properties

M. Pt. 2300°C **Specific gravity** 2.222

Solubility Water: decomp.

Occupational exposure

UN No. 1402 **HAZCHEM Code** 4YE **Conveyance classification** substance which in contact with water emits flammable gas

Supply classification highly flammable

Risk phrases Contact with water liberates extremely flammable gases (R15)

Safety phrases Keep out of reach of children (if sold to general public) – Keep container dry – In case of fire, use dry powder or sand never use water (S2, S8, S43)

Ecotoxicity

Invertebrate toxicity

Heterotrophic microorganisms were depressed 81% in 1 hr by the application of fresh carbide waste to a cave stream mudbank. The effect was temporary as the toxicity was removed after neutralisation (1).

Environmental fate

Carbonaceous inhibition

Escherichia coli, *Bacillus subtilis*, *Saccharomyces cerevisiae* inhibited in 15 min by 1% solution of waste carbide (1).

Legislation

Limited under EC Directive on Drinking Water Quality 80/778/EEC. Calcium: guide level 100 mg l⁻¹ (as calcium) (2).

Not permitted in trade effluent discharges in Britain.

Other comments

Reviews on experimental toxicology, human health effects, ecotoxicology and physico-chemical properties listed (3).

References

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CCaO₃

Mol. Wt. 100.09

CAS Registry No. 471-34-1

Synonyms agricultural limestone; chalk; dolomite; limestone; marble; Portland stone; lithographic stone

EINECS No. 207-439-9

RTECS No. EV 9580000

Uses Manufacture of paint, rubber, plastics, paper, dentifrices, inks, ceramics, putty, polishes, insecticides and shoe dressings. Filler in the production of adhesives, matches, pencils, crayons, linoleum, insulating compounds and welding rods. Foods. Cosmetics. Pharmaceuticals. Antibiotics. Removal of acidity from wines.

Therapeutically as an antacid, calcium supplement. Nutrient and/or dietary supplement. General purpose food additive. Native calcium carbonate *Calcareo carbonica* is used in homoeopathic medicine.

Occurrence Exists in nature as the minerals aragonite, calcite and vaterite. About 7% of the earth's crust is calcite, calcium carbonate in the form of limestone, marble and chalk.

Physical properties

M. Pt. 825°C (decomp.; aragonite); 898.6°C (decomp.; calcite) **Specific gravity** 2.93 (aragonite); 2.71 (calcite)

Solubility Water: insoluble in water

Occupational exposure

FR-VME 10 mg m⁻³

UK-LTEL 10 mg m⁻³ (total inhalable dust); 4 mg m⁻³ (respirable dust)

US-TWA 10 mg m⁻³

Mammalian & avian toxicity

Acute data

LD₅₀ oral rat 6450 mg kg⁻¹ (1).

Metabolism and toxicokinetics

Converted into calcium chloride by gastric acid. Some calcium (as calcium salts) is absorbed but ≈80% is further converted into insoluble salts and excreted in faeces (2,3).

Irritancy

Dermal rabbit (24 hr) 500 mg caused moderate irritation and 750 µg instilled into rabbit eye caused severe irritation (1).

Other effects

Other adverse effects (human)

In two cases, hypersensitivity resulted from an interaction between calcium carbonate with vitamin D and thiazide diuretics; calcium carbonate was being consumed unknown to the general practitioner (4).

A case of marked hypercalcaemia was reported in a 67-yr-old woman consuming large amounts of a proprietary medicine containing calcium carbonate in addition to hydrochlorothiazide for the treatment of epigastric distress (5).

In humans hypercalcaemia and alkalosis can occur following regular use of calcium carbonate (3).

The milk-alkali syndrome (hypercalcaemia, alkalosis and renal dysfunction) has occurred in patients taking large doses 4-60 g day⁻¹ (6).

There may be a silicosis risk in using impure limestone containing 3-20% quartz for stone dusting in coal mines (7).

Legislation

Limited under EC Directive on Drinking Water Quality 80/778/EEC. Calcium: guide level 100 mg l⁻¹ (8).

Other comments

Commercial calcium carbonate produced by chemical means is 98-99% pure.

Pure calcium carbonate dust is considered harmless (9).

Reviews on experimental toxicology, human health effects and workplace experience listed (10).

Insoluble in water but solubility can be increased by the presence of carbon dioxide or ammonium salts. Soluble with effervescence in acetic, hydrochloric and nitric acids.

References

1. Marhold, J. V. *Sbornik Vysledku Toxikologickeho Vysetreni Latek A Pripravku* 1972, 267, Prague, Czechoslovakia.
2. Gilman, A. C. et al *Goodman Gilman's The Toxicological Basis of Therapeutics* 1985, 7th ed., Macmillan Publ., New York, USA.
3. *Martindale: The Extra Pharmacopoeia* 31st ed., 1996, The Royal Pharmaceutical Society, London, UK.
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c26 calcium chlorate



CaCl₂O₆

Mol. Wt. 206.98

CAS Registry No. 10137-74-3

Synonyms chloric acid, calcium salt

EINECS No. 233-378-2

RTECS No. FN 9800000

Uses Herbicide. Insecticide. Seed disinfectant.

Physical properties

M. Pt. 100°C **Specific gravity** 2.711

Solubility Water: 1780 g l⁻¹ at 8°C. Organic solvents: acetone, ethanol

Occupational exposure

UN No. 1452

UN No. 2429 (solution) **HAZCHEM Code** 1YE **HAZCHEM Code** 2S (solution) **Conveyance classification** oxidising substance

Mammalian & avian toxicity

Acute data

LD₅₀ oral rat 4500 mg kg⁻¹ (1).

LD_{Lo} intraperitoneal rat 625 mg kg⁻¹ (2).

Legislation

Included in Schedule 6 (Release into Land: Prescribed Substances) of Statutory Instrument No. 472, 1991 (3).
Limited under EC Directive on Drinking Water Quality 80/778/EEC. Calcium: guide level 100 mg Ca l⁻¹.
Chloride: guide level 25 mg Cl l⁻¹ (approximate concentration above which effects might occur 200 mg l⁻¹).
Pesticides and related products: maximum admissible concentration 0.1 µg l⁻¹ (4).

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c27 calcium chlorite



CaCl₂O₄

Mol. Wt. 174.98

CAS Registry No. 14674-72-7

Synonyms chlorous acid, calcium salt

RTECS No. EV 9850000

Uses Purification of waste gases. Starch purification. Heat stabiliser for synthetic rubbers. Building materials.
Fruit and vegetable preservative

Physical properties

Specific gravity 2.71

Solubility Water: decomp.

Occupational exposure

UN No. 1453 **HAZCHEM Code** 1Y **Conveyance classification** oxidising substance

Legislation

Limited under EC Directive on Drinking Water Quality 80/778/EEC. Calcium: guide level 100 mg l⁻¹ (as calcium) (1).

Other comments

Inhibitory effect on strains of *Staphylococcus* sp. (2).

Experimental toxicology and human health effects reviewed (3).

Strong oxidiser. Ignites on contact with potassium thiocyanate. Reacts with chlorine to produce ClO₂.

References

1. *EC Directive Relating to the Quality of Water Intended for Human Consumption* 1982, 80/778/EEC, Office for Official Publications of the European Communities, 2 rue Mercier, L-2985 Luxembourg.
2. Mikhailova, M. A. et al *Antibiotiki Moscow* 1979, 24(1), 828-831 (Russ.) (*Chem. Abstr.* 92, 34999x).
3. *BIBRA Toxicity Profiles* 1991, British Industrial Biological Research Association, Carshalton, UK

**CaCrO₄****Mol. Wt.** 156.07**CAS Registry No.** 13765-19-0

Synonyms calcium chromate(vi); calcium chrome yellow; calcium chromium oxide; calcium monochromate; chromic acid, calcium salt (1:1); yellow ultramarine

EINECS No. 237-366-8**RTECS No.** GB 2750000

Uses Manufacture of chromium. Oxidising agent. Pigment. Used in battery depolarisation. Corrosion inhibitor.

Physical properties

M. Pt. 200°C**Solubility** Water: 163.9 g l⁻¹ at 20°C. Organic solvents: dimethyl sulfoxide, ethanol

Occupational exposure

FR-VME 0.05 mg m⁻³ (as Cr)**JP-OEL** 0.05 mg m⁻³ (as Cr)**SE-LEVL** 0.02 mg m⁻³ (as Cr)**UK-LTEL MEL** 0.05 mg m⁻³ (as Cr)**US-TWA** 0.05 mg m⁻³ (as Cr)**Supply classification** toxic**Supply classification** dangerous for the environment

Risk phrases May cause cancer – Harmful if swallowed – Very toxic to aquatic organisms, may cause long-term adverse effects in the aquatic environment (R45, R22, R50/53)

Safety phrases Avoid exposure – obtain special instruction before use – In case of accident or if you feel unwell, seek medical advice immediately (show label where possible) – This material and/or its container must be disposed of as hazardous waste – Avoid release to the environment. Refer to special instructions/safety data sheet – Restricted to professional users (S53, S45, S60, S61)

Ecotoxicity

Bioaccumulation

Bioconcentration factor oysters, blue mussels, molluscs and polychaetes 125-236 (1).

Bioconcentration factor rainbow trout <3 (2).

Total chromium bioconcentration factors for benthic algae, phytoplankton and zooplankton were 1600-2300, and bioconcentration factors for crustacean muscle and fish muscle were 70-440 (3).

Environmental fate

Adsorption and retention

Chromium(vi) is not strongly adsorbed by soil components but does bind to activated carbon. Chromium(vi) is reduced to chromium(III), which is a very stable species, especially in poorly drained soil (4).

Mammalian & avian toxicity

Acute data

LD₅₀ oral rat 327-746 mg kg⁻¹ (5).

Carcinogenicity and chronic effects

Sufficient evidence for carcinogenicity to humans and animals for hexavalent chromium compounds, IARC classification group 1 (6).

Squamous metaplasia was observed in rats exposed to chromium (vi) compounds. Squamous metaplasia is

considered to be a transforming state from which squamous carcinoma may arise. However, bronchial squamous carcinoma was only observed in rats receiving chromium compounds which were sparingly soluble in water (7). Implant rat (2 yr) 12.5 mg calcium chromate induced fibrosarcomas and sarcomas of ileocecal lymph nodes (8). Intramuscular and intrapleural implant of 25 mg calcium chromate in 50 mg fat in rats caused tumours of the spine, pelvis, thoracic wall, ribs, lungs and heart, liver and lymph nodes (9). Administration of 19 mg calcium chromate for 20 wk by wkly intramuscular injection in rats induced spindle cell or pleomorphic cell sarcoma (10). Nasal sinus and nasopharyngeal cancers have been described in chromate workers (11). Workers engaged in the production of chromate salts and pigments are at increased risk of developing bronchial carcinoma, although no detailed data on dose-response relationships are available (12).

Genotoxicity

Salmonella typhimurium TA1535, TA1537, TA1538, TA97, TA98, TA100, TA102 with and without metabolic activation positive (13). Calcium chromate caused positive induction of chromosomal aberrations in Chinese hamster ovary cells and C3H10T_{1/2} mouse embryo cells, due to the chromate binding to DNA and interacting with chromatin randomly (14,15). Mouse lymphoma L5178Y tk⁺/tk⁻ without metabolic activation cell forward mutation assay positive (16). Calcium chromate induced genotoxic effects including 6-thioguanine resistance at cytotoxic concentrations in diploid human fibroblastic cells (17). Syrian hamster embryo cells *in vivo* and *in vitro* without metabolic activation morphological transformation positive (18,19). Calcium chromate induced dose-dependent cytotoxicity and mutation to 6-thioguanine, but did not induce ouabain resistance in Chinese hamster ovary cells or morphological transformation in C3H10T_{1/2} mouse embryo cells (20). BALB/c mice (5 wk) dominant lethal test significant reduction in the number of pregnancies (21).

Legislation

The Water Supply (Water Quality) Regulation S.I. 1989 No. 1147; maximum concentration as chromium ion 50 µg l⁻¹ (22). Chromium (vi) is specified as special waste under the control of pollution (Special Waste Regulation, 1980 SI 1980/1709) (23). Limited under EC Directive on Drinking Water Quality 80/778/EEC. Chromium: maximum admissible concentration 50 µg l⁻¹. Calcium: guide level 100 mg l⁻¹ (24). Covered in the UK by the Control of Carcinogenic Substances, Control of Substances Hazardous to Health Regulations, 1988 (25).

Other comments

Reviews on human health effects, experimental toxicology, ecotoxicology, physico-chemical properties, environmental effects and exposure levels listed (26). Chromium genotoxicity is reviewed (27). Reviewed in IARC monographs under chromium and compounds (6,28). Effluents from chromate manufacturing plants usually contain residual chromium(vi). Solid chromium(vi) residues in landfills can by desorption contaminate surrounding water sources (29). May occur in wastes associated with its production or use (30).

References

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3. Lowman, F. G. et al *Radioactivity in the Marine Environment* 1971, 169-199.
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24. *EC Directive Relating to the Quality of Water Intended for Human Consumption* 1982, 80/778/EEC, Office for Official Publications of the European Communities, 2 rue Mercier, L-2985 Luxembourg.
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26. *ECETOC Technical Report No. 71* 1996, European Centre for Ecotoxicology and Toxicology of Chemicals, 4 Avenue E. Van Nieuwenhuyse (Bte 6), B-1160 Brussels, Belgium.
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c29 calcium cyanamide

CaNCN

CCaN₂

Mol. Wt. 80.10

CAS Registry No. 156-62-7

Synonyms cyanamide, calcium salt (1:1); aero-cyanamid; calcium carbimide; lime-nitrogen; nitrolime

EINECS No. 205-861-8

RTECS No. GS 6000000

Uses Fertiliser, defoliant, herbicide, pesticide. Used in the manufacture and refining of iron. Manufacture of calcium cyanide, melamine and dicyandiamide. Anthelmintic in veterinary medicine. Used as an adjunct in the treatment of chronic alcoholism.

Physical properties

M. Pt. 1340°C **B. Pt.** >1150°C (sublimes) **Specific gravity** 2.29 at 20°C with respect to water at 4°C
Solubility Water: decomp.

Occupational exposure

DE-MAK 1 mg m⁻³ (inhalable fraction of aerosol)

FR-VME 0.5 mg m⁻³

UK-LTEL 0.5 mg m⁻³

UK-STEL 1 mg m⁻³

US-TWA 0.5 mg m⁻³

UN No. 1403 HAZCHEM Code 4YE Conveyance classification substance which in contact with water emits flammable gas

Supply classification harmful

Risk phrases Harmful if swallowed – Irritating to the respiratory system – Risk of serious damage to eyes (R22, R37, R41)

Safety phrases Keep out of reach of children (if sold to general public) – Do not breathe dust – In case of contact with eyes, rinse immediately with plenty of water and seek medical advice – Wear suitable protective clothing, gloves and eye/face protection (S2, S22, S26, S36/37/39)

Mammalian & avian toxicity

Acute data

LD₅₀ oral rat 158 mg kg⁻¹ (1).

LC_{Lo} (4 hr) inhalation rat 86 mg m⁻³ (2).

LD₅₀ dermal rabbit 590 mg kg⁻¹ (3).

LD₅₀ intravenous rat, mouse 125, 282 mg kg⁻¹, respectively (1).

Carcinogenicity and chronic effects

National Toxicology Program tested rats and mice via feed. No evidence of carcinogenicity in ♂ or ♀ rats or mice (4).

Teratogenicity and reproductive effects

Administration of 3 mg l⁻¹ calcium cyanamide to pregnant rabbits (1 hr day⁻¹) and guinea pigs (2 hr day⁻¹) caused weight loss and changes in maternal blood, damage to the liver of foetuses, and abortion (5).

Metabolism and toxicokinetics

Dissolved by mucosal secretions giving rise to free cyanamide (CN-NH₂), ammonia and, through reaction with CO₂, calcium carbonate which has a dehydrating effect. Has been suggested that catalase is responsible for activating cyanamide to a metabolite which is a potent inhibitor of aldehyde dehydrogenase (species unspecified) (6).

Irritancy

Can cause skin irritation in humans; lesions vary from erythema to eczema. Ulcers and burning of skin, nose, and throat, conjunctivitis, rhinitis and gingivitis have been reported (7).

Sensitisation

Sensitising dermatitis has been reported in humans (7).

Genotoxicity

Salmonella typhimurium TA98, TA100, TA1535, TA97/TA1537 with and without metabolic activation positive (8,9).

Other effects

Other adverse effects (human)

May cause drowsiness, dizziness, fatigue, skin rash, tinnitus, mental depression and impotence (10).

Exposed workers may develop a transient vasomotor disturbance of the upper part of the body. There appears to be a wide variation to susceptibility to this effect that is increased by intake of ethanol and is called "Cyanamid flush" (11).

Chronic rhinitis with perforated nasal septum have been reported in subjects exposed to calcium cyanamide dust for many years (12).

Calcium cyanamide (administered in its citrated form CAS RN = 8013-88-5) has been used as a deterrent in the treatment of chronic alcoholism. Calcium cyanamide inhibits aldehyde dehydrogenase to produce raised acetaldehyde concentrations in the blood (13).

Chronic alcoholics treated with calcium cyanamide had distinctive hepatic lesions characterised by inclusions in the hepatocytes (14).

In a study of 39 patients who had received calcium cyanamide for periods of 2 months to 7 yr, liver biopsy showed characteristic cytoplasmic inclusion bodies in the liver cells, fibrosis and disruptions of the parenchymal-connective tissue interface. None of the patients had evidence of alcoholic liver disease and the stage of liver lesion correlated with duration of treatment (15).

Oral human 50 mg twice daily produced a reaction to a challenge dose of alcohol in an alcoholic who did not react while on 600 mg day⁻¹ disulfiram (16).

Any other adverse effects

Potentially dangerous cardiovascular changes have been reported during calcium cyanamide-alcohol reaction (species unspecified) (17).

In animals (species unspecified) inhibition of aldehyde dehydrogenase is maximal 1-2 hr after administration (concentration unspecified) and 80% activity was restored within 24 hr (13).

Legislation

Included in Schedule 6 (Release into Land: Prescribed Substances) of Statutory Instrument No. 472, 1991 (18).

Limited under EC Directive on Drinking Water Quality 80/778/EEC. Calcium: guide level 100 mg l⁻¹. Pesticides and related products: maximum admissible concentration 0.1 µg l⁻¹ (19).

Other comments

Reviews on experimental toxicology, human health effects, ecotoxicology, physico-chemical properties, epidemiology, and workplace experience listed (20).

Review of the ethanol deterrents calcium cyanamide and disulfiram (13,21,22).

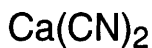
Disposition and pharmacokinetics discussed (23).

Solutions of calcium cyanamide cannot be obtained with any known solvent without decomposition occurring. Decomposes in cold water to evolve ammonia.

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C30 calcium cyanide



C_2CaN_2

Mol. Wt. 92.11

CAS Registry No. 592-01-8

Synonyms Calcid; Calcyan; Cyangas

EINECS No. 209-740-0

RTECS No. EW 0700000

Uses Fumigant. Rodenticide. Stainless steel manufacture. Leaching ores for precious metals. Stabiliser for cement.

Physical properties

M. Pt. $>350^\circ\text{C}$ (decomp.)

Occupational exposure

DE-MAK 5 mg m^{-3} (as CN) (inhalable dust fraction)

FR-VME 5 mg m^{-3} (as HCN)

SE-CEIL 5 mg m^{-3} (as CN)

UK-LTEL 5 mg m^{-3} (as CN)

US-STEL ceiling limit 5 mg m^{-3} (as CN)

UN No. 1575 Conveyance classification toxic substance

Supply classification very toxic

Risk phrases Very toxic if swallowed – Contact with acids liberates very toxic gas (R28, R32)

Safety phrases Keep locked up and out of the reach of children (if sold to general public) – Keep container tightly closed and dry – Do not breathe spray – Wear suitable protective clothing and gloves – In case of accident or if you feel unwell, seek medical advice immediately (show label where possible) (S1/2, S7/8, S23, S36/37, S45)

Mammalian & avian toxicity

Acute data

LD₅₀ oral rat 39 mg kg^{-1} (1).

Legislation

Regulations on prohibition of land disposal of certain hazardous wastes (3rd schedule wastes) are amended under the Federal Resources Conservation and Recovery Act (2).

Included in Schedule 6 (Release into Land: Prescribed Substances) of Statutory Instrument No. 472, 1991 (3).

Limited under EC Directive on Drinking Water Quality 80/778/EEC. Calcium: guide level 100 mg l^{-1} . Cyanides: maximum admissible concentration 30 $\mu\text{g l}^{-1}$. Pesticides and related products: maximum admissible concentration 0.1 $\mu\text{g l}^{-1}$ (4).

Other comments

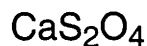
Very poisonous.

Reviews on experimental toxicology and human health effects, ecotoxicology, physico-chemical properties, environmental effects, exposure and exposure levels listed (5).

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c31 calcium dithionite



CaO_4S_2

Mol. Wt. 168.21

CAS Registry No. 15512-36-4

Synonyms calcium hydrosulfite; dithionous acid, calcium salt (1:1)

EINECS No. 239-540-9

Uses Reducing agent in leather substitutes and urethane rubbers. Polymerisation catalyst in the manufacture of high purity solutions.

Occupational exposure

UN No. 1923 HAZCHEM Code 2R Conveyance classification spontaneously combustible substance

Legislation

Limited under EC Directive on Drinking Water Quality 80/778/EEC. Calcium: guide level 100 mg l⁻¹ (1).

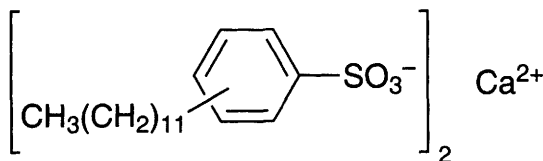
Other comments

Spontaneously combustible substance.

References

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c32 calcium dodecylbenzenesulfonate



$\text{C}_{36}\text{H}_{58}\text{CaO}_6\text{S}_2$

Mol. Wt. 691.06

CAS Registry No. 26264-06-2

Synonyms benzenesulfonic acid, dodecyl-, calcium salt; Ablusol DBC; Tensaryl SB Ca; Arylan CA; Nansa EVM 70/B; Emulson CAL; Surfac CABS70; Witconate 605A

EINECS No. 247-557-8

Uses Anionic detergent. Used in toxic chemical agent decontamination emulsions.

Mammalian & avian toxicity

Irritancy

May cause skin irritation (1).

Other effects

Other adverse effects (human)

Damaging potential of calcium dodecylbenzene sulfonate on humans (1).

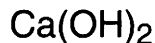
Legislation

Limited under EC Directive on Drinking Water Quality 80/778/EEC. Calcium: guide level 100 mg l⁻¹ (2).

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c33 calcium hydroxide



CaH_2O_2

Mol. Wt. 74.09

CAS Registry No. 1305-62-0

Synonyms calcium hydrate; hydrated lime; slaked lime; Red Hot Pellets; Limbux; Limil

EINECS No. 215-137-3

RTECS No. EW 2800000

Uses In mortar, plaster, cement and other building and paving materials. In lubricants, drilling fluids, pesticides, fireproofing coatings, water paints. Egg preservative. Manufacture of paper pulp. Styrene butadiene rubber vulcanisation. Water treatment. Dehairing hides. Therapeutically used as an astringent.

Physical properties

M. Pt. loses water at 580°C **B. Pt.** decomp. **Specific gravity** 2.240

Solubility Water: 0.8 g l⁻¹ at 0°C

Occupational exposure

FR-VME 5 mg m⁻³

UK-LTEL 5 mg m⁻³

US-TWA 5 mg m⁻³

Environmental fate

Adsorption and retention

Strong interaction with humic acids (1).

Mammalian & avian toxicity

Acute data

LD₅₀ oral redwing blackbird 111 mg kg⁻¹ (2).

LD₅₀ oral rat 7340 mg kg⁻¹ (3).

Irritancy

A severe eye irritant, a skin, mucous membrane and respiratory system irritant (4).

10 mg instilled into rabbit eye caused severe irritation (4).

Sensitisation

Has been reported to cause dermatitis in humans (2).

Other effects

Other adverse effects (human)

Produces third-degree alkali burns (with a pH as high as 12.9) after 2 hr of contact (5).

Legislation

Limited under EC Directive on Drinking Water Quality 80/778/EEC. Calcium guide level 100 mg l⁻¹ (6).

Other comments

Low levels cause physiological toxicity in a nitrogen-fixing strain of the cyanobacterium *Aphanizomenon flos-aquae*.

Limited cell membrane damage (as potassium release), release of dissolved organic carbon and of the odour compound, geosmin, was observed (7).

Use in restorative dentistry reviewed (8).

Reviews on experimental toxicology, human health effects and workplace experience listed (9).

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1. van den Hoop, M. A. G. T. *Anal. Chem. Acta* 1990, **232**(1), 141-148.
2. Schafer, E. W. et al *Arch. Environ. Contam. Toxicol.* 1983, **12**, 355-382.
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c34 calcium hypochlorite



CaCl₂O₂

Mol. Wt. 142.98

CAS Registry No. 7778-54-3

Synonyms hypochlorous acid, calcium salt; lime chloride; calcium chlorohydrochlorite; Induclor; Pi Habs; Pulsar; Swim Clear; CCH; HTH; Pittchlor

EINECS No. 231-908-7

RTECS No. NH 3485000

Uses Algicide. Bactericide. Deodorant. Disinfectant. Fungicide. Oxidising agent. Bleaching agent.

Physical properties

M. Pt. 100°C (decomp.) Specific gravity 2.35

Occupational exposure

UN No. 1748 (dry)

UN No. 2880 (hydrated) HAZCHEM Code 2WE (dry) HAZCHEM Code 2W (hydrated)

Conveyance classification oxidising substance

Supply classification oxidising, corrosive

Risk phrases Contact with combustible material may cause fire – Contact with acids liberates toxic gas – Causes burns (R8, R31, R34)

Safety phrases Keep locked up and out of the reach of children (if sold to general public) – In case of contact with eyes, rinse immediately with plenty of water and seek medical advice – In case of fire, use water – In case of accident or if you feel unwell, seek medical advice immediately (show label where possible) (S1/2, S26, S43, S45)

Ecotoxicity

Fish toxicity

LC₅₀ (24 hr) striped bass larvae 0.5 mg l⁻¹ static bioassay, 70% (hypochlorite) (1).

LC₁₀₀ (24 hr) green sunfish 3.6 mg l⁻¹ (as Cl₂) in pond water (2).

Invertebrate toxicity

EC₅₀ Photobacterium phosphoreum bioluminescence bioassay 6.1 ppm (3).

Toxic to algae exposed to levels of 2 mg l⁻¹ for 72 hr (4).

Mammalian & avian toxicity

Acute data

LD₅₀ oral rat 850 mg kg⁻¹ (5).

Irritancy

Severe irritant to skin and mucous membranes. Emits fumes capable of causing pulmonary oedema. Severe irritant to respiratory tract, can cause ulcers, nasal septal necrosis and laryngeal oedema (6).

Sensitisation

Has been reported to cause dermatitis and conjunctivitis in humans (6).

Genotoxicity

Salmonella typhimurium TA92, TA94, TA98, TA100, TA1537 with metabolic activation positive (7).

In vitro Chinese hamster fibroblast without metabolic activation positive (7).

Reports indicate that calcium hypochlorite is clastogenic *in vitro* but not *in vivo* (8).

Other effects

Any other adverse effects

Systemic effects include coughing, sore throat, gingivitis, teeth damage, laboured breathing, laryngitis and pulmonary oedema (6).

Legislation

Information regarding the US re-registration of pesticide products containing calcium hypochlorite (9).

Included in Schedule 6 (Released into Land: Prescribed Substances) Statutory Instrument No. 472, 1991 (10).

Limited under EC Directive on Drinking Water Quality 80/778/EEC. Chlorides: guide level 25 mg l⁻¹ (11).

Other comments

Primary municipal wastewater sludge treated with calcium hypochlorite 3% active Cl₂ (based on sludge dry matter) gives a product suitable for agricultural land application, improves dewatering by filtration and eliminates the unpleasant odour of unstabilised sludge (12).

Calcium hypochlorite successfully precipitated copper from wastewater containing Cu-EDTA. Treatment resulted in a sludge with lower heavy metal ion content (13).

Physical and chemical characteristics, toxicity and irritant effects reviewed (14,15).

Fire and explosion hazards, physical, chemical properties and toxicity detailed (16,17).

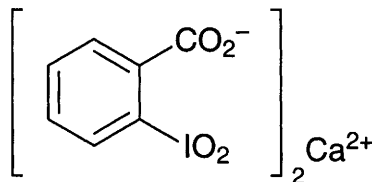
May explode or ignite spontaneously (18).

Reviews on experimental toxicology, human health effects, ecotoxicology, physico-chemical properties, environmental effects and exposure levels of calcium hypochlorite (Cl >39%) listed (19).
Effective in the detoxifying of the food toxin flavobacterium toxin A from *Flavobacterium farinofermentans* (20).
Bulk material may ignite or explode in storage. Traces of water may initiate reaction.

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c35 calcium o-iodoxybenzoate



$C_{14}H_8CaI_2O_8$

Mol. Wt. 598.10

CAS Registry No. 59643-77-5

Synonyms benzoic acid, 2-iodyl-, calcium salt

EINECS No. 261-835-6

Uses Reducing agent.

Occupational exposure

Supply classification explosive

Risk phrases Explosive when dry (R1)

Safety phrases Keep out of reach of children (if sold to general public) – This material and its container must be disposed of in a safe way (S2, S35)

Legislation

Limited under EC Directive on Drinking Water Quality 80/778/EEC. Calcium: guide level 100 mg l⁻¹ (1).
Included in Schedule 6 (Release into Land: Prescribed Substances) of Statutory Instrument No. 472, 1991 (2).

References

1. *EC Directive Relating to the Quality of Water Intended for Human Consumption* 1982, 80/778/EEC, Office for Official Publications of the European Communities, 2 rue Mercier, L-2985 Luxembourg.
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c36 calcium nitrate



CaN₂O₆

Mol. Wt. 164.09

CAS Registry No. 10124-37-5

Synonyms nitric acid, calcium salt; calcium dinitrate; Nitrosprint

EINECS No. 233-332-1

RTECS No. EW 2985000

Uses Used in the manufacture of explosives, fertilisers, matches and pyrotechnics. In the production of incandescent mantles and radio tubes. Corrosion inhibitor in diesel fuels.

Physical properties

M. Pt. 560°C **Specific gravity** 2.504 at 18°C

Solubility Water: very soluble. Organic solvents: acetone, ethanol, methanol

Occupational exposure

UN No. 1454 **HAZCHEM Code** 1 $\frac{+}{-}$ **Conveyance classification** oxidising substance

Environmental fate

Nitrification inhibition

Laboratory experiment 76-day duration to determine the availability of nitrogen in ¹⁵N- labelled fungi, soil microbial biomass and above-ground plant biomass. Only 2% of the total ¹⁵N was found in the microbial biomass two days after the addition of calcium nitrate. At 76 days 17% of ¹⁵N remaining in soil was found in the microbial biomass. The authors conclude that nitrogen in the native soil biomass is resistant to mineralisation and plant uptake (1).

Anaerobic effects

The effects of calcium nitrate on bacterial leaching of heavy metals from anaerobically digested sludge were studied in the batch process using a strain of *Thiobacillus ferrooxidans*. Addition of a nitrogen source to the sludge increased the metal solubilisation efficiency to a very small extent (2).

Mammalian & avian toxicity

Acute data

LD₅₀ oral redwing blackbird 99 mg kg⁻¹ (3).

Other effects

Other adverse effects (human)

Nitrate salts are more toxic than other neutral salts; if not promptly absorbed from the gastro-intestinal tract, they

may be reduced to nitrites by bacteria in the bowel. Cyanosis among infants who drink well water with high nitrate levels is a frequently encountered clinical manifestation of nitrate toxicity (4).

Legislation

Limited under EC Directive on Drinking Water Quality 80/778/EEC. Nitrates: guide level 25 mg l⁻¹ maximum admissible concentration 50 mg l⁻¹ as NO₃⁻ (5).

Other comments

Health hazards are discussed in terms of toxic or destructive effects and first aid measures (6).

Revised edition of report CIS 68-1694: classification of nitrate fertilisers hazard categories, safety rules, general information on explosion and fire hazards (7,8).

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c37 calcium oxide

CaO

CaO

Mol. Wt. 56.08

CAS Registry No. 1305-78-8

Synonyms burnt lime; quicklime; lime; calcia; calx; Fluorox; Garosorb; Caloxol; Dynacal; Desical; E-Z Spread; Morta-Lok

EINECS No. 215-138-9

RTECS No. EW 3100000

Uses Strong caustic agent. Used in bricks, plaster and other building materials. Manufacture of steel, aluminium, magnesium. Used in fungicides and insecticides. In laboratories to absorb carbon dioxide. Desiccant.

Physical properties

M. Pt. 2580°C B. Pt. 2850°C Specific gravity 3.37

Solubility Organic solvents: glycerol

Occupational exposure

DE-MAK 5 mg m⁻³ (inhalable fraction of aerosol)

FR-VME 2 mg m⁻³

SE-LEVL 2 mg m⁻³

SE-STEL 5 mg m⁻³

UK-LTEL 2 mg m⁻³

US-TWA 2 mg m⁻³

UN No. 1910

Mammalian & avian toxicity

Sub-acute and sub-chronic data

Repeated exposure study inhalation rat 413 mg m⁻³ or a single exposure of 1026 mg m⁻³ (durations unspecified). No deaths, and no marked changes in behaviour, body weight or food intake. No significant difference in haematologic results and serum biochemical analysis or urine analysis (1).

Irritancy

Strongly caustic and may cause severe irritation of skin and mucous membranes (2).

Tends to form clumps in the conjunctival sac which are dangerous and difficult to wash out (3).

Coarse dust causes skin erosion and ulceration while fine dust is injurious to the mouth, nose and eyes (4).

Prolonged exposure may cause dermatitis with desquamation and vesicular rash. Can cause severe irritation to eyes, oedema, hyperaemia, lachrymation, blurred vision, corneal opacities, ulceration and perforation and loss of vision (5).

Other effects

Any other adverse effects

Systemic effects include sore throat, coughing, dyspnoea and, after severe exposure, pulmonary oedema. Contact with moist skin can cause redness and ulceration. Fatal burns have been reported after massive exposure.

Prolonged exposure can cause inflammation and ulceration of the nasal and buccal mucosa with possible bronchial and gastro-intestinal disturbances. Death results from asphyxia and circulatory collapse (5).

Legislation

Included in Schedule 6 (Release into land: Prescribed Substances) Statutory Instrument No. 472 (6).

Limited under EC Directive on Drinking Water Quality 80/778/EEC. Calcium: guide level 100 mg l⁻¹ (7).

Other comments

Produced by the kiln-roasting of limestone. Reacts with water with the evolution of heat to form calcium hydroxide, thus reaction on the skin or in the mouth produces both a thermal and a caustic burn (3).

Decrease of lime dust and silt by acidic leaching and increase in coarse sand was characteristic for soils of a *Quercus Mongolica* forest with a *Corylus heterophylla*, *C. mandshurica*, and *Rhododendron sichonensis* undergrowth under the impact of acid rain. The transported silt formed a powdery layer on the subsoil layer. Calcium oxide occurred in organomineral forms and accumulated in humus. The most severe acidic leaching led to dispersion of the accumulated humus and its efflux in the form of low molecular compounds (8).

Reviews on experimental toxicology, human health effects, epidemiology and workplace experience listed (9).

Ineffective even at concentrations of 600 ppm in controlling the fish ectoparasite *Argulus* sp. (10).

DNA-damaging activity of natural food additives was investigated (11).

The powdered oxide may react explosively with water.

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c38 calcium permanganate



CaMn_2O_8

Mol. Wt. 277.95

CAS Registry No. 10118-76-0

Synonyms permanganic acid (HMnO_4), calcium salt

EINECS No. 233-322-7

RTECS No. EW 3860000

Uses Antiseptic. Disinfectant. Deodoriser. Used with calcium fluoride as binder for welding electrode coatings and fluxes.

Physical properties

M. Pt. decomp. Specific gravity 2.4

Solubility Water: 3310 g l⁻¹ at 14°C

Occupational exposure

UN No. 1456 HAZCHEM Code 1Y Conveyance classification oxidising substance

Mammalian & avian toxicity

Acute data

LD_{Lo} intravenous rabbit 50 mg kg⁻¹ (1).

Legislation

Limited under EC Directive on Drinking Water Quality 80/778/EEC. Manganese: guide level 20 µg l⁻¹, maximum admissible concentration 50 µg l⁻¹ (2).

Included in Schedule 6 (Release Into Land: Prescribed Substances) of Statutory Instrument No. 472, 1991 (3).

Other comments

Uses, hazards, physical and chemical properties reviewed (4).

A strong oxidant. May explode on contact with acetic acid or acetic anhydride. Ignites on contact with cellulose.

Incompatible with hydrogen peroxide.

References

1. *Ueber die Wirkung des Braunsteins* 1933, Paul Thessen Dissertation, Pharmakologischen Institut der Tierärztlichen Hochschule, Berlin, Germany.
2. *EC Directive Relating to the Quality of Water Intended for Human Consumption* 1982, 80/778/EEC, Office for Official Publications of the European Communities, 2 rue Mercier, L-2985 Luxembourg.
3. *S.I. 1991 No. 472 The Environmental Protection (Prescribed Processes and Substances) Regulations* 1991, HMSO, London, UK.
4. *Fire Prevention* 1981, 145, 47-48

c39 calcium peroxide



CaO_2

Mol. Wt. 72.08

CAS Registry No. 1305-79-9

Synonyms calcium dioxide; Fertilox; Oxy-Gro-G; Oxy-Gro-T

EINECS No. 215-139-4

RTECS No. EW 3865000

Uses Stabiliser for rubber. Antiseptic.

Physical properties

M. Pt. 692°C

Occupational exposure

UN No. 1457 HAZCHEM Code 1Y Conveyance classification oxidising substance

Legislation

Limited under EC Directive on Drinking Water Quality 80/778/EEC. Calcium: guide level 100 mg l⁻¹ (1).
Included in Schedule 6 (Release into Land: Prescribed Substances) of Statutory Instrument No. 472, 1991 (2).

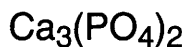
Other comments

Review of calcium peroxide as an oxygen-generating agent for plant growth, use in live fish transport and other agricultural applications (3).
Reacts with moisture to form slaked lime.

References

1. EC Directive Relating to the Quality of Water Intended for Human Consumption 1982, 80/778/EEC, Office for Official Publications of the European Communities, 2 rue Mercier, L-2985 Luxembourg.
2. S. I. 1991 No. 472 *The Environmental Protection (Prescribed Processes and Substances) Regulations 1991*, HMSO, London, UK.
3. Ino, K. *Gypsum Lime* 1990, 22, 47-50 (Japan.) (*Chem. Abstr.* 112, 134336d)

c40 calcium phosphate



$\text{Ca}_3\text{O}_8\text{P}_2$

Mol. Wt. 310.18

CAS Registry No. 7758-87-4

Synonyms calcium phosphate tribasic; tricalcium orthophosphate; tricalcium phosphate; tertiary calcium phosphate; Ajax

EINECS No. 231-840-8

Uses Manufacture of fertilisers. Used in the production of milkglass, polishing and dental powders, pottery. Animal feeds. Non-caking agent. Textile industry. Has been used as a dietary supplement and as an antacid. Calcium replenisher in homoeopathic medicines.

Occurrence Occurs in nature as the minerals apatite, hydroxyapatite, voelicherite and whitlockite.

Physical properties

M. Pt. 1670°C Specific gravity 3.14

Other effects

Any other adverse effects

Intraperitoneal exposure to injected dust resulted in initial foreign body irritation followed by nodules with no necrosis or cellular proliferation (1).

Legislation

Limited under EC Directive on Drinking Water Quality 80/778/EEC. Phosphorus: guide level 400 µg l⁻¹ maximum admissible concentration 5000 µg l⁻¹ (2).

Other comments

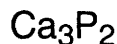
The technical product is known as bone ash.

Useful non-hygroscopic diluent for powders and vegetable extracts (3).

References

1. Miller, J. W. et al *Public Health Reports* 1936, 51(49), 1677-1688.
2. *EC Directive Relating to the Quality of Water Intended for Human Consumption* 1982, 80/778/EEC, Office for Official Publications of the European Communities, 2 rue Mercier, L-2985 Luxembourg.
3. *Martindale: The Extra Pharmacopoeia* 31st ed., 1996, The Royal Pharmaceutical Society, London, UK

c41 calcium phosphide



Ca₃P₂

Mol. Wt. 182.18

CAS Registry No. 1305-99-3

Synonyms Arrex Toupeira; Polytanol; Polythanol

EINECS No. 215-142-0

RTECS No. EW 3870000

Uses For signal fires. Rodenticide. Used in the purification of copper and copper alloys.

Physical properties

M. Pt. >1600°C Specific gravity 2.238 at 25°C

Occupational exposure

UN No. 1360 **Conveyance classification** substance which in contact with water emits flammable gas, toxic

Supply classification highly flammable, very toxic

Risk phrases Contact with water liberates toxic, extremely flammable gas – Very toxic if swallowed (R15/29, R28)

Safety phrases Keep locked up and out of the reach of children (if sold to general public) – Do not breathe dust – In case of fire, use dry powder or carbon dioxide – never use water – In case of accident or if you feel unwell, seek medical advice immediately (show label where possible) (S1/2, S22, S43, S45)

Legislation

Limited under EC Directive on Drinking Water Quality 80/778/EEC. Phosphorus: guide level 400 µg l⁻¹ maximum admissible concentration 5000 µg l⁻¹ (1).

Other comments

Reviews on human health effects, experimental toxicology, ecotoxicology and physico-chemical properties listed (3).

Phosphine poisoning in man briefly listed. Topics include its production from calcium phosphide (4).

Decomposes to evolve phosphine.

References

1. *EC Directive Relating to the Quality of Water Intended for Human Consumption* 1982, 80/778/EEC, Office for Official Publications of the European Communities, 2 rue Mercier, L-2985 Luxembourg.
2. *S. I. 1991 No. 472 The Environmental Protection (Prescribed Processes and Substances) Regulations* 1991, HMSO, London, UK.
3. *ECETOC Technical Report No. 71* 1996, European Centre for Ecotoxicology and Toxicology of Chemicals, 4 Avenue E. Van Nieuwenhuyse (Bte 6), B-1160 Brussels, Belgium.
4. Flury, F. *Anzeiger Fuer Schadlingskinde* 1937, **13**, 26-20

c42 calcium polysulfides



CAS Registry No. 1344-81-6

Synonyms calcium sulfide; lime sulfur; Orthorix; Eau Grison; Neviken

EINECS No. 215-709-2

RTECS No. EW 4155000

Uses Fungicide. Insecticide.

Physical properties

Specific gravity >1.28 at 15°C

Occupational exposure

Supply classification irritant

Risk phrases Contact with acids liberates toxic gas – Irritating to eyes, respiratory system and skin (R31, R36/37/38)

Safety phrases Keep out of reach of children (if sold to general public) – After contact with skin, wash immediately with plenty of water (S2, S28)

Mammalian & avian toxicity

Sensitisation

May cause eye damage and skin irritation in mammals (1).

Reported to be an irritant and sensitising agent in humans (2).

Legislation

Included in Schedule 4 (Release into Air: Prescribed Substances) Statutory Instrument No. 472, 1991 (3).

Limited under EC Directive on Drinking Water Quality 80/778/EEC. Calcium: guide level 100 mg l⁻¹. Sulfates: guide level 25 mg l⁻¹, maximum admissible concentration 250 mg l⁻¹ (4).

Other comments

Reviews on experimental toxicology, human health effects, ecotoxicology and physico-chemical properties listed (5).

Corrosive. May yield hydrogen sulfide on decomposition.

References

1. *The Pesticide Manual* 11th ed., 1997, The British Crop Protection Council, Farnham, UK.
2. Gosselin, R. E. et al *Clinical Toxicology of Commercial Products*, 5th ed., 1984, Williams & Wilkins, Baltimore, MD, USA.
3. S. I. 1991 No. 472 *The Environmental Protection (Prescribed Processes and Substances) Regulations* 1991, HMSO, London, UK.
4. *EC Directive Relating to the Quality of Water Intended for Human Consumption* 1982, 80/778/EEC, Office for Official Publications of the European Communities, 2 rue Mercier, L-2985 Luxembourg.
5. *ECETOC Technical Report No. 71* 1996, European Centre for Ecotoxicology and Toxicology of Chemicals, 4 Avenue E. Van Nieuwenhuysse (Bte 6), B-1160 Brussels, Belgium

c43 calcium silicate



CaO_3Si

Mol. Wt. 116.16

CAS Registry No. 1344-95-2

Synonyms silicic acid, calcium salt; calcium hydrosilicate; calcium monosilicate; calcium polysilicate; Micro-Cel; Extrusil; Keical-Ace; Silasorb; Vansil

EINECS No. 215-710-8

RTECS No. VV 9115000

Uses Anti-caking agent. Absorbent for liquids, gases and vapours. Reinforcing agent in elastomers and plastics. Binder for refractory material. Used in chromatography. Road construction. Antacid.

Occurrence Usually as hydrated form, in various minerals, such as okenite and tobermorite.

Physical properties

M. Pt. 1540°C

Occupational exposure

UK-LTEL 10 mg m⁻³ (total inhalable dust); 4 mg m⁻³ (respirable dust)

US-TWA 10 mg m⁻³

Mammalian & avian toxicity

Carcinogenicity and chronic effects

Inhalation rat (1 yr) 10 mg m⁻³ of respirable dust, no discernible effect on length of survival of treated animals compared with controls (1).

Irritancy

A 23-yr-old man developed an irritant skin contact reaction after being employed for three days in a pharmaceutical company warehouse where a food additive for pigs and poultry was packaged and stored. The food was a white powder made of virginiamycin, carboxymethyl cellulose and calcium silicate. Microscopic examination of the dust revealed sharp edged particles of calcium silicate which were thought to be causing the reaction due to their physical properties. The author classifies the compound as an airborne irritant contact reactant (2).

Other effects

Any other adverse effects

Calcium silicate composites induced cellular and biochemical changes in rat lung tissue which were dose dependent (3).

Legislation

Limited under EC Directive on Drinking Water Quality 80/778/EEC. Calcium: guide level 100 mg l⁻¹. Silica: covered under Article 8 (4).

Other comments

Forms a siliceous gel with mineral acids.

References

1. Bolton, R. E. et al *Environ. Res.* 1986, **39** 20-43.
2. Lachapelle, J. M. et al *Environ. Res.* 1984, **10**(4), 250-251.
3. Richards, R. T. et al *Environ. Res.* 1981, **26**(2), 243-257.
4. *EC Directive Relating to the Quality of Water Intended for Human Consumption* 1982, 80/778/EEC, Office for Official Publications of the European Communities, 2 rue Mercier, L-2985 Luxembourg

c44 calcium sulfate



CaO₄S

Mol. Wt. 136.14

CAS Registry No. 7778-18-9

Synonyms anhydrous sulfate of lime; anhydrous gypsum; sulfuric acid, calcium salt (1:1); Franklin Fibre; Andricite; Compactrol; Delaflo

EINECS No. 231-900-3 (natural)

RTECS No. WS 6920000

Uses Used in cement formulations and as a paper filler. An inert additive in pharmaceuticals and insecticides.

Occurrence Anhydrous calcium sulfate occurs naturally as the mineral anhydrite.

Physical properties

M. Pt. 1450°C **Specific gravity** 2.964

Solubility Water: 2 g l⁻¹ at 25°C. Organic solvents: glycerol

Occupational exposure

DE-MAK 6 mg m⁻³ (respirable fraction of aerosol)

US-TWA 10 mg m⁻³

Mammalian & avian toxicity

Carcinogenicity and chronic effects

Intratracheal ♀ hamster (5 wk) 2 mg wk⁻¹ calcium sulfate fibre, animals were observed for 2 yr post-exposure.

3/20 animals exposed to calcium sulfate fibre developed tumours. Primary sites were in the pleural cavity, kidney, adrenal gland, bladder and uterus (1).

Genotoxicity

Salmonella typhimurium TA102 with and without metabolic activation negative (2).

Other effects

Other adverse effects (human)

Airborne calcium sulfate emitted from coal-fired power plants was a suspected causative agent of acute asthma in Derby, UK (3).

Prolonged eye exposure may cause conjunctivitis (4).

Systemic effects include unpleasant nasal passage deposits and coughing. Prolonged exposure may cause chronic rhinitis, laryngitis, pharyngitis, impaired sense of taste and smell, epistaxis and reactions from tracheal and bronchial membranes in exposed workers (4).

Gastric irritation due to osmotic disturbances may occur after ingestion (4).

Legislation

Included in Schedule 4 (Release into Air: Prescribed Substances) Statutory Instrument No. 472, 1991 (5).

Limited under EC Directive on Drinking Water Quality 80/778/EEC. Calcium: guide level 100 mg l⁻¹. Sulfate: guide level 25 mg l⁻¹; maximum admissible concentration 250 mg l⁻¹ (6).

Other comments

A review of published data found no fibrous effects produced by natural dusts of calcium sulfate. Changes in lung tissues of animals and humans occurred only when calcium sulfate was contaminated with silicon dioxide (7).

Hydration reactions in relation to mechanism of Portland Cement reviewed (8).

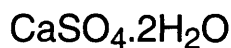
Reviews on experimental toxicology, human health effects, epidemiology and workplace experience listed (9).

A low-temperature soluble anhydride exists, known as Drierite. It is used as a commercial desiccant. Reacts violently with aluminium when heated. Can react explosively with diazomethane. Mixtures with phosphorus ignite at high temperatures.

References

1. Adachi, S. et al *Environ. Res.* 1991, **54**(1), 52-73.
2. Fujita, H. et al *Tokyo-toritsu Eisei Kenkyusho Kenkyu Nenpo* 1988, **39**, 343-350 (Japan.) (*Chem. Abstr.* **110**, 230308a).
3. Brown, H. M. et al *Experientia Suppl.* 1987, **51**, 261-266.
4. *Pestline* 1991, **1**, 175-176, Occupational Health Services, Van Nostrand Reinhold, New York, USA.
5. *S. I.* 1991, No. 472 *The Environmental Protection (Prescribed Processes and Substances) Regulations* 1991, HMSO, London, UK.
6. *EC Directive Relating to the Quality of Water Intended for Human Consumption* 1982, 80/778/EEC, Office for Official Publications of the European Communities, 2 rue Mercier, L-2985 Luxembourg.
7. Einbrodt, H. J. *Wiss. Umwelt.* 1988, **4**, 179-181 (Ger.) (*Chem. Abstr.* **112**, 144726v).
8. Gartner, F. M. *Mater. Sci. Concr.* 1989, **1**, 95-125.
9. *ECETOC Technical Report No. 71* 1996, European Centre for Ecotoxicology and Toxicology of Chemicals, 4 Avenue E. Van Nieuwenhuyse (Bte 6), B-1160 Brussels, Belgium

c45 calcium sulfate dihydrate



CaH₄O₆S

Mol. Wt. 172.17

CAS Registry No. 10101-41-4

Synonyms sulfuric acid, calcium salt (1:1), dihydrate; gypsum; Terra Alba 114836

RTECS No. EW 4150000

Uses Used in the manufacture of Portland Cement. Soil treatment to neutralise alkali carbonates and to prevent loss by volatilisation and leaching of dissolved nitrogenous compounds. Manufacture of plaster of Paris, artificial marble. Used in paints, enamels, pharmaceuticals, paper, insecticide dusts, yeast manufacture, water treatment, polishing powders and certain porous polymers.

Occurrence Occurs naturally as gypsum.

Physical properties

M. Pt. 128°C (loses water) **B. Pt.** 163°C (loses water) **Specific gravity** 2.32

Solubility Water: 2.4 g l⁻¹. Organic solvents: glycerol

Occupational exposure

FR-VME 10 mg m⁻³

UK-LTEL 10 mg m⁻³ (total inhalable dust); 4 mg m⁻³ (respirable dust)

Legislation

Included in Schedule 4 (Release into Air: Prescribed Substances) Statutory Instrument No. 472, 1991 (1).

Limited under EC Directive on Drinking Water Quality 80/778/EEC. Calcium: guide level 100 mg l⁻¹. Sulfate: guide level 25 mg l⁻¹, maximum admissible concentration 250 mg l⁻¹ (2).

Other comments

Considered a nuisance dust. Relationship between industrial dust and damage to the respiratory system has been evaluated (3).

Toxicity evaluated as nuisance, non-toxic dust (4).

References

1. S. I. 1991 No. 472 *The Environmental Protection (Prescribed Processes and Substances) Regulations 1991*, HMSO, London, UK.
2. *EC Directive Relating to the Quality of Water Intended for Human Consumption 1982*, 80/778/EEC, Office for Official Publications of the European Communities, 2 rue Mercier, L-2985 Luxembourg.
3. Schmidt, W. *Hals-, Nasen-, und Ohrenheilkunde* 1949, 1-58 (Ger.).
4. *Chemical Safety Information Sheet* 1990, 1, Canadian Centre for Occupational Health and Safety, Ontario, Canada

CaS

CaS

Mol. Wt. 72.14

CAS Registry No. 20548-54-3

Synonyms calcium monosulfide; calcic liver of sulfur; sulfurated lime

EINECS No. 243-873-5

Uses Phosphors. Lubricant additive. Luminous paints or varnishes.

Physical properties

M. Pt. >2000°C Specific gravity 2.59

Solubility Water: 0.21 g l⁻¹ at 15°C (decomp.)**Occupational exposure**

Supply classification irritant

Risk phrases Contact with acids liberates toxic gas – Irritating to eyes, respiratory system and skin (R31, R36/37/38)

Safety phrases Keep out of reach of children (if sold to general public) – After contact with skin, wash immediately with plenty of water (S2, S28)

Mammalian & avian toxicity

Irritancy

Strong irritant to skin and mucous membranes in humans (1).

Other effects

Any other adverse effects

If gastric acidity is high, the ingestion of sulfide salts may result in their decomposition to form hydrogen sulfide in the stomach with subsequent systemic poisoning (1).

LegislationLimited under EC Directive on Drinking Water Quality 80/778/EEC. Calcium: guide level 100 mg l⁻¹ (2).**Other comments**

Description and uses of inorganic sulfides, fire and explosion hazards, hazardous reactions, toxic effects, safety precautions and physico-chemical data (3).

Reviews on experimental toxicology, human health effects, ecotoxicology and physico-chemical properties listed (4).

Reacts violently with chromyl chloride, lead dioxide, potassium chlorate (mild explosion), potassium nitrate (violent explosion). Incompatible with oxidants.

References

1. Gosselin, R. E. et al *Clinical Toxicology of Commercial Products* 1984, 5th ed., Williams & Wilkins, Baltimore, MD, USA.
2. *EC Directive Relating to the Quality of Water Intended for Human Consumption* 1982, 80/778/EEC, Office for Official Publications of the European Communities, 2 rue Mercier, L-2985 Luxembourg.
3. *Safety Practitioner* 1983, 1(5), 20-21.
4. *ECETOC Technical Report No. 71* 1996, European Centre for Ecotoxicology and Toxicology of Chemicals, 4 Avenue E. Van Nieuwenhuyse (Bte 6), B-1160 Brussels, Belgium

Cl₂Hg₂

Mol. Wt. 472.09

CAS Registry No. 10112-91-1

Synonyms mercury(i) chloride; dimercury dichloride; mercurous chloride; mercury subchloride

EINECS No. 233-307-5

RTECS No. OV 8750000

Uses Fungicide. Insecticide. Used in coloured paper, porcelain paints and calomel electrodes. Formerly given as a laxative and was applied topically as an antibacterial. Used in the treatment of syphilis in the pre-antibiotic era.

Physical properties

M. Pt. 400-500°C Specific gravity 7.15

Solubility Water: 2 mg l⁻¹ at 25°C

Occupational exposure

JP-OEL 0.05 mg m⁻³ (as Hg)SE-LEVL 0.03 mg m⁻³US-TWA 0.024 mg m⁻³

Supply classification harmful

Risk phrases Harmful if swallowed – Irritating to eyes, respiratory system and skin (R22, R36/37/38)

Safety phrases Keep out of reach of children (if sold to general public) – Keep away from food, drink and animal feeding stuffs – Avoid contact with skin and eyes – If swallowed seek medical advice immediately and show this container or label (S2, S13, S24/25, S46)

Ecotoxicity

Invertebrate toxicity

Exposure to the housefly, *Musca domestica* (5 day) and larvae of the cabbage looper moth, *Trichoplusia ni* (48 hr) to the minimally acute LC₅ dose of 0.005% (w/v for *M. domestica* and w/w for *T. ni*) caused no reduction of glutathione levels, and no significant change in the protein carbonyl content in *M. domestica*, but significant increase in the protein carbonyl content (i.e. induced protein oxidation) in *T. ni* (1).

LC₅₀ *Musca domestica* 1.17% w/v concentration (2).LC₅₀ *Trichoplusia ni* 5.15% w/w concentration (2).

Environmental fate

Abiotic removal

Decomposes slowly in sunlight. Under aqueous conditions slowly decomposes to mercury and mercuric chloride (3).

Mammalian & avian toxicity

Acute data

LD₅₀ oral rat 250 mg kg⁻¹ (3).LD₅₀ dermal rat 1500 mg kg⁻¹ (4).LD₅₀ intraperitoneal mouse 10 mg kg⁻¹ (4).

Carcinogenicity and chronic effects

Inadequate evidence for carcinogenicity to humans, limited evidence for carcinogenicity to animals, IARC classification group 3 (5).

Genotoxicity

In vitro Chinese hamster ovary cells induced sister chromatid exchanges (6).

Legislation

Included in Schedule 5 and 6 (Release into Water/Land: Prescribed Substances) Statutory Instrument No. 472, 1991 (7).

Limited under EC Directive on Drinking Water Quality 80/778/EEC. Mercury: maximum admissible concentration $1 \mu\text{g l}^{-1}$ (8).

Other comments

EPA toxicity class II (3). Toxic to fish (1).

Reviews on experimental toxicology, human health effects, ecotoxicology and physico-chemical properties listed (9).

References

1. Zaman, K. et al *Toxic. Subst. J.* 1994, 13(2), 129-140.
2. Zaman, K. et al *Arch. Environ. Contam. Toxicol.* 1994, 26(1), 114-118.
3. *The Pesticide Manual* 11th ed., 1997, The British Crop Protection Council, Farnham, UK.
4. *Gig. Tr. Prof. Zabol.* 1981, 25(7), 27.
5. *IARC Monograph* 1993, 58, 239-345.
6. *Environ. Mutagen.* 1985, 7, 381.
7. S. I. 1991 No. 472 *The Environmental Protection (Prescribed Substances) Regulations* 1991, HMSO, London, UK.
8. *EC Directive Relating to the Quality of Water Intended for Human Consumption* 1982, 80/778/EEC, Office for Official Publications of the European Communities, 2 rue Mercier, L-2985 Luxembourg.
9. *ECETOC Technical Report No. 71* 1996, European Centre for Ecotoxicology and Toxicology of Chemicals, 4 Avenue E. Van Nieuwenhuysse (Bte 6), B-1160 Brussels, Belgium

c48 camphechlor

$\text{C}_{10}\text{H}_{10}\text{Cl}_8$

Mol. Wt. 413.81

CAS Registry No. 8001-35-2

Synonyms chlorinated camphene (67-69% chlorine); octachlorocamphene; phenacide; polychlorocamphene; toxaphene

EINECS No. 232-283-3

RTECS No. XW 5250000

Uses Superseded insecticide, rodenticide and acaricide.

Physical properties

M. Pt. 65-95°C (softens) **B. Pt.** 155°C (decomp.) **Flash point** 135°C (closed cup)

Specific gravity 1.65 at 25°C **Volatility** v.p. 3.3×10^{-5} mmHg at 25°C

Solubility Water: 3 mg l⁻¹ (temp. unspecified). Organic solvents: acetone, aromatic hydrocarbons, carbon tetrachloride, ethanol, hexane

Occupational exposure

FR-VME 0.5 mg m⁻³

US-TWA 0.5 mg m⁻³

Supply classification toxic

Supply classification dangerous for the environment

Risk phrases Harmful in contact with skin – Toxic if swallowed – Irritating to respiratory system and skin – Possible risk of irreversible effects – Very toxic to aquatic organisms, may cause long-term adverse effects in the aquatic environment (R21, R25, R37/38, R40, R50/53)

Safety phrases Keep locked up and out of the reach of children (if sold to general public) – Wear suitable protective clothing and gloves – In case of accident or if you feel unwell, seek medical advice immediately (show label where possible) – This material and/or its container must be disposed of as hazardous waste – Avoid release to the environment. Refer to special instructions/safety data sheet (S1/2, S36/37, S45, S60, S61)

Ecotoxicity

Fish toxicity

LC₅₀ (96 hr) rainbow trout, coho salmon 7-10 µg l⁻¹ (1).

LC₅₀ (96 hr) bluegill sunfish 7 µg l⁻¹ (2).

LC₅₀ (96 hr) sheepshead minnow, pinfish 0.5-1.1 µg l⁻¹ (3,4).

Extensive data on fish toxicity are available (5-7).

Invertebrate toxicity

EC₅₀ (48 hr) *Daphnia magna* 10-19 µg l⁻¹ at 15°C (1).

LC₅₀ (96 hr) grass shrimp 4.4 µg l⁻¹ (4).

LC₅₀ (48 hr) *Anodonta imbecilis* 0.74 mg l⁻¹ (8).

Bioaccumulation

Camphechlor concentrates in the adipose tissue of chickens, bioaccumulation factor 5 (9).

Oysters (36 wk) 1 µg l⁻¹ concentration of camphechlor in tissue at 36 wk was 8 mg kg⁻¹ (10).

In fathead minnows and channel catfish the maximum reported bioconcentration factors were 69,000 and 50,000, respectively (11).

Bioconcentration factors for shrimp of 400-1200, algae 6920, and snail 9600 have been reported (12,13).

Environmental fate

Degradation studies

Depuration t_{1/2} lake trout, single intraperitoneal injection 3.5 or 7 µg g⁻¹, 232 and 322 days, respectively (14).

Depuration t_{1/2} white sucker, 524 days (14).

Microbial degradation of camphechlor by natural microorganisms was enhanced in soil kept under anaerobic (flooded) conditions. Calculated t_{1/2} for 10 ppm camphechlor is 3 wk (15).

t_{1/2} soil 70 day-12 yr depending on soil type and climate (16).

Abiotic removal

Estimated hydrolysis t_{1/2} >10 yr at pH 5-8 and 25°C (17).

Direct photolysis has been reported to be insignificant for removal of camphechlor from the environment (18).

Mammalian & avian toxicity

Acute data

LD₅₀ oral sharptailed grouse 10-20 mg kg⁻¹ (19).

LD₅₀ oral mouse, hamster 112, 200 mg kg⁻¹, respectively (20,21).

LD_{Lo} oral human 28 mg kg⁻¹ (22).

LC_{Lo} (2 hr) inhalation mouse 2000 mg m⁻³ (23).

LD₅₀ dermal rabbit >4000 mg kg⁻¹ side-effects included moderate skin irritation (24).

LD₅₀ intraperitoneal mouse 42 mg kg⁻¹ (25).

LD₅₀ (7 day) oral mallard duck 31 mg kg⁻¹ (26).

Carcinogenicity and chronic effects

Oral rats (lifetime) 25, 100 and 400 mg kg⁻¹. High doses of 100 and 400 mg kg⁻¹ diet caused hypertrophy of liver, increased microsomal enzyme activity, and histological changes in the liver including centrilobular hepatic cell

enlargement with increased oxyphilia and peripheral margination of basophilic granules (27).
No adequate data for carcinogenicity to humans, sufficient evidence for carcinogenicity to animals, IARC classification group 2B (28).
B6C3F1 mice (90-91 wk) 99 or 198 mg kg⁻¹ in diet, induced hepatocellular carcinomas (28).
Oral rats (108-110 wk) 550 and 1100 mg kg⁻¹ in diet, induced follicular-cell carcinoma and adenoma of the thyroid (29).

Teratogenicity and reproductive effects

Camphechlor caused significant maternal weight reduction or maternal lethality in rats and supernumerary ribs were observed in the offspring (30).
Oral gravid CD-1 mice (8-12 days) 75 mg kg⁻¹ in corn oil reduced maternal weight gain (31).
Reproduction study rats, duration unspecified, 0.5 ppm caused no reproductive effects, but toxic effects included depressed weight gain, elevated system cholesterol, increased liver and kidney weight (32).

Metabolism and toxicokinetics

Accumulates temporarily in body fat of mammals (species unspecified), and is eliminated as unchanged camphechlor, hydroxylated and dechlorinated metabolites in urine and faeces (28).
Mice were given a single dose of ¹⁴C camphechlor: distribution after 4 hr to adrenals, kidney, liver, heart and adipose tissue (33).

Irritancy

TD_{Lo} dermal human 657 mg kg⁻¹ after systemic exposure caused dermatitis and allergic reactions (34).

Genotoxicity

Salmonella typhimurium TA98, TA100, TA1535, TA1537 with and without metabolic activation positive (35).
Escherichia coli prophage λ with and without metabolic activation positive (36).
Human lymphocyte sister chromatid exchange positive (37).
Chinese hamster lung cells significant increase in sister chromatid exchange (38).

Other effects

Other adverse effects (human)

A study conducted on 622 white men with newly diagnosed non-Hodgkin's lymphoma and 1245 population-based controls in Iowa and Minnesota showed that elevated risks of developing the disease were associated with handling, mixing, or application of camphechlor (39).
Complex reproducible mixture of 177 C₁₀ polychloro derivatives.
In human poisoning incidents victims suffered convulsions, respiratory arrest and death (28).

Any other adverse effects

Induced rat hepatic ornithine decarboxylase activity (40).
Acute and sub-acute doses of camphechlor caused liver hypertrophy in adult ♂ guinea pig livers. Histological and ultrastructural studies showed hypoxic and anoxic changes and disfigurement of myelin in the brain, chronic venous congestion and fatty changes in the hepatocytes of liver and degeneration of glomerular cells with increase in the number of mitochondria in kidney tubular epithelial cells. The phospholipid content of the brain and liver was significantly reduced, but with increased neutral lipid content. Brain cholesterol levels were increased. Liver accumulated more camphechlor than kidney during sub-acute treatment (41,42).
Camphechlor (250 μmol kg⁻¹) administered intramuscularly to white leghorn roosters had anti-oestrogenic activity as measured by its effect on oestrogen-regulated mRNA stabilising factor. Even at higher concentrations (145 μmol kg⁻¹) camphechlor did not show oestrogen agonist activity (43).

Other comments

Camphechlor has potential endocrine disrupting activities which may affect reproductive health and increase the risk of carcinogenesis (44).
Endocrine disruption effects reported in wildlife. Avian adult growth reduced, shortened egg-laying period, reduced hatchability; fish growth reduced, vertebral anomalies (45).

Reviewed in IARC Monograph (46).

Physical, chemical properties, experimental toxicology, human health effects and environmental fate of camphechlor have been reviewed (47-52).

Camphechlor poses a risk to the environment because, like PCBs and DDT metabolites, it bioaccumulates. Long-range atmospheric transport is possible (53).

Use and effects of camphechlor reviewed, with special reference to Egypt (54).

Workgroup report on environmental transport and fate of camphechlor (55).

IC₅₀ 0.3 µmol l⁻¹ in the *in vitro* Ca²⁺-transport-ATPase test system using human erythrocyte membranes (56).

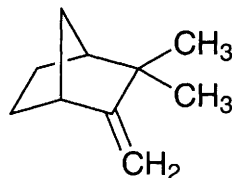
The use of camphechlor as a pesticide was discontinued in the USA in 1989. Undergoes dechlorination in strong sunlight, with iron catalysts and on heating to 150°C. Non-corrosive in absence of moisture. Incompatible with alkaline materials.

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C49 camphene



C₁₀H₁₆

Mol. Wt. 136.24

CAS Registry No. 79-92-5

Synonyms 2,2-dimethyl-3-methylenebicyclo[2.2.1]heptane; 2,2-dimethyl-3-methylenebornene; 2,2-dimethyl-3-methylenenorbornane; 3,3-dimethyl-2-methylenenorcamphane

EINECS No. 201-234-8

RTECS No. EX 1055000

Uses Used in the formulation of antiseptics.

Occurrence Component of essential oils, including turpentine, cypress oil, camphor oil, bergamot, citronella, neroli, ginger and valerian.

Physical properties

M. Pt. 51-52°C **B. Pt.** 158.5-159.5°C **Specific gravity** 0.842 (all physical data refer to *dl*-form)

Solubility Organic solvents: chloroform, cyclohexane, cyclohexene, diethyl ether, ethanol

Mammalian & avian toxicity

Acute data

LD₅₀ oral redwing blackbird >96 mg kg⁻¹ (1).

Genotoxicity

Concentrations of 1336-3418 mg l⁻¹ were obtained from pulverised particle board. Exposure of *Salmonella typhimurium* TA98, TA100, TA1535, TA1537 to samples proved mixture was biologically active. A number of other compounds, formaldehyde, benzene, toluene, xylenes, styrene, α -pinene, limonene, nonanal, tetradecane and *n*-butanol were also present, but not in all samples (2).

Salmonella typhimurium TA100 with metabolic activation 0.05-100 μ l rat body fluid assay, weak mutagenic activity (3).

Legislation

Limited under EC Directive on Drinking Water Quality 80/778/EEC. Substances extractable in chloroform: guide level 0.1 mg l⁻¹ dry residue (4).

Other comments

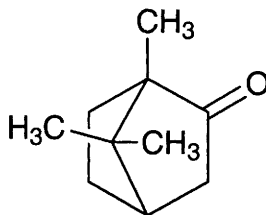
Staphylococcus aureus positive antimicrobial activity (5).

Reviews on experimental toxicology and human health effects listed (6).

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C50 camphor



C₁₀H₁₆O

Mol. Wt. 152.24

CAS Registry No. 76-22-2

Synonyms bicyclo[2.2.1]heptan-2-one, 1,7,7-trimethyl-; 2-bornanone; 2-camphanone; 2-oxo-1,7,7-trimethylbicyclo[2.2.1]heptane; 1,7,7-trimethylnorcamphor

EINECS No. 200-945-0

RTECS No. EX 1225000

Uses Plasticiser. Lacquers and varnishes. Explosives. Pyrotechnics. Preservative in pharmaceuticals and cosmetics. Moth repellent. Embalming fluids. Topical anti-infective, topical antipruritic.

Occurrence All parts of the camphor tree, *Cinnamomum camphora*.

Physical properties

M. Pt. 180°C **B. Pt.** 204°C **Flash point** 65.5°C (closed cup) **Specific gravity** 0.992 at 25°C with respect to water at 4°C **Volatility** v.p. 0.18 mmHg at 20°C ; v.den. 5.24

Solubility Water: 0.8 g l⁻¹ at 25°C. Organic solvents: acetone, benzene, chloroform, diethyl ether, ethanol, glacial acetic acid

Occupational exposure

DE-MAK 2 ppm (13 mg m⁻³)

FR-VME 2 ppm (12 mg m⁻³)

UK-LTEL 2 ppm (13 mg m⁻³)

UK-STEL 3 ppm (19 mg m⁻³)

US-TWA 2 ppm (12 mg m⁻³)

US-STEL 4 ppm

UN No. 2717 HAZCHEM Code 1 $\frac{2}{+}$ Conveyance classification flammable solid

Ecotoxicity

Fish toxicity

Exposure to 5 ppm was non-toxic to bluegill sunfish, yellow perch and goldfish. Test conditions: temperature 30°C; dissolved oxygen 7.5 ppm; total hardness (soap method) 300 ppm; alkalinity 310 ppm (methyl orange); free carbon dioxide 5 ppm (1).

LC₅₀ (96 hr) fathead minnow 110 mg l⁻¹ at 18-22°C (2).

Invertebrate toxicity

LC₅₀ (24, 48 hr) *Acanthoscelides obtectus* (Say) 31.6 and 28.9 mg l⁻¹, respectively (3).

Mammalian & avian toxicity

Acute data

LD_{Lo} oral rabbit 2000 mg kg⁻¹ (4).

LC_{Lo} (3 hr) inhalation mouse 400 mg m⁻³ (5).

LD₅₀ intraperitoneal mouse 3000 mg kg⁻¹ (4).

LD_{Lo} intraperitoneal rat 900 mg kg⁻¹ (6).

LD_{Lo} oral infant 70 mg kg⁻¹ (4).

Metabolism and toxicokinetics

In humans, hydroxylated in the liver to yield hydroxycamphor metabolites which are then conjugated with glucuronic acid and excreted in the urine (7).

Rapid absorption through mucous membranes with toxic level achieved within a few minutes after ingestion.

Removed from the bloodstream by the liver or fatty tissues (8).

After ingestion by mothers, camphor was detected in maternal blood 15 min after ingestion, but not after 8 hr. At delivery, 36 hr later, it was present in amniotic fluid, cord and foetal blood, foetal brain, liver and kidneys (9).

Alimentary absorption of pure camphor or of alcoholic solution is quite rapid, but from the oil preparation absorption rate is constant. Slowly absorbed from subcutaneous or intramuscular depots (10).

Mainly eliminated as the oxidised camphorol in urine, although some appears in breath, sweat and faeces (species unspecified) (11).

Other effects

Other adverse effects (human)

A small quantity applied to the nostrils of an infant may cause immediate collapse (8,12).

Ingestion of 2 g produced toxic effects in an adult, caused congestion of the gastro-intestinal tract, kidneys and brain. Caused stimulation of central nervous system and convulsions (13).

Any other adverse effects

In oxygenated mouse bone marrow cells, administration of camphor reduces radiation-induced DNA damage and it is therefore concluded that it could be useful to test as a potential radiomodifying agent in cancer therapy (14).

Other comments

Toxicity reviewed (15,16).

Toxicology of plastics additives used in the medical sector is reviewed (17).

Reviews on human health effects, epidemiology, workplace experience and experimental toxicology listed (18).

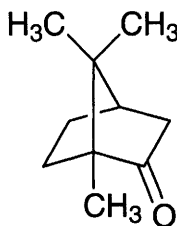
75% of camphor sold in the US is produced synthetically from pinene and sold in its racemic form.

Sublimes at room temperature.

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c51 (+)-camphor



C₁₀H₁₆O

Mol. Wt. 152.24

CAS Registry No. 464-49-3

Synonyms D-camphor; (1R)-(+)-camphor; 2-oxobornane; 1,7,7-trimethylbicyclo[2.2.1]-2-heptanone

EINECS No. 207-355-2

RTECS No. EX 1260000

Uses Pharmaceutical and industrial products. Plasticiser for cellulose esters and ethers. Insect repellent.

Manufacture of incense, lacquers and varnishes, explosives, embalming fluids and plastics.

Occurrence In pine oil (from leaves, twigs, stems of camphor tree of China, Taiwan, Japan) (1).

Physical properties

M. Pt. 179°C **B. Pt.** 207°C **Flash point** 65°C **Specific gravity** 0.990 at 25°C with respect to water at 4°C

Volatility v.p. 1 mmHg at 41.5°C (2)

Solubility Organic solvents: acetone, diethyl ether, ethanol

Ecotoxicity

Fish toxicity

LC₅₀ (1-96 hr) fathead minnow 145-110 mg l⁻¹, static bioassay in Lake Superior water at 18-22°C (2).

Mammalian & avian toxicity

Acute data

LD₅₀ oral mouse 1310 mg kg⁻¹ (3).

LD₅₀ (3 hr) inhalation mouse 400 mg m⁻³ (4).

LD_{Lo} subcutaneous rat 1700 mg kg⁻¹ (5).

LD₅₀ intraperitoneal mouse 3000 mg kg⁻¹ (6).

Metabolism and toxicokinetics

Metabolised by hydroxylation and excreted in the urine mainly as the glucuronide of 2-hydroxy- and 3-hydroxy-camphor. Oxidation also occurs at the 7-position yielding a small amount of the carboxylic acid. Hydroxycamphor metabolites then undergo conjugation with glucuronic acid (species unspecified) (7).

Removed from bloodstream by liver or lipid deposits (8).

Oxidation of (+)-camphor by cytochrome P₄₅₀ enriched intact cells of *Streptomyces griseus* resulted in the formation of major metabolite 6-*endo*-hydroxycamphor and minor metabolites 3-*endo*-hydroxycamphor; 5-*endo*-hydroxycamphor; 5-*exo*-hydroxycamphor; 2,5-diketobornane and camphorquinone (9).

Other effects

Other adverse effects (human)

The fatal dose in a 1-yr-old child is stated to be about 1 g of camphor, although some children have survived the ingestion of 5 g. In adults, doses in the region of 2 g are likely to produce toxic symptoms and doses of 4 g or more may be lethal, although a man survived ingestion of as much as 30 g in the form of 150 ml of camphorated oil. A plasma concentration of 1.7 µg ml⁻¹ was reported in a severely poisoned subject, 12 hr after ingestion of about 18 g of camphor, the patient recovered after treatment by haemoperfusion (10).

A serum concentration of 19.5 µg ml⁻¹ was observed 7 hr after the ingestion 0.7 g of camphor in a moderately poisoned 3-yr-old child (11).

Symptoms of poisoning include nausea, vomiting, colic, headache, dizziness, a feeling of warmth, delirium, muscle twitching, epileptiform convulsions, depression of the central nervous system (4,12).

Camphor was detected in maternal blood 15 min after ingestion but not after 8 hr. At delivery 36 hr later camphor was present in amniotic fluid, cord and foetal blood, foetal brain, liver and kidneys (13).

Other comments

A local irritant (4).

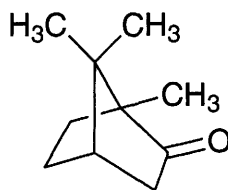
Camphor is readily absorbed by all routes of administration. Camphor crosses the placenta.

Should not be used in treatment of hepatic disorders, gall stones, or urinary tract infections (7).

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C52 (-)-camphor



C₁₀H₁₆O

Mol. Wt. 152.24

CAS Registry No. 464-48-2

Synonyms (-)-1,7,7-trimethylbicyclo[2.2.1]heptan-2-one; (1S)-(-)-camphor; L-(-)-camphor

EINECS No. 207-354-7

RTECS No. EX 1250000

Uses Chiral intermediate, used to synthesise analogues of the fungal sesquiterpenoids, *cis*-sativenediol and helminthosporal.

Physical properties

M. Pt. 178-180°C

Occupational exposure

UN No. 2717 HAZCHEM Code 1 $\frac{2}{+}$ Conveyance classification flammable solid

Mammalian & avian toxicity

Acute data

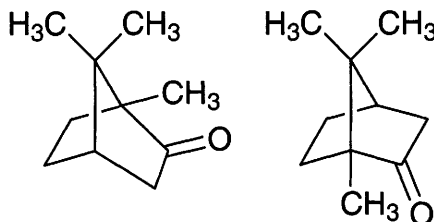
LD_{Lo} oral rat 800 µg kg⁻¹ (1).

LD₅₀ intravenous mouse 320 mg kg⁻¹ (2).

References

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C53 (±)-camphor



C₁₀H₁₆O

Mol. Wt. 152.24

CAS Registry No. 21368-68-3

Synonyms (±)-1,7,7-trimethylbicyclo[2.2.1]heptan-2-one; DL-camphor

EINECS No. 244-350-4

RTECS No. EX 1234000

Uses Used in anti-inflammatory topical pharmaceuticals.

Physical properties

M. Pt. 175-177°C B. Pt. 204°C Flash point 64°C

Occupational exposure

UN No. 2717 HAZCHEM Code 1 $\frac{2}{2}$ Conveyance classification flammable solid

Environmental fate

Degradation studies

Pseudomonas sp. Cam1040 degraded camphor (concentrations unspecified) (1).

Mammalian & avian toxicity

Acute data

LD₅₀ intraperitoneal mouse 884 mg kg⁻¹ (2).

LD₅₀ intraperitoneal rat 956 mg kg⁻¹ (2).

LD₅₀ subcutaneous mouse, rat 3020, 3040 mg kg⁻¹, respectively (2).

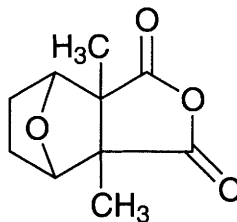
Carcinogenicity and chronic effects

Prechronic studies completed by National Toxicology Program. Chemical in review for further evaluation (3).

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C54 cantharidin



C₁₀H₁₂O₄

Mol. Wt. 196.20

CAS Registry No. 56-25-7

Synonyms cantharides camphor; cantharidine; cantharone; *exo*-1,2-*cis*-dimethyl-3,6-epoxyhexahydrophthalic anhydride; 2,3-dimethyl-7-oxabicyclo[2.2.1]heptane-2,3-dicarboxylic anhydride; hexahydro-3a,7a-dimethyl-4,7-epoxyisobenzofuran-1,3-dione; 4,7-epoxyisobenzofuran-1,3-dione, hexahydro-3a,7a-dimethyl-(3a,α,4β,7β,7α)

EINECS No. 200-263-3

RTECS No. RN 8575000

Uses Rubefacient. Counter-irritant and vesicant. Previously used to stimulate hair growth.

Occurrence Obtained from cantharides, especially *Cantharis vesicatoria*.

Physical properties

M. Pt. 218°C

Solubility Organic solvents: acetone, chloroform, diethyl ether, ethyl acetate

Mammalian & avian toxicity

Acute data

LD_{Lo} oral human 428 µg kg⁻¹ (1).

LD₅₀ intraperitoneal mouse 1 mg kg⁻¹ (2).

Lethal dose oral adult human 65 mg (3).

Carcinogenicity and chronic effects

No adequate data for evidence of carcinogenicity to humans, limited evidence for carcinogenicity to animals, IARC classification group 3 (4).

A 0.25% solution painted onto mouse skin inhibited tumour induction (5).

Irritancy

Extreme irritant and vesicant, contact with skin results in intense blister formation (3).

Other effects

Other adverse effects (human)

After ingestion there is a burning pain in the throat and stomach, difficulty in swallowing, nausea, vomiting, haematemesis, abdominal pain, bloody diarrhoea and tenesmus, renal pain, frequent micturition, haematuria, uraemia, severe hypotension and circulatory failure. Direct acting nephrotoxin (3).

Any other adverse effects

♂ Albino rats were injected intraperitoneally with cantharidin, and killed 35 min later. Examination revealed extensive damage to epithelial cells of oesophagus, stomach, small intestine, large intestine, bladder and ureter (6).

Legislation

Limited under EC Directive on Drinking Water Quality 80/778/EEC. Substances extractable in chloroform: guide level 0.1 mg l⁻¹ dry residue (7).

Other comments

Reviews on experimental toxicology and human health effects listed (8).

Toxic properties of cantharidin reviewed (9).

Has been employed unsuccessfully as an aphrodisiac (*Spanish fly*), its use can cause renal failure (10).

Carcinogenicity and adverse biological effects in mice reviewed (11).

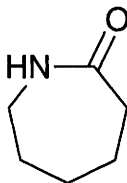
Report on physico-chemical data, toxicity and hazard information (12).

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c55 caprolactam



C₆H₁₁NO

Mol. Wt. 113.16

CAS Registry No. 105-60-2

Synonyms aminocaproic lactam; hexahydro-2H-azepine-2-one; ε-caprolactam; 2-ketohexamethyleneimine; 2-oxohexamethyleneimine; 6-aminohexanoic acid, cyclic lactam; 2-azacycloheptanone; 1-aza-2-cycloheptanone

EINECS No. 203-313-2

RTECS No. CM 3675000

Uses Intermediate in Nylon 6 manufacture. Production of film, coatings and synthetic leather. Curing agent for polyurethanes.

Physical properties

M. Pt. 69-71°C **B. Pt.** 270°C **Flash point** 125°C (open cup) **Specific gravity** 1.05 (liquid 70% aqueous solution) at 25°C with respect to water at 4°C **Volatility** v.p. 0.001 mmHg at 20°C ; v.den. 3.91
Solubility Water: very soluble. Organic solvents: benzene, chloroform, ethanol

Occupational exposure

DE-MAK 5 mg m⁻³ (inhalable fraction of aerosol)

FR-VME 5 ppm (20 mg m⁻³)(vapour); 1 mg m⁻³(dust)

SE-LEVL 5 mg m⁻³ (dust plus vapour)

UK-LTEL 1 mg m⁻³ (dust); 5 ppm (23 mg m⁻³) (vapour)

US-TWA 1 mg m⁻³ (particulate); 5 ppm (23 mg m⁻³) (vapour)

SE-STEL 10 mg m⁻³ (dust plus vapour)

UK-STEL 3 mg m⁻³ (dust); 10 ppm (47 mg m⁻³) (vapour)

US-STEL 3 mg m⁻³ (particulate); 10 ppm (46 mg m⁻³) (vapour)

Supply classification harmful

Risk phrases Harmful by inhalation and if swallowed – Irritating to eyes, respiratory system and skin (R20/22, R36/37/38)

Safety phrases Keep out of reach of children (if sold to general public) (S2)

Ecotoxicity

Fish toxicity

Catfish exposed to increasing concentrations, 1000 mg l⁻¹ no-effect level 30 days; 10,000 mg l⁻¹ no effect reported after 10 hr (1,2).

Environmental fate

Degradation studies

Activated sludge with compound as sole carbon source, COD 93.4%; 16 mg COD g dry inoculum⁻¹ hr⁻¹ (1).
Biodegradable (3).

Mammalian & avian toxicity

Acute data

LD₅₀ oral rat 2140 mg kg⁻¹ (4).
LD₅₀ oral mouse 930 mg kg⁻¹ (5).
LC₅₀ (2 hr) inhalation rat 65 ppm (6).
LD_{Lo} dermal rabbit 1440 mg kg⁻¹ (7).
LD₅₀ intraperitoneal mouse 650 mg kg⁻¹ (8).

Sub-acute and sub-chronic data

Inhalation ♂ rat (10 wk) 124 mg m⁻³ 4 hr day⁻¹ caused increased excitability, changes in spermatogenesis, decreased respiratory rate, decreased urinary excretion observed. Lowest no-adverse-effect level (10 wk) 10.6 mg m⁻³ (9).

Carcinogenicity and chronic effects

No adequate data for carcinogenicity to humans, evidence suggesting lack of carcinogenicity in animals, IARC classification group 4 (10).

Oral ♂, ♀ B6C3F mice (2 yr) 7500 or 15,000 mg kg⁻¹ in feed. Slight decrease in body weight gains observed but no treatment-related tumours (11).

Oral ♂, ♀ Fischer 344 rats (2 yr) 3750 or 7500 mg kg⁻¹. Slight decrease in body weight gains observed but no treatment-related tumours (11).

Teratogenicity and reproductive effects

Inhalation ♀ rat (1-5 day, 6-12 day gestation or day-13 parturition) 30 or 100 ppm 4 hr day⁻¹ caused increased pre- and post-implantation intra-uterine deaths, reduced foetal body weight and premature birth (12).

Metabolism and toxicokinetics

Pregnant ♀ Swiss-Webster mice oral intubation 6.5-6.7 mg kg⁻¹ ¹⁴C-caprolactam. Rapid transfer of the radioactivity across the placenta with almost complete elimination from foetal and maternal compartments within 24 hr (13).

Oral ♂, ♀ mice 6.4-6.9 mg kg⁻¹ ¹⁴C-caprolactam. Radioactivity rapidly absorbed and distributed throughout the entire animal. After 3 hr efficient elimination had occurred via kidneys and liver. No evidence of resorption via the enterohepatic circulation (13).

Detoxification rate in rats 60-70 mg kg⁻¹ hr⁻¹ (14).

Single intraperitoneal injection rabbit 400 mg kg⁻¹, 9-22% of dose excreted unchanged in urine and faeces (15).

Irritancy

Dermal rabbit (24 hr) 500 mg caused mild irritation and 20 mg instilled into rabbit eye caused moderate irritation (16).

Dermal irritation and sensitisation reported in humans (17).

Genotoxicity

Salmonella typhimurium TA98, TA100, TA1535, TA1537, TA1538 with and without metabolic activation negative (18).

Salmonella typhimurium TA102 with and without metabolic activation negative (19).

Saccharomyces cerevisiae D61M without metabolic activation aneuploidy equivocal (20).

In vitro Chinese hamster ovary cells with and without metabolic activation, induction of 6-thioguanine-resistant mutants negative (20).

In vitro Syrian hamster embryo cell transformation negative (20).

Mouse bone marrow micronucleus assay (0-350 mg kg⁻¹) negative (21).

Drosophila melanogaster sex-linked recessive lethal (SLRL) assay (6500 ppm in feed, 15,000 ppm injection) negative (22).

Induces somatic-cell mutations in *Drosophila melanogaster* and some evidence of chromosomal aberrations in cultured human cells and point mutations in yeast (23).

Other effects

Other adverse effects (human)

Functional disorders of the nervous system, genito-urinary tract and cardiovascular system reported in ♀ humans occupationally exposed in the manufacture of Kapron fibres (exposure, duration and concentrations unspecified) (24).

A case history of allergic contact dermatitis in a textile worker is reported. The worker had been employed in the industry for 29 yr. He presented with a 18-month history of itchy, erythematous scaly patches of eczema, involving mainly the face, neck, chest and limbs. An open test and patch test study were performed and occupational contact dermatitis was confirmed to caprolactam. The authors report this is the first case of occupational contact dermatitis due to caprolactam (25).

Legislation

FDA, 1984, permits the use of caprolactam-graft polymers as a component of side-seam cements intended for use in contact with food. Nylon 6 may be used for processing, handling and producing food (23).

The US EPA has amended (effective from June 18, 1996) the list of hazardous air pollutants in the Clean Air Act Section 112(5) (1) by removing caprolactam (26).

Other comments

Compound can be hydrolysed, N-alkylated, O-alkylated, nitrosated and halogenated (27).

Reviews on experimental toxicology and human health effects are listed (28,29).

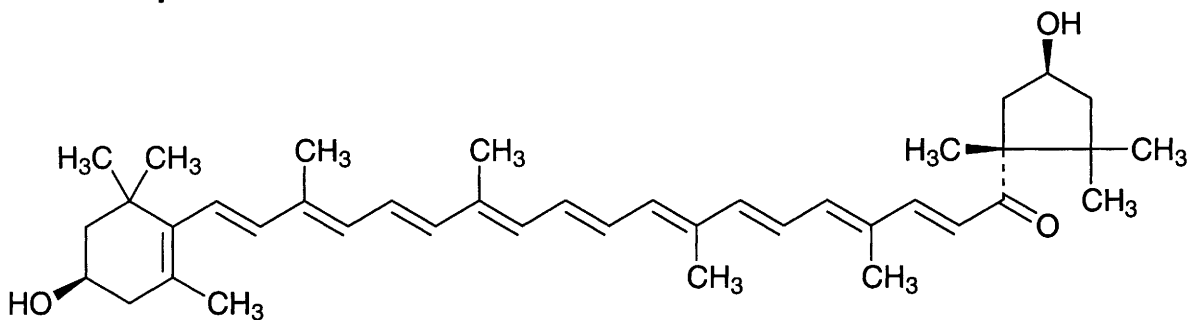
Hygroscopic.

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C56 capsanthin



$C_{40}H_{56}O_3$

Mol. Wt. 584.88

CAS Registry No. 465-42-9

Synonyms (3*R*,3'*S*,5'*R*)-3,3'-dihydroxy- β,κ -caroten-6'-one

EINECS No. 207-364-1

Occurrence Carotenoid pigment isolated from paprika.

Physical properties

M. Pt. 181-182°C

Solubility Organic solvents: miscible with acetone, chloroform; soluble in benzene, diethyl ether, ethanol, methanol

Ecotoxicity

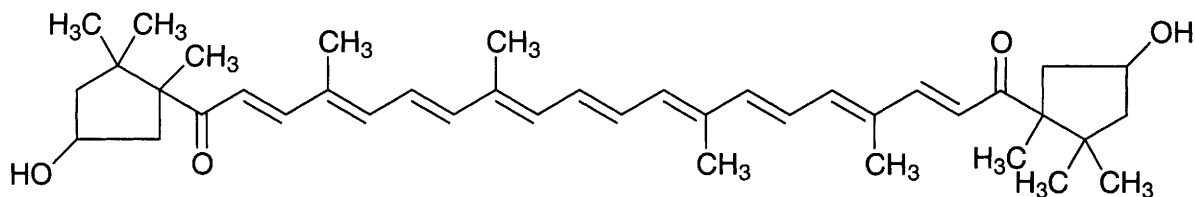
Invertebrate toxicity

0.1% capsanthin very toxic to *Paramecium caudatum* (1).

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c57 capsorubin



$C_{40}H_{56}O_4$

Mol. Wt. 600.88

CAS Registry No. 470-38-2

Synonyms κ,κ -carotene-6,6'-dione, 3,3-dihydroxy-(3S3'5R5'R)-; 2,4,6,8,10,12,14,16,18-eicosanonaene-1,20-dione, 1,20-bis(4-hydroxy-1,2,2-trimethylcyclopentyl)-4,8,13,17-tetramethyl-, (1R,1R,4S,4S)-(all-E)-; all-*trans*-capsorubin

EINECS No. 207-425-2

RTECS No. GW 4900000

Occurrence Constituent of paprika.

Physical properties

M. Pt. 201°C

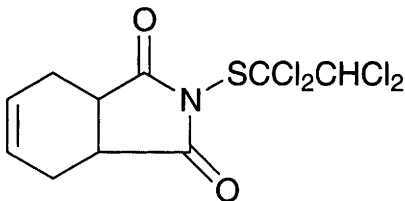
Other comments

Experimental toxicology and human health effects reviewed (1).

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c58 captafol



$C_{10}H_9Cl_4NO_2S$

Mol. Wt. 349.06

CAS Registry No. 2425-06-1

Synonyms 1*H*-isoindole-1,3(2*H*)-dione, 3a,4,7,7a-tetrahydro-2-[(1,1,2,2-tetrachloroethyl)thio]-; *N*-1,1,2,2-tetrachloroethylmercapto-4-cyclohexene-1,2-carboximide; difolatan; Foltaf; Haipen; Merpafol; Ortho Difolatan; Sanspor; Santar SM

EINECS No. 219-363-3

Uses Fungicide. Wood preservative in timber industry.

Physical properties

M. Pt. 160-161°C

Solubility Water: 1.4 mg l⁻¹ at 20°C. Organic solvents: acetone, benzene, toluene

Occupational exposure

FR-VME 0.1 mg m⁻³

UK-LTEL 0.1 mg m⁻³

US-TWA 0.1 mg m⁻³

Supply classification toxic

Risk phrases May cause cancer – May cause sensitisation by skin contact (R45, R43)

Safety phrases Restricted to professional users – Avoid exposure – obtain special instruction before use – In case of accident or if you feel unwell, seek medical advice immediately (show label where possible) (S53, S45)

Ecotoxicity

Fish toxicity

LC₅₀ (96 hr) rainbow trout 0.5 mg l⁻¹ (1).

LC₅₀ (96 hr) goldfish 3.0 mg l⁻¹ (1).

Common carp endotrophic embryos were exposed for 13 days to 0.0, 0.25, 0.5, and 2.0 mg l⁻¹. Posthatch no-observed-effect concentrations on survival and motility were 1 and 0.5 mg l⁻¹, respectively, at pH 6.9 and 2 and 1 mg l⁻¹ at pH 7.8. By days 12 and 13 these levels had decreased to 0.25 mg l⁻¹ at pH 7.8 and < 0.25 mg l⁻¹ at pH 6.9 (2).

Invertebrate toxicity

The relative acute toxicity of captafol was found to be *Semisulcospira libertina* > *Lusiola cruciata* > *Macronema radiatum* > *Cheumatopsyche brevilineata* (3).

LC₅₀ (96 hr) *Gammarus lacustris* 0.8 mg l⁻¹ (4).

LC₅₀ (96 hr) *Pteronarcys californica* 0.4 mg l⁻¹ (5).

EC₅₀ (5 min) *Photobacterium phosphoreum* 6.96 ppm Microtox test (6).

Mammalian & avian toxicity

Acute data

LD₅₀ oral rat 2500 mg kg⁻¹ (7).

LD_{LO} intraperitoneal mouse 3 mg kg⁻¹ (8).

LD₅₀ dermal rabbit >15 g kg⁻¹ (9).

Sub-acute and sub-chronic data

LC₅₀ (10 day) pheasant >23 g kg⁻¹ (1).

LC₅₀ (10 day) mallard duck >101 g kg⁻¹ in diet (1).

Oral B6C3F1 mice (12 wk) 0, 0.3, 0.625, and 1.25% captafol in diet. Decrease in body weight gain, increase in relative weight of liver and cytoplasmic vacuolar degeneration in liver of both sexes observed (10).

Carcinogenicity and chronic effects

In 2-yr feeding studies the no-adverse-effect levels in diet for rats and dogs were 500 mg kg⁻¹ and 10 mg kg⁻¹, respectively (10).

Administration of 0.3% captafol to B6C3F mice caused significant increases in the development of neoplastic lesions in heart, spleen, forestomach, small intestine and liver (11).

Liver identified as target organ for carcinogenicity in mice (12).

Teratogenicity and reproductive effects

Single intraperitoneal injection of 1.5 or 3.0 mg kg⁻¹ to ♂ mice. The results of wkly matings with untreated virgin ♀ disclosed no increase in early embryonic death among conceptuses obtained from ♀ mated with treated ♂ (8).

Metabolism and toxicokinetics

Following oral administration in unspecified mammals, captafol is hydrolysed to tetrahydrophthalimide and

dichloroacetic acid. Tetrahydrophthalimide is further degraded to tetrahydrophthalimidic acid, phthalic acid and ammonia (13).

Irritancy

Skin contact in humans may cause phototoxic irritation and itching, erythema, vesiculation and local oedema on hands, face and eyelids. Prolonged eye exposure may cause chemical or allergic conjunctivitis (9).

Sensitisation

Pulmonary and skin sensitiser (9).

Genotoxicity

Salmonella typhimurium TA102 without metabolic activation positive (direct mutagen) (14).

Escherichia coli B/r try WP2, WP2 try hcr without metabolic activation positive (14).

Bacillus subtilis H17, M45 gene conversion and mitotic recombination positive (15).

Salmonella typhimurium TA1535, TA1536, TA1537, TA1538 with metabolic activation negative (15).

Salmonella typhimurium Ames test and SOS chromotest, with and without metabolic activation, positive (16).

In vitro Chinese hamster ovary cells, clastogenic, sister chromatid exchanges positive (17).

Other effects

Other adverse effects (human)

Systemic effects include wheezing, stomatitis and painful bronchitis (9).

Any other adverse effects

Rats treated with captafol had decreased body weight; blood serum activities of aspartate and alanine, aminotransferases, lactate dehydrogenase, and levels of blood urea nitrogen and triglycerides increased. Total binding albumin value in the serum and liver and total ATPase activity in the liver and kidney also increased (18).

Legislation

Limited under EC Directive on Drinking Water Quality 80/778/EEC. Pesticides: maximum admissible concentration 0.1 µg l⁻¹ (19).

Included in Schedule 6 (Release into Land: Prescribed Substances) Statutory Instrument No. 472, 1991 (20).

Other comments

IC₅₀ 2 µmol l⁻¹ in the *in vitro* Ca²⁺- transport-ATPase test system using human erythrocyte membranes (21).

Reviews on experimental toxicology and human health effects listed (22).

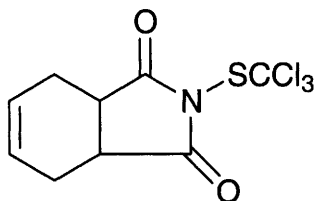
The toxicity of 16 pesticides, including captafol, to photosynthesis in natural freshwater plankton was determined. No relationship was found between pesticide toxicity and molecular weight, solubility, or log K_{ow} (23).

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c59 captan



C₉H₈Cl₃NO₂S

Mol. Wt. 300.59

CAS Registry No. 133-06-2

Synonyms Orthocide-406; *N*-trichloromethylmercapto-4-cyclohexene-1,2-dicarboximide; 4-cyclohexene-1,2-dicarboximide, *N*-[(trichloromethyl)thio]-; 1*H*-isoindole-1,3(2*H*)-dione, 3a,4,7,7a-tetrahydro-2-[(trichloromethyl)thio]-; Alfrocap; Agrocap; Belpron C; Bio Strike; Cafudan; Cap; Goldenon; Merpan; Orthocid; Philocap; Santhane; Seftal

EINECS No. 205-087-0

RTECS No. GW 5075000

Uses Fungicide. Bacteriostat in soap.

Physical properties

M. Pt. 172°C **Specific gravity** 1.74 at 20°C **Partition coefficient** log *P*_{ow} 2.35 **Volatility** v.p. <9.75 × 10⁻⁶ mmHg at 25°C

Solubility Water: 500 µg l⁻¹ at 20°C. Organic solvents: acetone, chloroform, dioxane, ethanol, toluene

Occupational exposure

FR-VME 5 mg m⁻³

UK-LTEL 5 mg m⁻³

UK-STEL 15 mg m⁻³

US-TWA 5 mg m⁻³

Supply classification harmful

Risk phrases Irritating to the eyes – Possible risk of irreversible effects – May cause sensitisation by skin contact (R36, R40, R43)

Safety phrases Keep out of reach of children (if sold to general public) – Wear suitable protective clothing and gloves (S2, S36/37)

Ecotoxicity

Fish toxicity

LC₅₀ (96 hr) harlequin fish 0.3 mg l⁻¹ (1).

LC₅₀ (96 hr) brook trout, bluegill sunfish 0.034-0.072 mg l⁻¹ (1).

Growth rates of the earthworm *Aporrectodea caliginosa* were measured over a 100-day period in soil culture chambers treated with three common biocides. The biocides were applied at 14-day intervals. Captan applied alone had a smaller effect on growth and mortality than either glyphosate or azinphos-Me (2).

Invertebrate toxicity

EC₅₀ (48 hr) *Daphnia pulex* 1.5 mg l⁻¹ (3).

LC₅₀ (48 hr) contact earthworm 73-80 ppm (4).

Toxic to bees (5).

ED₅₀ (oral) 91, (contact) 788 µg bee⁻¹ (1).

Environmental fate

Degradation studies

Degradation of captan in soil incubated under laboratory conditions started early, continued at an exponential rate for 35 days and then stopped. After 60 days of incubation 57-64% of the original captan was recovered (6).

Abiotic removal

t_{1/2} hydrolysis at 20°C pH 7 is 32 hr and pH 10 is <2 min (1).

Mammalian & avian toxicity

Acute data

LD₅₀ oral mallard duck, pheasant >5000 mg kg⁻¹ (1).

LD₅₀ oral redwing blackbird 100-104 mg kg⁻¹ (7).

LC₅₀ oral bobwhite quail >2400 mg kg⁻¹ (8).

LD_{Lo} oral human 1070 mg kg⁻¹ (9).

LD₅₀ oral rat 9000 mg kg⁻¹ (10).

LD₅₀ oral rabbit 740 mg kg⁻¹ (11).

LC₅₀ (2 hr) inhalation mouse 5000 mg m⁻³ (12).

LD₅₀ intraperitoneal mouse 462 mg kg⁻¹ (12).

Carcinogenicity and chronic effects

No adequate evidence for carcinogenicity to humans, limited evidence for carcinogenicity to animals, IARC classification group 3 (13).

No-effect level for rats 2000 mg kg⁻¹ in diet in 2-yr feeding studies (2).

Predicted as a carcinogen in agreement with experimental result in computer automated structure evaluation (CASE) (14).

National Toxicology Program investigated captan. Negative results in carcinogenicity studies in ♂ and ♀ rats, tumours found in intestine and colon in ♂ and ♀ mice when administered via food (15).

♂ F344 rats were pretreated 4 wk with three known carcinogens (diethylnitrosamine, *N*-methyl-*N*-nitrosourea, and *N*-bis(2-hydroxypropyl) nitrosamine) to induce neoplastic changes in a number of organs, then given captan in the diet for a further 16 wk. Neoplastic and pre-neoplastic lesions occurred in the forestomach, kidney, and thyroid. Based on these results the authors considered captan to be a carcinogen (16).

Teratogenicity and reproductive effects

Shown to cause congenital malformations in experimental animals (17).

Pregnant animal feeding studies (duration and concentrations unspecified) reported foetal death, still births, developmental abnormalities of the muscular, skeletal and cardiovascular systems and other effects in the foetus and newborn. Maternal problems included effects on the uterus, cervix and vagina (18).

Oral, intraperitoneal ♂ rat (5 day) 500 mg kg⁻¹ produced negligible antifertility effects and a minimal reduction in the mean number of total implants in pregnancy (19).

Gavage ♂ DBA/2J mice (5 day) 50 or 100 mg kg⁻¹ day⁻¹ caused slight decreases in fertility, significant decrease in 1st generation total offspring numbers (but this was not observed in 2nd generation study) and decreased average weaning weight (20).

Metabolism and toxicokinetics

In two human volunteers following oral administration of 1 mg kg⁻¹ captan, tetrahydrophthalimide was detectable in the urine for 72 hours, but most was eliminated within 24 hours (21).

Sensitisation

Skin sensitiser (species unspecified) (17).

Genotoxicity

Salmonella typhimurium TA102 without metabolic activation negative; TA104 without metabolic activation positive (22).

Salmonella typhimurium TA100, TA1535, with and without metabolic activation positive; TA98, TA102, TA1538 without metabolic activation positive, with metabolic activation negative (23).

Salmonella typhimurium Ames test and SOS chromotest, with and without metabolic activation, positive (24).

Escherichia coli WP2 hcr⁺ hcr⁻ with metabolic activation positive base mutation (25).

Bacillus subtilis H17 rec⁺ M45 rec⁻ without metabolic activation positive recombination assay (25).

In vitro embryonic human lung inhibition of mitosis induced (26).

In vitro human lymphocyte induced sister chromatid exchange (26).

In vitro human fibroblast with or without metabolic activation induced unscheduled DNA synthesis (27).

Mice bone marrow, induced micronuclei and chromosome aberrations, in testes caused abnormalities to spermatogonia, spermocytes and sperm morphology (28).

In vitro experiments using human diploid fibroblasts showed that captan can interact with DNA at a number of levels which could provide the basis for captan genotoxicity. The extreme cytotoxicity of captan, however, could be due to other effects since at the IC₅₀ for cell killing, 0.8 µM, no genotoxic events were detected (29).

Other effects

Other adverse effects (human)

A study conducted on 71 floriculturists exposed to pesticides, including captan, and a control group of 75 healthy blood donors living in the same area (Liguria, Italy) showed the floriculturists to have a significant increase in micronucleated lymphocytes compared with controls (8.57 vs. 6.67, p < 0.05) (30).

Ingestion of large quantities may cause vomiting, diarrhoea, respiratory irritation and bronchitis (31).

Poisoning may effect the cardiovascular system, liver and kidneys (18).

Any other adverse effects

Toxic effects of captan were studied in the presence and absence of glutathione. Rats were given 20 mg kg⁻¹ by intraperitoneal injection with and without pretreatment of 100 mg kg⁻¹ reduced glutathione administered intraperitoneally 1 hr prior to captan treatment. The animals were sacrificed at 24 hr post treatment and serum and microsomal enzyme activities were assessed. Microsomal cytochrome P₄₅₀ levels in µg g⁻¹ protein were 165, 72, 146 and 146 for control, captan treated, glutathione treated and glutathione pretreated captan treated animals, respectively (32).

Legislation

Limited under EC Directive on Drinking Water Quality 80/778/EEC. Pesticides: maximum admissible concentration 0.1 µg l⁻¹ (33).

WHO Toxicity Class III (34).

EPA Toxicity Class IV (1).

Other comments

Report on the safety assessment of captan (35).

Toxicity, carcinogenicity and hazards reviewed (36-38).

The growth of *Azolla pinnata* was inhibited by captan at concentrations up to 100 µg ml⁻¹. Complete death was recorded at this concentration after 21 days. 1 µg ml⁻¹ caused slight stimulation of chlorophyll metabolism after 14 and 21 days of treatment (39).

Inhibitory effects of captan on nitrogenase and hydrogen photoproduction of *Rhodobacter sphaeroides* and *Rhodospseudomonas palustris* described (40).

IC₅₀ 20 µmol l⁻¹ in the *in vitro* Ca²⁺-transport-ATPase test system using human erythrocyte membranes (41).

IC₅₀ (96 hr) *Chlorella pyrenoidosa* Chick. 44.5 mg l⁻¹ (42).

Incompatible with alkaline materials.

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c60 carbachol chloride



$\text{C}_6\text{H}_{15}\text{N}_2\text{O}_2\text{Cl}$

Mol. Wt. 182.65

CAS Registry No. 51-83-2

Synonyms Carbacholin; Coleytl; Jestryl; Lentin; Moryl; Vasoperif; ethanaminium, 2-[(aminocarbonyl)oxy]-*N,N,N*-trimethyl-, chloride; carbocholine; choline chloride carbamate

EINECS No. 200-127-3

RTECS No. GA 0875000

Uses Parasympathomimetic agent in veterinary medicine. Used in the treatment of post-operative intestinal atony and urinary retention. Has been given to stop supraventricular paroxysmal tachycardia. Also used in glaucoma treatment.

Physical properties

M. Pt. 200-203°C

Solubility Water: 1 g ml⁻¹. Organic solvents: ethanol

Mammalian & avian toxicity

Acute data

LD₅₀ oral mouse, rat 15, 40 mg kg⁻¹, respectively (1,2).

LD_{L0} subcutaneous guinea pig, dog 75-100 µg kg⁻¹ (3,4).

LD₅₀ subcutaneous mouse, rat 3, 4 mg kg⁻¹, respectively (2).

LD₅₀ intravenous rat 100 µg kg⁻¹ (2).

LD₅₀ intraperitoneal rat 2 mg kg⁻¹ (5).

Other effects

Other adverse effects (human)

Carbachol intoxication (dose unspecified) caused life-threatening attacks of profuse sweating, intestinal cramps, explosive defecation, hypothermia, hypotension and bradycardia in a 36-yr-old man (6).

A 10-yr-old boy died following similar attacks associated with repeated carbachol ingestion (6).

Cholinergic stimulation of human lymphocytes with carbachol chloride initially stimulated E-rosette formation (7).

Carbachol chloride enhanced the spontaneous adhesion of human lymphocytes *in vitro* (8).

Any other adverse effects

Carbachol chloride stimulated DNA synthesis via muscarinic acetylcholine receptors in primary astrocytes derived from perinatal rat brain, in an age-dependent fashion (9).

Other comments

Toxicology and pharmacology discussed (2).

Physico-chemical data, toxicity and hazard data reported (10).

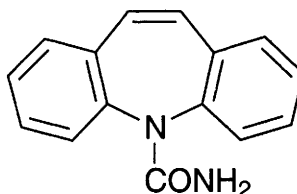
Hygroscopic.

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c61 carbamazepine



$C_{15}H_{12}N_2O$

Mol. Wt. 236.27

CAS Registry No. 298-46-4

Synonyms 5*H*-dibenzo[*b,f*]azepine-5-carboxamide; Biston; Stazepin; Tegretal; Telesmin; Timonil

EINECS No. 206-062-7

RTECS No. HN 8225000

Uses Medicinal treatment of schizophrenia. Antiepileptic. Analgesic.

Physical properties

M. Pt. 190-193°C

Solubility Organic solvents: acetone, ethanol, propylene glycol

Mammalian & avian toxicity

Acute data

LD₅₀ oral rat, guinea pig, mouse, rabbit 920-2680 mg kg⁻¹ (1-3).

LD₅₀ intraperitoneal mouse, rat 270, 293 mg kg⁻¹, respectively (1,4).

Teratogenicity and reproductive effects

Study of 48 children born alive to women treated with carbamazepine prenatally showed that carbamazepine is teratogenic from the incidence of craniofacial defects (11%), fingernail hypoplasia (26%) and developmental delay (20%) (5).

Metabolism and toxicokinetics

Phase I: hydroxylation, oxidation; Phase II: conjugation with glucuronide (species unspecified) (6).

Slowly absorbed from the gastro-intestinal tract. Primary metabolite is carbamazepine-10,11-epoxide. Excreted in the urine in the form of its metabolites. Widely distributed throughout the body, ≈75% bound to plasma proteins. Plasma t_{1/2} ≈20 hr (species unspecified) (6).

Irritancy

Generalised erythematous rashes, which may be severe, occur in about 3% of patients given carbamazepine and may cause treatment to be withdrawn (6).

Severe dermatological reaction reported (7).

Sensitisation

In vitro lymphocyte proliferation induced by carbamazepine; lymphocytes from all hypersensitive patients responded by enhanced DNA synthesis when compared with control subjects (8).

Photosensitivity reactions, urticaria, exfoliative dermatitis, erythema multiforma, lupus erythematosus and Stevens-Johnson syndrome have been reported (9).

Genotoxicity

The effect of carbamazepine on human chromosomes was studied to determine mutagenic potential. Analysis of chromosomal breakage, sister chromatid exchanges (SCE) and cell cycle studies were performed on peripheral lymphocyte cultures. *In vivo* studies failed to detect any significant increase of chromosomal aberrations or SCE or any slowing of the cell cycle. A significant dose-dependent increase in chromosomal aberrations but not in SCE was observed *in vitro* (10).

Other effects

Other adverse effects (human)

In humans common side-effects in the initial stages of therapy include dizziness, drowsiness and ataxia.

Disturbances of cerebellar and oculo-motor function (with ataxia, nystagmus and diplopia) are also symptoms of excessive plasma concentrations and may disappear with continued treatment at reduced dosage. Gastro-intestinal symptoms include dry mouth, gastric distress and abdominal pain, nausea and vomiting, anorexia and diarrhoea or constipation (9).

Blood disorders, including agranulocytosis, aplastic anaemia, eosinophilia, leucopenia, leucocytosis, thrombocytopenia, purpura, and abnormalities of liver and kidney function have occasionally been reported (9).

Fatal agranulocytosis in one patient was attributed to the use of carbamazepine started one month earlier (11).

Renal failure caused by acute tubular necrosis was reported in a patient taking 400 mg carbamazepine 4 × day⁻¹.

Three other cases of oliguria, dysuria and haematuria were reported (12).

Dystonia was reported in patients treated with carbamazepine (13,14).

May cause aplastic anaemia, hallucinations, distorted perceptions, nausea, vomiting, somnolence, dermatitis, ataxia, urine volume increase and agranulocytosis (15).

It has been hypothesised that disruption of glucuronidation of endogenous compounds by drugs represents a potential mechanism for pathogenesis of adverse drug reactions. Carbamazepine was found to have little effect on the UDPGT activities in human and rabbit liver microsomes studied *in vitro* (16).

All-*trans* retinoic acid deficiency resulting from ethanol interference with its synthesis from retinol has been suggested to cause the malformations of the foetal alcohol syndrome. The authors show that in patients given therapeutic doses of carbamazepine all-*trans* and all-*cis* retinoic acid concentrations are significantly lowered and propose that the drug should be considered as a potential teratogen (17).

Other comments

Carbamazepine reviewed (18).

Toxicity reviewed (19).

Neurotoxicity factors discussed (20).

The chemistry, pharmacology, toxicity, indications, dosage and side-effects of carbamazepine were reported in experimental and clinical studies (21).

Evaluation of carbamazepine on a probe in screening for host-factor influence on human drug metabolism.

Clearance of total plasma and plasma inbound carbamazepine reported (22).

Sensitisation reported (23).

Fatal overdose of carbamazepine; case report and literature review (15).

Case report of child with pure red cell aplasia (24).

Medicinal treatment of schizophrenia (25).

Adverse effects to liver reported (26-28).

Adverse effects to skin reported (29-32).

Clinical pharmacokinetics of carbamazepine and epoxide metabolite reviewed (33).

Use in psychiatric disorders reviewed (34,35).

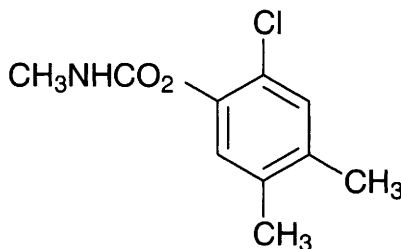
Allergic and hypersensitivity reactions to carbamazepine reported (36-38).

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c62 carbanolate



$C_{10}H_{12}ClNO_2$

Mol. Wt. 213.66

CAS Registry No. 671-04-5

Synonyms 2-chloro-4,5-dimethylphenyl methylcarbamate; chloroxylam; phenol, 2-chloro-4,5-dimethyl-, methylcarbamate; 6-chloro-3,4-xylyl methylcarbamate

Physical properties

M. Pt. 121-126°C

Mammalian & avian toxicity

Acute data

LD₅₀ oral redwing blackbird 2.4-6.0 mg l⁻¹ (1,2).

LD₅₀ oral quail 7.5 mg kg⁻¹ (1).

LD₅₀ oral rat 30 mg kg⁻¹ (3).

LD₅₀ intraperitoneal rat 11 mg kg⁻¹ (4).

LD₅₀ intramuscular rat 24 mg kg⁻¹ (5).

Other effects

Any other adverse effects

Cholinesterase inhibitor (6).

Legislation

Included in Schedule 6 (Release into Land: Prescribed Substances) Statutory Instrument No. 472, 1991 (7).

Limited under EC Directive on Drinking Water Quality 80/778/EEC. Pesticide: maximum admissible concentration 0.1 µg l⁻¹ (8).

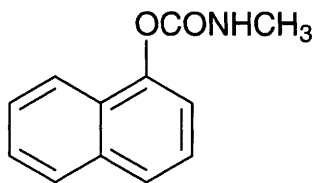
Other comments

Believed to be no longer manufactured or marketed (9).

Toxicity reviewed (4).

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C₁₂H₁₁NO₂

Mol. Wt. 201.22

CAS Registry No. 63-25-2

Synonyms 1-naphthyl N-methylcarbamate; carbattox-60; sevin; methylcarbamate, 1-naphthyl-; 1-naphthalenyl N-methylcarbamate; Afracid; Arvin; Basev; Carbal; Dicarbam; Eltarin; Karbaril; Laivin

EINECS No. 200-555-0

RTECS No. FC 5950000

Uses Contact insecticide. Animal ectoparasiticide.

Physical properties

M. Pt. 142°C **Specific gravity** 1.232 at 20°C with respect to water at 20°C **Partition coefficient** log P_{ow} 1.59

Volatility v.p. <4 × 10⁻⁵ mmHg at 25°C

Solubility Water: 120 mg l⁻¹ at 30°C. Organic solvents: acetone, cyclohexanone, dimethylformamide, dimethyl sulfoxide, isopropanol, xylene

Occupational exposure

DE-MAK 5 mg m⁻³ (inhalable fraction of aerosol)

FR-VME 5 mg m⁻³

JP-OEL 5 mg m⁻³

US-TWA 5 mg m⁻³

Supply classification harmful

Risk phrases Harmful if swallowed (R22)

Safety phrases Keep out of reach of children (if sold to general public) – Do not breathe dust – Avoid contact with the skin (S2, S22, S24)

Ecotoxicity

Fish toxicity

LC₅₀ (96 hr) trout, salmon, carp, bluegill sunfish, perch, bass 690-7100 µg l⁻¹ (technical material) (1).

LC₅₀ (96 hr) goldfish, green sunfish, fathead minnow, channel catfish, black bullhead 13-20 mg l⁻¹ (technical material) (1).

LC₅₀ (96 hr) fathead minnow 28-31 days old 6-10 mg l⁻¹ at 26°C in flow-through bioassay as the pure substance (2).

LC₅₀ (96 hr) zebrafish 46.0 µmol l⁻¹ (3).

LC₅₀ (96 hr) guppy 12.5 µmol l⁻¹ (3).

The histopathological effects on the testes of the teleost *Anabas testudineus* (Bloch) after 4, 10, 15 and 30 days of exposure to 5 mg l⁻¹ carbaryl were observed. Primary spermatogonia, spermatocytes, spermatids and spermatozoa showed clumping and shrinkage. Exposure of 30 days caused complete arrest of spermatogenesis. The walls of seminiferous tubules, connective tissue septa and germinal epithelium all showed degenerative changes. Interstitial cells were shrunken and blood capillaries contained clumped erythrocytes (4).

Invertebrate toxicity

Sublethal concentrations induced persistent hyperplasia and proliferation of mucosal epithelium to the midgut of the freshwater crab *Paratelphusa masoniana* (5).

LC₅₀ (96 hr) freshwater shrimp 22-26 µg l⁻¹ (technical material) (1).

LC₅₀ (96 hr) crayfish 1.9 mg l⁻¹ (technical material) (6).

Inhibited acetylcholinesterase activity in penaeid prawn (7).

LC₅₀ (96 hr) concentration in carp causes kidney damage such as hypertrophy of renal cells, changes in nuclear structure, formation of vacuoles, necrosis and degeneration of renal components (8).

LC₅₀ (48 hr) manure worm 10-19 µg cm⁻² filter paper test (9).

Carbaryl solution (0.106%) sprayed at 6 µl cm⁻² concentration caused 9/9 mortality in female rove beetles (10).

LD₅₀ (48 hr) oral bees 3.8-4.5 ppm in food (11).

Two 1 hr exposures of carbaryl caused significantly fewer symptoms of intoxication than a 2-hr continuous exposure in the midge *Chironomus riparius* if at least 2 to 6 hr in clean water was provided between doses (12).

Toxicity to other species

Tadpole (24 hr) 3.5, 5.0 or 7.2 mg l⁻¹. Activity diminished by 90% at 3.5 mg l⁻¹ and ceased at 7.2 mg l⁻¹. Sprint speed and sprint distance were significantly decreased at all exposure levels (13).

LD₅₀ (96 hr) frog *Rana tigrina* 640 mg kg⁻¹ (14).

LD₅₀ (unspecified duration) oral bullfrog 4000 mg kg⁻¹ (15).

Results of a long-term greenhouse trial of pesticide mixtures containing 4, 48 and 487 µg carbaryl on forest species (the deciduous *Carpinus betulus* and *Fagus sylvatica*, and the coniferous *Abies alba* and *Picea excelsa* species) suggest that changes in physiological parameters (transpiration, photosynthesis, stomatal conductance and chlorophyll) are indicative of complex effects of pesticides on plant metabolism (16).

Bioaccumulation

Bioconcentration factors reported for algae 4000, duckweed 3600, snails 300, catfish 140 and crayfish 260 (11).

0.02-5.8 ppm carbaryl detected in dead bees exposed to carbaryl (17).

Environmental fate

Nitrification inhibition

Threshold inhibition of nitrification/denitrification 10 mg l⁻¹ with activated sludge (18).

Carbonaceous inhibition

Acinetobacter sp. degraded carbaryl as a sole carbon source (19).

Degradation studies

Hydrolyses to 1-naphthol, further degradation by *Fluorobacter* sp. to hydroxycinnamic acid and salicylic acid, while photolytic decomposition yields 1-naphthoxide ion (20).

Soil microbes, *SF-10*, *Paecilomyces lilacinus*, *Aeolus elegans* degraded 3-70% carbaryl within 4 days. Degradation products included carbon dioxide, hydroxymethylcarbaryl and 5,6-dihydro-5,6-dihydroxycarbaryl (21).

Soil t_{1/2} 4 days in a Pliocene sand, an organic-rich orchard soil, and an agricultural soil, at pH 7.38-7.7; t_{1/2} 20 days in soil from a volcanic area, pH 4.86 (22).

Incubation with activated sludge caused 30% degradation within 5 days (23).

Abiotic removal

99% hydrolysed in water, pH 7, within 70 days (24).

Mammalian & avian toxicity

Acute data

LD₅₀ oral mallard duck, pheasant, Canada goose 1790-2200 mg kg⁻¹ (15).

LD₅₀ oral rat 230 mg kg⁻¹ (25).

LD₅₀ oral rat 500-850 mg kg⁻¹ (26).

LD₅₀ dermal rabbit >2000 mg kg⁻¹ (26).

LD₅₀ dermal rat >4000 mg kg⁻¹ (27).

LD₅₀ oral Japanese quail 2230 mg kg⁻¹ (26).

Carcinogenicity and chronic effects

No adequate evidence for carcinogenicity to humans, limited evidence for carcinogenicity to animals, IARC classification group 3 (28,29).

Rats fed for 2 yr on a diet containing 200 mg kg⁻¹ suffered no adverse effects (30).

Teratogenicity and reproductive effects

Gravid CD-1 mice (8-12 day) oral 100 mg kg⁻¹ in corn oil (the maximum tolerated dose) no adverse effect reported in *in vivo* teratology screening test (31).

Oral ♂ albino rats (90 days) 50 or 100 mg kg⁻¹, 5 days wk⁻¹ caused histopathological changes in the testes at both exposure levels. The testicular enzyme associated with postmeiotic spermatogenic cells, sorbitol dehydrogenase, decreased, and lactate dehydrogenase increased with the observed degeneration of spermatogenic cells. γ -Glutamyl transpeptidase, associated with premeiotic spermatogenic or Sertoli cells increased, while glucose 6-phosphate dehydrogenase levels decreased. These were dose-dependent effects and occurred together with lowered epididymal sperm count and percentage sperm motility, and increased abnormal sperm morphology (32).

Oral gavage ♀ mice (day 8 or 12 of pregnancy or daily from day 6 to 15) 0, 100, 150, 200 mg kg⁻¹ in corn oil. At the two highest doses, maternal and foetal toxicity and increased maternal mortality were observed at all stages of pregnancy. Total weight gain was reduced in mice given 200 mg kg⁻¹ on day 8 or day 12 of gestation. Treatment reduced litter size and foetal weight, increased the number of resorbed fetuses and the incidence of open eye, visceral abnormalities and reduced ossification. More aberrations occurred in mice treated throughout pregnancy than in those given single doses (33).

Oral ♀ mice, *Mus musculus* (7 wk) and *Peromyscus maniculatus* (1 wk), bran baits treated with 5% carbaryl formulation caused significantly increased time to delivery in *M. musculus*, and no observed effect in *P. maniculatus* (34).

Metabolism and toxicokinetics

Intraperitoneal rats and chickens 70 and 900 mg kg⁻¹, respectively, caused 47% inhibition of brain cholinesterase activity in rats, and 57% inhibition in chickens, 60 min after exposure. Signs of toxicity were more severe in rats than in chickens. Carboxylesterase activity in the brain, liver and plasma was also inhibited in both species. Clearance of carbaryl in chickens, after intravenous administration of 5 mg kg⁻¹ was 0.26 l kg⁻¹ min⁻¹, 5.7 times faster than that reported in the rat (35).

In mammals, carbaryl does not accumulate in body tissues, but is rapidly metabolised to non-toxic substances, particularly 1-naphthol. This, together with the glucuronic acid conjugate, is eliminated predominantly in urine and faeces (26).

Oral gavage rat, single dose of 400 mg kg⁻¹ in corn oil to rats which were sacrificed 1-8 days later, had 190% increase in liver cytochrome P₄₅₀ levels on day 1, reducing to 82% by day 8 (27).

Carbaryl is hydrolysed by rat liver, lung and skin microsomal fractions at a lower rate than by cytosolic fractions or by plasma (36).

Detected in foetus of pregnant rats and mice, carbaryl was concentrated in the eye, liver and brain of foetus (37). Carbaryl was administered to rats as single oral dose of 1.5, 30 or 300 mg kg⁻¹. 94% was absorbed within 12 hr, with 15-46% excreted in bile, 10-40% in urine and <1% in faeces (38).

In isolated human red blood cells, 1 μ g l⁻¹ carbaryl induced 20% inhibition of acetylcholinesterase. Oral human 1 mg kg⁻¹, plasma t_{1/2} 0.79 hr, clearance rate 5.4 l min⁻¹. Peak plasma concentration induced 27% inhibition of red blood cell acetylcholinesterase activity, and 20% inhibition was achieved by a concentration of 0.02 μ g ml⁻¹ (39). Carbaryl was absorbed after direct application to forearms of human volunteers, 74% of the dose was excreted in the urine (29).

Within 48 hr of intraperitoneal administration to rats, carbaryl was excreted in the urine (65%), exhaled air (25%), faeces (2%) and 8% was retained in the liver, kidneys, heart and in the blood (40).

Irritancy

Dermal rabbit (24 hr) 12 mg caused severe irritation (41).

Genotoxicity

Salmonella typhimurium TA98, TA100, TA1535, TA1537 with metabolic activation negative, detectable activity observed without metabolic activation (42).

Other effects

Other adverse effects (human)

Human toxicity includes nausea, vomiting, diarrhoea, bronchoconstriction, blurred vision, excessive salivation, muscle twitching, cyanosis, convulsions, coma and respiratory failure (43).

Any other adverse effects

Injection of single acute and sub-acute doses in the cockroach *Periplaneta americana* caused a decrease in total carbohydrates, glycogen and pyruvate levels, and cytochrome C-oxidase activity. Levels of lactate and glutamine increased, as did activities of lactate-, glutamate-, malate-, and succinate-dehydrogenase. The greatest change was seen at 3 hr after administration, and all values returned to control levels by 24 hr (44).

Legislation

Limited under EC Directive on Drinking Water Quality 80/778/EEC. Pesticides: maximum admissible concentration 0.1 µg l⁻¹ (45).

Included in Schedule 6 (Release into Land: Prescribed Substances) of Statutory Instrument No. 472, 1991 (46).

Other comments

Endocrine disruption effects reported in wildlife. Avian reproduction impaired, fish reproduction impaired (47).

Review of laboratory earthworm toxicity tests compared with field studies (48).

Toxicology reviewed (49,50).

Toxicity and hazards reviewed (51).

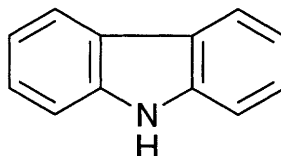
Reproductive toxicity reviewed (52).

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C64 carbazole



$C_{12}H_9N$

Mol. Wt. 167.21

CAS Registry No. 86-74-8

Synonyms 9-azafluorene; 9H-carbazole; dibenzopyrrole; diphenyleneimine

EINECS No. 201-696-0

RTECS No. FE 3150000

Uses Reagent for lignin, carbohydrates, formaldehyde. Used for making photographic plates sensitive to ultraviolet light. Important dyestuff intermediate.

Physical properties

M. Pt. 245°C **B. Pt.** 355°C (sublimes) **Specific gravity** 1.10 at 18°C with respect to water at 4°C

Partition coefficient log P_{ow} 3.72 **Volatility** v.p. 400 mmHg at 323°C

Solubility Organic solvents: acetone, benzene, diethyl ether, pyridine, quinoline

Ecotoxicity

Fish toxicity

Trout, bluegill sunfish and goldfish exposed to 5 ppm died within 7 hr. Test conditions: temperature 30°C; dissolved oxygen 7.5 ppm; total hardness (soap method) 300 ppm; alkalinity 310 ppm (methyl orange); free carbon dioxide 5 ppm (1).

Invertebrate toxicity

EC₅₀ (5, 15, 30 min) *Photobacterium phosphoreum* 11.6 ppm Microtox test (2).

Bioaccumulation

Bioconcentration factor *Daphnia pulex* 115 (wet weight) (3).

Non-accumulative or low accumulative (4).

Environmental fate

Degradation studies

Pseudomonas stutzeri with 15 g l⁻¹ (90 mM) carbazole as sole carbon and nitrogen source, produced 7.9 g l⁻¹ (58 mM) anthranilic acid (5).

Mammalian & avian toxicity

Acute data

LD_{Lo} oral rat 500 mg kg⁻¹ (6).

LD₅₀ intraperitoneal mouse 200 mg kg⁻¹ (7).

Carcinogenicity and chronic effects

No adequate evidence for carcinogenicity to humans, limited evidence for carcinogenicity to animals, IARC classification group 3 (8).

The effect of carbazole administered subsequent to a single dose of 2,2'-dioxo-*N*-nitrosodipropylamine on the development of putative preneoplastic lesions in Syrian golden hamsters was investigated. Carbazole gave rise to considerable numbers of enzyme altered foci, enhanced carcinogenesis in the liver and inhibited carcinogenesis in the pancreas. It induced hyperplastic and papillomatous lesions in the forestomachs of treated animals, independent of prior 2,2'-dioxo-*N*-nitrosodipropylamine treatment. The authors conclude that carbazole has carcinogenic potential for the liver and forestomach of experimental animals (9).

Teratogenicity and reproductive effects

Dermal ♀ Sprague-Dawley rats (days 0-20 gestation) administered 2.5, 25.0, and 250.0 mg kg⁻¹ carbazole showed no signs of maternal or developmental toxicity (10).

Genotoxicity

The mutagenicity of the photochemical reaction products of carbazole in the presence of nitrogen dioxide and nitrocarbazole was investigated in *Salmonella typhimurium* TA98. The results suggest that the weakly mutagenic mononitrocarbazole and mutagenic dinitrocarbazole and other high potency mutagens are formed by the photochemical reaction of carbazole with NO₂ and irradiation by light (11).

Other comments

Safety, toxicology, environmental hazard potential of carbazole reviewed (12).

Evaluation of the carcinogenic risk to humans (13).

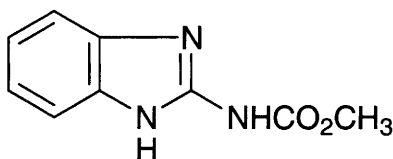
Reviews on experimental toxicology, human health effects and ecotoxicology listed (14).

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c65 carbendazim



C₉H₉N₃O₂

Mol. Wt. 191.19

CAS Registry No. 10605-21-7

Synonyms carbendazime; carbendazol; carbamic acid, 1*H*-benzimidazol-2-yl-, methyl ester;
2-benzimidazolecarbamic acid, methyl ester

EINECS No. 234-232-0

RTECS No. DD 6500000

Uses Fungicide.

Physical properties

M. Pt. 302-307°C (decomp.) **Specific gravity** 1.45 at 20°C **Partition coefficient** log *P*_{ow} 1.51 or 1.77 (pH 7) (1)

Volatility v.p. 6.75 × 10⁻⁷ mmHg at 20°C

Solubility Water: 28 mg l⁻¹ at 20°C and pH 4. Organic solvents: acetone, chloroform, dimethylformamide, ethanol

Occupational exposure

Supply classification harmful

Risk phrases Possible risk of irreversible effects (R40)

Safety phrases Keep out of reach of children (if sold to general public) – Wear suitable protective clothing and gloves (S2, S36/37)

Ecotoxicity

Fish toxicity

LC₅₀ (96 hr) carp 0.61 mg l⁻¹ (1).

LC₅₀ (96 hr) rainbow trout 0.83 mg l⁻¹ (1).

LC₅₀ (48 hr) channel catfish 0.44 µg g⁻¹. Toxicity is altered by changes in water temperature pH and water hardness. Bronchial and biliary excretion were major pathways for excretion by fish. Fast elimination of carbendazim indicates that excessive bioconcentration in fish is unlikely (2).

LC₅₀ (96 hr) guppy 4.5 mg l⁻¹ (3).

Invertebrate toxicity

Carbendazim toxicity was studied in *Asellus aquaticus* and *Daphnia magna* after 1, 2, 3, 6, 24, 48 and 96 hr and after 5, 6 and 24 days. Carbendazim was practically non-toxic for *Asellus aquaticus*. LC_{50} (96 hr) *A. aquaticus* 891.3 mg l^{-1} , *D. magna* 0.27 mg l^{-1} (3).

Environmental fate

Degradation studies

Degradation is enhanced in soil with a high content of organic matter, alkalinity and high sand content (4).

At 40°C persistence in soil was 90 days, at lower temperatures persistence increased to 135 days (5).

Soil pretreatment with microbes enhanced fast degradation. High temperature, acid pH and high moisture level in the soil in the presence of microbes also enhanced degradation (6).

Environmental $t_{1/2}$ 6-12 months on bare soil, $t_{1/2}$ 3-6 months on turf, $t_{1/2}$ 2 and 25 months in water under aerobic and anaerobic conditions, respectively. 2-Aminobenzimidazole is a product of degradation and is further decomposed by microorganisms. Soil $t_{1/2}$ 8-32 days under outdoor conditions (1).

Abiotic removal

At 22°C hydrolysis $t_{1/2}$ > 35 days at pH 5 – pH 7 which increased to 124 days at pH 9 (7).

Mammalian & avian toxicity

Acute data

LD_{50} oral rat, mouse, guinea pig, rabbit 700-10,000, 7700, 4150, 8160 mg kg^{-1} , respectively (8).

Inhalation (4 hr) rat, rabbit, guinea pig, cat no effect with 10 g l^{-1} as suspension in water (1).

LD_{50} dermal rabbit >10,000 mg kg^{-1} (1).

LD_{50} intraperitoneal ♂, ♀ rat 7320 and 15,000 mg kg^{-1} , respectively (1).

LD_{50} intraperitoneal mouse, rat 1225, 1720 mg kg^{-1} , respectively (8).

Sub-acute and sub-chronic data

Gavage weanling Wistar rats (90 days) 0, 16, 32 or 64 mg kg^{-1} caused dose-dependent increase in erythrocytes and decrease in leukocytes. After 30 days increased neutrophil and decreased lymphocyte count, no change in whole blood cholinesterase but increased alkaline phosphatase activity was observed in ♂ rats. After 90 days, blood sugar and urea levels were significantly increased and higher serum bilirubin concentrations were attributed to liver parenchymal cell damage as evidenced by increased glutamic-pyruvic transaminase and glutamic-oxaloacetic transaminase activities. Damage to liver and kidney reported (9).

Carcinogenicity and chronic effects

In 2-yr feeding trials the no-effect level for dogs was 300 mg kg^{-1} diet (6-7 mg kg^{-1} body weight) (1).

Teratogenicity and reproductive effects

Carbendazim was administered by gavage at dose levels of 250, 500 or 1000 mg kg^{-1} for 5 days to mice. Results showed no effect on body weights, but testes weights were reduced. Flow cytometric measurements on testicular and epididymal sperm cells showed that spermatogenesis was affected at high doses resulting in altered ratio of testicular cell types. Additionally, abnormalities were seen in sperm head morphology and chromatin structure (10,11).

Administration of carbendazim (50, 100, 200 or 400 mg kg^{-1}) (route and duration unspecified) was found to cause a dose-related elevation in serum follicle stimulating hormone and pituitary luteinising hormone in ♂ rats (12).

Oral rat (duration unspecified) 400 mg kg^{-1} day $^{-1}$ caused degeneration of testicular tissue and decreased spermatogenic activity (13).

Intraperitoneal rat (prepubertal and postpubertal) 164 mg kg^{-1} . Little damage was observed in prepubertal rats but in adult rats sloughing of the seminiferous epithelium was observed. Higher levels of carbendazim were observed in adult testes (210.2 nmol g^{-1} wet weight) than in prepubertal testes (67.77 nmol g^{-1} wet weight) (14).

Metabolism and toxicokinetics

Studies on the metabolic fate of carbendazim administered as a single dose of 12 mg kg^{-1} by the intraperitoneal or oral route in the rat showed that the major urinary metabolite was 5-hydroxy-2-benzimidazole carbamate, with 2-

aminobenzimidazole being a minor urinary metabolite. No significant accumulation of the parent compound or its metabolites occurred in rat tissues (15).

Irritancy

Shows no skin resorption effects but application as a concentrated emulsion affected the mucous membrane (8).

Genotoxicity

Salmonella typhimurium TA97, TA98, TA100, TA1535, TA1537, TA1538 with metabolic activation positive (16,17).
Saccharomyces cerevisiae D61.M *Saccharomyces cerevisiae* D7 with and without metabolic activation negative (17,18).
Clastogenic to Chinese hamster ovary cells (19).
Mycobacterium smegatis induced transection inhibition (20).
In vitro human lymphocytes induced a very low frequency of sister chromatid exchanges (20).
In vivo mouse bone marrow induced micronuclei formation (20).
Drosophila melanogaster test results from FIX and ZESTE systems. Aneuploidy was not induced (21).

Other effects

Any other adverse effects

HepG2 cells treated with 1.25-20 µg ml⁻¹ (24 hr) showed increased ethoxycoumarin deethylase activity.
Ethoxyresorufin deethylase activity was unaffected (22).

Legislation

Limited under EC Directive on Drinking Water Quality 80/778/EEC. Pesticides: maximum admissible concentration 0.1 µg l⁻¹ (23).
Included in Schedule 6 (Release into Land: Prescribed Substances) of Statutory Instrument No. 472, 1991, (24).
WHO Toxicity Class Table 5 (25).
ADI (JMPR) 0.03 mg kg⁻¹ body weight (26).

Other comments

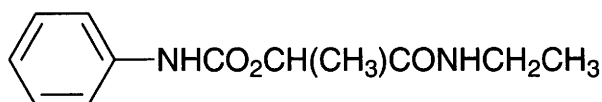
Possesses gonadotoxic and teratogenic action. Recommended maximum permissible level in the workplace 0.1 mg m⁻³, and in water reservoirs 0.1 mg l⁻¹ (8).
Sub-chronic administration of carbendazim in rats designed to assay the possible toxicity to vital organs, e.g. the haemopoietic system, liver and kidneys, discussed (27).

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c66 carbetamide



$C_{12}H_{16}N_2O_3$

Mol. Wt. 236.27

CAS Registry No. 16118-49-3

Synonyms D-(-)-carbanilic acid, 1-ethylcarbamoyl-, ethyl ester; propanamide, N-ethyl-2-[[[(phenylamine)carbonyl]oxy]-,(R)-; lactamide, N-ethylcarbanilate (ester), D-; Carbeetamide; Carbetamax; Legurame

EINECS No. 240-286-6

RTECS No. FD 8900000

Uses Herbicide.

Physical properties

M. Pt. 119°C **Partition coefficient** $\log P_{ow}$ -1.59 (1)

Solubility Water: 3.5 g l⁻¹ at 20°C. Organic solvents: acetone, dichloromethane, dimethyl formamide, ethanol, methanol

Ecotoxicity

Fish toxicity

LC₅₀ (96 hr) harlequin fish 165 mg l⁻¹ (2).

Environmental fate

Nitrification inhibition

Heterotrophic nitrogen fixation was slightly inhibited by carbetamide in a clay loam soil (3).

Degradation studies

Estimated t_{1/2} in soil 1 month (1).

Mammalian & avian toxicity

Acute data

LD₅₀ oral rat, mouse 1100, 1200 mg kg⁻¹, respectively (4).

LC₅₀ (4 hr) inhalation rat >130 mg m⁻³ (5).

LD₅₀ dermal rabbit >500 mg kg⁻¹ (5).

Sub-acute and sub-chronic data

In 90-day feeding studies the no-observable-adverse-effect level in diet of rat was 3200 mg kg⁻¹ and dog 12,800 mg kg⁻¹ (5).

Legislation

Limited under EC Directive on Drinking Water Quality 80/778/EEC. Pesticides: maximum admissible concentration 0.1 µg l⁻¹ (6).

Included in Schedule 6 (Release into Land: Prescribed Substances) of Statutory Instrument No. 472, 1991 (7).

WHO Toxicity Class Table 5 (8).

EPA Toxicity Class (formulation) IV (1).

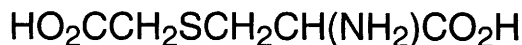
Other comments

Biodegradation of carbetamide has been studied in soil and plants (9,10).

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C67 carbocysteine



C₅H₉NO₄S

Mol. Wt. 179.20

CAS Registry No. 638-23-3

Synonyms 3-(carboxymethyl)thioalanine; S-(carboxymethyl)-L-cysteine; Mucopront; Mucodyne

EINECS No. 211-327-5

RTECS No. AY 4342000

Uses Mucoregulation and antiinflammatory drug.

Physical properties

M. Pt. 204-207°C (L-form)

Mammalian & avian toxicity

Acute data

LD₅₀ oral mouse 8400 mg kg⁻¹ (1).

LD₅₀ intraperitoneal mouse, rat 1400, 7800 mg kg⁻¹, respectively (1,2).

LD₅₀ subcutaneous mouse, rat 9000, 10,300 mg kg⁻¹, respectively (1).

Metabolism and toxicokinetics

Phase I, S-oxidation (3).

Carbocysteine is rapidly and well absorbed after oral administration in humans, peak serum concentrations being reached between 1 and 1.7 hr after administration. Peak values after 1.5g dose were 13.38 mg l⁻¹ and plasma t_{1/2} was estimated at 1.33 hr (4).

Metabolic pathways identified in humans include alkylation, decarboxylation and sulfoxidation. A minor metabolite is a glucuronic acid conjugate but the majority of the drug is eliminated unchanged in the urine (4).

Other effects

Other adverse effects (human)

Human systemic effects including gastric discomfort, nausea, gastro-intestinal bleeding, diarrhoea, headache and skin rashes have occasionally been reported with use of carbocysteine (5).

A patient with compromised thyroid function suffered transient hypothyroidism associated with the use of carbocysteine (6).

A study of 200 healthy volunteers given a single unspecified dose of carbocysteine showed a 100-fold variation in the amount of sulfoxide metabolites excreted in the urine. Family studies suggest this may be due to a genetic effect (7).

Ten patients with gastro-intestinal phytobezoars were treated with carbocysteine. In one patient the bezoar completely disappeared within three days (8).

A double-blind study of 109 patients with chronic bronchitis showed treatment with carbocysteine (750 mg day⁻¹ orally) for 6 months had improved peak expiratory flow rates (9).

A similar study on 36 patients reported inconclusive evidence on lung function and sputum viscosity (10).

Other comments

Carbocysteine is currently used in the management of respiratory diseases characterised by accumulation of excessive secretions (4).

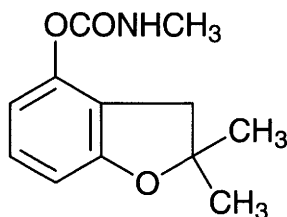
The use of carbocysteine on patients with secretory otitis media has been investigated (11).

Incompatible with Pholcodine (CAS RN 509-67-1) linctus which causes carbocysteine to precipitate from solution (5).

Recommended that carbocysteine be used with caution in patients with a history of peptic ulcers (5).

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C₁₂H₁₅NO₃

Mol. Wt. 221.26

CAS Registry No. 1563-66-2

Synonyms 2,3-dihydro-2,2-dimethylbenzofuran-7-yl methylcarbamate; methylcarbamic acid, 2,3-dihydro-2,2-dimethyl-7-benzofuranyl ester; 7-benzofuranol, 2,3-dihydro-2,2-dimethyl-, methylcarbamate; Barclay Carbosect; Benocarb; Candor; Diafuran; Evastin; Furacarb; Furdan; Garrot; Intrasol; Kenofuran; Overdyn

EINECS No. 216-353-0

RTECS No. FB 9450000

Uses Insecticide. Acaricide. Nematicide.

Physical properties

M. Pt. 153-154°C **Specific gravity** 1.180 at 20°C with respect to water at 20°C **Partition coefficient** log *P*_{ow} 1.52 at 20°C (1) **Volatility** v.p. 2×10^{-5} mmHg at 33°C
Solubility Water: 0.32 g l⁻¹ at 20°C. Organic solvents: acetone, benzene, dimethylformamide, ethanol

Occupational exposure

FR-VME 0.1 mg m⁻³

UK-LTEL 0.1 mg m⁻³

US-TWA 0.1 mg m⁻³

Supply classification very toxic

Risk phrases Very toxic by inhalation and if swallowed (R26/28)

Safety phrases Keep locked up and out of the reach of children (if sold to general public) – Wear suitable protective clothing and gloves – In case of accident or if you feel unwell, seek medical advice immediately (show label where possible) (S1/2, S36/37, S45)

Ecotoxicity

Fish toxicity

LC₅₀ (72 hr) mosquito fish 0.52 mg l⁻¹ (2).

LC₅₀ (96 hr) sheeps head minnow 386 µg l⁻¹ (3).

LC₅₀ (69 hr) goldfish 7.9 mg l⁻¹ (4).

Acmaea testudinalis were subjected to 156 mg l⁻¹ and 0.56 mg l⁻¹ concentrations of carbofuran. Results showed a persistent increase in aspartate and alanine aminotransferase activities in liver, kidney and intestine (5).

Channel catfish exposed to 0.5 ppm carbofuran (commercial grade) for six months exhibited varying degrees of histopathological changes, including cytoplasmolysis, nuclear pyrenolysis and necrosis, leading to complete exhaustion and disintegration of hepatocytes. Induction of tumours were indicative of the carcinogenic action of the pesticide (6).

0.1 mg l⁻¹ was toxic to the ovary of carp minnows. Severe damage to the peritoneal lining, vacuolation of the cytoplasm of immature oocytes, damage to yolk vesicles in mature oocytes and disintegration of cortical alveoli and yolk (7).

Newly hatched fathead minnow larvae were exposed for four days to carbofuran at levels approximating to half

the LC₅₀ and a much lower, level similar to that experienced by minnow in the waters of the Colusa Basin Drain. The higher level caused reduction in swimming capacity, an increased sensitivity to electric shock, a reduction in upper lethal temperature, and a reduction in acetylcholinesterase activity. The lower level of exposure caused no measurable effect (8).

Invertebrate toxicity

IC₅₀ (growth inhibition of 50% of algal population) (96 hr) *Chlorella pyrenoidosa* 204.48 mg l⁻¹ (4).

Lethal dose *Synechococcus elongatus*, *Scenedesmus bijugatus* 5 µg ml⁻¹ (9).

EC₅₀ (5 min) *Photobacterium phosphoreum* 20-90 ppm Microtox test (10).

Earthworm *Megascolex mauritii* 0.5, 1.0, 1.5, 2.0, 2.5 ppm carbofuran solution in 6 kg garden soil caused 38, 52, 36, 86, 72% mortality after 15 days, respectively. Paddy earthworm *Malabarica paludicola* 0.05, 0.1, 0.2, 0.25, 0.5, 1.0 ppm carbofuran caused 0, 0, 0, 40, 100, 100% mortality one day after treatment, respectively, and 0, 20, 20, 40, 60, 100% mortality after three days, respectively. Paddy gastropod *Cerastes* sp. 0.25, 0.5, 1.0, 1.5, 2.0 ppm carbofuran caused 100% mortality at all concentrations one day after treatment (11).

Two 1-hr exposures of carbofuran caused significantly fewer symptoms of intoxication than a 2-hr continuous exposure in the midge *Chironomus riparius* if at least 2 to 6 hr in clean water was provided between doses (12).

Toxic to bees (1).

Bioaccumulation

Tilapia nilotica exposed to 0.1-0.2 mg kg⁻¹ carbofuran resulted in equilibrium concentration of 0.09 mg kg⁻¹ in 17 hr. *Anodonta woodiana* exposed to 0.1-0.2 mg kg⁻¹ resulted in 0.39 mg kg⁻¹ equilibrium concentrations in seven days. Rapidly depurated from fish and clams on transfer to clear water (13).

Environmental fate

Nitrification inhibition

Nostoc muscorum 25 mg l⁻¹ enhanced survival, growth and nitrogen fixation, gradual inhibition from 50-1000 mg l⁻¹ (14).

Westiellopsis prolifica cyanobacterium 10 ppm of 3% carbofuran increased growth and nitrogen fixation; >20 ppm had an inhibitory effect and 1500 ppm suppressed oxygen evolution (15).

Aulosira fertilissima nitrogen fixation was stimulated in soil for 6 wk at all levels after application of ≥200 µg l⁻¹ (16).

Degradation studies

In soil estimated t_{1/2} 60-75 days at pH 6.5 (17).

890-950 µg 20 g⁻¹ of soil was initially present. After six days at 35°C >20% of the original level remained and 25% remained after 30 days at 25°C (18).

Mineralisation in soil proceeds with little or no acclimation phase (19).

Degradation products in soil include 3-ketocarbofuran and 3-hydroxycarbofuran (20).

Carbofuran is degraded more rapidly by soils that have been pretreated with it than by untreated soils. Tests using ¹⁴C-labelled carbofuran indicate that the major metabolic route in pretreated soil is hydrolysis of the ester bond; this releases the carbofuran phenol, which binds to soil organic matter, and the carbonyl moiety, which degrades to release CO₂ (21).

The cyanobacteria *Anabaena oryzae* and *Phormidium fragile* were incubated with 25 ppm radiolabelled carbofuran for seven days at 30°C. Degradation was 91.4% and 92.1%, respectively, for the two species and the principal metabolite was 2,3-dihydro-7-hydroxy-2,2-dimethylbenzofuran. Minor metabolites detected were 2,3-dihydro-3-hydroxy-2,2-dimethyl-7-benzofuranyl methylcarbamate and 2,3-dihydro-7-hydroxy-2,2-dimethyl-3-ketobenzofuran. Parent material accounted for 3.2% and 0.49% of applied dose, respectively (22).

Aspergillus niger and *Fusarium graminearum* degrade carbofuran in liquid culture to form 3-hydroxycarbofuran, 3-ketocarbofuran and 3-ketocarbofuran phenol. The t_{1/2} of carbofuran in liquid culture is 10.4 and 12 days for *A. niger* and *F. graminearum*, respectively (23).

Abiotic removal

In soil suspensions in water t_{1/2} 1-2 days. The main process of degradation is abiotic hydrolysis at the carbamate linkage (24).

Under laboratory conditions at 25°C volatilisation from sandy loam soil was 0.5% after 60 days and in sand it was 36% after 60 days (25).

In ponds sprayed with carbofuran the insecticide concentrations were 9-32 $\mu\text{g l}^{-1}$ after 16 hr and 3-12 $\mu\text{g l}^{-1}$ after 124 hr (26).

Mammalian & avian toxicity

Acute data

LD₅₀ oral redwing blackbird 0.42 mg kg⁻¹ (27).

LD₅₀ oral mallard duck 0.415 mg kg⁻¹ (28).

LD₅₀ oral rat 5300 $\mu\text{g kg}^{-1}$ (29).

LD₅₀ dermal rat, rabbit 120, 885 mg kg⁻¹, respectively (30,31).

LD₅₀ intravenous mouse 450 $\mu\text{g kg}^{-1}$ (32).

Sub-acute and sub-chronic data

Oral rat (duration unspecified) >50 ppm in diet caused growth depression in both ♂ and ♀. Results of haematology, urine analysis, organ weight and gross and microscopic pathology were unchanged (33).

Oral rat (15 day) 4.5 mg kg⁻¹ daily a decrease in liver total lipids and triglycerides, and hyperglycaemia, which is attributed to decreased glucose utilisation and increased liver glycogen mobilisation (34).

Oral rat (90 day) 10 and 25 ppm in diet induced moderate reversible changes in the liver (35).

Oral rat (180 day) 10 and 25 ppm in diet induced no cumulative toxic effects that could be detected (36).

Carcinogenicity and chronic effects

Oral mouse (12 month) 0, 3 and 8 ppm in drinking water caused 6.6%, 3.3% and 10% lymphosarcomas and 2.5%, 2.5% and 1.6% lung adenomas in the control and two carbofuran treated groups, respectively. No statistically significant difference observed between the groups. Malignant tumours of other types were few and scattered without preponderance in groups dosed with carbofuran. The authors conclude that carbofuran is not carcinogenic in ICR mice (37).

Teratogenicity and reproductive effects

Pregnant F₂ dihybrid mice received either a vehicle-control or one of two doses 0.01 or 0.50 mg kg⁻¹ carbofuran daily in the diet throughout gestation. All mothers gave birth to viable, overtly normal offspring at term (38).

Oral rat (8 wk before pregnancy) 25 ppm in diet induced no external and/or internal malformations (33).

Oral ♂ rats (60 days) 0.1, 0.2, 0.4 or 0.8 mg kg⁻¹, 5 days wk⁻¹. At all doses, except the lowest, a dose-dependent decrease in body weight, and significant decreases in the weights of epididymides, seminal vesicles, ventral prostate and coagulating glands occurred. Morphological abnormalities were seen in spermatozoa, as well as decreased sperm motility and reduced epididymal sperm count. Changes in enzyme activity were observed: decreased activity of sorbitol dehydrogenase and glucose-6-phosphate dehydrogenase, increased activity of lactate dehydrogenase and γ -glutamyl transpeptidase. Histological examination showed dose-dependent effects on testes, such as oedema, congestion and damage to Sertoli cells and germ cells. The no-effect level for ♂ rat reproductive toxicity is 0.1 mg kg⁻¹ (39).

♀ Mink were fed 0.05 mg kg⁻¹ in diet from before mating until weaning. No effect on fertility was observed compared to controls (40).

Metabolism and toxicokinetics

In vivo dermal penetration 120 hr was 43% for young and 18% for adult ♀ Fischer 344 rats, urinary excretion was 95% (41).

Rapidly detoxified in the liver and excreted in the urine in experimental animals (42).

Irritancy

Skin irritant, effects include sweating and fasciculations at site of contact. Eye irritant, effects include hyperaemia, lachrymation, meiosis, blurred vision and ciliary muscle spasm (43).

Genotoxicity

Salmonella typhimurium TA1538, TA98 with metabolic activation positive (44).

Escherichia coli WP2 *hcr* with and without metabolic activation negative (44).

Human lymphocyte sister chromatid exchange positive (45).

Hamster lung V-79 cells without metabolic activation weak direct acting mutagen, with metabolic activation mutation frequency negative (46).

Other effects

Other adverse effects (human)

A case study on two men who developed Parkinson's disease. Both had exposure to chemicals including carbofuran (47). Systemic effects include wheezing, dyspnoea, chest discomfort and nasal hyperaemia after inhalation. Other effects include nausea, vomiting, diarrhoea, headache, abdominal cramps, vertigo, ocular pain and sight inhibition (43).

Six prairie grain farmers were monitored for pesticide exposure and related adverse effects while they mixed or sprayed carbofuran. Exposure was 99.8% dermal and 0.2% via inhalation. No acute adverse effects were observed during exposure and for four days after exposure (48).

Any other adverse effects

Collared turtle dove exhibited cholinesterase inhibition in muscle, kidney, ovary, liver, intestine, pancreas and spleen after exposure to carbofuran (dose unspecified) (49).

Potent anticholinesterase agent (50).

IC₂₅ and IC₅₀ of 0.22 and 33.0 µg l⁻¹ produced 25% or 50% inhibition of cholinesterase activity in rat plasma, respectively (51).

Catfish exposed to carbofuran exhibited delayed formation of spermatids and sperm (52).

Measurement of the consumption of grasshoppers (*Melanoplus sanguinipes*) by clay-coloured sparrows (*Spizella pallida*), together with results from a field study suggests that adults and nestlings are able to tolerate exposure to carbofuran through ingestion of grasshoppers sprayed at the rate of 134 g ha⁻¹ (assuming an intake of ~0.2 mg kg⁻¹ per bird and an LD₅₀ of 1.43 mg kg⁻¹) (53).

House sparrow, 0.2-0.8 mg kg⁻¹ caused severe damage to ovary and hampered the normal reproductive process (54).

Legislation

Limited under EC Directive on Drinking Water Quality 80/778/EEC. Pesticide: maximum admissible concentration 0.1 µg l⁻¹ (55).

Included in Schedule 6 (Release into Land: Prescribed Substances) Statutory Instrument No. 472, 1991 (56).

WHO Toxicity Class Ib (57).

EPA Toxicity Class (formulation) I (Furadan 4F), II (Furadan G) (1).

ADI (JMPR) 0.002 mg kg⁻¹ (58).

Other comments

Toxicity and hazards reviewed (59).

Toxicity in mammals reviewed (60).

Unstable in alkaline media, cholinesterase inhibitor (1).

Reviews on human health effects, experimental toxicology, environmental effects and ecotoxicology are listed (61).

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c69 carbonylhydrazide



$\text{CH}_6\text{N}_4\text{O}$

Mol. Wt. 90.08

CAS Registry No. 497-18-7

Synonyms carbonic dihydrazide; 1,3-diaminourea; 4-aminosemicarbazide; carbazide

EINECS No. 207-837-2

RTECS No. FF 2625000

Uses Oxygen scavenger for boiler feed waters. Corrosion inhibitor.

Physical properties

M. Pt. 153-154°C (decomp.)

Solubility Water: miscible

Mammalian & avian toxicity

Acute data

LD₅₀ intravenous mouse 120 mg kg⁻¹ (1).

LD₅₀ intraperitoneal mouse 167 mg kg⁻¹ (2).

Other comments

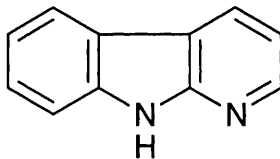
Reviews on experimental toxicology and human health effects listed (3).

The pH of a 1% solution is 7.4. Gradually decomposed on heating. Reacts with nitrous acid to form the highly explosive carbonylazide, $\text{CO}(\text{N}_3)_2$ (4).

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c70 α -carboline



$\text{C}_{11}\text{H}_8\text{N}_2$

Mol. Wt. 168.20

CAS Registry No. 244-76-8

Synonyms 1H-pyrido[2,3-b]indole; 9H-pyrido[2,3-b]indole; 1-azacarbazole; 1,9-diazafluorene; 9H-1,9-diazafluorene

EINECS No. 205-960-6

Physical properties

M. Pt. 210-225°C B. Pt. 363.6°C

Environmental fate

Degradation studies

Kitasatosporia setae transformed α -carboline by *N*-methylation. Product identified as α -isocarboline (1).

Mammalian & avian toxicity

Carcinogenicity and chronic effects

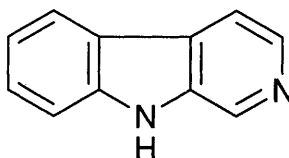
α -Carboline was evaluated for antitumour activity against sarcoma 180 in mice. Injection route mice (14 day) 50-100 mg kg⁻¹ had significant inhibitory effects upon the development of sarcoma 180 (2).

The anticancer activity potential of α -carboline was tested in mice and rats. α -Carboline was inactive against B16 melanoma, Lewis lung carcinoma, plasmacytoma MP26, colon carcinoma 26 and mammary carcinoma 16/C in mice and Walker carcinosarcoma 256 in rats (3).

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c71 β -carboline



C₁₁H₈N₂

Mol. Wt. 168.20

CAS Registry No. 244-63-3

Synonyms 9H-pyrido[3,4-b]indole; 2-azacarbazole; 2,9-diazafluorene; Carbazoline; Norharman; Norharmane

EINECS No. 205-959-0

RTECS No. UU 9350000

Physical properties

M. Pt. 198-200°C

Mammalian & avian toxicity

Acute data

LD₅₀ intravenous mouse 100 mg kg⁻¹ (1).

Sub-acute and sub-chronic data

Oral mouse (4 wk) 0.1% in diet resulted in DNA adducts in the kidney, glandular stomach and large intestine but not in the liver or brain (2).

Carcinogenicity and chronic effects

The modifying effects of β -carboline on liver carcinogenesis were investigated in σ rats initially treated with *N*-nitrosodiethylamine, single intraperitoneal dose 200 mg kg⁻¹. Two wk after administration of *N*-

nitrosodiethylamine rats were given 1000 or 200 ppm β -carboline for 6 wk. Marked retardation of body weight gain and increased liver weight was observed in high-dose (1000 ppm) animals. No toxicity-related liver lesions were detected but severe renal toxic tubular lesions and regeneration were evident (3).

Metabolism and toxicokinetics

Metabolism by hamster hepatic microsomes gave the corresponding hydroxylamine and *N*-oxide (4).

Genotoxicity

Salmonella typhimurium umu-test without metabolic activation weakly positive (5).

Escherichia coli trp E9777 frameshift mutation positive (5).

Escherichia coli B/r WP2 without metabolic activation β -carboline enhances UVC (254 nm) – induced mutagenesis (6).

In vitro human HeLa cells with metabolic activation equivocal (7).

Other effects

Any other adverse effects

Six-week-old σ^7 F344/DuCrj rats (2 or 4 wk) 0, 500 or 1000 ppm in diet. The high dose caused body weight retardation, increased consumption of water, increased urinary sugar levels and increased activity of *N*-acetyl- β -D-glucosaminidase and lactate dehydrogenase. Activity of γ -glutamyl transpeptidase and alkyl phosphatase decreased. Serum biochemical parameters showed renal toxicity, and histopathology showed renal degenerative/necrotic and regenerative lesions (8).

Other comments

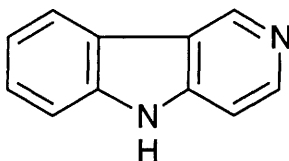
Food contaminant.

Weak inhibitory activity toward cholinesterases and pseudocholinesterases (9).

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C72 γ -carboline



$C_{11}H_8N_2$

Mol. Wt. 168.20

CAS Registry No. 244-69-9

Synonyms 5*H*-pyrido[4,3-*b*]indole; 3-azacarbazole

Physical properties

M. Pt. 225°C

Solubility. Organic solvents: miscible with methanol, soluble in ethanol

Environmental fate

Degradation studies

Kitasatospora setae transformed γ -carboline by *N*-methylation. Product identified as γ -isocarboline (1).

Genotoxicity

In vitro L1210 cells induced DNA breaks (2).

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C73 carbon black

C

Mol. Wt. 12.01

CAS Registry No. 1333-86-4

Synonyms acetylene black; furnace black; lamp black

EINECS No. 215-609-9

RTECS No. FF 5800000

Uses In rubber industry.

Occupational exposure

FR-VME 3.5 mg m⁻³

SE-LEVL 3 mg m⁻³

UK-LTEL 3.5 mg m⁻³

UK-STEL 7 mg m⁻³

US-TWA 3.5 mg m⁻³

Mammalian & avian toxicity

Carcinogenicity and chronic effects

Inadequate evidence for carcinogenicity to humans, inadequate evidence for carcinogenicity to animals for carbon blacks, IARC classification group 3. Sufficient evidence for carcinogenicity to animals for carbon black extracts, IARC classification group 2B (1).

Carcinogenic potential of carbon black was studied in mice. The animals were observed for tumour development and histopathological changes for up to 314 days. Six advanced squamous cell carcinomas observed in 212 animals treated with carbon black extracts (2).

Effect of dust overloading of lungs was examined in a variety of sub-chronic and chronic inhalation investigations in rats after exposure to carbon black, and other benign or slightly toxic insoluble materials. Animals inhaled one of the test materials for up to 2 yr at aerosol concentrations 1-64 mg m⁻³. Retardation of alveolar clearance started when retained mass in lungs reached a level of 0.5 mg lung⁻¹. Results of chest overloading were: alveolar clearance retardation, increased retention of material in lung, increased lung weight, accumulation of dust laden macrophages, persistent inflammation, increased epithelial permeability, and elevated infiltration of neutrophils (3).

Irritancy

Reported irritant to rabbit eye (4).

Genotoxicity

Salmonella typhimurium TA98, TA1537, TA1538 with metabolic activation positive (5)

Other effects

Other adverse effects (human)

Studies of workers exposed to carbon blacks showed respiratory symptoms including impaired lung function from the deposition of dust in the lungs (4).

Mortality in 1422 ♂ carbon black process workers with a minimum of 12 months exposure was recorded from 1947-1980. Excess deaths from lung cancer were observed but interpretation was complicated by the incomplete data from 2/5 populations studies (6).

Detailed job histories were obtained for 857 incident cases with histologically confirmed lung cancer, 1360 cancer controls and 533 population controls in a population-based case-control study in Montreal, Canada. Logistic regression analyses adjusted for smoking and other occupational and non-occupational potential confounders indicated no significant increase in risk with relatively low exposure to carbon black. Some increase for all lung cancers was apparent with relatively high exposure using cancer or population controls. Individuals with relatively high exposure had a significantly greater risk of oat-cell carcinoma using either or both control groups and the results provide some evidence for an association between carbon black exposure and lung cancer (7).

Any other adverse effects

Mildly toxic by ingestion, inhalation and skin contact. Inhalation by experimental animals has been reported to cause adverse effects to liver, spleen, kidneys, heart and lung (4).

Intratracheal rats (dose and duration unspecified) caused pneumoconiosis 3-9 months after administration (8).

Legislation

Included in Schedule 4 (Release into Air: Prescribed Substances) Statutory Instrument No. 472, 1991 (9).

Other comments

Carbon black is a generic term applicable to a family of high purity colloid carbons commercially produced by controlled pyrolysis of gaseous or liquid hydrocarbons. The range of products include furnace blacks, thermal blacks, acetylene blacks, channel blacks, gas blacks, and lamp blacks. The latter three substances are products from oil gasification processes.

Reviews on experimental toxicology, human health effects, workplace experience, environmental effects, and exposure listed (10).

Carcinogenicity reviewed (11).

History, physical properties, uses, chemistry and toxicity of carbon black are reviewed (12,13).

A nuisance dust in high concentrations. While particles of carbon black contain some carcinogenic substances, the carcinogens are apparently bound tightly and not eluted by hot or cold water, gastric juices or blood plasma.

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C74 carbon dioxide



CO₂

Mol. Wt. 44.01

CAS Registry No. 124-38-9

Synonyms carbonic acid gas; carbonic anhydride; dry ice

EINECS No. 204-696-9

RTECS No. FF 6400000

Uses Carbonation of beverages. Manufacture of carbonates. Fire prevention and extinction. Used to make flammable materials inert during manufacture, handling and transfer. Rice fumigant. Respiratory stimulant. Propellant in aerosols. Dry ice for refrigeration. Stage smoke. Antiseptic in bacteriology and the frozen food industry.

Occurrence Constituent of carbonate type minerals. Product of animal metabolism. Occurs in the atmosphere of many planets in our solar system. Needed for the respiratory cycle of plants and animals.

Physical properties

M. Pt. -56.5°C at 3952 mmHg **B. Pt.** -78.5°C (sublimes) **Specific gravity** 1.988 (liquid) **Volatility** v.den. 1.527 (gas in air)

Solubility Water: 0.145 g ml⁻¹ at 25°C. Organic solvents: acetone, ethanol

Occupational exposure

DE-MAK 5000 ppm (9100 mg m⁻³)

JP-OEL 5000 ppm (9000 mg m⁻³)

SE-LEVL 5000 ppm (9000 mg m⁻³)

UK-LTEL 5000 ppm (9150 mg m⁻³)

US-TWA 5000 ppm (9000 mg m⁻³)

SE-STEL 10000 ppm (18000 mg m⁻³)

UK-STEL 15,000 ppm (27,400 mg m⁻³)

US-STEL 30,000 ppm (54,000 mg m⁻³)

UN No. 1013

UN No. 2187 (refrigerated liquid) **HAZCHEM Code** 2RE **Conveyance classification** non-flammable non-toxic gas

Ecotoxicity

Fish toxicity

Exposure of carp to carbon dioxide (initial concentration unspecified) showed that the fish could be anaesthetised for up to 10 hr and subsequently remain sedated (1).

Invertebrate toxicity

The nitrogenase activity of the unicellular cyanobacterium *Synechococcus* RF-1 is inhibited by 50% after exposure to 1% CO₂ for 3 hr in light conditions. The inhibitory effect persists for several hours. The elevated CO₂ level also leads to an increase in photosynthetic CO₂ assimilation (2).

Environmental fate

Nitrification inhibition

The effect of carbon dioxide on 31 strains of *Candida albicans* was studied in serum and in a defined medium containing urea, ammonium chloride, asparagine, glutamine, or acetamide as the nitrogen source. The results suggest that the induction of germ tubes and mycelial growth is essentially a physical phenomenon caused by the intracellular accumulation of carbon dioxide in limited nutrient conditions (3).

Carbonaceous inhibition

The effect of inhibitors on carbon dioxide assimilation by methanotrophic, ammonium oxidising, thionic and heterotrophic bacteria was studied. The mode and degree of inhibition was shown to depend upon the inhibitor concentration and the taxonomic type of microorganism (4).

Anaerobic effects

The efficiency of nitrogen fixation in the presence of *Azotobacter chroococcu*lii WR146 and *Azospirillum lipo*terum WR116 and in the presence of different levels of carbon dioxide established (5).

Mammalian & avian toxicity

Acute data

LC_{Lo} (5 min) inhalation human 9 pph (6).

LC_{Lo} (5 min) inhalation unspecified mammal 90,000 ppm (7).

Inhalation rhesus monkey *Macaca mulatta* concentrations of 5%, 7.5% and 10% for 180 min produced significant dose-dependent increases in respiratory rate and cortisol, growth hormone and prolactin levels (8).

Genotoxicity

♀ *Drosophila melanogaster* homozygous for X-linked recessive markers, y and w, were exposed to CO₂ for 90 minutes and mated with y+ w+/Y ♂s. The frequency of nondisjunction XXY mutants was 100 × above control in the first day brood but did not increase above control level in the second to sixth broods. CO₂ is an extremely potent inducer of nondisjunction in mature oocytes during meiotic metaphase 1 but is not harmful to immature oocytes (9).

Other effects

Other adverse effects (human)

In humans, concentrations above 6% give rise to headaches, dizziness, mental confusion, palpitations, hypertension, dyspnoea, increased depth and rate of respiration, and depression of central nervous system (10). Concentrations of 30% may produce convulsions. Higher concentrations are depressant, inhalation of 50% carbon dioxide is reported to produce central nervous system effects similar to anaesthetics. Inhalation of high concentrations may lead to respiratory acidosis. Abrupt withdrawal of carbon dioxide after prolonged inhalation commonly produces pallor, hypotension, dizziness, severe headache, nausea or vomiting (10). Toxic listed as asphyxiant, prolonged exposure (42 days) to concentrations of about 15,000 ppm may cause mild stress and behavioural changes (11).

Legislation

Included in Schedule 4 (Release into Air: Prescribed Substances) Statutory Instrument No. 472, 1991 (12). HMIP Approved Codes of Practice and Other Guidelines. Integration Pollution Regulation Notes 13 IPR1 (13).

Other comments

Industrial by-product in the manufacture of lime, constituent of exhaust gases and industrial emissions. Soybean (Glycine max) plants exposed to 450 µl l⁻¹ at the flowering stage, 12 hr day⁻¹ for 5 days, showed no change in photosynthetic rate, 18% reduction in specific root nodule nitrogenase activity, 23% decrease in foliar nitrogen, and an increase in chlorophyll-a and -b (14).

150 µl l⁻¹ CO₂ has a protective effect on soybean plants exposed to 40 nl l⁻¹ ozone. CO₂ alone increases grain oil content and reduces protein content, neither of which are affected by ozone (15).

Studies of aliphatic epoxide and ketone metabolism by *Xanthobacter* strain Py2 have revealed that CO₂ plays a central role as a cosubstrate in this process, which involves two new classes of carboxylates (16).

Carbon dioxide fixation reviewed (17).

Reviews on experimental toxicology, human health effects, epidemiology, workplace experience, and exposure listed (18).

Autotrophic carbon dioxide fixation in chemotrophic anaerobic bacteria reviewed (4).

The biochemistry and molecular regulation of carbon dioxide metabolism in cyanobacteria reviewed (19).

Humans cannot breathe air containing more than 10% carbon dioxide without losing consciousness. Contact with dry ice causes frost bite and blisters.

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C75 carbon disulfide



CS₂

Mol. Wt. 76.14

CAS Registry No. 75-15-0

Synonyms carbon bisulfide; dithiocarbonic anhydride; carbon sulfide; sulfocarbonic anhydride

EINECS No. 200-843-6

RTECS No. FF 6650000

Uses In the manufacture of viscose rayon, cellophane, carbon tetrachloride, and electronic vacuum tubes.

Flotation agent, soil disinfectant and industrial solvent. Used as an insecticide and veterinary parasiticide.

Occurrence Natural product of anaerobic degradation, especially in oceans.

Physical properties

M. Pt. -108 to -116°C **B. Pt.** 46°C **Flash point** -16°C (closed cup) **Specific gravity** 1.263 at 20°C with respect to water at 4°C **Partition coefficient** log P_{ow} 1.84-2.16 (calc.) (1) **Volatility** v.p. 360 mmHg at 25°C; v.den. 2.64

Solubility Water: 2200 ppm at 25°C. Organic solvents: miscible with benzene, carbon tetrachloride, chloroform, diethyl ether, ethanol

Occupational exposure

DE-MAK 5 ppm (16 mg m⁻³)

FR-VME 10 ppm (30 mg m⁻³)

JP-OEL 10 ppm (31 mg m⁻³)

SE-LEVL 5 ppm (16 mg m⁻³)

UK-LTEL MEL 10 ppm (32 mg m⁻³)

US-TWA 10 ppm (31 mg m⁻³)

FR-VLE 25 ppm (75 mg m⁻³)

SE-STEL 8 ppm (25 mg m⁻³)

UN No. 1131 HAZCHEM Code 3WE Conveyance classification flammable liquid, toxic

Supply classification highly flammable, toxic

Risk phrases Highly flammable – Irritating to eyes and skin – Toxic: danger of serious damage to health by prolonged exposure through inhalation – Possible risk of impaired fertility – Possible risk of harm to the unborn child (R11, R36/38, R48/23, R62, R63)

Safety phrases Keep away from sources of ignition – No smoking – Take precautionary measures against static discharges – Wear suitable protective clothing and gloves – In case of accident or if you feel unwell, seek medical advice immediately (show label where possible) (S16, S33, S36/37, S45)

Ecotoxicity

Fish toxicity

LC₅₀ (24-96 hr) mosquito fish 162-135 mg l⁻¹ (2).

Invertebrate toxicity

EC₅₀ (15 min) *Photobacterium phosphoreum* 340 ppm Microtox test (3).

Bioaccumulation

Calculated bioconcentration factor of 7-9 (4).

Environmental fate

Nitrification inhibition

35 mg l⁻¹ caused 75% inhibition of ammonia oxidation by activated sludge (5).

Limit concentration for inhibition of nitrification (Agar test) was 17.5 mg l⁻¹ (6).

Degradation studies

Absorption of carbon disulfide by moist unsterilised soil increased significantly after 3 hr and the time for complete sorption of the gas decreased with repeated dosing. This behaviour which did not occur with air-dried or sterilised soil has been ascribed to microbial utilisation of the chemical (7).

Abiotic removal

Evaporation from soil is significant due to the high vapour pressure and low soil adsorption (8).

Hydrolysis to carbon dioxide and hydrogen disulfide occurs in alkaline solution (9).

Estimated photochemical t_{1/2} 8-9 days (10).

Evaporation rate relative to *n*-butyl acetate which has been assigned a value of 1 (25°C) is 10.90 (11).

Mammalian & avian toxicity

Acute data

LD₅₀ oral guinea pig, mouse, rat 2125, 2780, 3188 mg kg⁻¹, respectively (12).

Sub-acute and sub-chronic data

Intraperitoneal rat (6 month) 5-25 mg kg⁻¹ once a wk caused concentration-dependent interstitial oedema, stasis, congestion, seminiferous tubule basement membrane thickening and spermatogenesis suppression (13).

Teratogenicity and reproductive effects

♀ mice (31 day) exposure route and concentration unspecified had reduced pregnancy rates and decreased F₁ generation survival rates. F₁ ovary development was retarded and behavioural development altered. Pregnancy rates of F₁ generation and survival rates of F₂ foetus were also significantly decreased (14).

Metabolism and toxicokinetics

Carbon disulfide is metabolised to 2-thiothiazolidine-4-carboxylic acid (TTCA) in rats and humans; this metabolite is used to monitor CS₂ exposure in workers (15).

Irritancy

Irritant to humans (16).

Genotoxicity

Salmonella typhimurium TA98, TA100 with and without metabolic activation negative (17).

Escherichia coli WP2 *uvrA* with and without metabolic activation negative (17).

Drosophila melanogaster test for X-linked recessive lethal negative (17).

Other effects

Other adverse effects (human)

In a study group of 116 male viscose rayon workers exposed to CS₂ for more than one year the CS₂ exposure varied from 4 to 112 mg m⁻³ and the working conditions and work practice for the workers had not altered since 1932. The control group consisted of 69 referents not exposed to CS₂ or other nephrotoxic chemicals. None of the subjects in the analysis used antidiabetic drugs or medication with possible renal side-effects. Urine samples were analysed for blood ureas, glucose, β -2-microglobulin and erythrocyte sedimentation rate; creatinine levels in serum and urine were also measured. Serum β -2-microglobulin was included as marker of impaired glomerular filtration rate, inflammatory disease or neoplastic disease. The serum β -2-microglobulin level and the number of red blood cells in the urinary sediment (19.4 mg l⁻¹, 18%) were significantly higher than those of controls (16.5 mg l⁻¹, 10.1%). The results suggest subclinical glomerular damage in CS₂ exposed subjects (18). Toxic effects may occur as a result of inhalation, ingestion or absorption through skin (16). In three studies of ♀ workers exposed to 1.7-32 mg m⁻³ carbon disulfide, menstruation disorders including irregular menstrual cycle, excessive bleeding, early menopause and spontaneous abortion reported (19-21).

A study of endocrine gland activity in exposed ♂ workers and a control group was undertaken. Average exposure duration was 10 yr \pm 8 yr at concentrations of 24-67 mg m⁻³. Serum triiodothyronine, serum thyroxine and urinary glucose levels remained unaltered, while levels of 17-hydroxycortisol in 24 hr urine samples and serum testosterone were significantly lower in the exposed group (22).

An ophthalmological examination of 128 viscose rayon workers exposed to 3-147 mg m⁻³ and 67 controls showed carbon disulfide influenced colour vision. Microaneurysms were found in subjects exposed to carbon disulfide levels exceeding the threshold limit value (TLV) (23).

A health survey of ♂ viscose rayon workers exposed to 4-112 mg m⁻³ carbon disulfide found a significant prevalence of eye pain, burning and photophobia (24).

Abnormalities in the blood of 237 women (age 37-48) who had been chronically exposed to 5-7 ppm carbon disulfide were seen in those over 39 years old. This group had a significant increase in levels of total cholesterol and low-density lipoprotein cholesterol, and a decrease in levels of high-density lipoprotein cholesterol (25). Mean total cholesterol levels were found to be highest in a group of non-exposed workers, while serum triglyceride values were highest in the group with the highest exposure to carbon disulfide, lower in the less-exposed group, and lowest in the non-exposed group. This is an important correlation, as triglycerides are specific markers in the development of atherosclerosis (26).

Examination of data from a 1979 study of 165 exposed and 245 unexposed ♂ workers in the textile industry found a significant and positive linear correlation between carbon disulfide exposure and low-density lipoprotein cholesterol concentration and diastolic blood pressure. Exposure levels were 0.6-11.8 ppm for 8 hr on average. No link between exposure and triglyceride level, high-density lipoprotein cholesterol, fasting glucose concentration or systolic blood pressure was found (27).

Exposure to carbon disulfide affects the central nervous system, the cardiovascular system and the gastro-intestinal system. CNS effects include headache, fatigue, insomnia, tremor, emotional lability, extrapyramidal disorders, manic-depressive psychoses and encephalopathy. Gastro-intestinal effects include anorexia, dyspepsia and ulcerative changes (16).

Two groups of 343 men were studied for effects of heart disease. Group 1 had been occupationally exposed to carbon disulfide for a minimum of 5 yr between 1950 and 1975. Group 2 had no exposure. Results showed death from coronary heart disease, non-fatal first myocardial infarctions, history of angina and prevalence of angina were all greater in group 1 (28).

A 3-yr follow-up where exposure duration was lowered and atmospheric concentrations reduced to 10 ppm showed lowered risk of heart disease amongst workers at risk (29).

A further 7-yr follow-up showed the relative risk of mortality from heart disease in exposed workers was reduced to that of the unexposed group during the period 1974-1982 (30).

A study of 247 workers in the viscose industry, exposed to <0.2-65.7 ppm for between 4 and 220 months, found no significant difference between exposed workers and 222 controls in the variation of blood pressure, lipoproteins, blood glucose, blood coagulation, and indicators of direct cardiotoxic effects (31).

The results of a neurobehavioural study of workers in a viscose rayon factory conducted from 1974 to 1990 show that exposure to CS₂ may induce absent mindedness and difficulties in perception, even at levels <8 mg m⁻³ (32). An extensive health survey of 119 viscose rayon workers exposed to 4-112 mg m⁻³ CS₂ found significantly higher prevalence of anorexia, vomiting and recent weight loss than in 79 unexposed workers. Exposed workers had lower median values for aspartate aminotransferase and alanine aminotransferase activities, and larger values for liver size and γ -glutamyltransferase activity than unexposed workers. Alkaline phosphatase activity did not vary significantly between the two groups (33).

Crosses placenta and may be present in mothers milk (34).

A group of 111 workers were exposed to a time-weighted 8 hr average of 4 to 112 mg m⁻³ of carbon disulfide (CS₂), measured with personal monitors. Working conditions had not changed since 1932 and it was possible to derive a cumulative exposure index for each employee. Workers were given a clinical neurological examination and electroneuromyography and completed a self-administered questionnaire. Data were analysed with multiple regression procedures and significant associations were found between the cumulative index and observed symptoms; these included polyneuropathy in the legs and abnormal recruitment pattern and decrease of motor conductor velocities in the peroneal nerves. Exposure to CS₂ levels below the threshold limit value (TLV) of 31 mg m⁻³ set by ACGIH were associated with significant decreases of motor conductor velocity (35).

Any other adverse effects

Carbon disulfide inactivated ATPase in synaptosome membranes from rat brain (36).

Legislation

Maximum permissible concentration in domestic water in former Soviet Union 1 mg l⁻¹ (37).

Other comments

Occurs in effluent discharges from the leather tanning, paint and ink, organics, plastics and synthetics, pulp and paper, pesticide manufacturing and waste water treatment industries.

Occupational exposures occur principally to workers in the viscose rayon industry (38).

Effects of carbon disulfide on cardiovascular disease, neurotoxicity and hepatotoxicity reviewed (17,39,40).

Occupational exposure to ototoxic organic solvents reviewed (41).

Reviews on environmental effects, experimental toxicology, physico-chemical properties, ecotoxicology, exposure levels, workplace experience, epidemiology and human health effects listed (42).

Toxicity and hazards reviewed (43,44).

Review of health hazards associated with exposure to carbon disulfide (45).

The vapour mixed with air in the proportions of 1% to 50% is explosive and can be ignited even by hot steam pipes.

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c76 carbon monoxide

CO

CO

Mol. Wt. 28.01

CAS Registry No. 630-08-0

Synonyms carbonic oxide; carbon oxide; exhaust gas; flue gas

EINECS No. 211-128-3

RTECS No. FG 3500000

Uses Reducing agent in metallurgy processes. Intermediate in organic synthesis. Manufacture of metal carbonyls. Component of rocket propellant. Tracer gas.

Physical properties

M. Pt. -207°C **B. Pt.** -191.3°C **Specific gravity** 1.250 g l⁻¹ (gas) at 0°C and 760 mmHg **Volatility** v.den. 1.0
Solubility Water: 2.3 ml in 100 ml at 20°C

Occupational exposure

DE-MAK 30 ppm (35 mg m⁻³)

FR-VME 50 ppm (55 mg m⁻³)

JP-OEL 50 ppm (57 mg m⁻³)

SE-LEVL 35 ppm (40 mg m⁻³)

SE-STEL 100 ppm (120 mg m⁻³)

UK-LTEL 30 ppm (35 mg m⁻³)

UK-STEL 200 ppm (232 mg m⁻³)

US-TWA 25 ppm (29 mg m⁻³)

UN No. 1016 HAZCHEM Code 2SE Conveyance classification toxic gas, danger of fire (flammable gas)

Supply classification extremely flammable

Supply classification toxic

Risk phrases May cause harm to the unborn child – Extremely flammable – Toxic by inhalation – Toxic: danger of serious damage to health by prolonged exposure through inhalation (R61, R12, R23, R48/23)

Safety phrases Avoid exposure – obtain special instruction before use – In case of accident or if you feel unwell, seek medical advice immediately (show label where possible) (S53, S45)

Environmental fate

Nitrification inhibition

Nitrosomonas sp. 4W30, NH₄⁺ 300 µl l⁻¹, carbon monoxide oxidation rate 1.344 µg hr⁻¹. *Nitrosomonas cryotolerans* 320 µg inhibited nitrification activity (1).

Nitrosomonas europaea, NH₄⁺ 330 µl l⁻¹ carbon monoxide oxidation rate 0.07 µg hr⁻¹. Effects of temperature, pH, nitrogen source, cell concentration and the interactions between NH₄⁺ and carbon monoxide were examined with respect to carbon monoxide oxidation by *Nitrosomonas* 4W30, *Nitrosomonas europaea* and *Nitrosococcus oceanus* (2).

Carbonaceous inhibition

A majority of aerobic bacteria and yeast activity was inhibited by 50% in the presence of carbon monoxide, however, most carboxy bacteria, *Pseudomonas denitrificans* and *Pseudomonas stutzeri* were carbon monoxide insensitive (3).

Degradation studies

Methanogenic and acetogenic bacteria can metabolise carbon monoxide (4).

Acinetobacter JC1 growth doubling times using carbon monoxide as a substrate was 19 hr at 30°C (pH 6) (5).

Oxidation of carbon monoxide by soil is a co-metabolic process unaffected by autotrophs and heterotrophs (6).

Mammalian & avian toxicity

Acute data

LC₅₀ (4 hr) inhalation rat, guinea pig 1807, 5718 ppm, respectively (7).

LC₅₀ (30 min) inhalation rat 4600 ppm (8).

Sub-acute and sub-chronic data

Inhalation mice (15 min) 0.5% carbon monoxide caused 33% mortality; 30 min after exposure, surviving mice were fully recovered. Immediately after exposure, blood lactate levels had increased significantly, and 30 min later, glucose levels also increased. Measurement of brain energy metabolites, including phosphocreatine and ATP, 4 hr, 1 day, 4 days and 8 days after exposure showed that these did not differ from controls (9).

Teratogenicity and reproductive effects

TD_{L0} (24 hr) inhalation rat (1-22 days pregnant) 150 ppm affected foetal growth; higher concentrations affected viability and reduced weight and growth rates (10,11).

Prenatal exposure in rats to 150 ppm carbon monoxide caused a functional deficit in the central nervous system of exposed offspring, but no evidence of overt teratogenesis (12).

Sprague-Dawley rats exposed to 1400 ppm carbon monoxide for 24 hr sustained significant damage during pregnancy, but carbon monoxide was not teratogenic in any experimental group (13).

Metabolism and toxicokinetics

Metabolism of carbon monoxide by colonic flora was investigated using human faecal homogenates. During

anaerobic incubations added carbon monoxide was rapidly consumed. Aerobic incubation resulted in a slow but definite release of carbon monoxide. It is possible that carbon monoxide uptake by colonic flora protects other faecal organisms and possibly the host from carbon monoxide liberated in the gut (14).

The metabolic effect of carbon monoxide on the heart is discussed, $t_{1/2}$ for elimination from blood 1 hr (15).

Genotoxicity

♀ Mice exposed to 1500, 2500, 3500 ppm for 10 min on days 5, 11, 16 of gestation showed micronuclei in the maternal bone marrow and foetal blood and increased incidence of sister chromatid exchanges in both mother and foetus (16).

Other effects

Other adverse effects (human)

A case of foetal death from carbon monoxide poisoning resulting from accidental non-lethal carbon monoxide intoxication has been reported (17).

Of 79 patients severely poisoned with carbon monoxide, hospital mortality was 30%, and 14% of patients discharged following long-term treatment had signs of brain damage (18).

Investigations have shown hyperbaric oxygen reduces the morbidity rate for carbon monoxide poisoning to under 5%, preventing late onset of neurological sequelae (19).

TC_{Lo} (45 min) inhalation human 650 ppm central nervous system and blood effects (20).

Neurophysical effects of low-level carbon monoxide exposure was investigated in healthy men. The authors conclude that carbon monoxide is probably not neurotoxic in normal healthy men (21).

Of 207 cases of acute carbon monoxide poisoning which were observed during the acute stage and for the following three months, 27 (13%) developed delayed encephalopathy; six significant risk factors for the development of delayed encephalopathy were determined (22).

In five healthy male smokers exposed to carbon monoxide inhalation (70 or 100 ppm) for 70 mins, the velocity of dark adaption and light sensitivity were lower than in age-matched healthy non-smoking men (23).

Inhalation causes methaemoglobinemia, carboxyhaemoglobinemia, weakness and dizziness followed by coma; the most common early aftermath of severe intoxication is cerebral oedema (24).

Concentrations of 500-1000 ppm, in humans (duration unspecified), caused the development of headache, nausea, weakness, dizziness, mental confusion, hallucination and cyanosis (25).

Any other adverse effects

Results of an inhalation study in rats suggest that leukocytes are responsible for the development of biochemical changes in the brain after carbon monoxide poisoning (26).

Extracellular changes in levels of dopamine, serotonin and their metabolites were measured in rats at 15 min intervals, before and after exposure to carbon monoxide. After exposure, dopamine levels increased to 3.8 times the baseline level, but the increase was cleared from the extracellular fluid within 45 min; levels of 3,4-dihydroxyphenylacetic acid and homovanillic acid decreased by 20-25%. Changes in levels of serotonin and 5-hydroxyindoleacetic acid were small (27).

The generation of partially reduced oxygen species was studied in rats exposed to 1% carbon monoxide for 30 min, and reoxygenated on air for 0-180 min. The partially reduced oxygen species formed in the brain after severe carbon monoxide intoxication may contribute to CO-mediated neuronal damage during reoxygenation (28).

Carbon monoxide reduced calcium concentration by 29% to 369 mmol g⁻¹ tissue in vascular smooth muscle (rat thoracic aorta segments) (29).

Legislation

Included in Schedule 4 (Release into the Air: Prescribed Substances) of Statutory Instrument No. 472, 1991 (30). HMIP (UK) Approved Codes of Practice for carbon monoxide (31).

Other comments

Produced by partial oxidation of hydrocarbon gases from natural gas or by the gasification of coal and coke.

Blood carboxyhaemoglobin (COHb) levels were measured in 100 male charcoal meat grill workers, before and after work the same day. The mean COHb level for smoking workers before work was 3.8% and for non-smoking workers was 2.4%; after work these had increased to 8.1% and 6.2%, respectively. 81.1% of smokers (36 men) and 51.8% of non-smokers (29 men) exceeded the WHO and NIOSH recommended maximum COHb level of 5% (32). Carbon monoxide is not a cumulative poison in the usual sense. Carboxyhaemoglobin is fully dissociable and once acute exposure is terminated the pigment will revert to oxyhaemoglobin, with carbon monoxide excreted via the lungs (33).

NIOSH has designated carbon monoxide an ototoxin. It can impair hearing by causing hearing loss, ringing in the ears or total deafness, and its toxicity can be exacerbated by combined exposure with noise (34).

Experimental toxicology and human health effects, including neurotoxicity, cardiovascular and reproductive hazards of carbon monoxide, have been extensively reviewed (15,35-45).

The role of carbon monoxide in the toxicity of fire atmospheres reviewed (46).

The metabolic and environmental fates of carbon monoxide have been extensively reviewed (47-55).

Reproductive toxicity reviewed (56).

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C77 carbon tetrabromide



Br_4C

Mol. Wt. 331.63

CAS Registry No. 558-13-4

Synonyms carbon bromide; tetrabromomethane; tetrabromide methane

EINECS No. 209-189-6

RTECS No. FG 4725000

Uses Catalyst. Fire retardant. In photoimaging materials. Organic synthesis.

Occurrence Isolated from the red alga *Asparagopsis toxiformis* found in the ocean near Hawaii (1).

Physical properties

M. Pt. 88-90°C **B. Pt.** 190°C **Specific gravity** 2.9609 at 10°C with respect to water at 14°C

Volatility v.p. 40 mmHg at 96.3°C ; v.den. 11.4

Solubility Organic solvents: carbon disulfide, chloroform, diethyl ether, ethanol

Occupational exposure

FR-VME 0.1 ppm (1.4 mg m⁻³)

UK-LTEL 0.1 ppm (1.4 mg m⁻³)

US-TWA 0.1 ppm (1.4 mg m⁻³)

UK-STEL 0.3 ppm (4.1 mg m⁻³)

US-STEL 0.3 ppm (4.1 mg m⁻³)

Mammalian & avian toxicity

Acute data

LD_{Lo} oral rat 1800 mg kg⁻¹ (1).

LD₅₀ subcutaneous mouse 300 mg kg⁻¹ (2).

LD₅₀ intravenous mouse 56 mg kg⁻¹ (3).

Sub-acute and sub-chronic data

Inhalation rat 0.07-74 ppm 4 hr day⁻¹ for 4 months caused metabolic changes in the liver. Even the lowest concentration caused irritation to the eyes and upper respiratory tract (4).

Metabolism and toxicokinetics

Under anaerobic conditions forms complexes with ferrous cytochrome P₄₅₀. Carbon monoxide detected as a metabolic product of the interactions (5).

Other effects

Other adverse effects (human)

Acute exposures to high concentrations caused upper respiratory irritation and injury to the lungs, liver and kidneys. Chronic exposure and low levels caused liver injury. The material is a potent lachrymator (6).

Any other adverse effects

Central nervous system depressant at high concentrations (species unspecified) (7).

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c78 carbon tetrachloride



CCl₄

Mol. Wt. 153.82

CAS Registry No. 56-23-5

Synonyms tetrachloromethane; perchloromethane

EINECS No. 200-262-8

RTECS No. FG 4900000

Uses Industrial and laboratory solvent. Used in the manufacture of CFCs including trichlorofluoromethane, dichlorodifluoromethane. Manufacture of refrigerants, aerosols and propellants. Former dry cleaning agent and fire extinguisher. Veterinary anthelmintic.

Physical properties

M. Pt. -22.6°C B. Pt. 76.8°C Specific gravity 1.589 at 25°C with respect to water at 25°C

Partition coefficient log P_{ow} 2.62 at 20°C Volatility v.p. 100 mmHg at 23°C ; v.den. 5.5

Solubility Water: 1160 mg l⁻¹ at 25 °C. Organic solvents: miscible with benzene, carbon disulfide, chloroform, diethyl ether, ethanol

Occupational exposure

DE-MAK 10 ppm (64 mg m⁻³)

FR-VME 2 ppm (12 mg m⁻³)

JP-OEL 5 ppm (31 mg m⁻³)

SE-LEVL 2 ppm (13 mg m⁻³)

UK-LTEL 2 ppm (13 mg m⁻³)

US-TWA 5 ppm (31 mg m⁻³)

FR-VLE 10 ppm (60 mg m⁻³)

SE-STEEL 3 ppm (19 mg m⁻³)

US-STEEL 10 ppm (63 mg m⁻³)

UN No. 1846 HAZCHEM Code 2Z Conveyance classification toxic substance

Supply classification toxic

Supply classification dangerous for the environment

Risk phrases Toxic by inhalation, in contact with skin and if swallowed – Possible risk of irreversible effects – Toxic: danger of serious damage to health by prolonged exposure through inhalation – Dangerous for the ozone layer – Harmful to aquatic organisms, may cause long-term adverse effects in the aquatic environment (R23/24/25, R40, R48/23, R59, R52/53)

Safety phrases Keep locked up and out of the reach of children (if sold to general public) – Do not breathe vapour – Wear suitable protective clothing and gloves – In case of accident or if you feel unwell, seek medical advice immediately (show label where possible) – Refer to manufacturer/supplier for information on recovery/recycling – Avoid release to the environment. Refer to special instructions/safety data sheet (S1/2, S23, S36/37, S45, S59, S61)

Ecotoxicity

Fish toxicity

LC₅₀ (14 day) guppy 67 ppm (1).

LC₅₀ (96 hr) bluegill sunfish, inland silverside 125-150 ppm (2).

Intraperitoneal injection of a sublethal dose of undiluted CCl₄ in juvenile channel catfish caused reversible and irreversible dose-dependent cell damage (3).

Exposure of the freshwater teleost *Sarotherodon mossambicus* to 26 ppm carbon tetrachloride for up to 30 days caused a decrease in total protein content, due to reduced protein synthesis activity. This decrease was greater in liver than in muscle, and significant changes in the soluble protein fractions (albumin and globulins) and in the free amino acid content were observed (4).

Invertebrate toxicity

Cell multiplication inhibition test *Pseudomonas putida* 30 mg l⁻¹, *Entosiphon sulcatum* 770 mg l⁻¹, *Scenedesmus quadricauda* 600 mg l⁻¹ (5).

Lowest-observed-effect concentration *Microcystis aeruginosa* 105 mg l⁻¹ (6).

EC₅₀ (24 hr) *Tetrahymena pyriformis* 830 mg l⁻¹ (7).

EC₅₀ (72 hr) *Chlamydomonas reinhardtii* 0.217-0.278 mg l⁻¹ closed test system (8).

EC₅₀ (5,15 min) *Photobacterium phosphoreum* 6, 33 ppm, respectively, Microtox test (9).

Bioaccumulation

Bioconcentration factor in rainbow trout 17.4 (10).

Environmental fate

Degradation studies

Denitrifying bacteria able to transform carbon tetrachloride were cultured from aquifer sediment. High nitrite concentration inhibits growth, and nitrate and/or nitrite slows the degradation of CCl₄ (11).

Estimated aerobic *in situ* removal from groundwater t_{1/2} 14 ± 4 yr (12).

Abiotic removal

Evaporation rate 90% in 37 min for 1 mg l⁻¹ at 25°C (13).

Evaporation rate relative to *n*-butyl acetate which has been assigned a value of 1 (25°C) is 7.52 (14).

Adsorption and retention

The flux of CCl₄ from atmosphere to soil determined to be around 8600 ± 5100 pmol m⁻²-day (Brookhaven National Laboratory, Long Island, New York) (12).

Mammalian & avian toxicity

Acute data

LD₅₀ oral rat 2920 mg kg⁻¹ (15).

LD₅₀ oral mouse 8260 mg kg⁻¹ (16).

LC₅₀ (4 hr) inhalation rat 8000 ppm (17).

LD₅₀ dermal rat 5070 mg kg⁻¹ (18).

LD₅₀ intraperitoneal rat, dog 1500 mg kg⁻¹ (19,20).

The approximate lethal dose via the intratracheal route in rats is 3.1% of the oral LD₅₀, and death is peracute (21).

Sub-acute and sub-chronic data

Oral BUB mice (2 wk) 0.1 mg (40% carbon tetrachloride) 3 × wk⁻¹ caused noticeable changes in smooth and rough endoplasmic reticulum, Golgi apparatus, lysosomes or the nucleus. Ultrastructural alterations induced in liver differed from those observed under acute or chronic injury in mice and rats (22).

Carcinogenicity and chronic effects

Inadequate evidence for carcinogenicity to humans, sufficient evidence for carcinogenicity to animals, IARC classification group 2B (23).

Suspected long-term carcinogen in man, producing either liver cancer and/or lymphatic leukaemia (24-27).

Teratogenicity and reproductive effects

Embryotoxic and foetotoxic in rats at 300-1000 ppm (route and duration unspecified). Suspected teratogen in humans, although supporting evidence is equivocal. High levels may cause damage to testes or ovaries (28-31). Oral mice (from day 1, 6 or 11 of pregnancy) 1% and 10% of LD₅₀ dose for 5 days showed no effect on maternal body weight, liver or kidney weight or pregnancy. Neonatal parameters such as pup weight and length were also unaffected, and their development post-partum was normal. 0.05 and 0.5 mM had no effect on *in vitro* fertilisation, but 1, 2, 5 and 10 mM caused a linear decrease in the fertilisation rate, and an increase in abnormal ovum forms (32).

Metabolism and toxicokinetics

♂ Sprague-Dawley rats 17.5 and 179 mg kg⁻¹ by inhalation (2 hr), constant gastric infusion (2 hr) or bolus gavage (aqueous emulsion); arterial blood CCl₄ levels were much higher in the oral bolus and inhalation groups than in the gastric infusion group. High levels of CCl₄ were also found in the portal blood of the oral bolus group, due to fast and extensive absorption from the gastro-intestinal tract, and hepatotoxicity was also significantly greater in this group (33).

Genotoxicity

Micronucleus induction in mouse bone marrow and peripheral blood negative (34).

Other effects

Other adverse effects (human)

Toxic to humans, exposure routes via inhalation, ingestion or dermal absorption. Systemic effects of acute exposure include nausea, vomiting, diarrhoea, headache, and renal damage leading to anuria, azotemia and liver injury. Chronic effects primarily cause liver damage and kidney injury. Contact with skin can cause dermatitis via defatting action (35).

Two ♂ workers suffered acute poisoning after inhaling carbon tetrachloride vapours present at >15% and 78% by weight in a fire-extinguishing liquid. They were admitted to hospital with severe hepatonephrotoxicity, hepatomegaly and anuria, increased serum transaminase activity and increased levels of blood urea nitrogen, creatine, γ-glutamyltranspeptidase, bilirubin and uric acid. The workers recovered in 3-4 wks, after haemodialysis treatment; they appeared to be more susceptible than fellow workers because of their high ethanol intake (120 and 250 g day⁻¹, compared with <50 g in co-workers) (36).

Any other adverse effects

Intra-ruminal sheep 0.5 ml kg⁻¹ caused a decrease in bile flow and a greater decrease in bile acid excretion; an increase in the bile bilirubin concentration was seen after acute liver damage (37).

♂ Wistar rats given 50% carbon tetrachloride from 5 to 13 wk of age showed an increase in the ratio of lipids to liver weight, increase in liver collagen content and in serum prolyl hydroxylase concentration; the livers of exposed rats were fatty and fibrotic (38).

Rats given 8 ml kg⁻¹ carbon tetrachloride showed signs of hepatotoxicity (decreased levels of plasma conjugated bilirubin, glucose and protein); 2 g kg⁻¹ vitamin C prevented this induced liver damage (39).

Cultured neurons and astrocytes from chick embryo cerebral hemispheres are able to metabolise carbon tetrachloride. The metabolic capacity of the neurons is higher than that of the astrocytes, although the higher initial glutathione and glutathione-S-transferase activity levels in the neurons does not protect them from carbon tetrachloride-induced peroxidative damage (40).

Liver slices from ♂ Sprague-Dawley rats were exposed to 0.57 mM carbon tetrachloride for 9 hr. After 15 min, conjugated diene formation was detected, indicating lipid peroxidation, and levels of cytochrome P₄₅₀ decreased over time. Leakage of glucose-6-phosphate dehydrogenase and β-glucuronidase from centrilobular hepatocytes was seen after 9 hr; the levels of the periportal enzymes lactate dehydrogenase and sorbitol dehydrogenase were unchanged (41).

Mammalian splenocytes incubated with 3.0 mM carbon tetrachloride for 3 hr showed no effect on spleen cell function, number or viability; carbon tetrachloride immunotoxicity requires metabolic activation (42).

Rats orally administered 3.35 mmol kg⁻¹ showed a marked decrease in hepatic microsomal cytochrome P₄₅₀ content and CYP2E1 activity after 3 hr. The hepatic glutathione content was reduced to a similar extent at 3 hr and continued to decrease reaching a minimum at 24 hr. Plasma alanine aminotransferase and aspartate aminotransferase activities were significantly elevated at 3 hr, reaching a maximum at 24 hr then decreasing; levels were still abnormal at 72 hr. Hepatic cells were found to be necrotic at 3 hr post-treatment. Necrosis was at a maximum at 24 hr and some necrotic cells remained at 72 hr post-treatment (43).

Legislation

Limited under EC Directive on Drinking Water Quality 80/778/EEC. Organochlorine compounds: guide level 0.1 µg l⁻¹ (44).

Included in Schedule 6 (Release into Land: Prescribed Substances) Statutory Instrument No. 472, 1991 (45).

Maximum permissible concentration in domestic water in the former Soviet Union 0.3 mg l⁻¹ (46).

Other comments

National Toxicology Program sub-chronic toxicity study of CCl₄ in a mixture of chemical drinking water contaminants, in F344 rats and B6C3F₁ mice 0.012-0.4 ppm, systemic/organ toxicity and biochemical/cellular/tissue effects report available (47).

Toxicity and hazards reviewed (48).

The role of tissue repair as an adaptive strategy in the repair of carbon tetrachloride-induced liver damage reviewed (49).

Reported to be weakly mutagenic in bacterial systems (50).

Reviews on experimental toxicology, human health effects, ecotoxicology, physico-chemical properties, environmental effects, exposure levels, epidemiology and workplace experience are listed (51).

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c79 carbon tetrafluoride



CF₄

Mol. Wt. 88.00

CAS Registry No. 75-73-0

Synonyms tetrafluoromethane; carbon fluoride; perfluoromethane

EINECS No. 200-896-5

RTECS No. FG 4920000

Uses Used as a propellant in fluorocarbon fire-extinguishers (1).

Low-temperature refrigerant. Gaseous insulator.

Physical properties

M. Pt. -184°C B. Pt. -130°C Specific gravity -195°C (solid); -183°C (liquid)

Mammalian & avian toxicity

Acute data

LC_{Lo} (15 min) inhalation rat 895,000 ppm (2).

Other effects

Other adverse effects (human)

Narcotic in high concentrations (3).

Legislation

Included in Schedule 6 (Release into land: Prescribed Substances) Statutory Instrument No. 472, 1991 (4).

Other comments

Used in fire extinguishers which have no/low potential to destroy the earth's protective ozone layer (1).

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c80 carbonyl fluoride



CF₂O

Mol. Wt. 66.01

CAS Registry No. 353-50-4

Synonyms carbonyl difluoride oxide; difluoroformaldehyde; carbonic difluoride; carbon oxyfluoride; fluoroformyl fluoride

EINECS No. 206-534-2

RTECS No. FG 6125000

Uses Catalyst activator.

Physical properties

M. Pt. -114°C B. Pt. -83°C Specific gravity 1.139 (liquid) at -114°C , 1.388 (solid) at -190°C

Occupational exposure

DE-MAK 2.5 mg m⁻³ (as F) (inhalable dust fraction)

FR-VME 2 ppm (5 mg m⁻³)

UK-LTEL 2.5 mg m⁻³ (as F)

US-TWA 2 ppm (5.4 mg m⁻³)

US-STEL 5 ppm (13 mg m⁻³)

UN No. 2417 Conveyance classification toxic gas, corrosive

Mammalian & avian toxicity

Acute data

LC₅₀ (1 hr) inhalation rat 360 ppm (1).

Sub-acute and sub-chronic data

Greenacres-Flora rats were exposed to 50 ppm carbonyl fluoride for 1 hr day⁻¹ for 5 days. On day 1 and 5 and on days 3, 7, 18 post-exposure, urine samples were collected and examined for fluoride excretion and glucose, protein and ketones. Kidney and lung tissue were tested for succinate dehydrogenase activity. Daily urinary fluoride excretion increased to 14 × normal levels on day 1 and remained 4 × normal levels post-exposure on day 18. On day 5, body weights dropped 30%, urine, glucose, protein and ketones were abnormal, succinate dehydrogenase activity had dropped to near zero in kidney and doubled in lung. On post-exposure day 18, these levels had returned to normal. The authors conclude that carbonyl fluoride produced fluoride toxicity. If death does not result, the metabolic inhibition due to fluoride poisoning is completely reversible (1).

Other effects

Any other adverse effects

Exposure produced haemorrhage and oedema in lungs, along with residual focal emphysema and interstitial fibrosis. Fatty liver degeneration was also observed. Exposure caused irreversible lung damage (species unspecified) (1).

Other comments

Prepared from carbon monoxide and fluorine or bromine trifluoride and carbon monoxide.

Reviews on experimental toxicology and human health effects listed (2).

Hygroscopic. Contact with moisture forms hydrogen fluoride.

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c81 carbonyl sulfide

COS

COS

Mol. Wt. 60.08

CAS Registry No. 463-58-1

Synonyms carbon oxide sulfide; carbon oxysulfide; oxycarbon sulfide

EINECS No. 207-340-0

RTECS No. FG 6400000

Occurrence Volatile organic sulfur compounds, including carbonyl sulfide, are formed in marine and freshwater lake environments (1).

Physical properties

M. Pt. -138°C B. Pt. -50°C **Specific gravity** Volatility v.den. 2.1

Solubility Water: 1000 mg l⁻¹. Organic solvents: ethanol

Occupational exposure

UN No. 2204 Conveyance classification toxic gas, danger of fire (flammable gas)

Ecotoxicity

Invertebrate toxicity

Investigated as an inhibitor of active inorganic carbon transport in the cyanobacterium *Synechococcus* PCC7942 adapted to growth at low inorganic carbon levels. Carbonyl sulfide inhibited both carbon dioxide and hydrogen carbonate transport processes in a reversible (short-term) and mixed competitive manner (2).

Environmental fate

Degradation studies

High concentrations of carbonyl sulfide were found in the hypolimnion of Lake Ciso, Spain. The concentrations dropped rapidly in the metalimnion dominated by plates of purple sulfur bacteria and *C. phaseolus*, indicating a rapid microbial degradation of this compound, most likely by chemotrophic bacteria (1).

Abiotic removal

Hydrolysed in water to carbon dioxide and hydrogen sulfide (3).

Mammalian & avian toxicity

Acute data

LC₅₀ (35 min) inhalation mouse 1200 ppm (4).

LD₅₀ intraperitoneal rat 23 mg kg⁻¹ (5).

Metabolism and toxicokinetics

Converted into hydrogen sulfide and hydrogen carbonate by carbonic anhydrase (3).

Other effects

Other adverse effects (human)

Two industrial accidents, one fatal, involving the inhalation of carbonyl sulfide are described. Exposure to high concentrations (dose unspecified) was fatal and caused nervous system paralysis without local inhalation or olfactory warning. Rapid reversibility of effects of exposure to non-lethal doses indicate that carbonyl sulfide is rapidly broken down in the body (6).

Any other adverse effects

Narcotic in high concentrations. Concentrations of 0.1% v/v and higher produced death within 2 hr (species unspecified) (3).

Legislation

Included in Schedule 4 (Release into Air: Prescribed Substances) Statutory Instrument No. 472, 1991 (7).

Other comments

Reviews on experimental toxicology and human health effects listed (8).

Carbonic anhydrase is the key enzyme for carbonyl sulfide consumption in higher plants (9).

Carbonyl sulfide, a substrate for carbonic anhydrase, inhibited the carbon dioxide-concentrating process of five species of unicellular green algae at pH 7 (10).

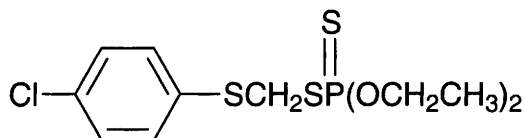
Toxic gas encountered during petroleum refining or destructive distillation of coal. May liberate highly toxic hydrogen sulfide upon decomposition. Emitted as a reduction product of sulfur gases from vegetation and soils.

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c82 carbophenothion



C₁₁H₁₆ClO₂PS₃

Mol. Wt. 342.87

CAS Registry No. 786-19-6

Synonyms S-[[[(4-chlorophenyl)thio]methyl] O,O-diethyl phosphorodithioate; phosphorodithioic acid, S-[[[(4-chlorophenyl)thio]methyl] O,O-diethyl ester; Trithion

EINECS No. 212-324-1

RTECS No. TD 5250000

Uses Insecticide. Acaricide. Also used as an animal ectoparasiticide.

Physical properties

B. Pt. 82°C at 0.01 mmHg **Specific gravity** 1.27 at 25°C with respect to water at 4°C

Volatility v.p. 8.02×10^{-6} mmHg at 25°C

Solubility Water: <40 mg l⁻¹. Organic solvents: acetone, ethanol, kerosene, methyl isobutyl ketone, vegetable oils, xylene

Occupational exposure

Supply classification toxic, dangerous for the environment

Risk phrases Toxic in contact with skin and if swallowed – Very toxic to aquatic organisms, may cause long-term adverse effects in the aquatic environment (R24/25, R50/53)

Safety phrases Keep locked up and out of the reach of children (if sold to general public) – After contact with skin, wash immediately with plenty of water – Wear suitable protective clothing and gloves – In case of accident or if you feel unwell, seek medical advice immediately (show label where possible) – This material and/or its container must be disposed of as hazardous waste – Avoid release to the environment. Refer to special instructions/safety data sheet (S1/2, S28, S36/37, S45, S60, S61)

Ecotoxicity

Fish toxicity

LC₅₀ (96 hr) bluegill 13 µg l⁻¹ acute static test (1).

LC₅₀ (96 hr) larval topmelt 19.4 µg l⁻¹ acute static test (2).

LC₅₀ (96 hr) inland silversides 35.3 µg l⁻¹ acute static test (2).

LC₅₀ (96 hr) Californian gunion 2.3 µg l⁻¹ flow-through toxicity test (3).

LC₅₀ (96 hr) sheepshead minnow 4.4 µg l⁻¹ flow-through toxicity test (3).

LC₅₀ (96 hr) Gulf toadfish 1.4 mg l⁻¹ produced 20% mortality in a static renewal test (3).

Invertebrate toxicity

LC₅₀ (96 hr) *Gammarus lacustris* 5.2 µg l⁻¹ (4).

Environmental fate

Degradation studies

50% degradation in soil occurs in 100 days or longer depending on soil type (5).

Abiotic removal

Photochemical degradation may occur (6).

Mammalian & avian toxicity

Acute data

LD₅₀ oral starling 5.6 mg kg⁻¹ (7).

LD₅₀ oral mouse 218 mg kg⁻¹ (8).

LD₅₀ oral rat 7 mg kg⁻¹ (9).

LD₅₀ dermal rat 27 mg kg⁻¹ (10).

LD₅₀ dermal rabbit 1250 mg kg⁻¹ (11).

LD₅₀ intraperitoneal rat 40 mg kg⁻¹ (12).

Teratogenicity and reproductive effects

Reported as causing malformations in chick and duck embryos (13).

Legislation

Limited under EC Directive on Drinking Water Quality 80/778/EEC. Pesticides: maximum admissible concentration 0.1 µg l⁻¹ (14).

WHO Toxicity Class Ib (15).

Other comments

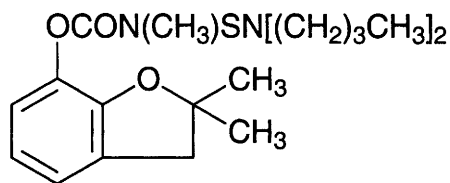
Moderately toxic to bees (8).

Hazards of organophosphorus pesticides to agricultural workers are reviewed (16).

Carbophenothion is believed to be no longer manufactured, or marketed for crop protection use (17).

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C₂₀H₃₂N₂O₃S

Mol. Wt. 380.55

CAS Registry No. 55285-14-8

Synonyms 2,3-dihydro-2,2-dimethylbenzofuranyl [(dibutylamino)thio]methylcarbamate; carbamic acid, [(dibutylamino)thio]methyl-, 2,3-dihydro-2,2-dimethyl-7-benzofuranyl ester; carbozulfan; Advantage; Gazette; Marshal; Posse; Sheriff; Zaprawa Marshal

EINECS No. 259-565-9

RTECS No. EZ 3815000

Uses Insecticide.

Physical properties

Specific gravity 1.056 at 20°C **Partition coefficient** log P_{ow} 3.3 (1) **Volatility** v.p. 3.07 × 10⁻⁴ mmHg

Solubility Water: 0.3mg l⁻¹ at 25°C. Organic solvents: miscible: acetone, chloroform, dichloromethane, hexane, methanol, xylene

Occupational exposure

Supply classification toxic, dangerous for the environment

Risk phrases Toxic by inhalation and if swallowed – May cause sensitisation by skin contact – Very toxic to aquatic organisms, may cause long-term adverse effects in the aquatic environment (R23/25, R43, R50/53)

Safety phrases Keep locked up and out of the reach of children (if sold to general public) – Avoid contact with the skin – Wear suitable gloves – In case of insufficient ventilation, wear suitable respiratory equipment – In case of accident or if you feel unwell, seek medical advice immediately (show label where possible) – This material and/or its container must be disposed of as hazardous waste – Avoid release to the environment. Refer to special instructions/safety data sheet (S1/2, S24, S37, S45, S60, S61)

Ecotoxicity

Fish toxicity

LC₅₀ (96 hr) bluegill sunfish, trout 15, 42 µg l⁻¹, respectively (1).

Invertebrate toxicity

LD₅₀ (24 hr) honey bee 0.145 µg bee⁻¹ at 32°C (2).

Single application caused significant reduction in soil microflora (3).

Environmental fate

Degradation studies

Concentrations of 680-785 µg 20 g soil⁻¹ in flooded alluvial soil declined to undetectable levels after six days at 35°C and to negligible levels after 30 days at 25°C (4).

Rapidly degraded in soil under both aerobic and anaerobic conditions, t_{1/2} 2-3 days (1).

Abiotic removal

Stable in water. No degradation observed in 24 hr (5).

Mammalian & avian toxicity

Acute data

LD₅₀ oral mallard duck 8.1 mg kg⁻¹ (1).

LD₅₀ oral pheasant 20 mg kg⁻¹ (1).

LD₅₀ oral quail 82 mg kg⁻¹ (1).
LD₅₀ oral rat 209 mg kg⁻¹ (1).
LC₅₀ inhalation (1 hr) rat, ♂ 1.53, ♀ 0.61 mg l⁻¹ air (1).

Carcinogenicity and chronic effects

Oral rats and mice (2 years) no-observable-effect level 20 mg kg⁻¹ in diet (1).

Irritancy

May cause skin irritation, localised sweating and fasciculations may occur at the site of contact. Direct contact with eye may cause pain, hyperaemia, lachrymation, twitching of the eyelids, miosis and impaired vision (species unspecified) (6).

Other effects

Other adverse effects (human)

Nausea, vomiting, anorexia, diarrhoea in humans may occur if ingested (6).

Any other adverse effects

Sub-lethal acute toxicity of carbosulfan was evaluated in Sprague-Dawley rats after intravenous and oral exposures. Maximum erythrocyte acetylcholinesterase inhibition was measured 45 min after an oral dose of 690 µg kg⁻¹. Full activity recovered after 5 hr. Erythrocyte acetylcholinesterase activity was maximally inhibited 1 min after intravenous administration 690 µg kg⁻¹. Full activity recovered after 4 hr. Systemic effects included urination, defecation, facial muscle fasciculations, salivation and tremors. Less toxic when given orally (7).

Legislation

Included in Schedule 6 (Release into Land: Prescribed Substances) of Statutory Instrument No. 472, 1991 (8).

Limited under EC Directive on Drinking Water Quality 80/778/EEC. Pesticides: maximum admissible concentration 0.1 µg l⁻¹ (9).

WHO Toxicity Class II (10).

ADI (JMPR) 0.01 mg kg⁻¹ body weight (11).

Other comments

LC₅₀ (24 hr) *Culex pipiens* larvae 120 ppm. Toxicity of carbosulfan was synergistically enhanced by its major metabolites carbofuran and 3-hydroxycarbofuran.

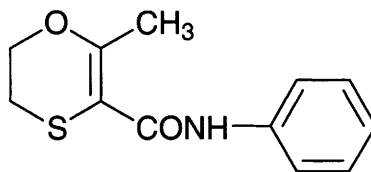
The toxicity of carbosulfan to overwintered adults (OA), adults of first generation (A1), and larvae of 1st generation (L1) in 3rd instar Colorado potato beetle was in the order: toxic to A1, slightly less to L1, and very low to OA. It was six times more toxic to A1 than to OA (12).

Metabolism, acid degradation and toxicity reviewed (13).

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C84 carboxin



C₁₂H₁₃NO₂S

Mol. Wt. 235.31

CAS Registry No. 5234-68-4

Synonyms 5-carboxanilido-2,3-dihydro-6-methyl-1,4-oxathiin; 1,4-oxathiin-3-carboxamide, 5,6-dihydro-2-methyl-N-phenyl; 1,4-oxathiin-3-carboxanilide, 5,6-dihydro-2-methyl-; Hexevax; Kemikar; Kisvax; Oxatin; Pro-Gro; Vitavax

EINECS No. 226-031-1

Uses Systemic fungicide. Wood preservative.

Physical properties

M. Pt. 91.5-92.5°C and 98-100°C depending on crystal structure **Specific gravity** 1.36 **Volatility** v.p. log P_{ow} 2.18 (25°C) (1) 187.5 × 10⁻⁶ mmHg at 25°C

Solubility Water: 170 mg l⁻¹ at 25°C. Organic solvents: acetone, benzene, dichloromethane, ethanol, methanol

Ecotoxicity

Fish toxicity

LC₅₀ (96 hr) rainbow trout 2 mg l⁻¹ (1).

LC₅₀ (96 hr) bluegill sunfish 1.2 mg l⁻¹ (1).

Invertebrate toxicity

EC₅₀ (48 hr) *Daphnia magna* 84.4 mg l⁻¹ (1).

Environmental fate

Degradation studies

46-72% degradation occurred in seven days, one degradation product, carboxin sulfoxide, is stable in anaerobic soil (2).

Rapidly metabolised: oxidation by flavin enzymes in fungi degraded 95% within seven days in aerobic soil. The major degradation product carboxin sulfoxide had a t_{1/2} in soil of 24 hr (1,3,4).

Carboxin is not readily adsorbed onto soil. Oxidised to carboxin sulfoxide and carboxin sulfone in seven days in aqueous solution (3,5).

Abiotic removal

49% of its major metabolite, carboxin sulfoxide, had photodegraded to unknown compounds within seven days (6).

In aqueous solution (pH 7) t_{1/2} for photodecomposition <3 hr (25°C), stable to hydrolysis pH 5-9 (1).

Mammalian & avian toxicity

Acute data

LC₅₀ (8 day) oral mallard duck >4640 mg kg⁻¹ diet (1).

LC₅₀ acute oral redwing blackbird 42.2 mg kg⁻¹ diet (7).

LD₅₀ oral rat 430 mg kg⁻¹ (8).

LD₅₀ dermal rat 1050 mg kg⁻¹ (8).

Sub-acute and sub-chronic data

Oral rats (90 day) 0-1000 mg kg⁻¹ in diet. No significant dose-related gross pathological changes observed (9).

Carcinogenicity and chronic effects

Oral rats (2 years) 600 mg kg⁻¹ in diet showed no ill-effects (1).

Teratogenicity and reproductive effects

In a three-generation reproduction study, rats were administered 0-30 mg kg⁻¹ day⁻¹ in diet. Evaluation of fertility, gestation, live birth and lactation indices, litter size and the physical appearance and growth of the pups was carried out. No compound-related effects on reproductive performance at any dose level were observed (9). Oral mallard duck (October to November (sexually inactive) or February to March (sexually active)) 2-5 g kg⁻¹. In the spring treated group ♂s showed reduced testosterone levels and ♀s reduced 17-β-estradiol levels. Egg production was reduced in both the autumn and spring treated groups (10).

Metabolism and toxicokinetics

Single oral dose by gavage to rabbits and rats, 10% and 40% excreted in the faeces, respectively. Principal metabolic pathway was *o*- or *p*-hydroxylation followed by glucuronidation. In rats, 32% was excreted in urine as glucuronides and 7% as unconjugated phenols. In rabbits, 85% excreted in urine as glucuronides and 3% free phenols (11).

Irritancy

Dermal rabbit (duration unspecified) 1500-3000 mg kg⁻¹ caused no obvious dermal irritation. A staining of the skin precluded readings for erythema (9).

Genotoxicity

Salmonella typhimurium TA1535, TA1537, TA1538, TA98, TA100 with and without metabolic activation negative (9).

Saccharomyces cerevisiae D4 with and without metabolic activation negative (9).

Primary rat hepatocytes 5-100 µg ml⁻¹ unscheduled DNA synthesis positive (9).

Carboxin was genotoxic *in vivo* in bone marrow cells in rats. Aberrations observed included chromatid breaks, chromatid fragments, ring chromosomes, dicentric chromosomes and chromosome fragments (12).

Other effects**Other adverse effects (human)**

A seven-year old boy developed headache and vomiting within 1 hr of ingesting wheat seed treated with carboxin (dose unspecified). He recovered in 2 hr, after treatment with Ipecac (an emetic) (9).

Any other adverse effects

Inhibits oxidative metabolism and succinate dehydrogenase activity in the mitochondria of liver and bone (species unspecified) (13).

Legislation

Limited under EC Directive on Drinking Water Quality 80/778/EEC. Fungicide: maximum admissible concentration 0.1 µg l⁻¹ (14).

WHO Toxicity Class Table 5 (15).

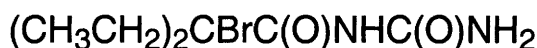
EPA Toxicity Class III (1).

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c85 carbromal



C₇H₁₃BrN₂O₂

Mol. Wt. 237.10

CAS Registry No. 77-65-6

Synonyms 2-bromo-2-ethylbutyrylurea; butanamide, *N*-(aminocarbonyl)-2-bromo-2-ethyl-; urea, 2-bromo-2-ethylbutyryl-; Karbromal

EINECS No. 201-046-6

RTECS No. YS 2975000

Uses Pharmaceuticals. Sedative. Hypnotic.

Physical properties

M. Pt. 116-119°C

Solubility Water: 0.33 g l⁻¹. Organic solvents: chloroform, diethyl ether, ethanol

Mammalian & avian toxicity

Acute data

LD₅₀ oral rat, mouse 316, 464 mg kg⁻¹, respectively (1).

LD_{Lo} oral rabbit 600 mg kg⁻¹ (2).

LD₅₀ intraperitoneal, intravenous rat 427 mg kg⁻¹ (3,4).

Carcinogenicity and chronic effects

Determined as non-carcinogenic in the Computer Automated Structure Evaluation (CASE) for predicting genotoxic and non-genotoxic carcinogens (5).

National Toxicology Program investigated carbromal via feed in ♂ and ♀ rats and mice. Results were negative in both species (6).

Metabolism and toxicokinetics

In humans rapidly absorbed following ingestion and metabolised with the formation of bromoethylbutyramide, ethyl butyrylurea and inorganic bromide. Serum concentrations of carbromal and its organic metabolites decline rapidly after single doses but serum bromide level may remain elevated for days or weeks (7).

Phase I hydroxylation involved in hepatic biotransformation of compound (8).

Irritancy

Characteristic purpuric skin reactions have been described in patients on prolonged therapeutic treatment (7).

Genotoxicity

Salmonella typhimurium TA98, TA100, TA1535, TA97/TA1537 with and without metabolic activation negative (9).

Other effects

Other adverse effects (human)

A sedative, hypnotic and central nervous system depressant. Prolonged use of carbromal preparations leads to chronic intoxication with bromide accumulation (10).

Toxic doses produce mental confusion, ataxia, loss of pupillary response, cyanosis and coma. Immediate death rarely occurs but because recovery from carbromal-induced coma is slow, fatal complications frequently supervene (7).

Continuous use of carbromal over long periods may give rise to symptoms of chronic toxicity including central nervous system depression, irritability and slurring of speech. Skin eruptions including non-thrombocytopenic purpura have been reported. Deaths have occurred after excessive dosage (11).

Reversible cataracts were observed in a man who had taken a half or one carbromal capsule every night for five years. (12).

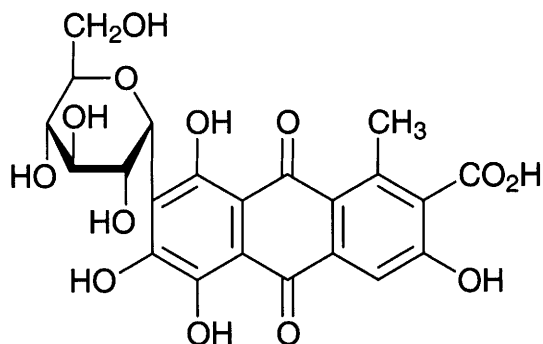
Six of seven patients who had ingested 26-60 g of carbromal and in whom routine gastric lavage had been unsuccessful survived after gastroscopic lavage had been performed (13).

Other comments

Prepared by heating urea to 50°C with α -bromo- β -ethylbutyryl bromide.

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C₂₂H₂₀O₁₃

Mol. Wt. 492.39

CAS Registry No. 1260-17-9

Synonyms 7-β-D-glucopyranosyl-9,10-dihydro-3,5,6,8-tetrahydroxy-1-methyl-9,10-dioxo-2-anthracenecarboxylic acid; 2-anthracenecarboxylic acid, 7-β-D-glucopyranosyl-9,10-dihydro-3,5,6,8-tetrahydroxy-1-methyl-9,10-dioxo; C.I. Natural Red 4; C.I. 75470

EINECS No. 215-023-3

Uses Free acid in colour photography. Pigment in paints. Bacteriological stain. Cosmetics. Reagent for aluminium. Complexing agent for cations.

Occurrence Glucosidal colouring matter from the scale insect *Coctus cacti* L.

Physical properties

M. Pt. 136°C (decomp.)

Solubility Water: soluble. Organic solvents: ethanol

Mammalian & avian toxicity

Carcinogenicity and chronic effects

♂ and ♀ B6C3F1 mice (2 yr) 0, 3, or 6% cochineal (of which carminic acid is an active principle) in diet. The incidences of tumours in treated and control groups were not significantly different (1).

Sensitisation

Caused increased responsiveness to histamine-induced asthmatic responses in humans (2).

Genotoxicity

Salmonella typhimurium with and without metabolic activation negative (3).

Salmonella reverse mutation, chromosomal aberrations, and sister chromatid exchanges *in vitro* on Chinese hamster ovary cells, and the mouse micronucleus test all negative (4). Carminic acid enhanced the antiviral activity of polyr(A-U) 9-13 fold using a human foreskin fibroblast-vesicular stomatitis virus bioassay (5).

The effect of carminic acid was studied in mice with Ehrlich ascites tumour. Administration intraperitoneally 1-2 days after tumour transplants induced cytostatic ultrastructural changes in the cytoplasm and nuclei (6).

Hepatocyte primary culture/DNA repair test suggests carminic acid is not a genotoxic carcinogen (7).

Other effects

Any other adverse effects

The antitumour effects of a mixture of 0.5% carminic acid and 1.4% lactic acid were studied in rats with Jensen's

sarcoma. A single treatment of 1 ml administered 2 wk after subcutaneous transplantation inhibited the tumour growth and led to tumour ulceration through the skin and its elimination (8).

Other comments

Found to be very toxic to *Paramecium caudatum*. The effects on leucine aminopeptidase, acid phosphatase and esterase *in vitro* were studied (9).

Experimental toxicology and human health effects reviewed (10).

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c87 carnauba wax

CAS Registry No. 8015-86-9

Synonyms Brazil wax; Carnicowax; Cire de Carnauba Poudre

EINECS No. 232-399-4

Uses Floor wax. Shoe polish. Plasticiser in dental impression compounds. Used to increase the melting point of other waxes. In pure form, used for cosmetic materials. Used in the last stage in tablet coating.

Occurrence An exudate from the pores of the leaves of the Brazilian wax palm tree, *Copernicia prunifera*.

Physical properties

M. Pt. 82-85.5°C **Flash point** 282°C **Specific gravity** 0.99

Mammalian & avian toxicity

Sub-acute and sub-chronic data

Oral rat short-term feeding studies (exact duration unspecified) 10% in diet no significant compound-related toxic effects observed (1).

Oral beagle dog (28 wk) 0.1, 0.3 and 1% in diet, no compound-related toxic effects observed (1).

Teratogenicity and reproductive effects

Oral rat 0.1, 0.3, and 1% in diet during gestation, no adverse effects observed in foetuses. Oral Wistar rats parent and F₁ generation study (13 wk) 0.1, 0.3, or 1% in diet. No adverse effects associated with the consumption of carnauba wax at levels up to 1% (1).

Irritancy

Two reports of dermatitis in humans caused by exposure to carnauba wax (1,2).

Genotoxicity

Salmonella typhimurium TA1537, TA1538 with metabolic activation equivocal positive responses (1).

Other effects

Other adverse effects (human)

Mortality pattern among 86 men was determined to investigate the hazards of polishing steel. The subjects had polished steel with polishing paste containing tallow, beeswax, carnauba wax, alendum, carborundum, ferric oxide and chalk for at least 5 yr. From the the total sample of 86 men, 18 had died between 1958-1976 compared with anticipated 13.3 deaths and 7 had developed cancer. Four men had died of stomach cancer (3,4).

Other comments

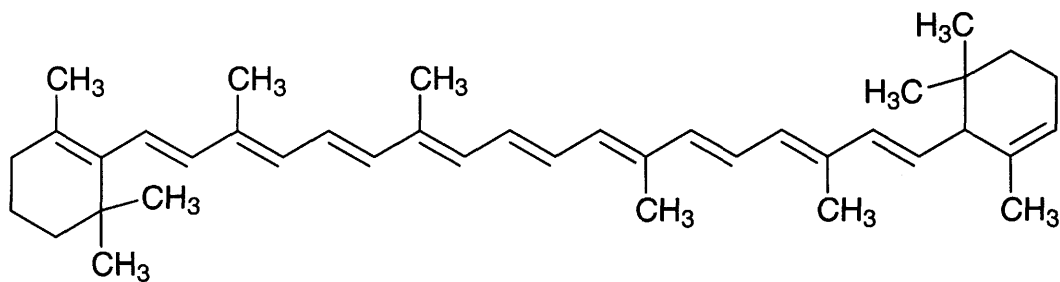
Experimental toxicology and human health effects reviewed (5).

Joint FAO/WHO Expert Committee on Food Additives allocated a TDI of 0-7 mg kg⁻¹ for carnauba wax (1).

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c88 α -carotene



C₄₀H₅₆

Mol. Wt. 536.88

CAS Registry No. 7488-99-5

Synonyms β,ϵ -carotene (6'R); α -carotene (natural)

Uses As a nutrient and dietary supplement. Vitamin A precursor.

Occurrence

Occurs in carrots, palm oil, and green leaves of various species.

Physical properties

M. Pt. 187.5°C **Specific gravity** 1.00 at 20°C with respect to water at 20°C

Solubility Organic solvents: miscible with carbon disulfide, chloroform; soluble in benzene, diethyl ether

Environmental fate

Abiotic removal

Absorbs oxygen from the air giving rise to colourless oxidation products. Oxidation in light is autocatalytic (1).

Mammalian & avian toxicity

Carcinogenicity and chronic effects

Topical application to mouse skin of carotenes derived from palm oil inhibited the 12-O-tetradecanoylphorbol-13-acetate-induced promotion of skin tumours after initiation by dimethylbenzo[*a*]anthracene. Carotenes also inhibited the proliferation of various types of malignant human cells *in vitro* (2).

Carotenoid and lipid peroxide concentrations in serum were detected in healthy adults aged 33-72 yr. A negative correlation was observed between the lipid peroxide and α - or β -carotene levels. It was concluded that serum α - and β -carotene may reduce lipid peroxidation in the body and contribute to the prevention of cancer (3).

Inhibits the proliferation of the human neuroblastoma cell line GOTO in a concentration- and time-dependent manner (4).

Other effects

Other adverse effects (human)

Five infants (8-11 months) with carotenaemia secondary to excessive consumption of carotene-containing foods were studied. Infants had white sclerae in spite of yellow skin discoloration. Elimination of foods led to normalisation of skin and carotene levels. All infants had normal vitamin A levels, white cell count, serum glucose, lipids, liver and thyroid function tests. The benign nature of the condition is emphasised (5).

Other comments

Occurs in breast secretion, colostrum distinctive yellow colour is due to the presence of carotenoids (6).

Has \approx 30-50% of the biological activity of β -carotene (1).

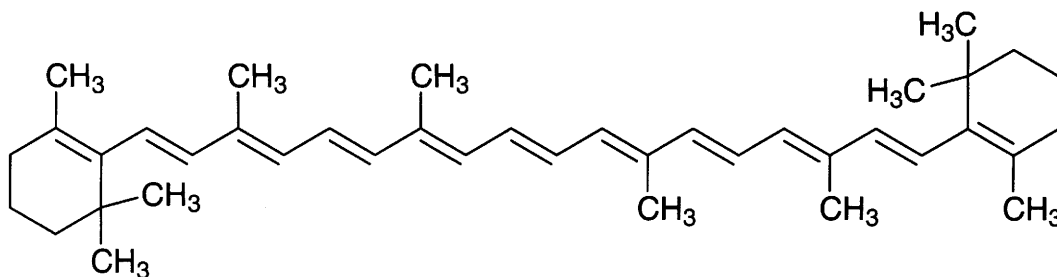
Serum concentration of α -carotene is significantly greater in σ^7 than φ (7).

Found in phytobenthos species (8).

Toxicology and human health effects reviewed (9).

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C₄₀H₅₆

Mol. Wt. 536.88

CAS Registry No. 7235-40-7

Synonyms β , β -carotene; Lucarotin 10% Feed; Solatene; Betatab

EINECS No. 230-636-6

RTECS No. FI 0329500

Uses Yellow colouring agent for foods. Vitamin A precursor.

Occurrence Widely distributed in plants, almost always occurs together with chlorophyll.

Physical properties

M. Pt. 178-179°C Specific gravity 1.00 at 20°C with respect to water at 20°C

Solubility Organic solvents: acetone, benzene, diethyl ether

Mammalian & avian toxicity

Carcinogenicity and chronic effects

β -Carotene reduced both the development of the tumour and urinary polyamine and erythrocyte polyamine levels (1).

Antioxidant β -carotene targeted localised tumour sites in the hamster cheek pouch tumour. Tumour cells took up liposomes containing β -carotene and were lysed, while normal cells did not (2).

Dietary β -carotene is inversely correlated with the incidence of prostate cancer in hospital patients. The smaller the dietary intake, the higher the risk of prostate cancer with a highly significant linear trend (3).

Histological changes attributed to β -carotene added *in vitro* to colorectal adenomas and adenocarcinomas were studied. The results showed significant increases in most cells and were associated with non-significant increases in plasma cells and lymphocytes (4).

It is suggested that β -carotene reduces the risk of some cancers. An *in vitro* study showed β -carotene administered for a period of 24 hr caused morphological differentiation without changing the level of melanin, and reduced basal and melanocyte-stimulated hormone, sodium fluoride and forskolin stimulated adenylate cyclase system activity. The adenylate cyclase system appears to be common site for antitumour-promoting vitamin activity (5). A 50% reduction in colon tumours (greater decrease in adenocarcinomas than adenomas) in ♀ Swiss Webster (ICR) mice was induced by 1,2-dimethylhydrazine when fed 2 or 22 mg kg⁻¹ β -carotene (6).

Metabolism and toxicokinetics

Carotene is metabolised in humans to vitamin A. Absorption depends on bile and fat in the gut. Chronic diarrhoea, steatorrhea or ingestion of mineral oil decrease absorption. Water-soluble dispersing agents enhance absorption (7).

Genotoxicity

Salmonella typhimurium TA92, TA94, TA98, TA100, TA1535, TA1537 with and without metabolic activation negative (8).

Other effects

Other adverse effects (human)

Five infants 8-11 months with carotenaemia, secondary to excessive consumption of carotene-containing foods, were studied. Infants had white sclerae in spite of yellow skin discoloration. Elimination of foods led to normalisation of skin and carotene levels. All infants had normal vitamin A levels, white cell counts, serum glucose, lipids, liver and thyroid function tests. The benign nature of the condition is emphasised (9).

Other comments

Mice (Skh:HR1 and CR:ORL Sencar) receiving a diet supplemented with 3% β -carotene had fewer tumours than mice in control groups, but this was only statistically significant in the Skh strain. β -Carotene showed a protective effect against 8-MOP phototoxicity in *in vitro* studies using BALBc 3T3 mouse fibroblasts (10).

β -Carotene has been shown to prevent death or ameliorate toxicity from acetaminophen in mice (11).

Experiments with mice suggest that β -carotene provides significant protection against the genotoxicity of cyclophosphamide (12,13).

Rats fed a diet supplemented with natural β -carotene (1 g kg⁻¹ diet) for 1 wk and then exposed to 0.5 MPa oxygen showed a significant increase in the latent period preceding oxygen seizures compared with rats fed a normal diet (38.5 ± 3.4 vs 16.8 ± 1.8 min, respectively) (14).

An exceptionally low mortality (2% after 69 wk) was found in hamsters receiving intratracheal intubation of benzo[a]pyrene and fed on a diet high in β -carotene (1% w/w) compared with animals receiving the same toxic treatment but fed on a normal diet (25% mortality after 69 wk). The exact cause of death of most of the hamsters could not be established but a 40% reduction of lipid peroxidation in the livers was found in the high β -carotene group (15).

β -Carotene and its antioxidant, genotoxic, teratogenic activities in mammalian bodies reviewed (16,17).

β -Carotene as a protective nutrient against cancer reviewed (6,18-23).

Effective absorption of carotenes requires dietary fat (23).

β -Carotene administration prevented genetic damage by mutagens in bacterial and cell culture assays. Large doses are not embryotoxic in rodents (24-30).

Potential harm of high intake on selected populations, biochemical antioxidant/prooxidant mechanisms at the cellular level, potential benefits of other carotenoids and antioxidants, and future directions for research reviewed (31).

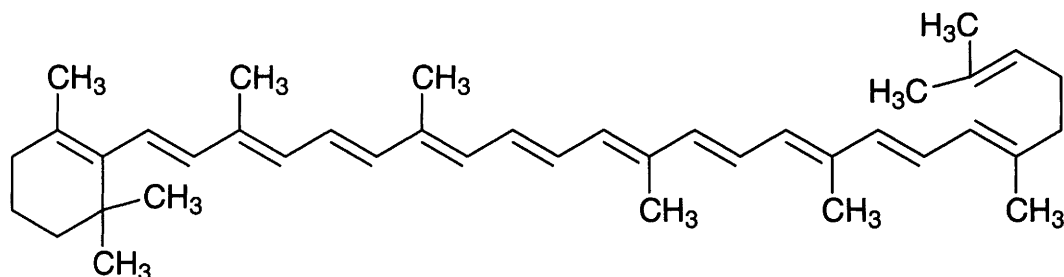
Experimental toxicology and human health effects reviewed (32).

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C90 γ -carotene



C₄₀H₅₆

Mol. Wt. 536.88

CAS Registry No. 472-93-5

Synonyms $\beta\psi$ -carotene

Uses A nutrient and dietary supplement. Vitamin A precursor.

Occurrence Occurs in *Penicillium sclerotiorum*. Has provitamin A activity. Occurs in small quantities in fruits and plant materials which contain β -carotene.

Physical properties

M. Pt. 152-153°C

Solubility Organic solvents: benzene, chloroform

Other comments

Experimental toxicology and human health effects reviewed (1).

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Synonyms Clarifloc; Ultrafloc; Stamere; Gelcarin; Gelloid; Gelodan; Lactarin; Sea Kem; Viscarin

EINECS No. 232-524-2

RTECS No. FI 0700000

Uses Gelling, emulsifying, stabilising agent. Demulcent. Food and feed additive. Used in cosmetics and pharmaceuticals.

Occurrence

Structural polysaccharide of the red seaweeds (Rhodophyceae); consists mainly of the calcium, potassium, magnesium and sodium sulfate esters of galactose and 3,6-anhydrogalactose copolymers.

Physical properties

Solubility Water: 33 ml l⁻¹ at 80°C

Mammalian & avian toxicity

Acute data

Oral gavage rat 0.5-10 mg (single doses) suppressed spleen and lymph node response (1-3).

LD_{Lo} intravenous rabbit 5 mg kg⁻¹ (4).

LD_{Lo} intravenous guinea pig 20 mg kg⁻¹ (5).

Sub-acute and sub-chronic data

The toxicity of native carrageenan was investigated in rats for 13-39 wk, administered in diet at 5% w/w. Except for minor changes, no evidence of any direct effect of carrageenan on the liver or gastro-intestinal tract (6).

κ-Carrageenan was nephrotoxic, shown by a progressive marked increase in serum creatinine and urea levels and in urinary *N*-acetyl-β-D-glucosaminidase activity. It was also hepatotoxic, evidenced by elevated serum aspartate aminotransferase activity 2-7 days after administration and by decreased circulating albumin concentration. λ- and ι-carrageenan had no clear effect on these urinary or serum enzyme activities (7).

Several studies in which carrageenan was administered to animals (guinea pigs, rabbits, rats, mice, pigs, rhesus monkeys) in drinking water (0.5%-2% for up to 14 wk) or in the diet (2%-5% for 12 wk) showed no ill-effects (8).

Carcinogenicity and chronic effects

No adequate data for carcinogenicity to humans, insufficient evidence of carcinogenicity to animals, IARC classification for native carrageenan group 3 (9).

Oral monkey (5 yr) 500 mg kg⁻¹ 6 day wk⁻¹ by gavage followed by unspecified amounts in diet for 2.5 yr, no gross microscopic or biochemical abnormalities reported (10).

Groups of 30 ♂ and 30 ♀ MRC outbred rats, 7 wk old, were given 0.5%, 2.5%, 5% native carrageenan in the diet for life. A group of 100 ♂ and 100 ♀ served as controls. Survival of the treated animals was not different to that of controls. No significant increase in tumour incidence was seen (11).

Oral rat (2 yr) 5%-25% carrageenan in diet, gut reported microscopically normal (12).

Teratogenicity and reproductive effects

In a three-generation reproduction study, groups of 40 ♂ and 40 ♀ Osborne-Mendel rats of each generation were fed diets containing 0.5%, 1.0%, 2.5% or 5.0% calcium, κ and λ degraded carrageenan for 12 wk before mating and thereafter. No effect was detected with respect to fertility, average litter size, average number of animals born live, survival of offspring. Developmental effects were studied in approximately 170 pregnant animals from each of the F₂ and F₃ generations. No external, skeletal or soft-tissue anomaly was correlated with treatment (13).

Pregnant rats (6-15 days) administered 40-600 mg kg⁻¹ day⁻¹ calcium and sodium salts by gavage, foetal development was studied and an increased number of early deaths recorded (14).

Metabolism and toxicokinetics

In guinea pigs and monkeys there are no adequate data demonstrating that native carrageenan is absorbed into tissue after oral administration (15).

Irritancy

Injection of 100 or 300 µg of carrageenan into the mouse paw or pleural cavity produced a delayed inflammatory reaction in 48 hr (16).

1% Carrageenan in water administered to rabbit eye caused irritant effects (17).

Carrageenan injected subcutaneously in the dorsum of the neck in albino rats produced inflammatory swellings which peaked after 16 hr (18).

Sensitisation

Initial dose 0.1-1.0 mg administered subcutaneously to mouse, strong allergic response exhibited when animal was challenged 10 days later with 2.5-40 µg (19).

Guinea pig given initial subcutaneous injection 1 mg showed a sensitisation reaction when challenged at 3, 5, and 8 wk with 50 mg of native or λ-carrageenan (20).

Genotoxicity

Salmonella typhimurium with and without metabolic activation negative (21).

Saccharomyces cerevisiae with and without metabolic activation negative (4).

Exposure of human embryonic cells *in vitro* to high concentrations of carrageenan salts induced chromosome damage. Oral rat (5 day) 5 g kg⁻¹ calcium carrageenan dominant lethal effect negative. Oral mouse *in vivo* (24 hr) 5 g kg⁻¹ chromosomal damage negative (22).

Other effects

Other adverse effects (human)

A patient with urticaria reported faintness and swelling of the lips and face after eating ice cream containing carrageenan (23).

Any other adverse effects

Single injection intraperitoneal rat 125 mg kg⁻¹ of ι, κ, λ-carrageenan decreased number of blood platelets and caused persistent anaemia and reticulocytosis (24).

In rodents 0.75% transbronchial injection of carrageenan in saline induced pneumonia and emphysema (25).

Oral rat (20 days) 2.5 g kg⁻¹ day⁻¹ administered ι, κ, κ-carrageenan in diet, reported increased bacterial activity indicative of an adverse effect on the gut wall (6).

Other comments

The three main copolymers in the food-grade material are ι-, κ- and λ-carrageenan. A commercial product 'degraded carrageenan' has been produced from extracts of *Eucheuma spinosum* seaweed. This product is thought to be no longer produced commercially. Degraded carrageenan was used as an antipeptic agent in Europe. Carrageenan varies in structure and composition, depending on its source, and has been studied in both native and degraded forms (26).

Experimental toxicology, metabolic fate and human health effects, including the immunotoxicity and carcinogenicity of native carrageenan have been extensively reviewed (27-33).

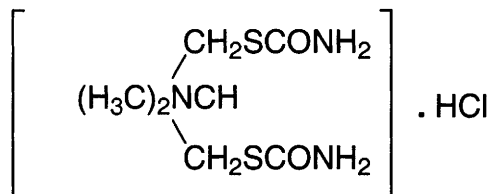
Native carrageenan as a contact allergen and sensitiser is discussed (23,34).

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c92 cartap hydrochloride



$\text{C}_7\text{H}_{16}\text{ClN}_3\text{O}_2\text{S}_2$

Mol. Wt. 273.81

CAS Registry No. 15263-52-2

Synonyms carbamothioic acid, S,S'-[2-(dimethylamino)-1,3-propanediyl] ester, monohydrochloride; 1,3-bis(carbamoylthio)-2-(N,N-dimethylamino)propane hydrochloride; Padan

EINECS No. 239-309-2

RTECS No. FD 1225000

Uses Insecticide.

Physical properties

M. Pt. 179-81°C (decomp.) **Volatility** v.p. negligible

Solubility Water: ~200 g l⁻¹ at 25°C. Organic solvents: very slightly soluble in ethanol and methanol

Occupational exposure

Supply classification harmful

Risk phrases Harmful in contact with skin and if swallowed (R21/22)

Safety phrases Keep out of reach of children (if sold to general public) – Wear suitable protective clothing and gloves (S2, S36/37)

Ecotoxicity

Fish toxicity

LC₅₀ (24, 48 hr) carp 1.6, 1.3 mg l⁻¹, respectively (1).

Invertebrate toxicity

EC₅₀ (48 hr) *Daphnia pulex* >40 mg l⁻¹ (2).

Moderately toxic to honey bees (1).

Environmental fate

Degradation studies

Estimated t_{1/2} in soil 3 days (1).

Abiotic removal

Stable under acidic conditions, hydrolysed under neutral or alkaline conditions (1).

Mammalian & avian toxicity

Acute data

LD₅₀ oral mouse, rat 165 and 250 mg kg⁻¹, respectively (3).

LD₅₀ dermal mouse >1000 mg kg⁻¹ (1).

LD₅₀ intravenous mouse 59 mg kg⁻¹ (4).

Sub-acute and sub-chronic data

Oral rat (3 month) 25 and 50 mg kg⁻¹ day⁻¹ in feed, no significant changes observed in urine, blood and tissues (1).

Carcinogenicity and chronic effects

Oral rat (2 yr) 10, 20, 40 mg kg⁻¹ day⁻¹ in feed, no pathological alterations observed in low dose and only a reduction in body weight gain in high dose animals (1).

Teratogenicity and reproductive effects

Ingestion of doses up to 100 mg kg⁻¹ during organogenesis caused minor skeletal changes, ascribed to maternal toxicity (species unspecified) (5).

Metabolism and toxicokinetics

In rats, the carbonyl carbon is hydrolysed and sulfur oxidised, with *N*-demethylation of methyl derivatives. No accumulation occurs in tissues. Excreted via urine (1).

Irritancy

Prolonged or repeated exposure of the skin may lead to insignificant dermatitis. Exposure to the eye over long periods may cause mild conjunctivitis (5).

Other effects

Any other adverse effects

Chronic inhalation (species unspecified) may cause respiratory problems (5).

Legislation

Included in Schedule 6 (Release into Land: Prescribed Substances) Statutory Instrument No. 472, 1991 (6).

Limited under EC Directive on Drinking Water Quality 80/778/EEC. Pesticides: maximum admissible concentration 0.1 µg l⁻¹ (7).

WHO Toxicity Class II (8).

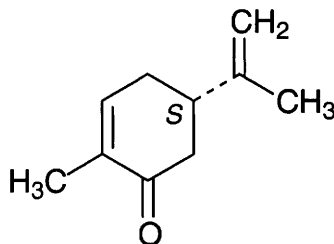
EPA Toxicity Class II (1).

Tolerable daily intake 0.1 mg kg⁻¹ body weight (1).

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C93 D-carvone



C₁₀H₁₄O

Mol. Wt. 150.22

CAS Registry No. 2244-16-8

Synonyms (S)-(+)-*p*-mentha-6,8,-dien-2-one; 2-cyclohexen-1-one, 2-methyl-5-(1-methylethenyl)-, (S)-; (+)-carvone; (S)-(+)-carvone; (S)-carvone; D-(+)-carvone

EINECS No. 218-827-2

RTECS No. OS 8670000

Uses As oil of caraway. Flavouring liqueurs. Perfumery and soaps. Therapeutic carminative .

Occurrence Caraway seed and dill seed oils. Exists as two isomers, D-carvone (CAS Reg No. 2244-16-8), found in caraway seed and dill seed oils, and L-carvone (CAS Reg No. 6485-40-1) found in spearmint and kuromoji oils.

Physical properties

B. Pt. 230-231°C **Flash point** 93°C **Specific gravity** 0.9645

Solubility Organic solvents: miscible in ethanol, soluble in chloroform, diethyl ether

Mammalian & avian toxicity

Acute data

LD₅₀ oral rat 3.7 mg kg⁻¹ (1).

Carcinogenicity and chronic effects

National Toxicology Program tested D-carvone in mice via gavage. No evidence of carcinogenic activity in ♂ or ♀ mice (no chemically-related increase in malignant or benign neoplasms) (2).

Irritancy

At 2% in petrolatum, no irritation after 48-hr closed-patch test on human subjects (1).

Genotoxicity

Salmonella typhimurium TA97, TA98, TA1535 and TA1537 with and without metabolic activation negative (3).

Legislation

Limited under EC Directive on Drinking Water Quality 80/778/EEC. Substances extractable in chloroform: guide level 0.1 mg l⁻¹ dry residue (4).

Other comments

Toxicity, irritation, sensitisation, metabolism, carcinogenicity and dermal absorption reviewed (1).

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c94 castor oil

CAS Registry No. 8001-79-4

Synonyms Cosmetol; Neoloid

EINECS No. 232-293-8

RTECS No. FI 4100000

Uses Raw material for many basic industrial chemicals including synthetic resins and fibres. Lubricants. Hydraulic fluids. Used therapeutically as a laxative and externally as an emollient.

Occurrence Fixed oil obtained by cold-pressing the seeds of *Ricinus communis* (Euphorbiacea).

Physical properties

M. Pt. -12°C **B. Pt.** 313°C **Flash point** 229.3°C (closed cup) **Specific gravity** 0.961-0.963 at 15.5°C with respect to water at 15.5°C

Solubility Organic solvents: miscible with chloroform, diethyl ether, glacial acetic acid; soluble in acetone, dimethyl sulfoxide, ethanol

Mammalian & avian toxicity

Carcinogenicity and chronic effects

National Toxicology Program post peer review technical report in progress. Toxicity study of rats, mice administration via feed (1).

Irritancy

Non-irritating to skin of humans and mildly irritating to rabbit skin (2).

When applied to the conjunctiva, castor oil delays irritation due to foreign bodies in the eye and has been used for making solutions of alkaloid bases for ophthalmic purposes (3).

Sensitisation

The seeds of *Ricinus communis* contain ricin, a toxic protein which can provoke allergic reactions (3).

Genotoxicity

Salmonella typhimurium TA97, TA98, TA100, TA1535, TA1537 with and without metabolic activation negative (4).

Other effects

Other adverse effects (human)

Castor oil in large doses can produce vomiting, nausea, colic and severe purgation. Castor oil may inhibit the absorption of fat-soluble vitamins (3).

Produces pelvic congestion and may induce abortions (5).

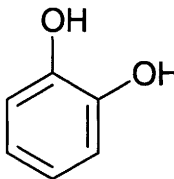
Other comments

Experimental toxicology and human health effects reviewed (2).

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C95 catechol



$C_6H_6O_2$

Mol. Wt. 110.11

CAS Registry No. 120-80-9

Synonyms pyrocatechol; *o*-benzenediol; *o*-hydroquinone; *o*-hydroxyphenol; 2-hydroxyphenol; 1,2-benzenediol

EINECS No. 204-427-5

RTECS No. UX 1050000

Uses Manufacture of polymerisation inhibitors and antioxidants. Photographic developing agent. Manufacture of pesticides and dyestuffs.

Occurrence Detected in onions, crude beet sugar, crude wood tar and coal.

Physical properties

M. Pt. 105°C **B. Pt.** 246°C **Flash point** 127°C (closed cup) **Specific gravity** 1.37 at 15°C with respect to water at 4°C **Partition coefficient** $\log P_{ow}$ 0.88-1.01 **Volatility** v.p. 10 mmHg at 118°C ; v.den. 3.8

Solubility Water: 451 g l⁻¹ at 20°C. Organic solvents: diethyl ether, ethanol

Occupational exposure

FR-VME 5 ppm (20 mg m⁻³)

SE-LEVL 5 ppm (20 mg m⁻³)

UK-LTEL 5 ppm (23 mg m⁻³)

US-TWA 5 ppm (23 mg m⁻³)

SE-STEL 10 ppm (40 mg m⁻³)

UN No. 2662 HAZCHEM Code 2Z **Conveyance classification** toxic substance

Supply classification harmful

Risk phrases Harmful in contact with skin and if swallowed – Irritating to eyes and skin (R21/22, R36/38)

Safety phrases Keep out of reach of children (if sold to general public) – Do not breathe dust – In case of contact with eyes, rinse immediately with plenty of water and seek medical advice – Wear suitable gloves (S2, S22, S26, S37)

Ecotoxicity

Fish toxicity

LC₅₀ (48 hr) goldfish 14 mg l⁻¹ (1).

LC₅₀ (96 hr) fathead minnow, rainbow trout 3-9 mg l⁻¹ (2).

Invertebrate toxicity

EC₅₀ (30 min) *Photobacterium phosphoreum* 29.6 mg l⁻¹ Microtox test (3).

Saccharomyces cerevisiae yeast test IC₅₀ 174 mg l⁻¹ (4).

In two yeast strains of *R. rubra* the proposed metabolic sequence for aromatic degradation is for phenol to be hydroxylated to form catechol prior to ring cleavage; catechol may then be further oxidised to *cis,cis*-muconic acid, muconolactone, β -keto-adipate enol-lactone and β -keto-adipic acid (5).

Bioaccumulation

Estimated bioconcentration factor of three based on a measured soil adsorption coefficient of 7.6 which suggests concentration in aquatic organisms is unlikely (6).

Environmental fate

Degradation studies

Adapted activated sludge (at 20°C) 96% COD, 55.5 mg COD g⁻¹ dry inoculum hr⁻¹ (1).

Aerobic degradation products include the pyruvate, succinate and acetaldehyde derivatives (1).

Six species of free-living nitrogen-fixing bacteria, *Azomonas agilis*, *Azospirillum brasilense*, *Azospirillum lipoferum*, *Azotobacter chroococcum*, *Azotobacter vinelandii*, and *Beijerinckia mobilis* are able to grow and to express nitrogenase activity using catechol as sole carbon source (7).

Abiotic removal

Autoxidation in aqueous environment t_{1/2} 447 hr at 25°C and pH 7 (1).

Non-ionised catechol will not be subject to significant direct photolysis since it does not significantly absorb light above 290 nm in methanol (8).

Estimated atmospheric t_{1/2} 14 hr (9).

Reaction of catechol with nitrate radicals at night may be a significant removal process (10).

Neutral pH and dissolved oxygen are critical factors for the stability of catechol. Oxidation reactions with molecular oxygen (also in the form of phosphate, nitrate, or nitrite) are catalysed by trace metal oxides as electron acceptors (11).

Adsorption and retention

Estimated soil adsorption coefficient of 72 suggests catechol will be highly mobile in soil (12).

Mammalian & avian toxicity

Acute data

LD₅₀ oral rat 260 mg kg⁻¹ (13).

LD₅₀ oral mouse 260 mg kg⁻¹ (4).

LD₅₀ intraperitoneal mouse 175 mg kg⁻¹ (14).

LD₅₀ percutaneous rabbit 800 mg kg⁻¹ (15).

Carcinogenicity and chronic effects

Inadequate evidence for carcinogenicity to humans, limited evidence for carcinogenicity to animals, IARC classification group 3 (16).

Oral σ , \varnothing rat (104 wk), σ , \varnothing mice (96 wk) 0.8% catechol induced glandular stomach adenocarcinomas in 54% and

43% of ♂ and ♀ rats, respectively, but not in mice. Under the same conditions, further work showed that catechol exerts carcinogenic activity in rat and mouse glandular stomach epithelium (17,18).

Oral ♂ Wistar, WKY, Lewis and SD strains of rats (104 wk) 0.8% catechol. Induction of glandular stomach adenocarcinomas occurred in 67, 73 and 77% of Wistar, Lewis and SD animals, respectively, but in only 10% of WKY rats. Forestomach papillomas were induced in 20% ($P < 0.05$), and squamous cell carcinomas in 3% of SD rats (19).

Oral ♂ F344 rats (2 yr) 0.8% catechol in diet. Retardation of body weight and elevated relative liver weights were observed (20).

Metabolism and toxicokinetics

Sulfate and glucuronide conjugation products detected in urine of chickens and dogs (21).

Metabolised to *o*-benzoquinone by human leucocytes (22).

Rapidly absorbed from gastro-intestinal tract and through skin. The conjugated fraction hydrolyses in urine forming free compound which is oxidised to a dark substance (23).

Sensitisation

Allergen and can cause dermatitis in man (21).

Genotoxicity

In vitro V79 Chinese hamster cells induced sister chromatid exchange. Mutations to 6-thioguanine resistance induced (24).

Oral mouse 200 mg kg⁻¹, *Escherichia coli* K-12 DNA repair host-mediated assay negative (25).

Intraperitoneal ♂ mice 40 mg kg⁻¹ induced micronuclei in bone marrow cells more readily than following oral administration (26).

Other effects

Other adverse effects (human)

Systemic effects from inhalation in man include sore throat, cough and dyspnoea (27).

At <1 mg l⁻¹ catechol acts as a redox catalyst on the myeloperoxidase-Cl⁻-hydrogen peroxide antimicrobial/cytotoxic system of the human neutrophil. Higher concentrations did not induce haemolysis.

Methaemoglobin formation was stimulated in a concentration-dependent fashion (28).

Exposure of human T lymphoblasts *in vitro* to 50 µM catechol decreased IL-2-dependent DNA synthesis and cell proliferation by >90% with no effects on cell viability. There is evidence that catechol may inhibit ribonucleotide reductase (29).

Any other adverse effects

♂ Rats administered 10-90 mg kg⁻¹ by gastric intubation induced ≥19-fold increase in ornithine decarboxylase activity with a maximum after 8 hr and ≥8-fold increase in replicative DNA synthesis with a maximum after 24 hr in the pyloric mucosa of the stomach. At 37-90 mg kg⁻¹ DNA single strand scission in the pyloric mucosa after 2 and 6 hr or unscheduled DNA synthesis after 2 and 12 hr did not occur (30).

Depression of central nervous system, hypertension, and methaemoglobinaemia have been reported (24,31).

Other comments

Combined treatment with ethanol and NaCl has a protective effect against catechol-induced forestomach and glandular stomach carcinogenesis in rats (32).

Human health effects, experimental toxicology, environmental effects, workplace experience and physico-chemical properties reviewed (33,34).

The underlying mechanisms of mutagenic, carcinogenic and chemopreventative effects of phenols and catechols reviewed (35).

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c96 celluloid

CAS Registry No. 8050-88-2

Uses Plastic material for manufacture of toilet articles, toys and photographic films. Substitute for amber, ivory, ebonite, tortoiseshell. In surgery for bandages. Dentistry as a substitute for rubber.

Physical properties

Specific gravity 1.35-1.60

Solubility Organic solvents: acetone

Occupational exposure

UN No. 2000

UN No. 2002 (scrap) **Conveyance classification** flammable solid **Conveyance classification** spontaneously combustible substance (scrap)

Other effects

Other adverse effects (human)

Autopsy of a painter employed in an aeroplane factory who died following exposure to a varnish made of cellulose or celluloid dissolved in carbon tetrachloride with amyl alcohol and benzene revealed liver and kidney alterations (1).

Peritoneal instillation of celluloid produced intense fibroblastic reaction in dogs (2).

Other comments

Prepared from nitrocellulose and camphor.

Prone to spontaneous decomposition which is retarded or prevented by the addition of urea, zinc oxide or magnesium carbonate.

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c97 cellulose

$(C_6H_{10}O_5)_n$

CAS Registry No. 9004-34-6

Synonyms β -amylose; Avicel

EINECS No. 232-674-9

RTECS No. FJ 5691460

Uses In fibrous form, the basic material for the textile and paper industries. Nitrated form, used for manufacture of explosives, celluloid, collodion, lacquers. In chromatography and ion exchange materials. In the food industry as stabiliser, thickener and texturiser.

Occurrence Chief constituent of fibre of plants. Cotton is the purest natural form.

Physical properties

Specific gravity 1.27-1.60

Occupational exposure

FR-VME 10 mg m⁻³

SE-LEVL 0.5 mg m⁻³

UK-LTEL 10 mg m⁻³ (total inhalable dust); 4 mg m⁻³ (respirable dust)
inhalable dust)

UK-STEL 20 mg m⁻³ (total

US-TWA 10 mg m⁻³

Environmental fate

Carbonaceous inhibition

Acetobacter xylinum synthesised cellulose at a high rate *in vitro* (1).

Degradation studies

Cellulomonas sp. ATCC 21399 utilises cellulose as a substrate (2).

Clostridium DC25 and mixed anaerobic bacterial cultures fermented cellulose producing different fermentation products including ethanol, acetate, formate, hydrogen, carbon dioxide, water and propionate (3).

Rates of decomposition of cellulose in meadow soil were 18% to 19%, 17% to 22% and 4.8%, respectively, in areas of strong, intermediate and low air-pollution. Intermediate and low pollution increased the concentration of mobile phosphorus five-fold and slightly decreased potassium. Hydrolytic acidity decreased and pH rose from pH 4.7 to pH 5.7 (4).

Biodegradation of cellulose by the microbial community occurred under aerobic conditions in aquifer solid samples by the conversion of substrate into carbon dioxide and incorporation into cell biomass (5).

Cellulose decomposition is not affected in soil treated with imazapyr or glyphosate. It is reduced by the direct application of imazapyr or glufosinate ammonium to the substrate and is slightly inhibited by paraquat applied either directly to the substrate or to the soil (6,7).

Aerobic decomposition of cellulosic material buried in soil is optimised when moisture is maintained at 100% field capacity and the temperature is within the range suited to mesophilic microorganisms. Addition of nutrients and an increase in the surface area of a sample both increase the rate of decomposition. The most readily degraded cellulosic samples contain less lignin and more cellulose (8).

Mammalian & avian toxicity

Sub-acute and sub-chronic data

Oral rat (6 months) via feed 330 mg kg⁻¹ powdered cellulose, no adverse effects (9).

Carcinogenicity and chronic effects

The gut microflora enzyme β -glucuronidase decreased in activity in rats fed cellulose. Cellulose decreased the incidence of colonic neoplasia development which may be due to decreased bacterial enzyme activation of carcinogens and co-carcinogens (10).

The effect of feeding cellulose on chemically induced colon cancer was investigated in rats. Rats fed cellulose had greater faecal bulk and lower β -glucuronidase activity and moderately reduced tumorigenicity was observed (11). The potential significance of certain colonic mutagens and secondary bile acids in the pathogenesis of colon cancer, the effect of types of supplemental fibre on faecal mutagens and bile acids were studied in human volunteers. Seventy-two healthy individuals consuming high fat, moderately low fibre diets were screened for faecal mutagenic activity using *Salmonella typhimurium* TA98, TA100, with and without metabolic activation. Results showed significantly lower faecal mutagenic activity during cellulose supplementation periods (12,13).

Other effects

Any other adverse effects

Hamsters were intratracheally instilled with respirable cotton dust particles for 6 wk at a dose equivalent to the maximum daily deposition in a high-dose aerosol study. Cellulose endotoxin and saline-instilled groups were positive and negative controls, respectively. Cellulose treated animals had decreased distensibility with normal surface forces, normal s-v ratio and significant numbers of granulomata. Respirable cellulose, although reported to have little effect on airways, may not be inert in the lung parenchyma (14).

Lipid and cholesterol metabolism were compared in experiments on rats given 3 to 15% dietary fibre for 30 to 200 days. Dietary fibre sources did not significantly affect blood serum cholesterol. All the fibre sources studied decreased total liver lipids. Cellulose decreased liver cholesterol only at the 3% level (15).

A single 15 mg intratracheal injection in rats caused fibrosing granulomatous alveobronchiolitis and an increase of IgA production in the bronchoalveolar lavage (16).

Rats administered cellulose intratracheally showed interstitial oedema as well as the initial signs of inflammation of the lung after the first day. Inflammation was still noted after 1 wk, partly interstitial and partly intra-alveolar. In the bronchoalveolar lavage fluid, protein, lactate dehydrogenase and acid phosphatase activities, phospholipid

and cell count were enhanced after days 1 and 3. After 1 month, the developing bronchioalveolitis was fibrous in character. However, cellulose did not damage rat peritoneal macrophages *in vitro* (17).

Other comments

Cellulose as a food additive is reported to be non-toxic in rats and mice (18).

Physiological effects of cellulose in the human large intestine reviewed (19).

Physico-chemical properties, human health effects, metabolism and absorption, teratogenic, mutagenic and carcinogenic effects reviewed (20).

Degradation of cellulose by rumen anaerobic microorganisms and enzymes reviewed (21).

Biodegradation of cellulose by cellulases reviewed (22).

Biodegradation of cellulose by actinomycetes reviewed (23).

Reviews on experimental toxicology and human health effects listed (24).

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c98 cellulose nitrate

(C₆H₇N₃O₁₁)_n

CAS Registry No. 9004-70-0

Synonyms cellulose tetranitrate; nitrocellulose; gun-cotton; nitrocotton; Waloran N; AS; Hercules AS; RS Nitrocellulose

RTECS No. GW 0970000

Uses Used in the preparation of collodions which are applied to the skin for the protection of small cuts and abrasions. Manufacture of celluloid, lacquers. In plastics.

Physical properties

Flash point 12.9°C **Specific gravity** 1.66

Solubility Organic solvents: acetone, diethyl ether, ethanol

Occupational exposure

UN No. 2059 **HAZCHEM Code** 2ME **Conveyance classification** flammable liquid

Supply classification explosive

Risk phrases Explosive when dry – Extreme risk of explosion by shock, friction, fire or other sources of ignition (R1, R3)

Safety phrases Keep out of reach of children (if sold to general public) – This material and its container must be disposed of in a safe way (S2, S35)

Environmental fate

Degradation studies

Resistant to environmental degradation (1).

Due to the fibrous nature of nitrocellulose, it blankets benthic habitats, limiting available oxygen (1).

Mammalian & avian toxicity

Acute data

LD₅₀ unreported route rat $\approx 5000 \text{ mg kg}^{-1}$ (1).

Metabolism and toxicokinetics

No absorption from the gastro-intestinal tract observed in rats (duration and concentration unspecified) (1).

Sensitisation

Reported to be allergenic in humans (2).

Other effects

Other adverse effects (human)

Occupational exposure during production suggests an association between nitrocellulose and rectal and digestive tract cancer (1).

Exposure over 7-8 months to nitrocellulose in a factory resulted in a worker developing atrophy of enamel and dentine in incisor teeth (3).

Any other adverse effects

Chronic toxicity studies in mice found the only physical effect was fibre impaction in the digestive tract (1).

Exposure in experimental animals resulted in diminished weight gain, increased respiratory rate and increased numbers of erythrocytes and leucocytes (4).

Legislation

Included in the UK List of Classified and Authorised Explosives 1994. UK Class and Division 3.2. Competent Authority Reference GB 32083 (5).

Other comments

Industrial air pollutant. Data on fish, macro-invertebrates and algae indicate nitrocellulose has limited toxicity (1).

Effects of water pollution from munitions factories on mammalian toxicology and aquatic organisms reviewed (6).

Reviews on experimental toxicology and human health effects listed (7).

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c99 cement, Portland

CAS Registry No. 65997-15-1

Synonyms Portland cement silicate; Italcementi; Lion; Parrot

EINECS No. 266-043-4

RTECS No. VV 8770000

Uses Civil engineering construction.

Occupational exposure

DE-MAK 5 mg m⁻³ (inhalable fraction or aerosol)

SE-LEVL 10 mg m⁻³ (total dust); 5 mg m⁻³ (respirable dust)

UK-LTEL 10 mg m⁻³ (total inhalable dust); 4 mg m⁻³ (respirable dust)

US-TWA 10 mg m⁻³ (total inhalable particulate matter containing no asbestos and <1% crystalline silica)

Mammalian & avian toxicity

Irritancy

Reported to cause nose bleeds and irritation to upper respiratory tract in man (1).

Other effects

Other adverse effects (human)

A study of respiratory symptoms and ventilatory function in Portland cement workers was conducted on 2736 workers, average exposure time was 10.9 yr. Cement workers had a significantly increased prevalence of dyspnoea. Prevalence of chronic phlegm was positively correlated with length of exposure (2).

The respiratory symptoms and function of 591 Portland cement workers from four production plants were studied using questionnaires and lung function tests. Chronic respiratory symptoms such as coughing and wheezing were more prevalent in the workers than in non-exposed controls. The workers exposed to cement dust also had lower cross-sectional lung function, with reduced ventilatory capacity. The mean airborne dust concentration in the work environment was 3.58 mg m⁻³ (3).

Legislation

Included in Schedule 4 (Release into Air: Prescribed Substances) Statutory Instrument No. 472, 1991 (4).

Other comments

Composed of compounds of lime, alumina, silica and iron oxide. Contains small amounts of magnesium, sodium, potassium, chromium and sulfur. Crystalline silica content < 1%.

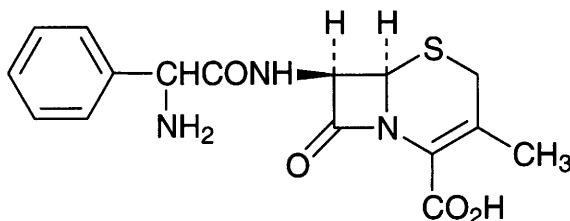
Reviews on experimental toxicology and human health effects listed (5).

Cement dust is a common air contaminant.

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C100 cephalixin



C₁₆H₁₇N₃O₄S

Mol. Wt. 347.39

CAS Registry No. 15686-71-2

Synonyms 7-(D- α -aminophenylacetamido)desacetoxycephalosporanic acid; 5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylic acid, 7-[(aminophenylacetyl)amino]-3-methyl-8-oxo-[6 α ,7 β R]; Keflex

EINECS No. 239-773-6

RTECS No. XI 0350000

Uses Cephalosporin antibiotic. Antibacterial agent.

Mammalian & avian toxicity

Acute data

LD₅₀ oral mouse 1495 mg kg⁻¹ (1).

LD₅₀ intraperitoneal mouse, rat 400 and 4000 mg kg⁻¹, respectively (2,3).

LD₅₀ subcutaneous rat 6100 mg kg⁻¹ (3).

LD₅₀ subcutaneous mouse 1150 mg kg⁻¹ (4).

Teratogenicity and reproductive effects

Treatment with cephalixin appears to pose no significant risk to the foetus although the possibility of sensitising the foetus during the 2nd or 3rd trimesters arises (5).

Metabolism and toxicokinetics

Almost completely absorbed from the gastro-intestinal tract in humans; peak plasma concentrations were reached 1 hr after administration. Cephalixin taken with food may result in delayed absorption, without altering total amounts absorbed. \approx 15% dose is bound to plasma proteins, $t_{1/2}$ of 30 min to 2 hr reported. 80% of a dose is excreted unchanged in the urine within 6 hr (6).

Average peak serum levels of 18 μ g ml⁻¹ are reached in humans approximately 1 hr after oral administration of 500 mg. Peak serum levels are usually well in excess of the minimum inhibitory concentration for susceptible organisms (7).

Cephalixin passes from the serum into maternal milk. In humans after a 500 mg oral dose of cephalixin, peak levels of 4 μ g ml⁻¹ of milk were found. These concentrations would be therapeutic against mastitis in nursing mothers (8).

Irritancy

Allergic reactions such as skin rashes, urticaria, eosinophilia, angioedema and anaphylaxis may occur and raised liver enzyme activities have been noted (6).

Other effects

Other adverse effects (human)

Supra-infection with resistant microorganisms particularly *Candida* may follow treatment (6).

Of 12,917 patients treated with cephalaxin in controlled clinical trials, 771 (6%) reported adverse effects leading to the withdrawal of the drug in 156 (1.2%). There was a probable or definite relationship to cephalaxin therapy in 385 patients and an uncertain relationship in 386. Adverse effects involving the gastro-intestinal system were reported by 379 patients and included nausea, vomiting, diarrhoea, gastro-intestinal upset or pain, anorexia, glossitis or stomatitis, oral candidiasis and pruritus. Hypersensitivity reactions including skin reactions, angioedema, or positive direct Coombs' test occurred in 36 patients. Only 21 of 462 patients with known penicillin sensitivity developed sensitivity to cephalaxin. Other adverse effects reported included headache, dizziness and genito-urinary effects (9).

A woman with uraemia treated with cephalaxin developed convulsions and toxic psychosis attributed to raised serum levels of cephalaxin ($120 \mu\text{g ml}^{-1}$). This patient returned to normal 11 days after cessation of treatment (10).

Other comments

Reports of nephrotoxicity associated with cephalaxin (8).

Pharmacokinetics of cephalaxin in pregnant women reported (11).

Absorption and fate of cephalaxin reviewed (12).

The significant *in vitro* characteristics of cephalaxin based on data published since 1967, including cephalaxin activity against recent clinical isolates, have been reviewed (13).

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C101 cerium

Ce

Ce

Mol. Wt. 140.12

CAS Registry No. 7440-45-1

EINECS No. 231-154-9

RTECS No. FK 4850000

Uses Catalyst in manufacture of ammonia. Manufacture of ferro-cerium for gas lighters. Strong reducing agent. Isotope ^{144}Ce as tracer in atomic warfare.

Occurrence Estimated abundance in the earth's crust: 20-46 ppm. Found in the minerals monazite, bastnaesite, and cerite; occurs as four natural isotopes ^{140}Ce , ^{142}Ce , ^{138}Ce and ^{136}Ce .

Physical properties

M. Pt. 795-798°C B. Pt. 3257°C Specific gravity 6.9 (cubic), 6.75 (hexagonal)

Occupational exposure

UN No. 3078 HAZCHEM Code 4M Conveyance classification substance which in contact with water emits flammable gas

Ecotoxicity

Fish toxicity

High tissue burdens of the metal are found in the gastro-intestinal tract and gill tissue, while the lowest concentrations are usually found in muscle tissue of fresh water and marine fish (1).

Toxicological study of the effect of radioactive isotopes in fresh water on animals and plants. Time and levels of accumulation and pathological changes are determined for yearling carp, *Daphnia* spp., higher aquatic plants and protoalgal algae *Scenedesmus* spp. exposed to long-lived emitter of cerium chlorides (2).

Bioaccumulation

Bioconcentration factor (cerium salts) for freshwater fish 500 and for marine fish 100 (1).

Environmental fate

Adsorption and retention

Cerium has a strong tendency to adsorb to particulate matter (1).

Mammalian & avian toxicity

Carcinogenicity and chronic effects

Long-term study in dogs showed that cerium caused pulmonary fibrosis, radiation pneumonitis, congestive heart failure and pulmonary haemangiosarcoma (concentration unspecified) (3).

Five rats exposed to high doses of ¹⁴⁴cerium hydroxide aerosols died between 263 and 607 days post exposure. Animals exhibited squamous cell carcinomas of lungs, and two animals had metastases in other organs (4).

Metabolism and toxicokinetics

Two groups of rats were experimentally exposed by inhalation to heat-treated ¹⁴⁴cerium hydroxide aerosols. Following initial rapid clearance ¹⁴⁴Ce had an effective t_{1/2} dose of 130 days in lung. Other target organs were skeleton, liver, tracheobronchial lymph nodes, and kidney (4).

¹⁴¹Ce (salt) was administered to suckling rats (6 days and 6-wk-old) orally or intraperitoneally for 2-12 days. The ileum was the main site of intestinal retention, although within each age group distribution of retention in the gut was element specific (5).

Other effects

Other adverse effects (human)

A case of rare earth pneumoconiosis in a 34-yr-old man was primarily due to cerium. Pulmonary function was unimpaired (6).

Inhalation may affect the central nervous system. Reported to produce polycythemia but cannot be used in treatment of anaemia because of its toxicity. Analysis of human hearts from patients who died from endomyocardial fibrosis showed a significantly greater concentration of cerium than in control hearts (7).

Lung retention of particles containing cerium in 459 subjects with and without previous occupational exposure to mineral dusts was evaluated. Particles containing cerium were found in <10% of subjects. The proportion of subjects with particles containing cerium in their biological samples did not differ between controls and subjects with previous occupational exposure to fibrous or non-fibrous mineral dusts (8).

Ce, La, and Nd concentrations in a subject exposed to carbon-arc lamp emissions in printing shops were higher than the average concentrations measured in 41 other workers who had died of cancer at various sites. The lung

content of other prismatic and compact particles did not show any statistically significant differences between the case and the control group (9).

Any other adverse effects

Cerium poisoning reported to cause fatty liver (species unspecified) (10).

Cerium was evaluated in an *in vitro* cytotoxicity assay system with adult ♂ Sprague-Dawley rat pulmonary alveolar macrophages, using the soluble chloride and insoluble oxide. The authors conclude cerium fumes should be considered cytotoxic to lung tissue and therefore potentially fibrogenic (11).

Legislation

Included in Schedule 4 (Release into Air: Prescribed Substances) Statutory Instrument No. 472, 1991 (12).

Other comments

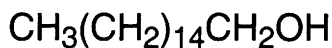
The toxicity of cerium is dependent on the ability of the organism to absorb it. Therefore, toxicity data refer to bioavailable forms, such as the ion in solution or particulate matter. The acute toxicity of cerium concentrate is presented (13).

Baseline concentrations together with biological variations of 29 trace elements, including cerium, have been investigated in the brown alga *Sargassum filipendula* collected from the western coast of Sri Lanka. Chemical abundance of the rare earth elements decreased approximately linearly with increasing atomic numbers (14). Specific pulmonary disorders resulting from exposure to metals discussed. Cerium may cause pneumoconiosis with sarcoid-like epithelioid granuloma (15).

Pharmacology, toxicology and clinical application of the stable and radioactive rare earths reviewed (16,17).

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C₁₆H₃₄O

Mol. Wt. 242.45

CAS Registry No. 36653-82-4

Synonyms 1-hexadecanol; ethal; ethol; palmityl alcohol; Hyfatol 16-98; Lanette 16; Nacol 16-98

EINECS No. 253-149-0

RTECS No. MM 0225000

Uses Emollient for cosmetics. Emulsion modifier. Coupling agent. Emulsifying and stiffening agent for pharmaceuticals. As surface film to reservoirs to reduce evaporation.

Physical properties

M. Pt. 49°C **B. Pt.** 344°C **Flash point** >110°C **Specific gravity** 0.8176 at 50°C with respect to water at 4°C

Volatility v.p. 1 mmHg at 123°C ; v.den. 8.36

Solubility. Organic solvents: chloroform, diethyl ether, ethanol. Miscible when melted with animal and vegetable oils, melted wool fat and liquid paraffin

Ecotoxicity

Fish toxicity

[¹⁴C]Cetyl alcohol was force fed to carp. Radioactivity was distributed mainly in the lipids of muscle, hepatopancreas, gill, intestine and skin, incorporated in phosphatidylcholine and triacylglycerols (1). Threespine stickleback, rainbow trout (24 hr) 10 mg l⁻¹ no loss of equilibrium or death (2).

Environmental fate

Anaerobic effects

Anaerobic growth occurred with sulfate-reducing bacteria Hxd3 (3).

Degradation studies

Anaerobic digestion after 4 wk at 35°C gave >90% degradation. After primary biodegradation by scission into alkyl and poly(ethylene glycol) moieties, further biodegradation of the latter appears to advance under aerobic conditions via oxidative or hydrolytic depolymerisation steps. Ultimate biodegradation leads to the formation of the gaseous end-products methane and carbon dioxide (4).

Using 55 g laboratory marine muddy sediment inoculated with active surface sediment sample from indoor mudflat model gave a daily anaerobic degradation rate of 0.12 mg g⁻¹ sediment (5).

Bench scale activated sludge after 6 hr, 0.3% of ThOD; 12 hr, 0.4% of ThOD; 24 hr, toxic (6).

After 10-20 days degradation rate ≈0.2 mg g⁻¹ day⁻¹ in muddy sediments with added nutrients. In sandy sediments biodegradation was not significant. Adsorption onto silt particles was an important factor in the process (7).

In a laboratory marine muddy sediment a daily degradation rate of 0.17 mg g⁻¹ sediment was observed. The specific surface of the sediment influenced the degradation rate (5).

Mammalian & avian toxicity

Acute data

LD₅₀ oral mouse, rat 3200, 6400 mg kg⁻¹, respectively (8).

Inhalation rat (6 hr) 2.22 mg l⁻¹ all died within two days; 0.41 mg l⁻¹ all survived (9).

LD₅₀ intraperitoneal mouse, rat 1600 mg kg⁻¹ (8).

Metabolism and toxicokinetics

Synthesised from palmitate via acyl-CoA and simultaneously oxidised back to free fatty acid in a fatty alcohol cycle in intact cultured human fibroblasts. Cells incubated in fatty acid-free medium with cetyl alcohol rapidly

oxidised it to palmitate; <2% of the cetyl alcohol was incorporated into the ether linkage of phosphatidylethanolamine and no incorporation into wax esters was detected (10).

Irritancy

Dermal guinea pig (duration unspecified) 100% caused well defined erythema and slight oedema (8).

Dermal human (3 day, intermittent) 75 mg caused well defined erythema and slight oedema (11).

Dermal rabbit (24 hr) 2600 mg kg⁻¹ caused well defined erythema and slight oedema and 82 mg instilled into eye caused mild irritation (12).

Sensitisation

Can cause hypersensitivity (13).

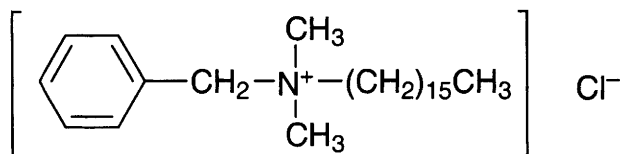
Other comments

Toxicity, safety and physical properties reviewed (14,15).

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C103 cetyldimethylbenzylammonium chloride



C₂₅H₄₆ClN

Mol. Wt. 396.10

CAS Registry No. 122-18-9

Synonyms cetalkonium chloride; benzylhexadecyldimethylammonium chloride; N-hexadecyl-N,N-dimethylbenzenemethanaminium chloride; Cetol; Sumquat 6050

EINECS No. 204-526-3

RTECS No. BO 6822450

Uses Cationic quaternary ammonium surfactant. Germicide. Fungicide. Leather processing. Textile dyeing. General antibacterial agent. Mildew preventive in silicone-based water repellent.

Physical properties

M. Pt. 59°C **Specific gravity** 0.988 at 20°C

Solubility Water: freely soluble. Organic solvents: acetone, carbon tetrachloride, diethyl ether, ethanol, glycerol, propylene glycol, sorbitol solution

Ecotoxicity

Invertebrate toxicity

LC₅₀ *Daphnia magna* 0.18 mg l⁻¹ (1).

EC₅₀ (30 min) *Photobacterium phosphoreum* 0.2 mg l⁻¹ Microtox test (1).

Toxicity to other species

LD_{Lo} parenteral frog 15 mg kg⁻¹ (2).

Environmental fate

Degradation studies

At a surfactant concentration of 2.5 mg l⁻¹ >80% biogradation occurred in 8-14 days. At 10 mg l⁻¹ surfactant <20% biogradation occurred after 19 days. [Determinations were conducted using the 'Ready Biodegradability: Modified OECD Screening Test' and the 'Inherent Biodegradability: Modified Zahn-Wellens Test'] (1).

Mammalian & avian toxicity

Acute data

LD₅₀ oral mouse 175 mg kg⁻¹ (3).

LD₅₀ oral guinea pig 200 mg kg⁻¹ (4).

Irritancy

Human skin 150 µg for three days caused mild irritation (5).

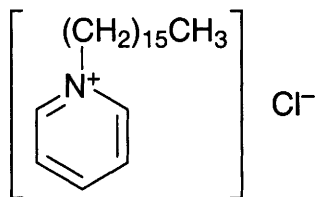
Legislation

Limited under EC Directive on Drinking Water Quality 80/778/EEC. Pesticides and related products: maximum admissible concentration 0.1 µg l⁻¹ (6).

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C104 cetylpyridinium chloride



$\text{C}_{21}\text{H}_{38}\text{ClN}$

Mol. Wt. 339.99

CAS Registry No. 123-03-5

Synonyms pyridinium, 1-hexadecyl-, chloride; hexadecylpyridinium chloride; Acetoquat CPC; Merocets; CPC

EINECS No. 204-593-9

RTECS No. UU 4900000

Uses Pharmaceutical. Preservative. Cationic surfactant. Topical anti-infective. Biocide in personal hygiene products. Charge-control additive in some reprographic toners.

Physical properties

M. Pt. 77-83°C

Solubility Water: freely soluble, pH (1% solution) 6.0-7.0. Organic solvents: chloroform, ethanol

Environmental fate

Anaerobic effects

A 7-day study of the inhibitory effects of 7.8-125 $\mu\text{g ml}^{-1}$ cetylpyridinium chloride at 37°C, showed *Leptotrichia buccallis* and Gram-positive anaerobic bacteria to be the most sensitive (1).

Mammalian & avian toxicity

Acute data

LD₅₀ oral mouse, rat 108, 200 mg kg⁻¹, respectively (2,3).

LD₅₀ oral rabbit 400 mg kg⁻¹ (4).

Inhalation rats (4 hr) 0.05, 0.07, 0.13 and 0.29 mg cetylpyridinium chloride l⁻¹ (aerosol), animals were observed for toxicity and ocular effects for 14 days after exposure. Clinical signs of toxicity included weight loss, nasal discharge, chromodacryorrhoea, respiratory difficulty and eye irritation. All clinical manifestations were reversible. Acute inflammation of the cornea, iris and/or aqueous humour were found in high-dose animals. LC₅₀ (4 hr) inhalation rat 0.09 mg l⁻¹ (5).

LD₅₀ intravenous rat 30 mg kg⁻¹ (6).

LD₅₀ intraperitoneal rat, mouse 6, 10 mg kg⁻¹, respectively (7,8).

LD₅₀ subcutaneous rat 250 mg kg⁻¹ (8).

LD_{Lo} dermal rabbit 2000 mg kg⁻¹ (9).

Teratogenicity and reproductive effects

♀ Oral rat (3 month) 7 or 35 mg kg⁻¹ day⁻¹ (diet) prior to mating and throughout pregnancy for three generations, fertility and incidence of malformations within normal limits (10).

Irritancy

Dermal rabbit (24 hr) 500 mg caused moderate irritation (11).

Dermal human (24 hr) cover patch test 0.2% and 1% concentrations caused irritation (12).

0.5-1.0 mg instilled into rabbit eye caused severe irritation and corneal damage (13).

Sensitisation

Inconclusive evidence of sensitisation (14).

Other effects

Any other adverse effects

Reported limb paralysis in experimental animals, convulsions and central nervous system depression at high doses (14).

Other comments

Use of a mouthwash containing cetylpyridinium chloride 0.05% reduced plaque accumulation in 100 subjects tested (15).

Chemistry, actions, uses and abuses of quaternary ammonium antiseptics reviewed (16,17).

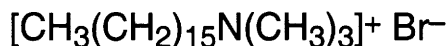
Experimental toxicology and human health effects reviewed (14,18).

The sensitivity of wild-type and mutant strains of *Escherichia coli* to cetylpyridinium chloride showed that the compound was most active against the mutant strains and least active against the wild type strains. The presence of a chelating agent considerably enhanced cetylpyridinium chloride activity (19).

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c105 cetyltrimethylammonium bromide



C₁₉H₄₂BrN

Mol. Wt. 364.45

CAS Registry No. 57-09-0

Synonyms hexadecyltrimethylammonium bromide; trimethylhexadecylammonium bromide; *N,N,N*-trimethyl-1-hexadecanaminium bromide; Quatrax CTAC; Querton 16CI-29; Varisoft 250; Arquad 16-29; Chemquat 16/50; Radiaquat 6444; Mackernium CTC-30; Surfac CAT176

EINECS No. 200-311-3

RTECS No. BQ 7875000

Uses Cationic surfactant and antiseptic.

Physical properties

M. Pt. 237-243°C

Solubility Water: 100 g l⁻¹. Organic solvents: acetone, ethanol

Ecotoxicity

Invertebrate toxicity

EC₅₀ (5 min) *Photobacterium phosphoreum* 9.81 ppm Microtox test (1).

LC₁₀ (3 day) *Poterochromonas malhamensis* 4.38 mg l⁻¹ (2).

Escherichia coli K-12 cells, damaged cells at the exponential phase more than those at the stationary phase (3).

EC₅₀ (96 hr) *Selenastrum capricornutum*, *Microcystis aeruginosa* 0.09, 0.03 mg l⁻¹, respectively (4).

Selenastrum capricornutum 2.5, 5 or 10 ppm, no living cells were observed in the cultures (5).

Environmental fate

Degradation studies

15 mg l⁻¹ in sewage was completely degraded after four days (6).

Rapidly and fully degraded at concentrations below 15 mg l⁻¹, biodegradation impaired at 20 mg l⁻¹ (7).

t_{1/2} in seawater 4 to 9 days (8).

BOD day⁻¹ 3.5 × 10⁻¹⁰ g l⁻¹ O₂ from an initial concentration of 1 mg l⁻¹ (9).

Mammalian & avian toxicity

Acute data

LD₅₀ oral rat 410 mg kg⁻¹ (10).

LD₅₀ intravenous rat 44 mg kg⁻¹ (11).

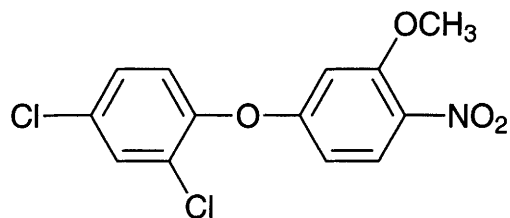
LD₅₀ intraperitoneal mouse, rabbit 106, 125 mg kg⁻¹, respectively (12,13).

LD₅₀ subcutaneous guinea pig, rabbit 100, 125 mg kg⁻¹, respectively (13,14).

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C106 chlomethoxyfen



C₁₃H₉Cl₂NO₄

Mol. Wt. 314.12

CAS Registry No. 32861-85-1

Synonyms 2,4-dichloro-1-(3-methoxy-4-nitrophenoxy)benzene; 5-(2,4-dichlorophenoxy)-2-nitroanisole; 2,4-dichlorophenyl 3-methoxy-4-nitrophenyl ether; 4-(2,4-dichlorophenoxy)-2-methoxy-1-nitrobenzene; Diphenex; Condore; Difenex; Ekkosugoni; Ikkokuso

EINECS No. 251-266-1

RTECS No. KN 8300000

Uses Herbicide.

Physical properties

M. Pt. 113-14°C **B. Pt.** 260°C at 25 mmHg **Specific gravity** 1.37 **Partition coefficient** log K_{ow} 3.34 at 20°C

Volatility v.p. 1.40×10^{-5} mmHg

Solubility Water: 0.3 mg l⁻¹ at 15°C. Organic solvents: acetone, benzene, dimethyl sulfoxide

Ecotoxicity

Fish toxicity

LC₅₀ (48 hr) mirror carp 237 mg l⁻¹ (1).

More than half of the herbicide residues in carp, tilapia, roach, and black silver carp were excreted within five days in clean water; a slight amount of residue remained after 30 days. Grass carp and eel showed almost negligible or non-detectable residues within three days in clean water (2).

Bioaccumulation

Bioconcentration factors (3-5 day exposures) have been determined for a number of freshwater creatures.

Bioconcentration factors are followed in parentheses by the concentration of pesticide in water, in µg l⁻¹, at which the experiments were conducted: tilapia 106 [30], loach 155 [30], grass carp 95 [5.0] and 30 [2.5], eel 1736 [5.0] and 4708 [2.5], black silver carp 391 [17.8] and 1109 [2.0], freshwater clam 58 [30.0], macrobranch shrimp 13 [20.0] and 13 [2.0] (2).

Mammalian & avian toxicity

Acute data

LD₅₀ oral rat >10,000 mg kg⁻¹ (1).

LD₅₀ oral mouse >33,000 mg kg⁻¹ (1).

LD₅₀ dermal rat >5000 mg kg⁻¹ (1).

Genotoxicity

Salmonella typhimurium YG1026 without metabolic activation positive, with metabolic activation negative (3).

Salmonella typhimurium YG1021 with and without metabolic activation positive (3).

Salmonella typhimurium TA98 and TA100 with and without metabolic activation negative (3).

Chlomethoxyfen induced significant sister chromatid exchanges in Chinese hamster cell line V9, but the dose-dependence was poor (4).

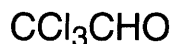
Legislation

Included in Schedule 6 (Release into Land: Prescribed Substances) Statutory Instrument No. 472, 1991 (5).
Limited under EC Directive on Drinking Water Quality 80/778/EEC. Pesticides: maximum admissible concentration $0.1 \mu\text{g l}^{-1}$ (6).
WHO Toxicity Class Table 5 (7).
EPA Toxicity Class (formulation) IV (1).

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c107 chloral



$\text{C}_2\text{HCl}_3\text{O}$

Mol. Wt. 147.39

CAS Registry No. 75-87-6

Synonyms trichloroacetaldehyde; anhydrous chloral; trichloroethanal

EINECS No. 200-911-5

RTECS No. FM 7870000

Uses Organic synthesis. Manufacture of chloral hydrate and DDT.

Physical properties

M. Pt. -57.5°C **B. Pt.** 97.8°C **Flash point** 75°C **Specific gravity** 1.510 at 20°C with respect to water at 4°C

Volatility v.p. 35 mmHg at 20°C ; v.den. 5.1

Solubility Water: miscible. Organic solvents: chloroform, diethyl ether, ethanol

Occupational exposure

UN No. 2075 HAZCHEM Code 2X Conveyance classification toxic substance

Ecotoxicity

Invertebrate toxicity

Toxicity threshold (cell multiplication inhibition test) *Pseudomonas putida* 1.6 mg l^{-1} , *Scenedesmus quadricauda* 2.8 mg l^{-1} , *Entosiphon sulcatum* 79 mg l^{-1} (1).

Environmental fate

Abiotic removal

Polymerises on exposure to light, forming the solid white trimer metachloral (2).

Photooxidation yields hydrogen chloride, carbon dioxide, carbon monoxide and carbonyl chloride. Photooxidation is a chain reaction catalysed by chlorine (3).

Reaction with photochemically produced hydroxyl radicals in the atmosphere $t_{1/2}$ 10.8 hr (4).

Mammalian & avian toxicity

Acute data

LD₅₀ oral mammal (species unspecified) 710 mg kg⁻¹ (5).

LD₅₀ intraperitoneal mouse 600 mg kg⁻¹ (6).

Genotoxicity

Salmonella typhimurium TA100 with metabolic activation weakly positive (7).

Saccharomyces cerevisiae D7, XV185-14C with metabolic activation reverse mutation positive (8).

Legislation

This substance may be habit forming and is listed in the US Code of Federal Regulations, Title 21 Part 329.1, 1987 (2).

WHO guideline value for drinking water 10 mg l⁻¹ (provisional) (9).

Other comments

Disinfection by-product. In chlorinated wood pulp and drinking water (9,10).

Intermediate in photolytic degradation of chloroalkanes and chloroalkenes in the atmosphere (11).

On addition to water forms chloral hydrate (2).

Reviews on human health effects, experimental toxicology, physico-chemical properties listed (12).

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c108 chloral hydrate



C₂H₃Cl₃O₂

Mol. Wt. 165.40

CAS Registry No. 302-17-0

Synonyms 2,2,2-trichloro-1,1-ethanediol; trichloroacetaldehyde monohydrate; Noctec Capsules; Somnos; Grasex; Luxan Teceal

EINECS No. 206-117-5

RTECS No. FM 8750000

Uses Manufacture of DDT. Therapeutic use as anaesthetic, hypnotic, narcotic and sedative.

Physical properties

M. Pt. 52°C B. Pt. 97.5°C Specific gravity 1.91 at 20°C with respect to water at 4°C

Solubility Water: $\geq 10 \text{ g l}^{-1}$ at 20°C. Organic solvents: freely soluble in acetone, benzene, carbon disulfide, diethyl ether, dimethyl sulfoxide, ethanol, glycerol, olive oil

Occupational exposure

UN No. 2831

Supply classification toxic

Risk phrases Toxic if swallowed – Irritating to eyes and skin (R25, R36/38)

Safety phrases Keep locked up and out of the reach of children (if sold to general public) – Avoid contact with the eyes – In case of accident or if you feel unwell, seek medical advice immediately (show label where possible) (S1/2, S25, S45)

Ecotoxicity

Invertebrate toxicity

EC₅₀ (48 hr) *Daphnia magna* 630 mg l⁻¹ (1).

Toxicity to other species

In vivo exposure of the newt, *Pleurodeles waltl* larvae to chloral hydrate resulted in a significant increase in the frequency of micronucleated erythrocytes (2).

Mammalian & avian toxicity

Acute data

LD₅₀ oral redwing blackbird, mallard duck, ring-necked pheasant >100 mg kg⁻¹ (3).

LD₅₀ oral starling >100 to >422 mg kg⁻¹ (3).

LD₅₀ oral rat 480 mg kg⁻¹ (4).

LD₅₀ intraperitoneal mouse 777 mg kg⁻¹ (5).

Sub-acute and sub-chronic data

Oral ♂ and ♀ Sprague-Dawley rats (90 days) 300, 600, 1200, or 2400 mg l⁻¹ administered continuously in drinking water. Significant decrease in food and water consumption and in weight gain was observed for the group that received 2400 mg l⁻¹ (168 mg kg⁻¹ day⁻¹). Several dose levels, but particularly the highest, caused minimal to mild hepatocellular necrosis. The oral no-observed-adverse-effect level was calculated to be 96 mg kg⁻¹ (600 mg l⁻¹) (6).

Carcinogenicity and chronic effects

Oral F344 ♂ rats (52 wk) 55 and 188 mg kg⁻¹ in drinking water produced no systemic toxicity, no gross lesions in the reproductive organs and no tumours in any tissues. Exposure to 188 mg kg⁻¹ chloral hydrate significantly decreased the percentage of both motile and progressively motile sperm (7).

Teratogenicity and reproductive effects

Sprague-Dawley rat embryos were explanted on gestational day 10 and cultured for 46 hr in the presence of chloral hydrate. A concentration-dependent decrease in growth and differentiation was observed along with an increase in the incidence of morphologically abnormal embryos (8).

Metabolism and toxicokinetics

Rapidly absorbed from the stomach (humans) and widely distributed throughout the body. Metabolised to trichloroethanol and trichloroacetic acid in erythrocytes, liver and other tissues. Excreted partly in urine as trichloroethanol, urochloralic acid and trichloroacetic acid. Significant amounts are also excreted in the bile. Trichloroethanol is the active metabolite and passes into the cerebrospinal fluid, milk and across the placenta. Trichloroethanol t_{1/2} ranges from 7-11 hr (9).

Liver microsomes from ♂ B6C3F1 mice metabolise chloral hydrate to malondialdehyde, formaldehyde, acetaldehyde, acetone, and propionaldehyde. It is suggested that cytochrome P₄₅₀ is the enzyme catalysing the metabolic activation leading to lipid peroxidation. CYP2E1 may be the major isoenzyme responsible (10).

Irritancy

Allergic reactions in humans include skin rashes and eosinophilia (9).

Genotoxicity

Saccharomyces cerevisiae D61.M induced mitotic malsegregation of chromosome VII (11).

In vivo mouse bone marrow cells chromosomal aberrations negative (12).

Drosophila melanogaster wing mosaic and sex-linked recessive lethal test following larval exposure positive (13).

Other effects

Other adverse effects (human)

Therapeutic dose side-effects have included gastric irritation, light-headedness, ataxia, nightmares, excitement and confusion (sometimes with paranoia). Chronic ingestion of high doses has been associated with gastritis, skin rashes, peripheral vasodilation, hypotension and myocardial depression. Renal damage has been reported (9).

Legislation

Limited under EC Directive on Drinking Water Quality 80/778/EEC. Organochlorine compounds; guide level 1 µg l⁻¹ (14).

Included in Schedule 6 (Release into Land: Prescribed Substances) of Statutory Instrument No. 472, 1991 (15).

US Drug Enforcement Administration: Schedule IV drug.

WHO Toxicity Class II.

EPA Toxicity Class II.

Other comments

By-product of water disinfection.

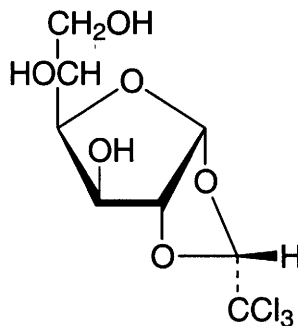
Hypnotic. Sedative. May be habit forming.

Potential carcinogenicity of chloral hydrate reviewed (16).

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c109 chloralose



C₈H₁₁Cl₃O₆

Mol. Wt. 309.53

CAS Registry No. 15879-93-3

Synonyms α-chloralose; (*R*)-1,2-*O*-(2,2,2-trichloroethylidene)-D-glucofuranose; α-D-glucochloralose; monotrachlorethylidene-α-D-glucose; Alfamat; All Muis Kill; Alphakil; Alta Musepulver; Eradic Corbeaux; Eradic-Taupe

EINECS No. 240-016-7

RTECS No. FM 9450000

Uses Rodenticide. Anaesthetic for laboratory animals.

Physical properties

M. Pt. 187°C

Solubility Water: 4.44 g l⁻¹ at 15°C. Organic solvents: diethyl ether, glacial acetic acid; slightly soluble in chloroform

Occupational exposure

Supply classification harmful

Risk phrases Harmful by inhalation and if swallowed (R20/22)

Safety phrases Keep out of reach of children (if sold to general public) – Keep away from sources of ignition – No smoking – Avoid contact with skin and eyes – After contact with skin, wash immediately with plenty of water (S2, S16, S24/25, S28)

Mammalian & avian toxicity

Acute data

LD₅₀ oral redwing blackbird, quail 31.6 mg kg⁻¹ (1).

LD₅₀ oral starling >76.9 mg kg⁻¹ (1).

LD₅₀ oral duck 42 mg kg⁻¹ (2).

LD₅₀ oral pigeon 178 mg kg⁻¹ (2).

LD₅₀ oral rat 400 mg kg⁻¹ (3).

LD_{Lo} oral mouse 32 mg kg⁻¹ (4).

LD_{Lo} subcutaneous rat 200 mg kg⁻¹ (5).

LD₅₀ intraperitoneal mouse 175 mg kg⁻¹ (6).

Metabolism and toxicokinetics

In animals, metabolised to chloral, oxidised to trichloroacetic acid, and reduced to trichloroethanol. The latter metabolite is responsible for the hypnotic effect (2).

Other effects

Any other adverse effects

Rodenticide acts by slowing down metabolism and lowering body temperature to a fatal level (3).

Legislation

US Code of Federal Regulations Title 21 Part 329.1, 1987 (7).

Limited under EC Directive on Drinking Water Quality 80/778/EEC. Pesticides: maximum admissible concentration $0.1 \mu\text{g l}^{-1}$ (8).

Included in Schedule 6 (Release into Land: Prescribed Substances) of Statutory Instrument No. 472, 1991 (9).

WHO Toxicity Class II (10).

EPA Toxicity Class (formulation) II (2).

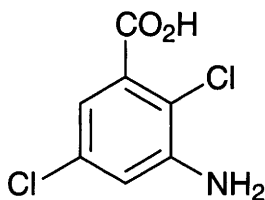
Other comments

Sedative. Hypnotic. May be habit forming (7).

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c110 chloramben



$\text{C}_7\text{H}_5\text{Cl}_2\text{NO}_2$

Mol. Wt. 206.03

CAS Registry No. 133-90-4

Synonyms 3-amino-2,5-dichlorobenzoic acid; 2,5-dichloro-3-aminobenzoic acid; Amiben

EINECS No. 205-123-5

RTECS No. DG 1925000

Uses Herbicide.

Physical properties

M. Pt. 200-201°C **Partition coefficient** $\log P_{\text{ow}}$ 2.32 (1) **Volatility** v.p. 7×10^{-3} mmHg at 100°C

Solubility Water: 700 mg l^{-1} at 25°C. Organic solvents: acetone, benzene, diethyl ether, dimethylformamide, dimethyl sulfoxide, ethanol, isopropanol, methanol

Ecotoxicity

Invertebrate toxicity

Chlorococcum sp. 50% decrease in oxygen evolution at 115 mg l⁻¹ (2).

Dunaliella tertiolecta 50% decrease in growth at 50 mg l⁻¹ and 50% decrease in oxygen evolution at 150 mg l⁻¹ (2).

Isochrysis galbana 50% decrease in growth at 15 mg l⁻¹ and 50% decrease in oxygen evolution at 100 mg l⁻¹ (2).

Phaeodactylum tricornutum 50% decrease in growth at 25 mg l⁻¹ and 50% decrease in oxygen evolution at 100 mg l⁻¹ (2).

Not toxic to bees (3).

Environmental fate

Degradation studies

Undergoes microbial degradation in soil. Duration of activity 6-8 wk (3).

Microbial degradation appears to operate via decarboxylation (4).

Abiotic removal

Undergoes photodegradation in sunlight, with total loss of phytotoxicity in two days. In dry soil about 30% is lost in two days (4).

A 0.02 mg l⁻¹ aqueous solution was tested for adsorption on 10 mg activated carbon at pH 3, pH 7 and pH 11.

Highest adsorption occurred at lowest pH, values were 50.5%, 12.4% and 5.2%, respectively (5).

Mammalian & avian toxicity

Acute data

LD₅₀ oral rat, mouse 3500, 3730 mg kg⁻¹, respectively (6,7).

LC₅₀ (1 hr) inhalation rat >200 mg l⁻¹ (1).

LD₅₀ dermal rabbit, rat 3136, 3160 mg kg⁻¹, respectively (8,9).

Sub-acute and sub-chronic data

LC₅₀ (8 day) oral mallard duck 4640 mg kg⁻¹ (3).

Carcinogenicity and chronic effects

Oral rats, dogs (2 yr) 10,000 mg kg⁻¹ in feed, no adverse effect reported (3).

National Toxicology Program (2 yr) study rats and mice. Negative in carcinogenicity studies in ♂ and ♀ rats.

Equivocal results in ♂ mice. Tumours found in liver of ♀ mice (concentration unspecified) (10,11).

Teratogenicity and reproductive effects

In a three-generation study of rats of both sexes, administration of up to 4500 mg kg⁻¹ in diet for 9 wk prior to breeding, during breeding and weaning periods, no adverse effects on fertility, gestation, viability and lactation were observed (1).

Another study reported increased foetal mortality and decreased foetal skeletal development following oral administration to ♀ rats at 225 mg kg⁻¹ day⁻¹. Administration of 75 mg kg⁻¹ day⁻¹ caused no increase in embryo mortality although there was a general reduction in skeletal development. No effects were observed at 25 mg kg⁻¹ day⁻¹ (1).

Gavage rabbits (6-18 day gestation) 1000 mg kg⁻¹ caused no teratogenic effects (12).

Metabolism and toxicokinetics

In rats the major metabolites were 3-amino-5-chlorobenzoic acid, 3-aminobenzoic acid, 2,5-dihydroxybenzoic acid, 3,5-dihydroxybenzoic acid and 2,5-dichloroaniline (route unspecified) (3).

Irritancy

A single application of 3 mg to rat skin caused mild irritation (3).

Genotoxicity

Salmonella typhimurium TA98, TA100, TA1535, TA1537, TA1538 with and without metabolic activation positive (13).

Did not induce unscheduled DNA synthesis in primary rat hepatocytes. *In vitro* cytogenetic assay using Chinese hamster ovary cells positive. Bone marrow cytogenetic assay *in vivo* negative (1).

Other effects

Any other adverse effects

In plants, converted into a highly stable *N*-glucoside which retards further degradation (3).

Legislation

Limited under EC Directive on Drinking Water Quality 80/778/EEC. Pesticides and related products: maximum admissible concentration 0.1 µg l⁻¹ (14).

WHO Toxicity Class Table 5 (15).

EPA Toxicity Class (formulation) IV (3).

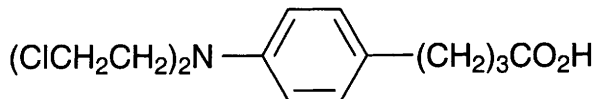
Other comments

Metabolic pathways reviewed (16).

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c111 chlorambucil



C₁₄H₁₉Cl₂NO₂

Mol. Wt. 304.22

CAS Registry No. 305-03-3

Synonyms 4-[bis(2-chloroethyl)amino]benzenebutanoic acid; 4-[*p*-[bis(2-chloroethyl)amino]phenyl]butyric acid; Chormanimophene; Chlorbutium; Leukeran

EINECS No. 206-162-0

RTECS No. ES 7525000

Uses Antineoplastic agent.

Physical properties

M. Pt. 64-66°C

Solubility Water: <1 g l⁻¹ at 20°C. Organic solvents: acetone, chloroform, diethyl ether, dimethyl sulfoxide, ethanol

Ecotoxicity

Invertebrate toxicity

Continuous exposure of sea urchin embryos (10⁻⁶ to 3 × 10⁻⁴ M) from the time of fertilisation delayed the first cleavage and hatching. Fertilisation was not affected. Developmental defects consisted mainly of blastula and gastrula-arrested embryos and in a limited number (25%) of plutei with malformed gut or skeleton. Post-hatching exposure resulted in malformed plutei only (1).

Mammalian & avian toxicity

Acute data

LD₅₀ oral rat, mouse 76, 100 mg kg⁻¹ respectively, (2,3).

LD₅₀ subcutaneous mouse 115 mg kg⁻¹ (3).

LD₅₀ intraperitoneal rat, mouse 17, 34 mg kg⁻¹, respectively (4,5).

Single intravenous dose 4 mg kg⁻¹ to dogs caused severe leucopenia, vomiting and diarrhoea within seven days (6).

Sub-acute and sub-chronic data

Repeated intraperitoneal injections of the maximum tolerated dose (unspecified) resulted in testicular atrophy and decreased spermatogenic activity in mice after 39 wk (7).

Intraperitoneal mice (1, 3, 4 and 14 days) 20 mg kg⁻¹ day⁻¹ cardiotoxic as determined by histochemical studies.

Creatine phosphokinase increases were observed in the blood before heart damage was detected (8).

Carcinogenicity and chronic effects

Sufficient evidence for carcinogenicity in humans and animals, IARC classification group 1 (9).

In a two-stage skin carcinogenesis experiment in which chlorambucil was applied wkly for 10 wk and croton oil wkly for 18 wk to 25 mice, 11 of 19 survivors developed skin papillomas compared with 0 of 17 controls treated with croton oil only (10).

Mice and rats administered up to 420 mg kg⁻¹ by intraperitoneal injection developed a dose-related incidence of lung tumours (7).

At least 34 cases of cancer have been reported following chlorambucil therapy for non-malignant diseases. Of these, 31 were acute leukaemias, and most were acute non-lymphocytic leukaemia. Although no controlled epidemiological study has been carried out, several studies and case reports point to the increased occurrence of acute non-lymphocytic leukaemia in patients treated with chlorambucil (4).

A randomised trial of therapy in 431 polycythemia vera patients showed a significant, 13-fold increase in the incidence of acute non-lymphocytic leukaemia in those receiving chlorambucil, which was 2.3 times higher than in patients receiving radioactive phosphorus. The excess was strongly related to dose and persisted throughout the first decade after treatment (11).

Chlorambucil administered to mice at doses of 1.0 mg kg⁻¹ 5 times wkly for 12 wk caused reduced survival in both sexes. The treatment induced an increase in lung and lymphoreticular system tumours in both sexes and mammary carcinomas in ♀ mice (12).

Teratogenicity and reproductive effects

Chlorambucil was administered to mice at 7.4 days of gestation (route and dose unspecified) and embryos were examined on days 9.3-9.4, 9.7-9.8 and 10.4. Neural tube defects of the brain were observed (13).

Found to be teratogenic and embryolethal in rats in several studies when given as intraperitoneal injections on days 11-14 of pregnancy at doses of 6-12 mg kg⁻¹. A wide spectrum of foetal abnormalities were produced including encephalocoele, exencephaly, cleft palate and deformed appendages, paws and tails (4).

A woman who received 10 mg day⁻¹ for 6 wk from 20 wk of pregnancy, followed by 6 intravenous injections of 20 mg nitrogen mustard gas during the 5th, 6th and 7th months had a normal infant (14).

Another woman who became pregnant while receiving 6 mg day⁻¹ and continued to receive it for another 10 wk, had a therapeutic abortion at 14 wk. The foetus had no left kidney or ureter (15).

Metabolism and toxicokinetics

After oral administration of ^{14}C -ring-labelled chlorambucil to rats, radioactivity was detected in most tissues within 1 hr. Plasma, liver and kidney showed the highest concentrations. Following intravenous administration most radioactivity was eliminated via urine. Chlorambucil is extensively metabolised in rodents by monodechloroethylation and by β -oxidation, forming the phenylacetic acid derivative which also has anti-cancer activity. Chlorambucil has been shown to bind covalently to proteins, and to be incorporated into the DNA and RNA in both normal and tumorous rat tissues using tritiated labelled compound. Chlorambucil has also been shown to cause polymerisation of RNA and an increase in nuclear protein phosphorylation (4).

In humans chlorambucil is readily absorbed following oral administration and is reported to have a plasma $t_{1/2}$ of about 90 min. It is extensively metabolised in the liver, primarily to active phenylacetic acid mustard which undergoes some further degradation. Chlorambucil is excreted in urine almost entirely as metabolites with <1% unchanged (16).

Genotoxicity

Salmonella typhimurium TA100, TA1535 without metabolic activation negative, with metabolic activation positive (17).

Salmonella typhimurium TA98, TA1537 with and without metabolic activation negative (17).

Induced mitotic gene conversion in the diploid strain D4 of *Saccharomyces cerevisiae* (18).

Induced mutations in the haploid wild-type (RAD.REV) strain of *Saccharomyces cerevisiae* (19).

Induced point mutations in *Escherichia coli* Sd-4-73 (20).

Induced chromosomal aberrations of the chromatid type in short-term *in vitro* cultures of human peripheral lymphocytes (21,22).

Induced sex-linked recessive lethal mutations in *Drosophila melanogaster* (13).

Other effects

Other adverse effects (human)

Pulmonary fibrosis induced in six human patients treated with chlorambucil (23).

Myelosuppression was observed in 67% of an uncontrolled sample of 495 patients treated for rheumatoid arthritis. Viral, fungal and bacterial infections, attributed to immunosuppression were, observed in about 30% of patients. There was a low incidence of skin and gastro-intestinal complaints (24).

Convulsions have been reported in ten children, two of whom accidentally received very large amounts (4).

Oligospermia, azoospermia and disappearance of testicular germinal cells have been observed in σ patients. The changes were dose-dependent. A minimum total dose of 400 mg was required to induce azoospermia.

Oligospermia appeared to be reversible in cases in which the total dose was <400 mg (25).

Sterility has been reported, particularly when given to boys before puberty (16).

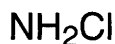
Reported to cause peripheral neuropathy of the sensorimotor type in human patients (26).

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c112 chloramine



ClH₂N

Mol. Wt. 51.48

CAS Registry No. 10599-90-3

Synonyms chloramide; chloroamine; monochloramide; monochloramine; monochloroammonia

EINECS No. 234-217-9

RTECS No. FN 0275000

Uses Disinfection of water supplies.

Physical properties

M. Pt. -66°C

Solubility Water: miscible

Ecotoxicity

Fish toxicity

Coho salmon early life stage toxicity test lowest observed effective concentration (LOEC) – no observed effective concentration (NOEC) 23-11 µg l⁻¹ fry survival and fry growth most sensitive responses (1).

Fathead minnow partial chronic toxicity test LOEC-NOEC 43-16 µg l⁻¹ reproduction and adult survival most sensitive responses (1).

LC₅₀ (2 hr) rainbow trout 0.66 mg l⁻¹ (2).

LC₅₀ (2 hr) channel catfish 0.44 mg l⁻¹ (2).

LC₅₀ (2 hr) emerald shiner 0.25 mg l⁻¹ (2).

Invertebrate toxicity

LC₅₀ (96 hr) *Gammarus pseudolimnaeus* 0.22 mg l⁻¹ (3).

LC₅₀ *Ceriodaphnia dubia* (24 hr static test) 0.012 mg l⁻¹, (continuous flow) 0.016 mg l⁻¹ (4).

Environmental fate

Carbonaceous inhibition

Inactivated 99.9% *Escherichia coli* culture at a concentration of 0.3 mg l⁻¹ for 4 hr at pH 8.5 and 25°C (5).

Mammalian & avian toxicity

Sub-acute and sub-chronic data

Oral rats (12 months) to 0, 1, 10 and 100 mg l⁻¹ in drinking water. At three months the red blood cell and haematocrit were significantly decreased while at ten months a significant decrease in haemoglobin concentration

was observed. Body weights were significantly reduced in the highest treatment group after 3 months (6). African green monkeys were exposed to 30 and 100 mg l⁻¹ in drinking water for 30 days. No detectable effect on haematology was observed. No evidence of thyroid suppression was detected in the serum (7). Oral rat (90 day) 200 mg l⁻¹ in drinking water was the lowest-observable-adverse-effect level; body and organ weights were reduced in both sexes and a small decrease in red blood cell count and calcium levels were observed in ♂ (8).

Carcinogenicity and chronic effects

The National Toxicology Program tested rats and mice via chloraminated water. No evidence of carcinogenicity in ♂ rats or ♂ and ♀ mice, equivocal evidence of carcinogenicity in ♀ rats (9).

Teratogenicity and reproductive effects

Following administration of up to 100 mg l⁻¹ in drinking water to ♀ rats 2-5 months prior to and during gestation, no teratogenic or embryotoxic effects were observed (10).

Metabolism and toxicokinetics

Reduced by thiocyanate ions, large concentrations of which are found in human saliva (11).

Reported to be reduced intracellularly by glutathione (12).

Irritancy

Allergic contact urticaria has been reported in a patient. Symptoms occurred within 20 min of contact and lasted for several days (13).

Genotoxicity

Salmonella typhimurium TA97a, TA100, TA102 with and without metabolic activation positive (11).

Bacillus subtilis 926 µg l⁻¹ DNA repair positive (12).

In vitro Chinese hamster ovary cells sister chromatid exchanges positive (14).

Other effects

Other adverse effects (human)

Chloramines have been reported to lead to the formation of methaemoglobin and depression of the hexose monophosphate pathway in red blood cells. They have also been reported to shorten human erythrocyte survival *in vivo* in patients undergoing haemodialysis and *in vitro* when cells are incubated in chloraminated water (15).

Haemolytic anaemia has frequently been a serious problem among long-term dialysis patients (16).

A trial of chloramine in drinking water was carried out in 48 healthy men; 0, 2 or 15 ppm in 1.5 l water day⁻¹ was consumed for 4 wk. Blood samples showed that the 2 ppm level had no significant effect on total cholesterol, triglycerides, high- or low-density lipoprotein cholesterol or on apoproteins A1, A2 or B. Thyroid function was also unaffected. The 15 ppm level caused an increase in levels of apolipoprotein B, while other parameters were unchanged (17).

Legislation

Limited under EC Directive on Drinking Water Quality 80/778/EEC, Article 8. Residual chlorine levels in water for human consumption must not be higher than the maximum admissible concentration (18).

Other comments

In vitro experiments with purified enzymes from mice found that 0.56-3.35 µM chloramine inhibits N¹⁰-formyl tetrahydrofolate dehydrogenase, and 2.7-100.8 µM inhibits formaldehyde dehydrogenase (19).

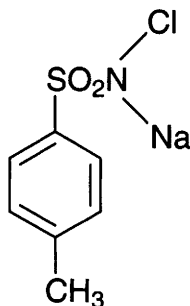
Dry material decomposes violently at -50°C.

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c113 chloramine T



$C_7H_7ClNNaO_2S$

Mol. Wt. 227.65

CAS Registry No. 127-65-1

Synonyms tosylchloramide sodium; *N*-chloro-*p*-toluenesulfonamide, sodium salt; sodium *p*-toluenesulfonylchloramide; Ketjensept

EINECS No. 204-854-7

RTECS No. XT 5616800

Uses Antibacterial agent.

Physical properties

M. Pt. 167-170°C

Occupational exposure

Supply classification corrosive

Risk phrases Harmful if swallowed – Contact with acids liberates toxic gas – Causes burns – May cause sensitisation by inhalation (R22, R31, R34, R42)

Safety phrases Keep locked up and out of reach of children (if sold to general public) – Keep container tightly closed – Do not breathe dust – In case of contact with eyes, rinse immediately with plenty of water and seek medical advice – Wear suitable protective clothing, gloves and eye/face protection – In case of accident or if you feel unwell, seek medical advice immediately (show label where possible) (S1/2, S7, S22, S26, S36/37/39, S45)

Ecotoxicity

Fish toxicity

LC₅₀ (72 hr) fathead minnow 0.15 mg l⁻¹ (1).

LC₅₀ (96 hr) rainbow trout, channel catfish, fathead minnow 2.80, 3.75, 7.30 mg l⁻¹, respectively (2).

The compound was more toxic to fish in warm water than in cold water for exposures of ≥24 hr; it was ≈6 × more toxic at pH 6.5 than at pH 9.5 (2).

Invertebrate toxicity

LC₅₀ (96 hr) *Gammarus pseudolimnaeus* 0.22 mg l⁻¹ (1).

EC₅₀ (24 hr) *Daphnia magna* 4.8 mg l⁻¹ (3).

NOEC (21 day) *Daphnia magna* 1.3 mg l⁻¹ (3).

EC₅₀ (48 hr) *Scenedesmus subspicatus* 0.31-0.58 mg l⁻¹ (4).

Toxicity to other species

LD_{Lo} parenteral frog 200 mg l⁻¹ (5).

Mammalian & avian toxicity

Acute data

LD_{Lo} intravenous rabbit 25 mg kg⁻¹ (5).

LD_{Lo} subcutaneous guinea pig 900 mg kg⁻¹ (5).

LD_{Lo} parenteral mouse 300 mg kg⁻¹ (5).

Genotoxicity

Escherichia coli WP2s(λ) Microscreen assay with metabolic activation positive (6).

In vitro Chinese hamster ovary cells with metabolic activation sister chromatid exchanges positive (7).

Legislation

Limited under EC Directive on Drinking Water Quality 80/778/EEC. Sodium: guide level 20 mg l⁻¹, maximum admissible concentration 150 mg l⁻¹. Organochlorine compounds: guide level 1 µg l⁻¹ (8).

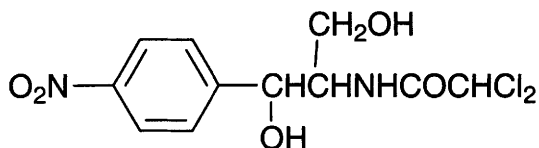
Other comments

May decompose violently if heated above 130°C.

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c114 chloramphenicol



$C_{11}H_{12}Cl_2N_2O_5$

Mol. Wt. 323.13

CAS Registry No. 56-75-7

Synonyms 2,2-dichloro-N-[2-hydroxy-1-(hydroxymethyl)-2-(4-nitrophenyl)ethyl]acetamide; 2,2-dichloro-N-[(α R, β R)- β -hydroxy- α -hydroxymethyl-4-nitrophenylethyl]acetamide; Chloramex; Econochlor

EINECS No. 200-287-4

RTECS No. AB 6825000

Uses Antibiotic.

Occurrence Obtained from cultures of the soil bacterium *Streptomyces venezuelae*.

Physical properties

M. Pt. 151°C

Solubility Water: 2.5 g l⁻¹ at 25°C. Organic solvents: acetone, butanol, diethyl ether, ethanol, ethyl acetate, methanol

Ecotoxicity

Invertebrate toxicity

EC₅₀ (24 hr) *Artemia salina*, *Streptocephalus proboscideus*, *Daphnia magna* and *Brachionus calyciflorus* 6.3, 0.9, 3.4 and 6.5 mmol l⁻¹, respectively (1).

EC₅₀ (5 min) *Photobacterium phosphoreum* 5.2 mmol l⁻¹ (Microtox test) (1).

Environmental fate

Nitrification inhibition

Did not inhibit nitrification using a recirculating system at 50 mg l⁻¹ (tested over 26 days) (2).

Degradation studies

For 3.3 mg COD g⁻¹ dry inoculum hr⁻¹ to adapted activated sludge, 86.2% COD removal reported at 20°C, when chloramphenicol was sole carbon source (3).

Biodegradable (4).

Abiotic removal

Undergoes photochemical decomposition (5).

Mammalian & avian toxicity

Acute data

LD₅₀ oral mouse 1500 mg kg⁻¹ (6).

LD₅₀ oral guinea pig 500 mg kg⁻¹ (7).

LD₅₀ intraperitoneal rat, mouse 1811, 1100 mg kg⁻¹, respectively (8,9).

LD₅₀ subcutaneous mouse, rat 400, 5000 mg kg⁻¹, respectively (10,11).

LD₅₀ intravenous rat, mouse, rabbit 110-170 mg kg⁻¹ (12).

LD₅₀ intravenous guinea pig 560 mg kg⁻¹ (13).

Sub-acute and sub-chronic data

Three groups of ten three-month-old mice were given daily intraperitoneal injections of 20, 40 or 100 mg kg⁻¹ for three months. During the second month, groups given the higher doses developed splenomegaly, hepatomegaly,

adenopathy and hypertrophy of the thymus. These pathological alterations were not found in animals receiving 20 mg kg⁻¹ until after the third month (14).

Carcinogenicity and chronic effects

Limited evidence for carcinogenicity to humans, inadequate evidence for carcinogenicity to animals, IARC classification group 2B (15).

Oral mice (duration and concentration unspecified) in drinking water increased incidence of lymphomas and hepatocellular carcinomas in two strains (16).

Teratogenicity and reproductive effects

Intraperitoneal ♂ ICR/Ha Swiss mice (duration unspecified) 333 and 666 mg kg⁻¹ caused no increase in early foetal deaths or pre-implantation losses (17).

Metabolism and toxicokinetics

Metabolites identified in rat and dog urine were unchanged chloramphenicol, glucuronide conjugate of the terminal hydroxyl group and a hydrolysis product (18).

The major route of elimination in the rat is via biliary excretion as the glucuronide. Gut bacteria can hydrolyse this metabolite, so that free chloramphenicol can be absorbed from the caecum and large intestine (19).

Following subcutaneous administration of 100 mg kg⁻¹ to rats, highest tissue concentrations of nitro-compounds were found in the kidney after 1-2 hr. In the guinea pig, the liver and kidneys contained low amounts of nitro-derivatives and high concentrations of aryl amines, due to the capacity of this species to reduce nitro-groups in the liver. Plasma t_{1/2} for a man given a 3 g oral dose was found to be ≈6 hr (20).

Following intramuscular administration of 90 mg kg⁻¹ to calf, the mean maximum serum concentration of 22.9 µg ml⁻¹ was reached in a mean time of 8.9 hr. The t_{1/2} for the same dose administered intravenously was 6.0 hr (21). Converted in mammals enzymatically into its monoacetylated form (22).

Genotoxicity

Salmonella typhimurium TA102, TA1535, TA1538 without metabolic activation negative (23).

Salmonella typhimurium TA98, TA100, TA1535, TA1537 with metabolic activation negative (24).

Induced chromosomal aberrations in human lymphocyte cultures and sister chromatid exchanges in human lymphocyte and hamster V79 cultures (25).

Negative results were reported for the induction of sex-linked recessive lethality and dominant lethal assay in *Drosophila melanogaster* (26).

Contradictory results reported for dominant lethal mutations in mice (27).

Increased the frequency of polyploid cells and caused chromosomal damage in chick bone-marrow (28).

Other effects

Other adverse effects (human)

A study of 487 patients with aplastic or hypoplastic anaemia or generalised cytopenia showed the primary toxic effect associated with chloramphenicol therapy is bone-marrow damage (29).

The incidence of blood disorders in patients was reported as one in 40,800 for women and one in 24,500 in men (30).

The death of a five-year-old boy was reported, due to acute myeloblastic leukaemia following a one-year history of aplastic anaemia after administration of chloramphenicol (31).

Three children aged 4-10 years developed acute leukaemia (1 lymphatic, 2 stem-cell) 8 months to 4 years after treatment (alone or with other drugs) at total doses of 18-230 g over periods ranging from 20 days to 3 years (32).

A further case of acute myeloblastic leukaemia was observed in a 6-year-old girl 6 months after receiving 5 g chloramphenicol (33).

Any other adverse effects

Lethal or near-lethal amounts given orally or parenterally to rats, mice, guinea pigs and dogs produced respiratory depression or failure, accompanied by a fall in blood pressure and anoxia (34). Reported to be nephrotoxic by interfering with the metabolism of ribosomal RNA and protein synthesis in rat kidney *in vivo* (35). Reported to be nephrotoxic by interfering with rat kidney lysosomal stability *in vivo* and *in vitro* (36).

In vivo administration of chloramphenicol to mice for 1, 3 or 6 days caused an increase in the activity of the low-

and high-substrate forms of *N*-nitrosodimethylamine demethylases (NDMA_I and II, respectively) in liver microsomes, and induction of hepatic cytochrome P₄₅₀. The activity of arylhydrocarbon (benzo[*a*]pyrene) hydroxylase was unaffected (37).

Legislation

Limited under EC Directive on Drinking Water Quality 80/778/EEC. Organochlorine compounds: guide level 1 µg l⁻¹ (38).

Included in Schedule 6 (Release into Land: Prescribed Substances) of Statutory Instrument No. 472, 1991 (39).

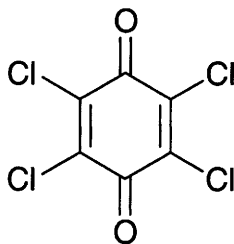
Other comments

Exerts its antibiotic effects through the inhibition of bacterial protein synthesis by binding specifically to bacterial ribosomes, preventing peptide chain extension (40).

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c115 chloranil



$C_6Cl_4O_2$

Mol. Wt. 245.88

CAS Registry No. 118-75-2

Synonyms tetrachloro-*p*-benzoquinone; 2,3,5,6-tetrachloro-1,4-benzoquinone; 2,3,5,6-tetrachloro-2,5-cyclohexadiene-1,4-dione; tetrachloroquinone; Vulklor

EINECS No. 204-274-4

RTECS No. DK 6825000

Uses Fungicide. Manufacture of chloranil electrodes for pH measurements. Reagent for pamaquine in urine. Vulcanising agent.

Physical properties

M. Pt. 290°C **Specific gravity** 1.97 at 20°C

Solubility Water: 250 mg l⁻¹ at 25°C. Organic solvents: diethyl ether

Occupational exposure

Supply classification irritant

Supply classification dangerous for the environment

Risk phrases Irritating to eyes and skin – Very toxic to aquatic organisms, may cause long-term adverse effects in the aquatic environment (R36/38, R50/53)

Safety phrases Keep out of reach of children (if sold to general public) – Wear suitable gloves – This material and/or its container must be disposed of as hazardous waste – Avoid release to the environment. Refer to special instructions/safety data sheet (S2, S37, S60, S61)

Ecotoxicity

Fish toxicity

LD₅₀ (96 hr) fathead minnow 0.01 mg l⁻¹ static bioassay (1).

Mammalian & avian toxicity

Acute data

LD₅₀ oral redwing blackbird >100 mg kg⁻¹ (2).

LD₅₀ oral rat 4000 mg kg⁻¹ (3).

LD_{Lo} intraperitoneal rat 500 mg kg⁻¹ (4).

Irritancy

May cause irritation to skin and mucous membranes in humans (5).

Genotoxicity

Salmonella typhimurium TA98, TA100 without metabolic activation negative; TA102, TA2637 with and without metabolic activation negative (6).

Legislation

Limited under EC Directive on Drinking Water Quality 80/778/EEC. Pesticides and related products: maximum admissible concentration 0.1 µg l⁻¹ (7).

Included in Schedule 6 (Release into Land: Prescribed Substances) of Statutory Instrument No. 472, 1991 (8).

Other comments

Prepared from *p*-phenylenediamine or phenol by treating with potassium chlorate and hydrochloric acid.

Believed to be no longer manufactured, or marketed for crop protection use (9).

Lake plankton from a mesotrophic lake were used to study pesticide toxicity. The concentrations of chloranil needed to cause a 50% reduction in relative uptake of carbon, phosphate and ammonium were 0.5, 3.5 and 2.5 mg l⁻¹, respectively (10).

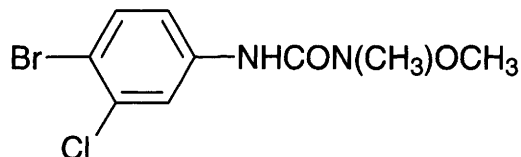
Did not affect seed germination of cereals and grasses when applied at a rate of 500 or 2500 mg kg⁻¹ soil (11).

Reviews on human health effects, experimental toxicology, ecotoxicology, physico-chemical properties and exposure levels listed (12).

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c116 chlorbromuron



C₉H₁₀BrClN₂O₂

Mol. Wt. 293.55

CAS Registry No. 13360-45-7

Synonyms 1-(3-chloro-4-bromophenyl)-3-methylmethoxyurea; Maloran; 3-(4-bromo-3-chlorophenyl)-1-methoxy-1-methylurea; *N'*-(4-bromo-3-chlorophenyl)-*N*-methoxy-*N*-methylurea

EINECS No. 236-411-9

RTECS No. YS 2800000

Uses Herbicide.

Physical properties

M. Pt. 95-97°C **Specific gravity** 1.69 at 20°C **Volatility** v.p. 4.0×10^{-7} mmHg at 20°C
Solubility Water: 35 mg l⁻¹ at 20°C. Organic solvents: acetone, benzene, dichloromethane, hexane, propan-2-ol

Ecotoxicity

Fish toxicity

LC₅₀ (96 hr) rainbow trout, bluegill sunfish 5 mg l⁻¹ (1).

LC₅₀ (96 hr) crucian carp 8 mg l⁻¹ (1).

Invertebrate toxicity

I₅₀ (50% inhibition of reproduction) *Chlorella fusca* 3×10^{-8} mol l⁻¹ (2).

Not toxic to bees (1).

Bioaccumulation

Chlorella fusca bioconcentration factor 1071.5 (2).

Environmental fate

Degradation studies

t_{1/2} in soil approximately 45-120 days (1).

Mammalian & avian toxicity

Acute data

LD₅₀ oral rat 2150 mg kg⁻¹ (3).

LC₅₀ (6 hr) inhalation rat >1.05 mg l⁻¹ air (1).

LD₅₀ dermal rat >2000 mg kg⁻¹ (1).

LD₅₀ dermal rabbit >10,000 mg kg⁻¹ (1).

Sub-acute and sub-chronic data

LC₅₀ (10 day) oral pheasant, mallard duck >10,250 mg kg⁻¹ diet (1).

Oral rat (90 day) 316 mg kg⁻¹ in feed (21.0 mg kg⁻¹ day⁻¹) caused no adverse effect (1).

Irritancy

50 mg instilled into rabbit eye caused moderate irritation (4).

Legislation

Limited under EC Directive on Drinking Water Quality 80/778/EEC. Pesticides and related products: maximum admissible concentration 0.1 µg l⁻¹ (5).

Included in Schedule 6 (Release into Land: Prescribed Substances) of Statutory Instrument No. 472, 1991 (6).

WHO Toxicity Class Table 5 (7).

EPA Toxicity Class (formulation) (1).

Other comments

In plants metabolism involves demethylation and deamination-decarboxylation to the corresponding aniline moiety (1).

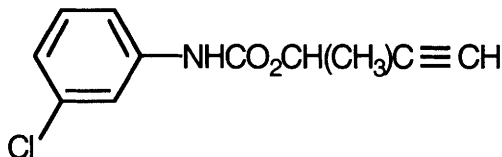
Metabolic pathways reviewed (8).

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c117 chlorbufam



$C_{11}H_{10}ClNO_2$

Mol. Wt. 223.66

CAS Registry No. 1967-16-4

Synonyms 1-methyl-2-propynyl (3-chlorophenyl)carbamate; *m*-chlorocarbanilic acid, 1-methyl-2-propynyl ester; 1-butyn-3-yl *m*-chlorophenylcarbamate; 1-methylprop-2-ynyl 3-chlorophenylcarbamate; 1-methylprop-2-ynyl 3-chlorocarbanilate; chlorbufame

EINECS No. 217-815-4

RTECS No. FD 8575000

Uses Superseded herbicide.

Physical properties

M. Pt. 45-46°C **Specific gravity** 1.22 **Volatility** v.p. 1.6×10^{-5} mmHg at 20°C

Solubility Water: 540 mg l⁻¹ at 20°C. Organic solvents: acetone, ethanol, methanol

Ecotoxicity

Invertebrate toxicity

Not toxic to bees (1).

Mammalian & avian toxicity

Acute data

LD₅₀ oral rat 2500 mg kg⁻¹ (2).

LD₅₀ intraperitoneal mouse 250 mg kg⁻¹ (3).

Sub-acute and sub-chronic data

Oral rat (4 month) 400 mg kg⁻¹ in diet no adverse effects observed (1).

Irritancy

Dermal rabbit (15 min) unspecified dose caused mild temporary erythema. Significant effects were observed after application for 20 hr (4).

Genotoxicity

Salmonella typhimurium TA98, TA100, TA1535, TA1538 with and without metabolic activation negative (5).

Other effects

Any other adverse effects

Activates acetylcholinesterase in the plasma of mice, but decreases acetylcholinesterase activity in the liver. No effect on acetylcholinesterase activity in the central nervous system (6).

Legislation

Limited under EC Directive on Drinking Water Quality 80/778/EEC. Pesticides: maximum admissible concentration $0.1 \mu\text{g l}^{-1}$ (7).

Included in Schedule 6 (Release into Land: Prescribed Substances) of Statutory Instrument No. 472, 1991 (8).
WHO Toxicity Class Table 5 (9).

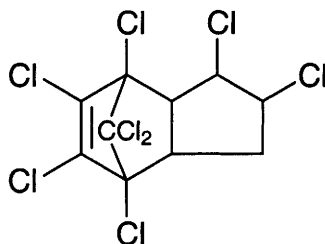
Other comments

Incompatible with alkaline materials (2).

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c118 chlordane



$\text{C}_{10}\text{H}_6\text{Cl}_8$

Mol. Wt. 409.78

CAS Registry No. 57-74-9

Synonyms 1,2,4,5,6,7,8,8-octachloro-2,3,3a,4,7,7a-hexahydro-4,7-methano-1H-indene; 1,2,4,5,6,7,8,8-octachloro-3a,4,7,7a-tetrahydromethanoindan; octachloro-4,7-methanotetrahydroindane; dichlorochlordene; chlordan; Corodane; Octachlor; Belt; Chlortox; Gold Crest; Intox; Synklor; Termi-Ded

EINECS No. 200-349-0

RTECS No. PB 9800000

Uses Non-systemic insecticide.

Physical properties

M. Pt. *cis*-isomer 106-107°C; *trans*-isomer 104-105°C **B. Pt.** 175°C at 1 mmHg **Specific gravity** 1.59-1.63 at 25°C **Volatility** v.p. 1×10^{-5} mmHg at 25°C

Solubility Water: 0.1 mg l^{-1} at 25°C. Organic solvents: miscible with most aliphatic and aromatic organic solvents

Occupational exposure

DE-MAK 0.5 mg m^{-3} (inhalable fraction of aerosol)

FR-VME 0.5 mg m⁻³

US-TWA 0.5 mg m⁻³

Supply classification harmful, dangerous for the environment

Risk phrases Harmful in contact with skin and if swallowed – Possible risk of irreversible effects – Very toxic to aquatic organisms, may cause long-term adverse effects in the aquatic environment (R21/22, R40, R50/53)

Safety phrases Keep out of reach of children (if sold to general public) – Wear suitable protective clothing and gloves – This material and/or its container must be disposed of as hazardous waste – Avoid release to the environment. Refer to special instructions/safety data sheet (S2, S36/37, S60, S61)

Ecotoxicity

Fish toxicity

LC₅₀ (96 hr) rainbow trout, bluegill sunfish 0.09, 0.07 mg l⁻¹, respectively (1).

LC₅₀ (96 hr) brook trout 47 µg l⁻¹ (2).

Invertebrate toxicity

EC₅₀ (48 hr) *Daphnia magna* 0.59 mg l⁻¹ (1).

LC₅₀ (96 hr) *Gammarus fasciatus* 40 µg l⁻¹ (3).

LC₅₀ (96 hr) *Palaemonetes kadiakensis* 4.0 µg l⁻¹ (3).

Toxic to bees (1).

Bioaccumulation

Bioconcentration factor *Oedogonium* (cyanobacteria) 90,000 (4).

Scenedesmus quadricauda 6,000 to 15,000 for both isomers at levels of 0.1 to 100 µg l⁻¹ water (5).

Environmental fate

Nitrification inhibition

Threshold concentration for inhibition of nitrification and denitrification, rotating disc and activated sludge 10 mg l⁻¹ (6).

Degradation studies

t_{1/2} in soil ~1 yr (1).

Removed from water using activated rotating biological contactor (7).

Mammalian & avian toxicity

Acute data

LD₅₀ oral rabbit, rat, mouse 300-590 mg kg⁻¹ (1).

LD₅₀ oral bobwhite quail 83 mg kg⁻¹ (1).

LC₅₀ (4 hr) inhalation cat 100 mg m⁻³ (8).

LD₅₀ dermal rabbit 200-2000 mg kg⁻¹ (1).

LD₅₀ dermal rat 217 mg kg⁻¹ (1).

LD₅₀ intraperitoneal ♂ rat 343 mg kg⁻¹ (9).

Oral human 100 mg kg⁻¹ was fatal (10).

Sub-acute and sub-chronic data

LC₅₀ (8 day) oral bobwhite quail 421 mg kg⁻¹ diet (1).

LC₅₀ (8 day) mallard duck 795 mg kg⁻¹ diet (1).

Carcinogenicity and chronic effects

Inadequate evidence for carcinogenicity in humans, sufficient evidence for carcinogenicity in animals, IARC classification group 2B (11).

Oral mice (10 month) concentrations up to 50 mg kg⁻¹ diet, there was a dose-related incidence of hepatocarcinomas (12).

Oral mice (80 wk) doses of up to 80 mg kg⁻¹ diet, a dose-related incidence of hepatocellular carcinomas was demonstrated. A parallel study in rats gave inconclusive results (13,14).

In 2-yr feeding trials in dogs no-effect level 3 mg kg⁻¹ diet. Serious chronic and cumulative toxicity occurs at higher levels, including liver and kidney damage (1).

The National Toxicology Program tested rats and mice via feed. No evidence of carcinogenicity in rats, positive evidence of carcinogenicity in ♂ and ♀ mice (15).

Teratogenicity and reproductive effects

Oral gravid CD-1 mice (8-12 day) 50 mg kg⁻¹ although 3 of 25 animals tested died, no effect was observed on the numbers and weight of pups (16).

Reported to have decreased fertility in ♀ and ♂ rats and ♀ mice (17).

Metabolism and toxicokinetics

Following oral administration to rats, metabolised via 1,2-dichlorochlordane and oxychlordane to 1-*exo*-hydroxy-2-chlorochlordene and 1-*exo*-hydroxy-2-*endo*-chloro-2,3-*exo*-epoxychlordene, and to various other hydroxylated products (18).

Being lipophilic, these compounds are stored mainly in the adipose tissue. Elimination takes place via urine and faeces. Breast milk is a supplementary excretory route in lactating women (11).

Induces hepatic drug metabolising enzymes (19).

Irritancy

Mild skin irritant and severe eye irritant in rabbits. Non-sensitising to skin of guinea pigs (1).

Genotoxicity

Salmonella typhimurium TA98, TA100, TA1535, TA1537, with and without metabolic activation negative (20).

Escherichia coli WP2 *uvrA*- with and without metabolic activation negative (21).

DNA repair test, rat, mouse and hamster hepatocytes, *in vitro*, without metabolic activation negative (22).

Gene mutation, mouse lymphoma L5178Y cells without metabolic activation positive (23).

Sister chromatid exchange, human lymphoid cells *in vitro* with and without metabolic activation positive (24).

Other effects

Other adverse effects (human)

Case reports have suggested a relationship between human exposure to chlordane or heptachlor (either alone or in combination with other compounds) and blood dyscrasia and acute leukaemia (16).

A study of 800 workers employed at a chlordane production plant for three months or more during the period 1946-1985 showed a slightly less than expected overall death rate and an inverse relationship of cancer mortality to length of employment (25).

Any other adverse effects

The effects of *cis*- and *trans*-chlordane on respiratory activities in hepatic mitochondria and on electron transport in sonicated submitochondrial particles were examined. Chlordanes did not appear to be specific inhibitors like cyanide, rotenone or antimycin A (24).

Toxic effects in rats include stimulation of central nervous system, stomach ulcers, inflammation of the intestine, nephritis, hepatitis, increase in liver weight, coma and fatality (dose and duration unspecified) (26).

Accumulates in body fat and lipid-containing organs (1).

Legislation

Limited under EC Directive on Drinking Water Quality 80/778/EEC. Pesticides: maximum admissible concentration 0.1 µg l⁻¹ (27).

Included in Schedule 6 (Release into Land: Prescribed Substances) of Statutory Instrument No. 472, 1991 (28).

The EPA has cancelled registration of pesticides containing this compound with the exception of its use through subsurface ground insertion for termite control and the dipping of roots or tops of non-food plants (29).

WHO Toxicity Class II (30).

EPA Toxicity Class (formulation) IIB (1).

Other comments

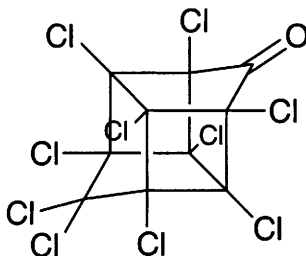
Toxicity and hazards reviewed (31).

Reviews on physico-chemical properties, human health effects, exposure levels, experimental toxicology, workplace experience, epidemiology and environmental effects listed (32).

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C119 chlordecone


$$\text{C}_{10}\text{Cl}_{10}\text{O}$$

Mol. Wt. 490.64

CAS Registry No. 143-50-0

Synonyms 1,1a,3,3a,4,5,5a,5b,6-decachlorooctahydro-1,3,4-metheno-2H-cyclobuta[cd]pentalen-2-one; decachlorotetrahydro-4,7-methanoindeneone; Kepone

EINECS No. 205-601-3

RTECS No. PC 8575000

Uses Superseded insecticide.

Physical properties

M. Pt. 350°C **Volatility** v.p. 5×10^{-5} mmHg at 20-25°C ; v.den. 16.9

Solubility Water: 4 g l⁻¹ at 100°C. Organic solvents: acetone, dimethyl sulfoxide, ethanol

Occupational exposure

Supply classification toxic

Risk phrases Toxic in contact with skin and if swallowed – Possible risk of irreversible effects (R24/25, R40)

Safety phrases Keep locked up and out of the reach of children (if sold to general public) – Do not breathe dust –

Wear suitable protective clothing and gloves – In case of accident or if you feel unwell, seek medical advice immediately (show label where possible) (S1/2, S22, S36/37, S45)

Ecotoxicity

Fish toxicity

Freshwater catfish exposed to 0.012, 0.024 or 0.04 mg l⁻¹ for 96 hr, 10-20 days or 30-60 days had decreased hepatic and muscle glycogen concentrations. Hyperglycaemia was evident with glycogenolytic changes in liver at 30 and 60 days (1).

Environmental fate

Degradation studies

Methanosarcina thermophila cultures degraded 86% of a chlordecone sample within 10 days, converting it into polar and nonpolar products. The titanium(III) citrate-reduced CO dehydrogenase enzyme complex isolated from *M. thermophila* converted chlordecone into a similar range of products as the whole cell cultures. Reduced vitamin B12, reduced corrinoid cofactor (factor III) from the CO dehydrogenase enzyme complex, and reduced coenzyme F430 from the Me coenzyme M methylreductase of *M. thermophila* also degraded chlordecone with a similar pattern of decomposition products (2).

Mammalian & avian toxicity

Acute data

LD₅₀ oral coturnix 237-316 mg kg⁻¹ (3).

LD₅₀ oral rabbit, rat 65, 95 mg kg⁻¹, respectively (4,5).

LD₅₀ dermal rat >2000 mg kg⁻¹ (6).

LD₅₀ dermal rabbit 345 mg kg⁻¹ (5).

Sub-acute and sub-chronic data

Oral mice, rats (2 wk) 50 mg kg⁻¹ diet induced hepatic mixed function oxidase activity (7).

Oral ♂ Sprague-Dawley rats (15 days) 1, 10, 50 or 100 ppm chlordecone in calcium-sufficient (Ca-S) or calcium-deficient (Ca-D) diet. No significant changes in serum total proteins were seen. At 50 or 100 ppm, serum non-protein nitrogen compounds (urea, uric acid and creatinine) and glutamic acid oxaloacetic transaminase, glutamic pyruvic transaminase, creatine kinase and alkaline phosphatase activities were all significantly increased, implying altered glomerular and hepatic functions; the increase was greater in rats fed on the Ca-D diet than in those on the Ca-S diet (8).

Carcinogenicity and chronic effects

No adequate data for carcinogenicity in humans, sufficient evidence for carcinogenicity in animals, IARC classification group 2B (9).

The National Toxicology Program tested mice and rats via feed. Positive evidence of carcinogenicity in ♂ and ♀ rats and mice (10).

Oral rats, mice (112 wk) TWA dietary concentrations up to 40 mg kg⁻¹ induced hepatocellular carcinomas in both sexes (11).

Oral rat at concentrations ≥80 mg kg⁻¹ diet, all ♂ and ♀ receiving 50 and 80 mg kg⁻¹ had died by 25 wk.

Hepatocellular carcinomas were seen in a significant number of survivors after 2 yr (12).

Teratogenicity and reproductive effects

♀ Mice maintained on 40 mg kg⁻¹ diet failed to reproduce. Animals appeared to be in constant oestrus and developed large ovarian follicles but no corpora lutea. The effects were consistent with a partial blockage of the release of luteinising hormone from the pituitary (13).

Chlordecone had an oestrogen-like effect on the oviducts of immature ♀ quail and on the testes of the ♂ (14).

Chlordecone was administered by gastric intubation at doses of 2, 6 and 10 mg kg⁻¹ day⁻¹ to rats and 2, 4, 8 and 12 mg kg⁻¹ day⁻¹ to mice on days 7-16 of gestation. In rats, 19% of those receiving the highest dose died. Foetuses of those which survived exhibited reduced body weight, reduced degree of ossification, oedema, undescended testes, enlarged renal pelvis and cerebral ventricles. Lower dose levels only reduced foetal weight and degree of ossification. In mice, foetotoxicity occurred only at the highest dose and was manifested by foetal mortality and clubfoot malformations (15).

Metabolism and toxicokinetics

After mice were exposed for 5 months (route unspecified), maximum accumulation occurred in the liver. Residues were also found in the brain, kidneys and body fat. On withdrawal, levels decreased. There was no evidence of metabolism (13).

When fed to dairy cows at 0.25-5.0 mg kg⁻¹ in feedstuff for 60 days, the highest residue level in milk was 0.44 mg l⁻¹. No measurable amounts were detected in milk 83 days after treatment was discontinued (16).

High concentrations were found in the liver and body fat and levels of 0.165-26 µg ml⁻¹ found in the blood of exposed workers (13,17).

The serum t_{1/2} in humans ranges from 63-148 days (18).

In humans, chlordecone has been shown to undergo extensive biliary excretion and enterohepatic circulation.

Excretion in faeces, unchanged and as chlordecone alcohol derivative, was the major route of elimination.

Administration of the anionic exchange resin cholestyramine increased faecal excretion (17).

Irritancy

Dermatitis was reported in 60% of industrial workers. Skin rashes were also seen in family members of the workers (19).

Genotoxicity

Salmonella typhimurium TA100, TA98, TA1535, TA1537 with metabolic activation negative (20).

Other effects

Other adverse effects (human)

Human workers exposed by inhalation, oral ingestion and skin contact, showed signs of nervousness, tremors, visual deficiencies, pleural pain, joint pain, weight loss, tachycardia and hepatomegaly. Abnormal liver function tests, changes in electroencephalogram and electromyogram patterns, demyelination of peripheral nerves and oligospermia with decreased sperm mobility were noted. The severity of symptoms was proportional to blood levels (19).

Any other adverse effects

Rats and mice fed high (unspecified) doses of chlordecone in chronic studies exhibited nervous tremors (11). Oral mice (duration unspecified) 30-100 mg kg⁻¹ diet caused increased liver size, focal necrosis, cellular hypertrophy, hyperplasia and congestion depending on the length of treatment (13). Chlordecone has been reported to impair biliary excretion (21). Chlordecone (50 µmol kg⁻¹) administered intramuscularly to white leghorn roosters had oestrogen agonist activity as measured by its effect on oestrogen-related mRNA stabilising factor (22).

Legislation

Limited under EC Directive on Drinking Water Quality 80/778/EEC. Pesticides: maximum admissible concentration 0.1 µg l⁻¹ (23).

Included in Schedule 6 (Release into Land: Prescribed Substances) of Statutory Instrument No. 472, 1991 (24).

Other comments

Degradation product of the insecticide Mirex.

Believed to be no longer manufactured, or marketed for crop protection use (25).

A strong correlation was shown between the neurotoxic effects of chlordecone and the inhibition of Mg²⁺-ATPases in fish brain and rat liver (26,27).

Health effects, toxicokinetics, human exposure and environmental fate reviewed (28).

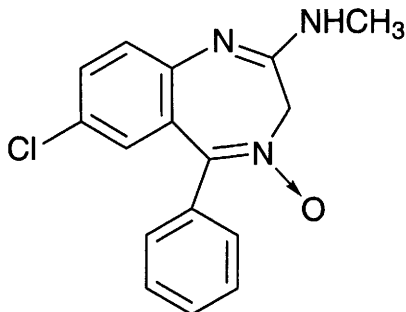
Oestrogenic activity is reviewed (29).

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c120 chlordiazepoxide



C₁₆H₁₄ClN₃O

Mol. Wt. 299.76

CAS Registry No. 58-25-3

Synonyms 7-chloro-2-methylamino-5-phenyl-3H-1,4-benzodiazepine 4-oxide; methaminodiazepoxide; Abboxide

EINECS No. 200-371-0

RTECS No. DE 9275000

Uses Tranquilliser. Anxiolytic. Used as a pharmaceutical and veterinary drug.

Physical properties

M. Pt. 236-236.5°C

Solubility Organic solvents: diethyl ether, ethanol

Mammalian & avian toxicity

Acute data

Non-toxic in oral toxicity tests redwing blackbird or starling at 100 mg kg⁻¹ (1).

LD₅₀ oral rat 548 mg kg⁻¹ (2).

LD₅₀ oral rabbit 590 mg kg⁻¹ (3).

LD₅₀ intravenous rat 165 mg kg⁻¹ (4).

LD₅₀ intraperitoneal mouse 207 mg kg⁻¹ (5).

LD₅₀ subcutaneous mouse 392 mg kg⁻¹ (6).

Teratogenicity and reproductive effects

A study of 50,282 children born to mothers exposed at some time during the first four months of pregnancy found no association between chlordiazepoxide and any type of malformation (7).

Metabolism and toxicokinetics

Phase I metabolism occurs via hydroxymethylation and N-demethylation while Phase II involves conjugation with glucuronides. Plasma t_{1/2} 6-28 hr (species unspecified) (8).

Other effects

Other adverse effects (human)

Aplastic anaemia has been reported in some patients. It has also been reported as being associated with cases of agranulocytosis (9).

Non-thrombocytopenic purpura occurred in a 65-yr-old woman following oral administration for at least 12 months in irregular courses of 10 mg twice daily for about 1 wk at \approx monthly intervals. The purpura reappeared within 48 hr of restarting dosage of 30 mg daily (10).

The most frequent adverse effects are drowsiness, sedation and ataxia. Less commonly, dizziness, vertigo, headache, confusion, mental depression, slurred speech and dysarthria, changes in libido, tremor, blurred vision, urinary retention or incontinence, gastro-intestinal disturbances, jaundice and occasional blood disorders have been reported. Overdose can cause central nervous system depression and coma (11).

Legislation

Controlled substance (depressant) listed in the US Code of Federal Regulations, Title 21 Part 1308.14, 1995 (12). Limited under EC Directive on Drinking Water Quality 80/778/EEC. Organochlorine compounds: guide level 1 $\mu\text{g l}^{-1}$ (13).

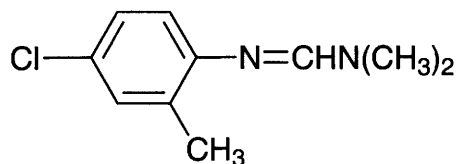
Other comments

The potential for drug dependence is less than that of, for example, barbiturates (11).

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c121 chlordimeform



$C_{10}H_{13}ClN_2$

Mol. Wt. 196.68

CAS Registry No. 6164-98-3

Synonyms *N'*-(4-chloro-2-methylphenyl)-*N,N*-dimethylmethanimidamide; *N'*-(2-methyl-4-chlorophenyl)-*N,N*-dimethylformamidine; *N'*-(4-chloro-*o*-tolyl)-*N,N*-dimethylformamidine; chlorophenamidine

EINECS No. 228-200-5

RTECS No. LQ 4375000

Uses Acaricide. Insecticide. Ovicide.

Physical properties

M. Pt. 35°C **B. Pt.** 156-157°C at 0.4 mmHg **Specific gravity** 1.105 at 25°C with respect to water at 4°C

Volatility v.p. 3.5×10^{-4} mmHg at 20°C

Solubility Water: 250 mg l⁻¹ at 20° C. Organic solvents: acetone, benzene, chloroform, ethyl acetate, hexane

Occupational exposure

Supply classification harmful

Risk phrases Harmful in contact with skin and if swallowed – Possible risk of irreversible effects (R21/22, R40)

Safety phrases Keep out of reach of children (if sold to general public) – Do not breathe dust – Wear suitable protective clothing and gloves (S2, S22, S36/37)

Ecotoxicity

Fish toxicity

LC₅₀ (24 hr) trout 11.7 mg l⁻¹ (1).

LC₅₀ (24 hr) bluegill sunfish 1 mg l⁻¹ (1).

LC₅₀ (24 hr) Japanese killifish 33 mg l⁻¹ (1).

Invertebrate toxicity

Chlordimeform alone is non-toxic to bees (2).

Environmental fate

Degradation studies

In non-sterile soil t_{1/2} estimate of 1 month (3).

Adsorption and retention

Adsorbed in soil by a cationic exchange mechanism. Fulvic acids adsorb in a lower proportion than humic acids (4).

Mammalian & avian toxicity

Acute data

LD₅₀ oral rat, mouse 160 mg kg⁻¹ (5,6).

LD₅₀ oral mouse 224 mg kg⁻¹ (7).

LD₅₀ oral rabbit 625 mg kg⁻¹ (8).

LD₅₀ dermal rat 640 mg kg⁻¹ (9).

LD₅₀ intraperitoneal rat 90-240 mg kg⁻¹ (10,11).

Sub-acute and sub-chronic data

Single intraperitoneal dose rats, mice 200 mg kg⁻¹ caused marked hyperexcitation after 5-10 min, followed by a gradual fall into a state of sedation. Recovery was complete within 24 hr. Some fatalities occurred during the early hyperexcitation (1-3 hr) (12).

Two of three cats given 50 mg kg⁻¹ subcutaneously daily for up to five days exhibited severe degeneration and sloughing of the bladder epithelium and other manifestations of kidney and liver injury (13).

Rabbit (route unspecified) (6 month) 8-40 µg kg⁻¹ caused moderate liver damage (14).

Carcinogenicity and chronic effects

No adequate data for carcinogenicity to humans, insufficient evidence for carcinogenicity to animals, IARC classification group 3 (15).

Oral rats, dogs (2 yr) 0.1 mg kg⁻¹ day⁻¹ in diet (rats) 6.25 mg kg⁻¹ day⁻¹ (dogs) no adverse effect reported (1).

Oral ♂ mouse 0, 20, 100 or 300 ppm in diet. Sarcomas (target organs unspecified) were observed in high-dose animals (16).

Results of oral administration tests on mice show that there is sufficient evidence for carcinogenicity to animals from the metabolite *p*-chloro-*o*-toluidine (17).

Teratogenicity and reproductive effects

Oral rat 100 µg kg⁻¹ day⁻¹ from day 5 of pregnancy. Except for an impaired ability in swimming between 7-17 days of age, the administration of chlordimeform during pregnancy caused no other behavioural effect (18).

Female rats given a single dose of 50 mg kg⁻¹ showed delayed ovulation, resulting in delayed breeding and significantly reduced litter size (19).

Metabolism and toxicokinetics

Rats, dogs and goats treated orally with radiolabelled chlordimeform (tolylmethyl-¹⁴C) rapidly metabolised the compound and eliminated the radioactivity primarily via the urine. In rats 85% of the dose was excreted in urine within 24 hr and 7.5% in faeces by 72 hr. The equivalent values for dogs and goats were 65% and 85%, and 0.6% and 1.8%, respectively. <25% (Rats) and 10% (dogs and goats) of the urinary radioactivity was soluble in organic solvents, most of the water soluble metabolites were glucuronides and/or ethereal sulfates. The following metabolites were identified: desmethyl chlorodimeform; *N*-formyl-*p*-chloro-*o*-toluidine; *p*-chloro-*o*-toluidine; *N*-formyl-5-chloroanthranilic acid; 5-chloroanthranilic acid; in addition to a number of other unidentified metabolites. Storage of ¹⁴C-chlordimeform and its metabolites in rat and dog tissue and its elimination in goat milk were negligible. *p*-Chloro-*o*-toluidine comprised only 0.9% of total radioactivity in selected tissues of rats sacrificed 72 hr after administration (20).

Rat liver microsomal enzymes catalyse the *N*-demethylation and hydrolysis of chlordimeform *in vitro*. The major product, 4'-chloro-*o*-formotoluidine, is further converted by a liver enzyme into *p*-chloro-*o*-toluidine (21).

¹⁴C-chlordimeform is also metabolised by human embryonic lung cells *in vitro* to 4'-chloro-*o*-formotoluidine (82%) and *p*-chloro-*o*-toluidine (2.3%) (22).

Irritancy

Dermal rabbit (duration unspecified) 500 mg caused mild irritation and 100 mg instilled into rabbit eye caused mild irritation (23).

Genotoxicity

Salmonella typhimurium TA98, TA100, TA1535, TA1537, TA1538 with and without metabolic activation negative (24).

Escherichia coli WP2 UVR A with and without metabolic activation negative (24).

Saccharomyces cerevisiae D3 system with and without metabolic activation induction of mitotic recombination negative. No induction of unscheduled DNA synthesis was found in W138 human lung fibroblasts (24).

Other effects

Other adverse effects (human)

It has not been established whether chlordimeform itself is a bladder irritant. The ability of its metabolite *p*-chloro-*o*-toluidine to cause urinary tract injury in humans has, however, been established (17).

In 9/22 cases of acute poisoning, exposed workers complained of dysuria, nocturia, gross haematuria, penile discharge, back ache, abdominal pain and 'feeling hot'. Other symptoms included drowsiness, skin rash, anorexia and a sweet taste in the mouth. All manifestations of illness, including cystitis, resolved slowly over 3-8 wk (25). Studies of three hospitalised workers revealed haematuria and pyuria, proteinuria, low creatine clearance, decreased serum complement level, elevated serum glutamic oxaloacetic transaminase activity, small urinary bladder capacity and ureteral reflux. Bladder biopsy showed severe haemorrhagic cystitis. Microscopic haematuria was also found in 1/6 farmers who had used chlordimeform, which had resolved itself after 3 wk (25).

Legislation

Limited under EC Directive on Drinking Water Quality 80/778/EEC. Pesticides: maximum admissible concentration 0.1 µg l⁻¹ (26).

Included in Schedule 6 (Release into Land: Prescribed Substances) Statutory Instrument No. 472, 1991 (27). WHO Toxicity Class II (28).

Other comments

Believed to be no longer manufactured, or marketed for crop protection use (1).

A sublethal dose (causing 1% mortality) in ♀ cabbage looper moths (*Trichoplusia ni*) stimulated calling behaviour and pheromone emission early in the scotophase, resulting in depleted pheromone reserves. The mating success of males was decreased; mated females laid fewer eggs and hatchability was lower than in untreated controls (29). The major metabolites in plants are *N*-(4-chloro-*o*-tolyl)*N*-methylformamidine, *N*-formyl-4-chloro-*o* toluidine and 4-chloro-*o*-toluidine (30).

Chlordimeform has an enhancing effect on permethrin, almost doubling its toxicity to honey bees one day after spraying onto cotton plant leaves (2).

Environmental health criteria reviewed (31).

Neurotoxicity in insects reviewed (32).

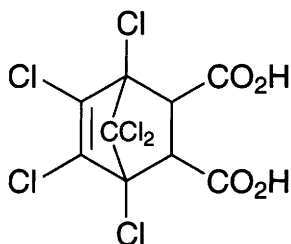
Metabolic fate and degradation in the presence of soil microorganisms reviewed (30).

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c122 chlorendic acid



C₉H₄Cl₆O₄

Mol. Wt. 388.84

CAS Registry No. 115-28-6

Synonyms 1,4,5,6,7,7-hexachloro-5-norbornene-2,3-dicarboxylic acid; 1,4,5,6,7,7-hexachlorobicyclo-[2.2.1]hept-5-ene-2,3-dicarboxylic acid; NCI-C55072; Het Acid

EINECS No. 204-078-9

RTECS No. RB 9000000

Uses Production of fire-resistant plastics, resins and adhesives.

Physical properties

M. Pt. 208-210°C **Specific gravity** 0.95

Solubility Water: 3 g l⁻¹ at 21°C. Organic solvents: acetone, benzene, ethanol, methanol

Mammalian & avian toxicity

Acute data

LD₅₀ oral rat 1770 mg kg⁻¹ (1).

Sub-acute and sub-chronic data

Oral rat (13 wk) up to 1% diet, and in mice up to 2% diet, decreased weight gain was observed in all groups. Dose-related histomorphological changes were noted in livers of ♂ and ♀ rats at 0.5 and 1.0% dose. Changes included cytomegaly and mitotic changes. In mice compound-related histomorphological changes were observed in the liver. For the highest dose, 10 ♂ and 2 ♀ exhibited centrilobular cytomegaly, 7 ♂ and 7 ♀ exhibited mitotic alteration, and 8 ♂ and 1 ♀ exhibited coagulative necrosis. Mitotic alteration was noted in mice for the lower doses (2).

Carcinogenicity and chronic effects

No adequate data for carcinogenicity to humans, sufficient evidence for carcinogenicity in animals, IARC classification group 2B (3).

The National Toxicology Program tested ♂ and ♀ rats and mice via feed. Clear evidence of carcinogenicity in ♂ and ♀ rats and ♂ mice, no evidence of carcinogenicity in ♀ mice (4).

Following oral administration of 620 and 1250 mg kg⁻¹ to rats and mice for 103 wk, hepatocellular adenomas and carcinomas were observed in ♂ mice and an increase in the incidence of alveolar/bronchiolar tumours and follicular-cell adenomas in animals of each sex and hepatocellular carcinomas in ♀; in ♂ rats it induced an increase in the incidence of alveolar/bronchiolar adenomas and of acinar-cell adenomas of the pancreas (5). Oral rat (2 yr) dietary trials of up to 1250 mg kg⁻¹ increased incidence of liver cystic degeneration and bile duct hyperplasia in ♂ and liver granulomatous inflammation and pigmentation and bile duct hyperplasia in ♀ were observed. Liver lesions were also reported in mice similarly treated, and increased incidences of necrosis in ♂ (5).

Metabolism and toxicokinetics

Following oral and intravenous administration to rats, distributed to various tissues, principally the liver. Excreted primarily through bile and faeces. Within one day 75% of dose was excreted in faeces. Some was also excreted in the bile and urine. Excretory products included the parent compound and conjugates resistant to β-glucuronidase and aryl sulfatase (6).

Irritancy

Dermal rabbit (24 hr) 500 mg caused mild irritation and 250 µg instilled into rabbit eye caused severe irritation (1).

Genotoxicity

Mouse lymphoma forward mutation assay with and without metabolic activation positive (7).

Legislation

Limited under EC Directive on Drinking Water Quality 80/778/EEC. Organochlorine compounds: guide level 1 µg l⁻¹ (8).

Included in Schedule 6 (Release into Land: Prescribed Substances) of Statutory Instrument No. 472, 1991 (9).

Other comments

May be released by hydrolytic degradation of polyesters incorporating it. Oxidation product of heptachlor and its metabolites.

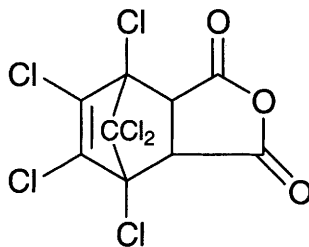
Reviews on human health effects, experimental toxicology and environmental effects listed (10).

Environmental health criteria reviewed (11).

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C123 chlorendic anhydride



$C_9H_2Cl_6O_3$

Mol. Wt. 370.83

CAS Registry No. 115-27-5

Synonyms 4,5,6,7,8,8-hexachloro-3a,4,7,7a-tetrahydro-4,7-methanoisobenzofuran-1,3-dione;
1,4,5,6,7,7-hexachlorobicyclo[2.2.1]hept-5-enedicarboxylic anhydride

EINECS No. 204-077-3

RTECS No. RB 9080000

Uses Used in the preparation of polyester resins.

Physical properties

M. Pt. 231-235°C

Solubility Water: miscible. Organic solvents: acetone, benzene, toluene

Occupational exposure

Supply classification irritant

Risk phrases Irritating to eyes, respiratory system and skin (R36/37/38)

Safety phrases Keep out of reach of children (if sold to general public) – Avoid contact with the eyes (S2, S25)

Mammalian & avian toxicity

Acute data

LD₅₀ oral rat, mouse 2300-2400 mg kg⁻¹ (1).

Teratogenicity and reproductive effects

Oral pregnant rats (6-15 day gestation) 400 mg kg⁻¹ caused dose-related decreases in maternal weight, foetal sex ratio and increased post-implantation losses (2).

Metabolism and toxicokinetics

Following oral administration to rats the primary route of excretion was the faeces, with 70% of the administered doses of up to 5.55 mg kg⁻¹ eliminated within 72 hr. 10% was eliminated in urine. After 192 hr maximum tissue residues were <0.1 ppm, except in fat (0.121 ppm) and liver (0.296 ppm). Blood concentrations peaked after 1 hr. t_{1/2} for fat was 22.5 days, and 2 days for other tissues (3).

Genotoxicity

Salmonella typhimurium TA98, TA100, TA1535, TA1537, TA1538 with and without metabolic activation negative (4).

Saccharomyces cerevisiae D4 with and without metabolic activation negative (4).

Legislation

Limited under EC Directive on Drinking Water Quality 80/778/EEC. Organochlorine compounds: guide level 1 µg l⁻¹ (5).

Included in Schedule 6 (Release into Land: Prescribed Substances) of Statutory Instrument No. 472, 1991 (6).

No-effect level for domestic water as determined in the former USSR from mammalian toxicity tests 50 µg kg⁻¹.

Maximum permissible concentration in domestic water in the former USSR 1.0 mg l⁻¹ (7).

Other comments

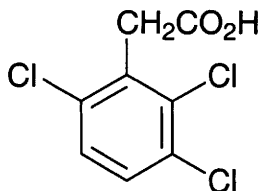
Reviews on human health effects, experimental toxicology, ecotoxicology, physico-chemical properties and environmental effects listed (8).

Environmental mental health criteria reviewed (9).

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c124 chlorfenac



$C_8H_5Cl_3O_2$

Mol. Wt. 239.48

CAS Registry No. 85-34-7

Synonyms 2,3,6-trichlorophenylacetic acid; Fenatrol; Kanepar; TCPA; Tri-fen; Fenab; Fenac

EINECS No. 201-599-3

RTECS No. AJ 8750000

Uses Herbicide.

Physical properties

M. Pt. 160°C Volatility v.p. 8.3×10^{-3} mmHg at 100°C

Solubility Water: 200 mg l⁻¹ at 28°C. Organic solvents: acetone, diethyl ether, ethanol

Occupational exposure

Supply classification harmful, dangerous for the environment

Risk phrases Harmful if swallowed – Toxic to aquatic organisms, may cause long-term adverse effects in the aquatic environment (R22, R51/53)

Safety phrases Keep out of reach of children (if sold to general public) – Wear suitable protective clothing – Avoid release to the environment. Refer to special instructions/safety data sheet (S2, S36, S61)

Ecotoxicity

Fish toxicity

LC₅₀ (96 hr) rainbow trout 11 mg l⁻¹ (1).

LC₅₀ (96 hr) bluegill sunfish 41 mg l⁻¹ (1).

LC₅₀ (96 hr) redear sunfish 12 mg l⁻¹ (1).

Mammalian & avian toxicity

Acute data

LD₅₀ oral ring-necked pheasant, Japanese quail, mallard duck >5000 mg kg⁻¹ (2).

LD₅₀ oral rat 1780 mg kg⁻¹ (3).

LD₅₀ dermal rabbit 1440-3160 mg kg⁻¹ (4).

Carcinogenicity and chronic effects

In a 2-yr feeding trial rats receiving 2000 mg kg⁻¹ diet showed no ill-effects (4).

Metabolism and toxicokinetics

52.8% of dose (unspecified) was excreted in urine of a lactating cow as 2,3,6-trichlorophenylacetic acid glucuronide ester, and 18.6% as the free acid. There was no excretion by the faecal or mammary routes. It was not metabolised by liver drug-metabolising enzymes or ruminal microflora (5).

Following oral application to lactating cattle, no decomposition was identified in the rumen for 7 hr and in a liver fraction for 1 hr. Residues were not detected in the milk or faeces, but were observed in the urine, 18.6% as free acid and 52.8% as conjugated acid (6).

Legislation

Limited under EC Directive on Drinking Water Quality 80/778/EEC. Pesticides and related products: maximum admissible concentration 0.1 µg l⁻¹ (7).

Included in Schedule 6 (Release into Land: Prescribed Substances) of Statutory Instrument No. 472, 1991 (8).

WHO Toxicity Class III (9).

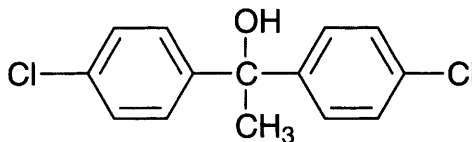
Other comments

Believed to be no longer manufactured, or marketed for crop protection use (10).

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C125 chlorfenethol



$C_{14}H_{12}Cl_2O$

Mol. Wt. 267.15

CAS Registry No. 80-06-8

Synonyms 1,1-bis(4-chlorophenyl)ethanol; benzenemethanol, 4-chloro- α -(4-chlorophenyl)- α -methyl-; dichlorodiphenylethanol; DCPC; DCPE; Dimite

EINECS No. 201-246-3

RTECS No. DC 7875000

Uses Superseded non-systemic acaricide. Insecticide.

Physical properties

M. Pt. 69-71°C

Solubility Organic solvents: benzene, diethyl ether, ethanol

Occupational exposure

Supply classification harmful

Risk phrases Harmful if swallowed (R22)

Safety phrases Keep out of reach of children (if sold to general public) – Wear suitable protective clothing (S2, S36)

Ecotoxicity

Fish toxicity

LC₅₀ (48 hr) carp 1.8 mg l⁻¹ (1).

Mammalian & avian toxicity

Acute data

LD₅₀ oral rat 500 mg kg⁻¹ (2).

LD₅₀ intraperitoneal rat 725 mg kg⁻¹ (3).

Sub-acute and sub-chronic data

Rats tolerated 1000 mg kg⁻¹ in diet for 10 days (4).

A powdered diet containing 0.1% chlorfenethol was well tolerated by growing rats during a 10-wk period; 0.25% was fairly well tolerated but 1% was quickly fatal (4).

Genotoxicity

Salmonella typhimurium TA98, TA100, TA1535, TA1537, TA1538 with and without metabolic activation negative (5).

Legislation

Limited under EC Directive on Drinking Water Quality 80/778/EEC. Pesticides: maximum admissible concentration 0.1 µg l⁻¹ (6).

Included in Schedule 6 (Release into Land: Prescribed Substances) of Statutory Instrument No. 472, 1991 (7). WHO Toxicity Class III (8).

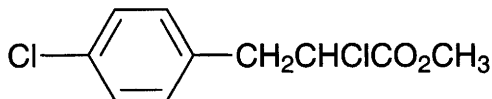
Other comments

Shows a marked synergistic activity when combined with DDT.

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c126 chlorfenprop-methyl



C₁₀H₁₀Cl₂O₂

Mol. Wt. 233.09

CAS Registry No. 14437-17-3

Synonyms Bidisin; Fatex EK80; methyl α ,4-dichlorobenzenepropanoate; methyl p,α -dichlorohydrocinamate

EINECS No. 238-413-8

RTECS No. UE 8840000

Uses Superseded post-emergence herbicide.

Physical properties

M. Pt. >-20°C **B. Pt.** 110-113°C at 0.1 mmHg **Specific gravity** 1.3 at 20°C with respect to water at 4°C

Volatility v.p. 6.975×10^3 mmHg at 50°C

Solubility Water: 400 mg l⁻¹ at 20°C. Organic solvents: acetone, diethyl ether

Occupational exposure

Supply classification harmful, dangerous for the environment

Risk phrases Harmful in contact with skin and if swallowed – Very toxic to aquatic organisms, may cause long-term adverse effects in the aquatic environment (R21/22, R50/53)

Safety phrases Keep out of reach of children (if sold to general public) – Wear suitable protective clothing and gloves – This material and/or its container must be disposed of as hazardous waste – Avoid release to the environment. Refer to special instructions/safety data sheet (S2, S36/37, S60, S61)

Ecotoxicity

Fish toxicity

LC₅₀ (24 hr) harlequin fish 1.85 mg l⁻¹ (1).

Mammalian & avian toxicity

Acute data

LD₅₀ oral rat 1070 mg kg⁻¹ (2).

LC₅₀ (4 hr) inhalation rat >1380 mg m⁻³ (3).

LD₅₀ dermal rabbit 756 mg kg⁻¹ (2).

Sub-acute and sub-chronic data

In 90-day feeding trials, rats fed 1000 mg kg⁻¹ diet suffered no ill-effects. Daily dermal application of 500 μ l kg⁻¹ to rabbits for 14 days was non-toxic (3).

Genotoxicity

Salmonella typhimurium TA97, TA98, TA100 with and without metabolic activation negative (4).

Salmonella typhimurium TA1535, TA1538 without metabolic activation negative (4).

Legislation

Limited under EC Directive on Drinking Water Quality 80/778/EEC. Pesticides and related products: maximum admissible concentration 0.1 µg l⁻¹ (5).

Included in Schedule 6 (Release into Land: Prescribed Substances) of Statutory Instrument No. 472, 1991 (6).

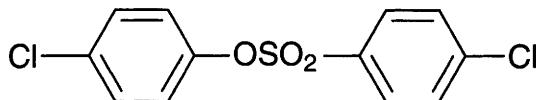
Other comments

Believed to be no longer manufactured, or marketed for crop protection use (7).

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7. *The Pesticide Manual* 11th ed., 1997, The British Crop Protection Council, Farnham, UK

c127 chlorfenson



C₁₂H₈Cl₂O₃S

Mol. Wt. 303.17

CAS Registry No. 80-33-1

Synonyms 4-chlorophenyl 4-chlorobenzenesulfonate; Corotran; Difenson; Estonmite; Ovex; Sappiran

EINECS No. 201-270-4

RTECS No. DB 5250000

Uses Superseded pesticide. miticide.

Physical properties

M. Pt. 86.5-86.8°C

Solubility. Organic solvents: acetone, carbon tetrachloride, cyclohexanone, ethanol, xylene

Occupational exposure

Supply classification harmful

Risk phrases Harmful if swallowed – Irritating to the skin (R22, R38)

Safety phrases Keep out of reach of children (if sold to general public) – Wear suitable gloves (S2, S37)

Ecotoxicity

Fish toxicity

LC₅₀ (48 hr) carp 3.2 mg l⁻¹ (1).

Mammalian & avian toxicity

Acute data

LD₅₀ oral chicken 3780 mg kg⁻¹ (1).
LD₅₀ oral rat, mouse 2000 mg kg⁻¹ (2,3).
LD₅₀ oral rabbit 5660 mg kg⁻¹ (4).
LD₅₀ oral guinea pig 640 mg kg⁻¹ (4).
LD₅₀ dermal rat >10,000 mg kg⁻¹ (1).

Sub-acute and sub-chronic data

Oral rat (130 day) 300 mg kg⁻¹ diet showed no apparent ill-effects (1).
Oral rat (130 day) 3000 mg kg⁻¹ in diet caused significant growth retardation, increased thyroid and liver size, with characteristic histological changes. Except for body growth in ♂, similar but lesser changes were induced with a dose of 1000 mg kg⁻¹. In mice respiratory difficulty and spasms were observed following oral administration of 2000 mg kg⁻¹. In some acutely poisoned mice, the only change noted was haemorrhage of the spleen (5).

Metabolism and toxicokinetics

In the presence of succinate or 2-ketoglutarate substrates chlorfenson did not alter oxygen uptake but increased ATP hydrolysis (in the presence of Mn, Mg and Ca) in metabolic studies of bluegill liver mitochondria (6).

Genotoxicity

Salmonella typhimurium TA98, TA100, TA1535, TA1537, TA1538 with and without metabolic activation negative (6).
Escherichia coli WP hcr with and without metabolic activation negative (7).

Legislation

Maximum permissible concentration in drinking water in the former USSR 0.2 mg l⁻¹ (8).
Limited under EC Directive on Drinking Water Quality 80/778/EEC. Pesticides: maximum admissible concentration 0.1 µg l⁻¹ (9).
Included in Schedule 6 (Release into Land: Prescribed Substances) of Statutory Instrument No. 472, 1991 (10).

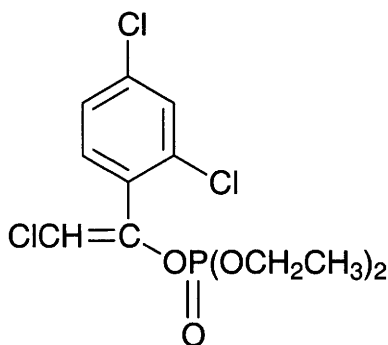
Other comments

Following injection into the cockroach abdomen, decomposition gave rise to *p*-chlorobenzenesulfonic acid. This metabolite was also identified in citrus sapling and soybean seedling (11).
Believed to be no longer manufactured or marketed for crop protection use (12).

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C128 chlorfenvinphos



C₁₂H₁₄Cl₃O₄P

Mol. Wt. 359.57

CAS Registry No. 470-90-6

Synonyms 2-chloro-1-(2,4-dichlorophenyl)vinyl diethyl phosphate; phosphoric acid, 2-chloro-1-(2,4-dichlorophenyl)ethenyl diethyl ester; *O,O*-diethyl *O*-[2-chloro-1-(2,4-dichlorophenyl)vinyl] phosphate; 2,4-dichloro- α -(chloromethylene)benzyl alcohol, diethyl phosphate; Apachlor; Binafos; Birlane; Enolofos; Fliefos; Leptox

EINECS No. 207-432-0

RTECS No. TB 8750000

Uses Insecticide.

Physical properties

M. Pt. -23 to -19°C **B. Pt.** 167-170°C at 0.5 mmHg **Specific gravity** 1.36 at 15.5°C with respect to water at 15.5°C **Partition coefficient** logP = 3.85 (*Z*-isomer), 4.22 (*E*-isomer) **Volatility** v.p. 7.5×10^{-6} mmHg at 25°C **Solubility** Water: 145 mg l⁻¹ at 23°C. Organic solvents: miscible with acetone, dichloromethane, ethanol, hexane

Occupational exposure

Supply classification very toxic, dangerous for the environment

Risk phrases Toxic in contact with skin – Very toxic if swallowed – Very toxic to aquatic organisms, may cause long-term adverse effects in the aquatic environment (R24, R28, R50/53)

Safety phrases Keep locked up and out of the reach of children (if sold to general public) – After contact with skin, wash immediately with plenty of water – Wear suitable protective clothing and gloves – In case of accident or if you feel unwell, seek medical advice immediately (show label where possible) – This material and/or its container must be disposed of as hazardous waste – Avoid release to the environment. Refer to special instructions/safety data sheet (S1/2, S28, S36/37, S45, S60, S61)

Ecotoxicity

Fish toxicity

LC₅₀ (24 hr) harlequin fish 360 µg l⁻¹ (1).

LC₅₀ (24,48 hr) guppy 1560-540 µg l⁻¹ (1,2).

Invertebrate toxicity

LC₅₀ (48 hr) *Paramecium caudatum* 48 mg l⁻¹ (2).

EC₅₀ (48 hr) *Daphnia magna* 18.5 mg l⁻¹ (2).

LC₅₀ (96 hr) *Mytilus galloprovincialis* 26.3 mg l⁻¹ (3).

In five experiments to investigate the effect of chlorfenvinphos (5-day exposure), at a concentration equivalent to the highest recommended dosage for practical use, on mated ♀ rove beetles, mortality was 89-100% and reduction in egg production 63-100% (4).

Slightly toxic to honey bees. Topical LD₅₀ (24 hr) 4.1 µg (1).

Environmental fate

Degradation studies

$t_{1/2}$ soil 2 months, 90% degradation occurred within 12 months (5).

On a peaty soil, chlorfenvinphos was very slowly degraded, 70% of the applied dose remaining after 21 wk and 30% after nearly 12 months, whereas on sandy soils it was much less persistent, only 3-15% remaining after 15 wk (6).

The DT_{50} (disappearance time) in laboratory experiments for single exposure was 15 days and for repeat exposure 6 days. Similar but not significant results were obtained under field conditions (7).

The $t_{1/2}$ range in soil was 12-28 days. Major metabolites detected were 2,4-dichlorophenacyl chloride, 2,4-dichlorobenzoic acid, 2-hydroxy-4-chlorobenzoic acid and 2,4-dihydroxybenzoic acid (8).

Abiotic removal

$t_{1/2}$ in aqueous solution was 86-103 and 40-55 days at -5 and 35°C, respectively (9).

Mammalian & avian toxicity

Acute data

LD₅₀ oral pigeon 14 mg kg⁻¹ (1).

LD₅₀ oral rat 9-14 mg kg⁻¹ (10-12).

LD₅₀ oral mouse 64 mg kg⁻¹ (11).

LD₅₀ intravenous rat 6 mg kg⁻¹ (10).

LC₅₀ rat 0.13 mg l⁻¹ (>1 µm-sized aerosol), 0.51 mg l⁻¹ (<1 µm-sized aerosol). [There was no qualitative difference in lethal profile in cardiorespiration between the two types of aerosol, and the higher lethality of micron-sized aerosols was ascribed to swallowed chlorfenvinphos.] (13).

Sub-acute and sub-chronic data

Intragastric rat 5% of LD₅₀ value given as a single dose or distributed over a 35-day period. Damage to hepatocytic organelles, liver necrosis and haemorrhages were observed (14).

Carcinogenicity and chronic effects

In 2-yr feeding trials, the no-effect level for rats and dogs was 50 µg kg⁻¹ day⁻¹ (1).

Metabolism and toxicokinetics

A single dose administered to rats was quantitatively eliminated in four days, 87.2% in the urine (67.5% in the first day), 11.2% in the faeces and 1.4% in the respired air (15).

Irritancy

No irritant action observed on rabbit skin (11).

Sensitisation

No sensitising action observed on guinea-pig skin (11).

Genotoxicity

Salmonella typhimurium TA98, TA100, TA1535, TA1537, TA1538 with and without metabolic activation negative (16-18).

Other effects

Any other adverse effects

An important factor determining the toxicity of chlorfenvinphos (and other organophosphorus pesticides) to birds is the production in the brain of the active oxon form of the pesticide which inhibits the brain acetylcholinesterases (19).

Oral rat pretreatment (15 mg kg⁻¹, 24 hr before) reduced the lethality of oral chlorfenvinphos greatly and that of intravenous administration to a lesser extent. Brain acetylcholinesterase inhibition by oral and intracranial administration was also decreased by pretreatment (20).

Legislation

Limited under EC Directive on Drinking Water Quality 80/778/EEC. Pesticides: maximum admissible concentration $0.1 \mu\text{g l}^{-1}$ (21).

Included in Schedule 6 (Release into Land: Prescribed Substances) Statutory Instrument No. 472, 1991 (22).

ADI (JMPR) $0.5 \mu\text{g kg}^{-1}$ body weight (23).

WHO Toxicity Class Ia (24).

EPA Toxicity Class (formulation) I (1).

Other comments

In its active form chlorfenvinphos is an inhibitor of 'B' esterases and can affect the activity of these enzymes in soil microorganisms (25).

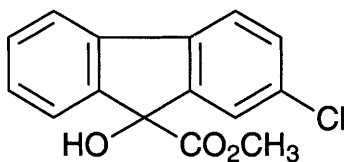
In a study of accumulation in the Mediterranean mussel *Mytilus galloprovincialis* bioconcentration factors were determined experimentally. The authors concluded that the bioaccumulation ability in living tissues represents a potential environmental risk to marine organisms and humans (26).

Metabolism and degradation in soil, water, plants and animals reviewed (27).

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c129 chlorflurenol-methyl



C₁₅H₁₁ClO₃

Mol. Wt. 274.70

CAS Registry No. 2536-31-4

Synonyms chlorflurenol methyl ester; methyl 2-chloro-9-hydroxyfluorene-9-carboxylate; Morphactin; Multiprop; Chlorfurecol; Curbiset

EINECS No. 219-800-8

RTECS No. LL 6070000

Uses Superseded plant growth regulator.

Physical properties

M. Pt. 152°C **Specific gravity** 1.496 at 20°C **Volatility** v.p. 5.0×10^{-5} mmHg at 25°C

Solubility Water: 18 mg l⁻¹ at 20°C. Organic solvents: acetone, benzene, carbon tetrachloride, cyclohexane, ethanol, methanol, propan-2-ol

Ecotoxicity

Fish toxicity

LC₅₀ (96 hr) bluegill sunfish, carp 7.2, 9 mg l⁻¹, respectively (1).

LC₅₀ (96 hr) rainbow trout 15 µg l⁻¹ (1).

Environmental fate

Degradation studies

t_{1/2} in soil approximately 1.5 days and in water ≈2 days. Loss from soil by microbial degradation and photolytic decomposition (1).

Abiotic removal

Under UV irradiation in benzene, 50% decomposition occurs in approximately 10 min (1).

Mammalian & avian toxicity

Acute data

LD₅₀ oral rat 3100 mg kg⁻¹ (2).

LD₅₀ oral quail >10,000 mg kg⁻¹ (1).

LD₅₀ intraperitoneal rat, mouse 1410, 1670 mg kg⁻¹, respectively (1).

LD₅₀ dermal rat >10,000 mg kg⁻¹ (1).

Carcinogenicity and chronic effects

Oral rat (2 yr) 3000 mg kg⁻¹ in diet and dogs receiving 300 mg kg⁻¹ in diet showed no ill-effects (1).

Metabolism and toxicokinetics

Oral rat (dose unspecified) almost complete elimination occurred within 24 hr (1).

Legislation

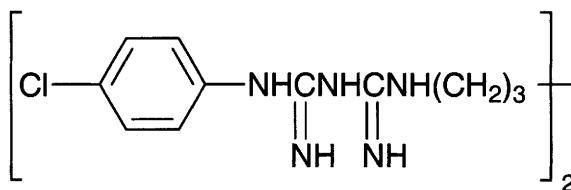
Limited under EC Directive on Drinking Water Quality 80/778/EEC. Pesticides: maximum admissible concentration 0.1 µg l⁻¹ (3).

Included in Schedule 6 (Release into Land: Prescribed Substances) of Statutory Instrument No. 472, 1991 (4).

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c130 chlorhexidine



$\text{C}_{22}\text{H}_{30}\text{Cl}_2\text{N}_{10}$

Mol. Wt. 505.45

CAS Registry No. 55-56-1

Synonyms 1,1'-hexamethylenebis[5-(4-chlorophenyl)biguanide]; *N,N'*-bis(4-chlorophenyl)-3,12-diimino-2,4,11,13-tetraazatetradecanediimidamide

EINECS No. 200-238-7

RTECS No. DU 1925000

Uses Topical antibacterial. Disinfectant.

Physical properties

M. Pt. 134-136°C

Solubility Water: 19 g l⁻¹ at 20°C. Organic solvents: ethanol, glycerol, propylene glycol, polyethylene glycol

Environmental fate

Abiotic removal

Almost complete removal of 0.02 mg l⁻¹ in a hospital wastewater treated by extended aeration, filtration and activated carbon adsorption (1).

Mammalian & avian toxicity

Acute data

LD₅₀ oral rat, mouse 9200, 9850 mg kg⁻¹, respectively (2).

Metabolism and toxicokinetics

Adult human metabolic experiments showed that chlorhexidine (2.0 g) may be hydrolysed to form 4-chloroaniline (3).

Irritancy

Dermal human treated intermittently for three days 1.5 mg caused mild irritation (4).

Tests on nine cationic preservatives (including chlorhexidine) used in ophthalmic formulations and cosmetics, with MDCK epithelial cell line and cultured rabbit corneal epithelial cells as ocular models, indicated that their cytotoxicity was greatly reduced in the presence of tear proteins (5).

Genotoxicity

Salmonella typhimurium TA1535, TA1538 without metabolic activation positive (6).

Other effects

Any other adverse effects

Reported to damage dog kidney cells *in vitro* (7).

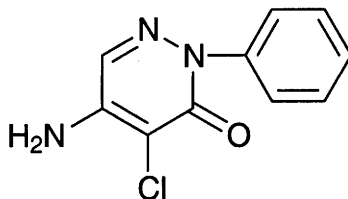
Reported to lyse >40% human and rat corneal epithelial cells *in vitro* when incubated for 15 min at concentrations used in topical ophthalmic medications (8).

Reported to be cytotoxic to both neutrophils and red blood cells over a narrow range of 0.01-0.02% *in vitro*. Serum provided significant protection against cytotoxicity (9).

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c131 chloridazon



C₁₀H₈ClN₃O

Mol. Wt. 221.65

CAS Registry No. 1698-60-8

Synonyms 1-phenyl-4-amino-5-chloropyridazin-6-one; 5-amino-4-chloro-2-phenylpyridazin-3(2H)-one; burex; PAC; PCA; Phenazon; Pyramin; Pyrazone; Suzon; Barbetol; Betamin; Better; Booster; Brek

EINECS No. 216-920-2

RTECS No. UR 6125000

Uses Herbicide.

Physical properties

M. Pt. 205-206°C (decomp.) **Partition coefficient** log P_{ow} 2.2 (1) **Volatility** v.p. <7.5 × 10⁻⁸ mmHg at 20°C

Solubility Water: 400 mg l⁻¹ at 20°C. Organic solvents: acetone, benzene, chloroform, cyclohexane, diethyl ether, dichloromethane, ethyl acetate, methanol

Occupational exposure

Supply classification irritant

Risk phrases May cause sensitisation by skin contact (R43)

Safety phrases Keep out of reach of children (if sold to general public) – Avoid contact with the skin – Wear suitable gloves (S2, S24, S37)

Ecotoxicity

Fish toxicity

LC₅₀ (96 hr) trout 27 mg l⁻¹ (for 65% wettable powder formulation) (1).

Environmental fate

Degradation studies

In soil microbial degradation involves cleavage of the phenyl group to give 5-amino-4-chloropyridazin-3(2H)-one, which is not active herbicidally. Persists in soil for 6-8 wk in sufficiently moist conditions (1,2).

Adsorption and retention

Freundlich isotherm for soil 10-500 µg l⁻¹ (3).

Forms stable complexes with montmorillonite (4).

Mammalian & avian toxicity

Acute data

LD₅₀ oral rat, guinea pig, mouse, rabbit 647, 760, 1000, 2000 mg kg⁻¹, respectively (1,5-7).

LC₅₀ (4 hr) inhalation rat >5.4 mg l⁻¹ air (7).

LD₅₀ dermal rat, rabbit >2000 mg kg⁻¹ (1,7).

LD₅₀ intraperitoneal rat, mouse 410, 600 mg kg⁻¹, respectively (5).

Carcinogenicity and chronic effects

Oral rat, mouse (2 yr) no-adverse-effect level for rats 150 mg kg⁻¹ diet, for mice 500 mg kg⁻¹ diet (1).

Teratogenicity and reproductive effects

Intravenous hamster, lowest toxic dose 175 mg kg⁻¹ on 8th day of gestation (foetal death) (8).

Irritancy

Slight skin irritant, non-irritating to rabbit eyes (1).

500 mg instilled into rabbit eye caused mild irritation (9).

Legislation

Limited under EC Directive on Drinking Water Quality 80/778/EEC. Pesticides: maximum admissible concentration 0.1 µg l⁻¹ (10).

Included in Schedule 6 (Release into Land: Prescribed Substances) Statutory Instrument No. 472, 1991 (11).

WHO Class Table 5 (12).

EPA Toxicity Class III (1).

Other comments

Metabolic pathways reviewed (13).

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c132 chlorinated paraffins

CAS Registry No. 63449-39-8

Synonyms chlorinated paraffin waxes; hydrocarbon waxes, chlorinated; Aloten; Cereclor S52; Cloparin; Cloparol; Hordaflex; Chlorez; Chlorowax; Flexchlor

EINECS No. 264-150-0

RTECS No. RV 0450000

Uses In luminescent and fire-retardant paints. Plasticisers, adhesives and binders, and fireproofing agents. Additives for lubricants.

Physical properties

Solubility Organic solvents: oils

Ecotoxicity

Fish toxicity

LC₅₀ (96 hr) rainbow trout 520-1630 ppm (1).

LC₅₀ (96 hr) bluegill sunfish >300 ppm (1).

Bleak exposed to 0.1 or 1.0 mg l⁻¹ (duration unspecified) caused neurotoxic effects including disorientation and tetanic spasm and some fatalities (2).

Investigations in carp show labelled C₁₄ chlorinated paraffins were metabolised to ¹⁴CO₂ (6% within 96 hr). Carp injected with labelled C₁₆ chlorinated paraffins showed strong labelling of bile and intestinal contents.

C₁₅ chlorinated paraffins are most probably biotransformed into biogenic molecules used in the anabolism of fish since labelling of tissues with high cell turnover rates was observed (3,4).

Bioaccumulation

Bioconcentration factor in freshwater fish 5.4 (Cereclor S52) (5).

Non-accumulative or low accumulative (6).

Accumulation in *Mytilus edulis* was 3250 ng g⁻¹ (1).

Environmental fate

Degradation studies

Confirmed non-biodegradable (6).

Mammalian & avian toxicity

Acute data

LD₅₀ oral rat >21.5 ml kg⁻¹ for a sample of average chain length C₁₂ and average degree of chlorination 59% (7).

LD₅₀ oral rat >4 g kg⁻¹ (8).

Sub-acute and sub-chronic data

Rats did not appear to be affected by dermal absorption of daily doses of 1 g for 42 day (8).

Oral rat (90 day) 200-300 ppm in food, no adverse effects observed. Concentrations >500 ppm caused weight decrease in a time-dependent manner (8).

Carcinogenicity and chronic effects

Chlorinated paraffins of average carbon-chain length C_{12} and average degree of chlorination approximately 60% are possibly carcinogenic to humans, IARC classification group 2B (9).

A sample (average chain length C_{12} , average degree of chlorination 60%) fed orally (duration and concentration unspecified) to mice increased the incidence of alveolar/bronchiolar carcinomas in ♂ and of follicular-cell tumours of the thyroid gland in ♀. In rats, it increased the incidences of hepatocellular tumours in animals of each sex – of follicular cell tumours of the thyroid in ♀, and of mononuclear cell leukaemia in ♂ (10).

A sample (average chain length C_{23} , average degree of chlorination 43%) fed orally (duration and concentration unspecified) increased the incidence of malignant lymphomas in ♂ mice and induced pheochromocytomas of the adrenal medulla in ♀ (10).

Both of the above studies were interpreted as equivocal evidence of carcinogenicity to animals (9).

Metabolism and toxicokinetics

Single oral dose mallard duck 10 g kg^{-1} (Cereclor S52) short-chain paraffins (C_{14} – C_{17}) detected primarily in feathers but also in liver, gut, heart, muscle and fat. Long-chain paraffins (C_{22} – C_{26}) accumulate in the same organs but to a much lesser extent (1).

Following intravenous or oral administration to mice of three ^{14}C -labelled chlorodecanes of different chlorine content (17.5%, 55.9% and 68.5%) there was a marked uptake of label in the liver fat, salivary glands, bone marrow and thymus. The concentration of radioactivity in the tissues and the amount of exhaled ^{14}C (carbon dioxide) were inversely related to the degree of chlorination of the paraffins (11).

Labelled C_{16} chlorinated paraffins administered to rats (dose unspecified), less than 3% of unchanged compound was excreted in bile. Metabolites with acidic or amphoteric properties were detected and the formation of mercapturic acid pathway metabolites was suggested (12,13).

Detected in human adipose tissue in concentrations of 200 ng g^{-1} (14).

Irritancy

Dermal rabbit (24 hr) 100 mg caused mild irritation and 100 mg instilled into rabbit eye caused mild irritation (duration unspecified) (15).

Genotoxicity

Salmonella typhimurium TA98, TA100, TA1535, TA1537 with and without metabolic activation negative (8,16).

In vivo rat bone marrow chromosomal aberrations negative (17).

Other effects

Any other adverse effects

Accumulation in grey seal 75 ng g^{-1} and in heron, guillemot and herring gull $100\text{--}900\text{ ng g}^{-1}$ (18).

Intravenous mouse (duration unspecified) $30\text{--}300\text{ mg kg}^{-1}$ caused significant decrease in motor capacity. Animals dosed with 300 mg kg^{-1} showed a decrease in rectal temperature of $1\text{--}3\text{ }^{\circ}\text{C}$ (19).

Legislation

Included in Schedule 6 (Release Into Land: Prescribed Substances) Statutory Instrument No. 472, 1991 (20).

Limited under EC Directive on Drinking Water Quality 80/778/EEC. Organochlorine compounds: guide level $1\text{ }\mu\text{g l}^{-1}$ (21).

Other comments

Analysis of water and sediment samples in the UK and Switzerland quantified the following amounts of chlorinated paraffins in water and sediment. Freshwater: not detectable – 2.5 ng g^{-1} ; freshwater sediment UK: not detectable – 100 ng g^{-1} and freshwater sediment Zurich: 5 ng g^{-1} . Marine water: not detectable – 6 ng g^{-1} ; marine sediment UK: not detectable – 100 ng g^{-1} and sewage sludge 30 ng g^{-1} (14,18).

Detected in marine and fresh water and in sediments in industrial areas. Residues have also been found in aquatic fauna (18).

Occupational exposure and health hazards reviewed (22).

Reviews on experimental toxicology and human health effects listed (23).

Chlorinated paraffins can be thermally transformed. At temperatures of 300-700°C in air and in air-deficient atmospheres, C₁₂ chlorinated paraffins (59% Cl) formed unchlorinated aromatic compounds (toluene, biphenyl, naphthalene) and chlorobenzene and dichlorostyrene. C₁₂ chlorinated paraffins (70% Cl) resulted in large amounts of polychlorinated aromatic compounds (24).

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c133 chlorinated paraffins (C₁₂, 60% Cl)

CAS Registry No. 108171-26-2

Synonyms alkanes, chlorinated; chloroalkanes, C10-C12; paraffin waxes and hydrocarbon waxes, chlorinated

RTECS No. RV 0480000

Uses Used in lubricants and detergents. Flame retardant. Plasticiser.

Physical properties

Specific gravity 1.36 at 25°C

Solubility Organic solvents: benzene, chloroform, diethyl ether, ethanol, tetrachloroethylene

Ecotoxicity

Bioaccumulation

No absorption in Atlantic salmon exposed to chlorinated paraffins adsorbed on silica (1).

Fingerling rainbow trout were fed a diet fortified with 10% chlorwax for up to 82 days. Chlorinated paraffin residues were found as high as 1.1 ppm in tissues. No gross toxicological effects were noted although weight gain was less than in controls (2).

Non-accumulative or low accumulative (3).

Accumulation in *Mytilus edulis* was 3250 ng g⁻¹ (4).

Environmental fate

Degradation studies

Confirmed non-biodegradable (3).

Abiotic removal

Undergoes photochemical decomposition (5).

Mammalian & avian toxicity

Acute data

LD₅₀ oral rat >21.5 ml kg⁻¹ (6).

Sub-acute and sub-chronic data

Oral rat (14 and 90 day) 100 mg kg⁻¹ day⁻¹ in diet caused enlarged livers and hepatocellular hypertrophy. In the 90-day studies chronic nephropathy and thyroid hyperplasia were also observed at doses of 100 mg kg⁻¹ day⁻¹ (7). Gavage rat (16 day) 7500 mg kg⁻¹ day⁻¹ caused deaths and reduced body weight gains in ♂ and ♀ rats, while all mice receiving doses of 3750 mg kg⁻¹ died. Gavage rat (90 day) 5000 mg kg⁻¹ day⁻¹ no deaths observed and gavage mice (90 day) 2000 mg kg⁻¹ day⁻¹ no deaths observed. However, liver weights were increased in rats and mice, and hypertrophy of hepatocytes was evident microscopically. Focal hepatic necrosis was observed in mice. Nephrosis was evident in high-dose rats (8).

Carcinogenicity and chronic effects

No adequate evidence for carcinogenicity in humans, sufficient evidence for carcinogenicity in animals, IARC classification group 2B (9).

Gavage rat (104 wk) non-neoplastic lesions, including minimal necrosis and hypertrophy of the liver, were associated with treatment. Severe chronic renal disease with secondary parathyroid hyperplasia and subsequent fibrous osteodystrophy and inflammation and hyperkeratosis of the forestomach were seen in ♂ rats.

Nephropathy was also increased in ♀ rats and mice (8).

National Toxicology Program (2 yr) testing in rats and mice (concentrations unspecified). Clear evidence of carcinogenicity in ♂ rats in haematopoietic system, kidney, liver and pancreas; in ♀ rats in haematopoietic system, liver and thyroid gland; in ♂ mice in liver, including liver, adenomas; in ♀ mice in liver (including adenomas) and thyroid gland (10).

Gavage mice, rats (103/104 wk) 0, 125 or 250 mg kg⁻¹ (mice) and 0, 312 or 625 mg kg⁻¹, (rats). In mice an increased incidence of hepatocellular tumours in both sexes, alveolar/bronchiolar carcinomas in ♂ and follicular cell tumours of thyroid gland in ♀, was observed. In rats there was an increased incidence of hepatocellular tumours in both sexes, and of follicular cell tumours of the thyroid in ♀ and of mononuclear cell leukaemia in ♂ (11).

Teratogenicity and reproductive effects

No teratogenic effects were observed in rats and rabbits treated by gavage on gestation days 6-19 and 6-27, respectively (doses unspecified) (7).

Metabolism and toxicokinetics

Following oral or intravenous administration to mice of ¹⁴C-labelled compound, exhaled ¹⁴C carbon dioxide was quantified in animals pretreated with cytochrome P450 inducers and inhibitors. These studies suggested that cytochrome P450 catalysed a dechlorination reaction which was followed by β-oxidation and incorporation of the carbon chain into endogenous metabolism (12).

Detected in human adipose tissue at concentrations of 200 ng g⁻¹ (13).

Irritancy

Do not appear to be irritants or sensitisers in humans (14).

Genotoxicity

Salmonella typhimurium TA98, TA100, TA1535, TA1537 with and without metabolic activation negative (15).

Did not induce dominant lethal mutations in rats *in vivo* (7).

Other effects

Any other adverse effects

Accumulation of C₁₀₋₂₀ chlorinated paraffins in grey seal liver and blubber 75 ng g⁻¹, and in heron, guillemot and herring gull livers 100-900 ng g⁻¹ (4).

Legislation

Included in Schedule 6 (Release into Land: Prescribed Substances) Statutory Instrument No. 472, 1991 (16).

Limited under EC Directive on Drinking Water Quality 80/778/EEC. Organochlorine compounds: guide level 1 µg l⁻¹ (17).

Other comments

Analysis of water and sediment samples in the UK and Switzerland quantified the following amounts of C₁₀₋₃₀ chlorinated paraffins in water and sediment. Freshwater: not detectable-2.5 ng g⁻¹; freshwater sediment UK: not detectable-100 ng g⁻¹ and freshwater sediment Zurich: 5 ng g⁻¹. Marine water: not detectable-6 ng g⁻¹; marine sediment UK: not detectable-100 ng g⁻¹ and sewage sludge 30 ng g⁻¹. In all analyses, C₁₀₋₂₀ chlorinated paraffin levels were slightly higher than C₂₀₋₃₀ levels (4,13).

Chlorinated paraffins can be thermally transformed. At temperatures of 300-700°C in air and in air-deficient atmospheres, C₁₂ chlorinated paraffins (59% Cl) formed unchlorinated aromatic compounds (toluene, biphenyl, naphthalene) and chlorobenzene and dichlorostyrene. C₁₂ chlorinated paraffins (70% Cl) resulted in large amounts of polychlorinated aromatic compounds (18).

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C134 chlorinated paraffins (C₂₃, 43% Cl)

CAS Registry No. 108171-27-3

Synonyms alkanes (C₂₂₋₂₆), chlorinated; chlorinated C₂₂₋₂₆ alkanes; paraffin waxes and hydrocarbon waxes, chlorinated

RTECS No. RV 0490000

Uses Plasticiser.

Physical properties

Solubility Organic solvents: mineral oils

Ecotoxicity

Bioaccumulation

Non-accumulative or low accumulative (1).

Accumulation of C₂₀₋₃₀ chlorinated paraffins in *Mytilus edulis* was 10 ng g⁻¹ (2).

Environmental fate

Degradation studies

Confirmed non-biodegradable (1).

Mammalian & avian toxicity

Acute data

No fatalities resulted from a single oral dose of 10 ml kg⁻¹ to rats (3).

Sub-acute and sub-chronic data

Gavage rat (14 and 90 day) no compound-related effects were reported in the 14-day study, but ♀ rats given doses of >100 mg kg⁻¹ in the 90-day study showed an increase in liver weight and lesions described as multifocal granulomatous hepatomas. ♂ Rats dosed at 3750 mg kg⁻¹ day⁻¹ showed increased nephrosis while ♀ had increased kidney mineralisation (4).

Gavage rats, mice (16 and 90 day) no significant toxicity was observed in the 16- or 90-day studies at doses up to 3750 mg kg⁻¹ day⁻¹ in rats and 7500 mg kg⁻¹ day⁻¹ in mice, with the exception of granulomatous inflammation of the livers in ♀ rats in the 90-day study (5).

Gavage rats, mice (14 day) 2 g kg⁻¹ day⁻¹ to ♂ rats and 1 g kg⁻¹ day⁻¹ to ♀ rats and mice of both sexes caused increased liver weight and proliferation of hepatic smooth endoplasmic reticulum (6).

Carcinogenicity and chronic effects

No adequate evidence for carcinogenicity to humans, limited evidence for carcinogenicity in animals, IARC classification group 3 (7).

Gavage rats, mice (2 yr) non-neoplastic lesions in rats of each sex included lymphocytic infiltration and granulomatous inflammation of the liver including the mesenteric and pancreatic lymph nodes, with associated lymphoid hypoplasia and splenic congestion. Increased kidney tubule pigmentation and nephropathy occurred in ♀ rats. No significant non-neoplastic lesion was seen in mice treated with up to 5000 mg kg⁻¹ day⁻¹ (5).

No evidence of carcinogenicity in ♂ rats, equivocal evidence in ♀ rats. Clear evidence in ♂ mice, tumours in haematopoietic system. Equivocal evidence in ♀ mice (8).

National Toxicology Program tested ♂, ♀ rats and mice via gavage. Clear evidence of carcinogenicity as evidenced by increase of malignant neoplasms, increase of a combination of malignant and benign neoplasms or marked increase in benign neoplasms in ♂ mice. Equivocal evidence in ♀ rats and mice and no evidence in ♂ rats (9).

Teratogenicity and reproductive effects

No teratogenic effect was observed in rats and rabbits treated by gavage on gestation days 6-19 and 6-27 respectively (dose unspecified) (4).

Metabolism and toxicokinetics

Detected in human adipose tissue at concentrations of 200 ng g⁻¹ (10).

Genotoxicity

Salmonella typhimurium (strains unspecified) with and without metabolic activation negative (7,9).

Did not induce chromosomal aberrations in rat bone marrow when administered by gavage at toxic doses of up to 5 g kg⁻¹ day⁻¹ for 5 days (4).

Other effects

Any other adverse effects

Accumulation of C₂₀₋₃₀ chlorinated paraffins in heron and herring gull livers 100-150 ng g⁻¹ (2).

Legislation

Included in Schedule 6 (Release into Land: Prescribed Substances) Statutory Instrument No. 472, 1991 (11).

Limited under EC Directive on Drinking Water Quality 80/778/EEC. Organochlorine compounds: guide level 1 µg l⁻¹ (12).

Other comments

Analysis of water and sediment samples in the UK and Switzerland quantified the following amounts of C₁₀₋₃₀ chlorinated paraffins in water and sediment. Freshwater: not detectable-2.5 ng g⁻¹; freshwater sediment UK: not detectable-100 ng g⁻¹ and freshwater sediment Zurich: 5 ng g⁻¹. Marine water: not detectable-6 ng g⁻¹; marine sediment UK: not detectable-100 ng g⁻¹ and sewage sludge 30 ng g⁻¹. In all analyses C₁₀₋₂₀ chlorinated paraffin levels were slightly higher than C₂₀₋₃₀ levels (2,10).

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Cl₂

Mol. Wt. 70.91

CAS Registry No. 7782-50-5

Synonyms molecular chlorine; dichlorine

EINECS No. 231-959-5

RTECS No. FO 2100000

Uses Manufacture of chlorinated lime. Reagent in synthetic chemistry. Military poison gas. Purifying water. Bleach. Disinfecting. De-tinning and de-zincing iron. Used in plastics manufacture.

Occurrence Ozone depleting species found in the stratosphere. Found in seawater and in igneous rock (95% of earth's crust).

Physical properties

M. Pt. -101°C **B. Pt.** -34.05°C **Specific gravity** 1.4085 at 5216 mmHg and 20°C with respect to water at 4°C

Volatility v.p. 4800 mmHg at 20°C ; v.den. 2.49

Solubility Water: 6.52 g l⁻¹ at 25°C

Occupational exposure

DE-MAK 0.5 ppm (1.5 mg m⁻³)

FR-VLE 1 ppm (3 mg m⁻³)

JP-OEL 1 ppm (2.9 mg m⁻³)

SE-LEVL 0.5 ppm (1.5 mg m⁻³)

SE-CEIL 1 ppm (3 mg m⁻³)

UK-LTEL 0.5 ppm (1.5 mg m⁻³)

UK-STEEL 1 ppm (2.9 mg m⁻³)

US-TWA 0.5 ppm (1.5 mg m⁻³)

US-STEEL 1 ppm (2.9 mg m⁻³)

UN No. 1071 **HAZCHEM Code** 2XE **Conveyance classification** toxic gas, fire intensifying hazard, corrosive
Supply classification toxic

Supply classification dangerous for the environment

Risk phrases Toxic by inhalation – Irritating to eyes, respiratory system and skin – Very toxic to aquatic organisms (R23, R36/37/38, R50)

Safety phrases Keep locked up and out of the reach of children (if sold to general public) – Keep container in a well ventilated place – In case of accident or if you feel unwell, seek medical advice immediately (show label where possible) – Avoid release to the environment. Refer to special instructions/safety data sheet (S1/2, S9, S45, S61)

Ecotoxicity

Fish toxicity

Fathead minnow exposed in partial chronic toxicity test. Lowest effective concentration and no-effect concentration were 42 and 14 µg l⁻¹, respectively. Fry survival was the most sensitive response (1).

LC₅₀ (96 hr) rainbow trout 0.17 mg l⁻¹ (total chlorine) (2).

LC₅₀ (96 hr) yellow perch 0.88 mg l⁻¹ (3).

LC₅₀ (96 hr) channel catfish 70 µg l⁻¹ (total chlorine) (3).

LC₅₀ (1 hr) coho salmon 0.20 mg l⁻¹ (3).

Invertebrate toxicity

LC₅₀ (96 hr) grass shrimp 0.22 mg l⁻¹ (3).

LC₅₀ (1 hr) *Daphnia magna* 6 µg l⁻¹ (4).

LC₅₀ (1 hr) *Gammarus affinis* 0.84 mg l⁻¹ (4).

LC₅₀ (static, 24 hr, added food) *Ceriodaphnia dubia* hypochlorous acid 0.14 mg l⁻¹, hypochlorite ion 0.08 mg l⁻¹.

However, free chlorine reacts very rapidly (<1 min) with the *C. dubia* food mix, so the standard toxicity test measured the toxicity of chlorinated food rather than the toxicity of free chlorine. Static tests without food showed

LC₅₀ hypochlorous acid 0.035 mg l⁻¹, hypochlorite ion 0.048 mg l⁻¹. The free chlorine still decayed rapidly (<7 hr) in the test solution. LC₅₀ (continuous flow, 24 hr) hypochlorous acid 0.005 mg l⁻¹, hypochlorite ion 0.006 mg l⁻¹ (5).

Environmental fate

Anaerobic effects

Activated sludge digestion is not affected by concentrations up to 10 mg l⁻¹ and the process may be gradually acclimatised up to 20 mg l⁻¹ (6).

Mammalian & avian toxicity

Acute data

LC₅₀ (1 hr) inhalation rat 293 ppm (7).

LC₅₀ (1 hr) inhalation mouse 137 ppm (7).

LC_{Lo} (4 hr) inhalation rabbit 660 ppm (8).

LC_{Lo} (7 hr) inhalation guinea pig 330 ppm (8).

Sub-acute and sub-chronic data

Chlorine was administered to rats in drinking water for 90 days. The highest dose of 250 mg l⁻¹ produced no observable adverse effects (9).

Chlorine was administered to pigeons in drinking water at 2.0 or 15 mg l⁻¹, with a normocholesterolemic diet with calcium reduced to 80% normal levels. At one and three months there was no evidence of any effect on circulating lipid levels or upon development of arteriosclerotic plaques (10).

Oral ♂ and ♀ B6C3F1 mice (90 days) 12.5, 25, 50, 100, 200 mg l⁻¹ in drinking water. Results suggested that chlorine induces its effects via an indirect mechanism, e.g. nutritional deficiencies, rather than by a direct toxicological effect on specific organs or tissues (11).

RD₅₀ mice (airborne concentration resulting in a 50% decrease in respiratory rate) 3.5 ppm. On the basis of a TLV-STEL equal to 0.1 RD₅₀ and a TLV-TWA equal to 0.3 RD₅₀, the authors propose that the current TLVs for chlorine (1 and 0.5 ppm, respectively) are too high and should be reduced to 0.5 and 0.1 ppm, respectively (12).

Carcinogenicity and chronic effects

Equivocal evidence for carcinogenicity (marginal increase in the incidence of mononuclear cell leukaemia) in ♀ rats administered chlorinated drinking water at the maximum chlorine concentration that the animals would accept. The equivalent chlorine concentration administered as bromodichloromethane induced neoplasms of the large intestine in rats. The authors suggest that organic by-products of chlorination are the chemicals of greatest concern in assessment of the carcinogenic potential of chlorinated drinking water (13).

In a seven-generation study, the incidence of malignant tumours in rats consuming drinking water containing free chlorine at 10 mg kg⁻¹ body weight day⁻¹ did not differ from that of controls (14).

Oral ♂, ♀ rats (2 yr) free chlorine in drinking water 13 or 26 and 53 or 106 mg kg⁻¹ day⁻¹, respectively. A dose-related depression in body weight gain was observed in all groups, and liver, brain and heart weights were depressed in ♂ at a dose of 13 mg kg⁻¹ day⁻¹. No adverse haematological effects or increase in non-neoplastic lesions were observed (15).

The National Toxicology Program tested rats and mice via drinking water. No evidence of carcinogenicity in mice and ♂ rats, equivocal evidence of carcinogenicity in ♀ rats (16).

F344 rats and B6C3F1 mice were exposed to chlorine gas – 0, 0.4, 1.0, or 2.5 ppm 6 h day⁻¹ – 5 days wk⁻¹ (mice and ♂ rats) or 3 alternate days wk⁻¹ (♀ rats). ♂ Mice and ♀ rats appeared more sensitive to chlorine than ♀ mice and ♂ rats, respectively. Exposure-dependent lesions were confined to the nasal passages in all sex and species groups. The incidence of neoplasia was not increased by exposure, indicating that inhaled chlorine in rats and mice is an upper respiratory tract toxicant but not a carcinogen (17).

Teratogenicity and reproductive effects

Mice administered drinking water containing 10 mg l⁻¹ residual chlorine (~ 1.9 mg kg⁻¹ body weight day⁻¹) showed no adverse reproductive effects (18).

Irritancy

Allergic dermatoses were observed among occupationally exposed workers (19).

Genotoxicity

In vivo oral mice (duration unspecified) 8 mg kg⁻¹ day⁻¹ did not cause any significant increases in erythrocyte micronuclei or chromosomal aberrations of bone marrow (20).

Other effects

Other adverse effects (human)

Human volunteers ingested progressively increasing doses of chlorine in drinking water every 3 days for 18 days at concentrations of 0, 0.1, 1.0, 5.0, 10.0, 18.0 and 24.0 mg l⁻¹. This was followed by daily ingestion of 5 mg l⁻¹ for 12 consecutive wk. No significant toxic effects were observed (21).

In humans, symptoms of acute respiratory distress resulting from chlorine inhalation include coughing, bloody sputum, chest pain, dyspnoea and cyanosis. Tracheobronchitis, pulmonary oedema and pneumonia may supervene later (22).

In humans, 0.2 ppm for 4-20 min caused itching of the nose; 1 ppm sore eyes, dry throat, coughing and a feeling of difficulty in inhaling. 1.3 ppm caused some subjects severe shortness of breath and violent headache after 30 min. Throat irritation was observed after exposure to 15 ppm and cough at 30 ppm. 1000 ppm was reported to be fatal after a few breaths (23).

Concentrations of up to 15 ppm caused a case of chronic poisoning after several years exposure (24).

Decreased lung capacity in workers 3 yr after moderately severe acute exposure (25).

Workers, 239, at risk from inhalational accidents involving chlorine ("puffs") were assessed. No relationship was found between persistent symptoms and the exposure variables studied. In workers who experienced more than 10 puffs with mild symptoms, repeated exposure to chlorine with acute respiratory symptoms was associated with a slight but significant reduction in expiratory flow rates, without long-term symptoms (26).

High atmospheric concentrations are asphyxiant by causing muscular spasms of the larynx (choking), swelling of the mucous membranes, nausea, vomiting, anxiety, syncope, and may be fatal (27).

Legislation

Limited under EC Directive on Drinking Water Quality 80/778/EEC, Article 8. Residual chlorine levels in water for human consumption must not be higher than the maximum admissible concentration (28).

Included in Schedule 4 (Release into Air: Prescribed Substances) Statutory Instrument No. 472, 1991 (29).

Maximum permitted concentration in UK drinking water supplies for combined concentration of chlorine dioxide, chlorite and chlorate 0.5 mg l⁻¹ as chlorine dioxide (30).

Other comments

Kentucky blue grass subjected to three applications of chemical solutions to simulate exposure to swimming pool run-off water containing chlorine did not have any phytotoxic effect. The highest concentrations used were 100-150 µg ml⁻¹ Cl (31).

Using *Salmonella typhimurium* TA1535/pSK1002 carrying the umu-lacZ fusion gene (which can detect genotoxicity via β-galactosidase activity) chlorine treatment of 10 amino acids (arg, gly, his, hyp, lys, met, phe, pro, ser, thr) was found to result in genotoxic amino acid derivatives. Derivatives of four other amino acids (ala, ile, leu, val) were not genotoxic (32).

When used in disinfection of water supplies, may react with trace organic compounds which can have varying organoleptic and toxic properties (33).

Mixtures with gases (e.g. hydrogen, oxygen) are explosive. Violent reaction with alcohols. Potentially dangerous reaction with hydrocarbons. Decomposes to hydrogen chloride gas.

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c136 chlorine dioxide



ClO_2

Mol. Wt. 67.45

CAS Registry No. 10049-04-4

Synonyms chlorine peroxide; chlorine oxide; chlorine(IV) oxide; chloroperoxyl; Anthium dioxide; Aromabator PC-80; Microbator PC-78; Carnebon 200

EINECS No. 233-162-8

RTECS No. FO 3000000

Uses Bleaching agent. Oxidising agent. Bactericide. Antiseptic. Disinfectant, taste and odour control in water supplies.

Physical properties

M. Pt. -59°C B. Pt. 11°C Specific gravity 1.642 at 0°C with respect to water at 4°C

Solubility Water: soluble in water

Occupational exposure

DE-MAK 0.1 ppm (0.28 mg m⁻³)

FR-VME 0.1 ppm (0.3 mg m⁻³)

SE-LEVL 0.1 ppm (0.3 mg m⁻³)

UK-LTEL 0.1 ppm (0.28 mg m⁻³)

US-TWA 0.1 ppm (0.28 mg m⁻³)

FR-VLE 0.3 ppm (0.8 mg m⁻³)

SE-STEEL 0.3 ppm (0.8 mg m⁻³)

UK-STEEL 0.3 ppm (0.84 mg m⁻³)

US-STEEL 0.3 ppm (0.83 mg m⁻³)

Ecotoxicity

Invertebrate toxicity

Embryos of *Strongylocentrotus purpuratus* purple sea urchin (48 hr) 250 mg l⁻¹ at 15°C caused developmental abnormalities. Fertilised eggs of *Paralabrax clathratus* (48 hr) ≥25 mg ClO₂ l⁻¹ at 20°C caused no adverse effects. Minimal toxicity is predicted from intermittent discharge of chlorine-treated waters into marine environment (1). LC₅₀ (7 days, intermittent exposure, 30 min day⁻¹) adult zebra mussel 13.0 mg l⁻¹. A single 30 min exposure to ≥20 mg l⁻¹ caused ≥50% mortality in adult zebra mussels (2).

Mammalian & avian toxicity

Acute data

LD₅₀ oral rat 292 mg kg⁻¹ (3).

LC_{Lo} (15 min) inhalation rat 500 ppm (4).

Sub-acute and sub-chronic data

Chlorine dioxide administered to rats in drinking water for 90 days produced a dose-related decrease in body and organ weight as low as 25 mg l⁻¹ but its most significant toxic effect was the induction of nasal lesions (5).

Rat pups were administered an oral dose of 14 mg kg⁻¹ day⁻¹ up to 20 days old. Body weight reductions were observed on postnatal days 11, 21 and 35. Forebrain weight and protein content were decreased on days 21 and 35, as were the DNA content on day 35 and the number of dendritic spines on cerebral cortical pyramidal cells. Otherwise cell proliferation in the forebrain, cerebellum and olfactory bulbs was normal, as were the migration and aggregation of neuronal cells in three areas of the cerebral cortex. Histopathology of the forebrain, cerebellum and brainstem showed no gross lesions (6).

♀ Sencar mice were treated with (1, 10, 100, 300, 1000 ppm) whole body exposure (except head) for a 10 min period for 4 days. Animals were killed on days 1, 2, 3, 4, 5, 8, 10 and 12 post-exposure. Chlorine dioxide at 1000 ppm induced hyperplastic responses in mouse skin by day 5 (7).

Rats exposed daily to 10 ppm died after 10-13 days exposure. Effects were nasal and ocular discharge and dyspnoea. Autopsy revealed purulent bronchitis. No adverse reactions were observed in rats exposed to about 0.1 ppm for 5 hr day⁻¹ for 10 wk (8).

Teratogenicity and reproductive effects

Long-Evans rats were dosed with 0.0, 2.5, 5.0, or 10.0 mg kg⁻¹ chlorine dioxide in deionised water, males for 56 days and females for 14 days prior to breeding and throughout the 10-day breeding period. Females continued to be dosed throughout gestation and until lactation day 21. The parent rats showed no clinical signs of toxicity or adverse effects on the reproductive organ weights. Litter size, pup viability and pup weights were not affected. F1 organ weights for testis, epididymis, uterus, and ovaries were not different between groups, but vaginal weight was significantly decreased for female weanlings in the 10 mg kg⁻¹ group relative to controls (9).

Irritancy

100 mg instilled into rabbit eye produced mild irritation (3).

Genotoxicity

In vivo rat bone marrow cells chromosome aberrations positive (10).

Other effects

Other adverse effects (human)

Exposure of a worker to 19 ppm was fatal (duration of exposure not specified) (11).
Repeated acute exposure of workers to undetermined concentrations caused eye and throat irritations, nasal discharge, cough, sneezing, bronchitis, and delayed onset of pulmonary oedema (12).

Legislation

Included in Schedule 4 (Release into Air: Prescribed Substances) of Statutory Instrument No. 472, 1991 (13).
Maximum permitted concentration in UK drinking water supplies for combined concentration of chlorine dioxide, chlorite and chlorate 0.5 mg l⁻¹ as chlorine dioxide (14).

Other comments

Macrocystis pyrifera (48 hr) 25-250 mg ClO₂ l⁻¹ at 15°C inhibited germination of meiospores (1).
Powerful explosive sensitive to spark, impact, sunlight, or heating rapidly to 100°C. Powerful oxidiser.
Concentrations of greater than 10% in air are explosive.
Reviews on experimental toxicology and human health effects listed (15).
Preoxidation by 1, 3 or 5 mg l⁻¹ chlorine dioxide enhanced alum flocculation of *Scenedesmus* spp. The authors conclude chlorine dioxide is suitable for water treatment (16).
Laboratory tests with humic acid solutions and field tests in the Aqueduct of Turin, Italy, were carried out to study the power of some oxidants including chlorine dioxide to produce mutagenicity in drinking water. Water chlorination (NaClO having a much greater effect than ClO₂) caused more mutagenic activity than ozonisation treatment (17).
Disinfection with chlorine dioxide in water treatment reviewed (18-20).

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C137 chlorine pentafluoride



ClF_5

Mol. Wt. 130.44

CAS Registry No. 13637-63-3

Synonyms chlorine fluoride

EINECS No. 237-123-6

RTECS No. FO 2975000

Uses Etching metals.

Occurrence In volcanic gases.

Physical properties

M. Pt. -103°C B. Pt. -13.1°C

Occupational exposure

DE-MAK 2.5 mg m^{-3} (as F) (total dust)

SE-LEVL 2 mg m^{-3} (as F)

UN No. 2548 Conveyance classification toxic gas, fire intensifying hazard, corrosive

Mammalian & avian toxicity

Acute data

LC₅₀ (1 hr) inhalation rat, mouse, monkey 57, 122, 173 ppm, respectively (1).

Irritancy

Dermal rabbit $10 \mu\text{l}$ caused severe irritation with destruction of the skin (2).

Other effects

Any other adverse effects

Inhalation rats, monkeys (1 hr) 10 ppm produced pale livers and kidneys in rats and congested lungs in monkeys (3).

In studies in rats, cats, guinea pigs and rabbits, 10, 25, 50 and $100 \mu\text{l}$ caused death in all species when given parenterally or orally. Intravenous infusion of 10 or $20 \mu\text{l}$ over 15 min to rabbits caused death in 8-12 hr with signs of massive haemorrhage and infarcts in the heart and lung. Slow infusion of $1 \mu\text{l}$ was tolerated as a single dose or when given for as many as 20 consecutive daily doses. In inhalation studies no rats survived 400 ppm for more than 10 min. 30 rats exposed to 200 ppm for 10 min survived 24 hr and almost all rats exposed to 100 ppm for 15 min daily up to 5 days survived, but these rats exhibited weight loss. Following administration of 10 or $20 \mu\text{l}$ in rabbits (route unspecified), respiratory enzyme activity in serum fell to undetectable concentrations. Following topical, parenteral or dermal administration alterations to protein structure were immediately apparent (2).

Legislation

Included in Schedule 4 (Release into Air: Prescribed Substances) Statutory Instrument No. 472, 1991 (4).

Other comments

Corrosive material, vigorous reaction in contact with water or anhydrous nitric acid. Violent reaction on contact with metals.

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c138 chlorine trifluoride



ClF₃

Mol. Wt. 92.45

CAS Registry No. 7790-91-2

Synonyms chlorotrifluoride

EINECS No. 232-230-4

RTECS No. FO 2800000

Uses Fluorinating agent used in the preparation of iron(III) fluoride. Used in nuclear reactor fuel processing. Igniter and propellant for rockets. Etching of silicon.

Physical properties

M. Pt. -76.34°C B. Pt. 11.75°C Specific gravity 4.057 g l⁻¹ at 25°C and 760 mmHg Volatility v.p. 740 mmHg at 11.5°C

Solubility Water: decomposes

Occupational exposure

DE-MAK 0.1 ppm (0.38 mg m⁻³)

FR-VLE 0.4 mg m⁻³

SE-LEVL 2 mg m⁻³ (as F)

UK-STEEL 0.1 ppm (0.38 mg m⁻³)

US-STEEL ceiling limit 0.1 ppm (0.38 mg m⁻³)

UN No. 1749 Conveyance classification toxic gas, fire intensifying hazard, corrosive

Environmental fate

Abiotic removal

Violently hydrolysed by water (1).

Mammalian & avian toxicity

Acute data

LC₅₀ (1 hr) inhalation mouse, monkey, rat 178, 230, 299 ppm, respectively (2,3).

LC_{Lo} (30 min) inhalation rat 400 ppm (4).

Sub-acute and sub-chronic data

Inhalation study on two dogs (6 months) 1.2 ppm 6 hr day⁻¹, 5 day wk⁻¹. Signs of toxicity included coughing, sneezing, rhinorrhea, lachrymation, salivation, panting-type respiration and occasionally coughing up of a frothy fluid. Both dogs developed pneumonia which caused one death on the 115th day (5).

Irritancy

Exposure to 21 ppm for 24 hr caused eye irritation in dogs and rats (6).

Other effects

Any other adverse effects

Inhalation (species, dose and duration unspecified) caused inflammation of the mucosal surfaces, burning of the skin and corneal ulceration. Lung damage was established from decreased release of carbon dioxide from the lung following administration of sodium hydrogen carbonate and from lowered blood pH (6).

Legislation

Included in Schedules 4 and 6 (Release into Air/Land: Prescribed Substances) of Statutory Instrument No. 472, 1991 (7).

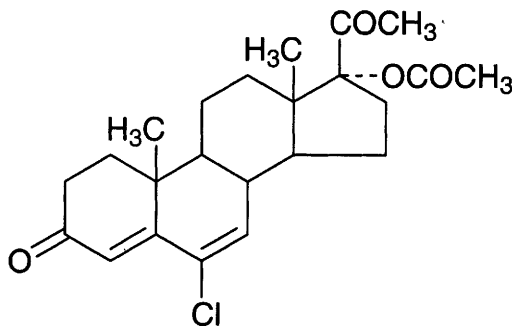
Other comments

Extremely reactive. Glass wool and organic matter burst into flames on contact with dilute vapours. Violently hydrolysed by water. Attacks quartz if traces of moisture are present.

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c139 chlormadinone acetate



$C_{23}H_{29}ClO_4$

Mol. Wt. 404.93

CAS Registry No. 302-22-7

Synonyms 17-acetoxy-6-chloro-6-dehydroprogesterone; 6-chloro-17-acetoxy-4,6-pregnadiene-3,20-dione; Cap; Chlordion; Lormin; Lutinyl

EINECS No. 206-118-0

RTECS No. TU 3750000

Uses Progestogen. Antineoplastic (hormonal). Oral contraceptive.

Physical properties

M. Pt. 212-214°C

Solubility Organic solvents: chloroform, diethyl ether, ethanol, methanol

Mammalian & avian toxicity

Acute data

LD₅₀ intraperitoneal mouse 3000 mg kg⁻¹ (1).

Carcinogenicity and chronic effects

No adequate data for carcinogenicity in humans, limited evidence for carcinogenicity in animals, IARC classification group 3 (2).

Following oral administration to mice for 80 wk at doses up to 400 × the human contraceptive dose (amounts unspecified) there was no increase in the incidence of tumours. When administered in combination with mestranol (25:1) there was a 5 to 10-fold increase in pituitary tumours (3).

Oral administration of 0.25 mg kg⁻¹ day⁻¹ to dogs for up to 7 yr induced mammary tumours (4).

Teratogenicity and reproductive effects

Oral administration of up to 50 mg kg⁻¹ to mice and rabbits resulted in dose-related incidence of malformations in offspring and embryoletality (5).

Metabolism and toxicokinetics

Readily absorbed from rat intestine; absorption is modulated by biliary constituents (6).

Metabolised in rabbits by two main pathways: 2-hydroxylation and dechlorination at C-6; and, to some extent, by hydrogenation of one or both of the ring double bonds. A small amount of metabolite oxidised at C-21 was detected (7).

Readily absorbed from gastro-intestinal tract. Distributed in body fat from which it is slowly released (8).

Sensitisation

Autoimmune dermatitis was reported in one patient following administration of chlormadinone acetate (9).

Genotoxicity

Salmonella typhimurium TA100, TA1535, TA1537, TA1538 with and without metabolic activation negative (10).

No chromosomal effects were observed when 0.1 to 100 µg ml⁻¹ were added to human lymphocytes *in vitro* (11).

Other effects

Other adverse effects (human)

Healthy young men were studied in a double-blind, cross-over trial to detect whether or not chlormadinone acetate augments hypoxic chemosensitivity. Seven days after administration inspiratory minute volume and tidal volume increased. Arterial carbon dioxide pressures and plasma bicarbonate levels decreased. Hypoxic ventilatory response increased. The study suggests that chlormadinone acetate augments hypoxic respiratory chemosensitivity (12).

Any other adverse effects

Continuous oral administration increased the incidence of breast nodules in beagle dogs (dose rate and duration unspecified) (9).

Following daily administration (14 days) (dose unspecified) to ♂ rats, ventral prostate and seminal vesical gland weights were increased. Androgenic activity observed (13).

Legislation

Use as oral contraceptive suspended in UK and US in 1970 (9).

Limited under EC Directive on Drinking Water Quality 80/778/EEC. Substances extractable in chloroform: guide level 0.1 mg l⁻¹ dry residue (14).

Other comments

There are wide variations in progestational activity among species (15).

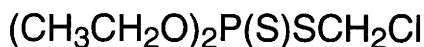
The high sensitivity of dogs may be related to its very slow metabolic breakdown in that species (16).

Prostatic cancer therapy reviewed (17).

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c140 chlormephos



$\text{C}_5\text{H}_{12}\text{ClO}_2\text{PS}_2$

Mol. Wt. 234.71

CAS Registry No. 24934-91-6

Synonyms S-chloromethyl O,O-diethyl phosphorodithioate; phosphorodithioic acid, S-chloromethyl O,O-diethyl ester; Dotan; Geodan

EINECS No. 246-538-1

RTECS No. TD 5170000

Uses Non-systemic insecticide.

Physical properties

B. Pt. 81-85°C at 0.1 mmHg **Specific gravity** 1.260 at 20°C **Volatility** v.p. 5.7×10^{-2} mmHg

Solubility Water: 60 mg l⁻¹ at 20°C. Organic solvents: miscible with most organic solvents

Occupational exposure

Supply classification very toxic

Risk phrases Very toxic in contact with skin and if swallowed (R27/28)

Safety phrases Keep locked up and out of the reach of children (if sold to general public) – After contact with skin, wash immediately with plenty of water – Wear suitable protective clothing and gloves – In case of accident or if you feel unwell, seek medical advice immediately (show label where possible) (S1/2, S28, S36/37, S45)

Ecotoxicity

Fish toxicity

LC₅₀ (96 hr) harlequin fish 2.5 mg l⁻¹ (1).

Invertebrate toxicity

Toxic to bees (2).

Mammalian & avian toxicity

Acute data

LD₅₀ oral rat 7 mg kg⁻¹ (3).

LD₅₀ dermal rat 27 mg kg⁻¹ (2).

LD₅₀ oral quail 260 mg kg⁻¹ (2).

Sub-acute and sub-chronic data

Oral rat (90 day) 0.39 mg kg⁻¹ diet no adverse effect (2).

Metabolism and toxicokinetics

Following oral administration to rats there is almost complete elimination in urine within 24 hr as diethyl phosphate and diethyl phosphorothioate (2).

Genotoxicity

Salmonella typhimurium TA98, TA100 with and without metabolic activation negative (4).

Escherichia coli WP2, WP2 *uvr A* with and without metabolic activation negative (4).

Legislation

Limited under EC Directive on Drinking Water Quality 80/778/EEC. Pesticides: maximum permissible concentration 0.1 µg l⁻¹ (5).

Included in Schedule 6 (Release into Land: Prescribed Substances) Instrument No. 472, 1991 (6).

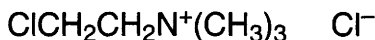
WHO Toxicity Class Ia (7).

EPA Toxicity Class (formulation) I (2).

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C141 chlormequat chloride



$\text{C}_5\text{H}_{13}\text{Cl}_2\text{N}$

Mol. Wt. 158.07

CAS Registry No. 999-81-5

Synonyms 2-chloro-*N,N,N*-trimethylethanaminium chloride; chlorocholine chloride; β -chloroethyltrimethylammonium chloride; (2-chloroethyl)trimethylammonium chloride; β -trimethylchloroethylammonium chloride; choline dichloride; Affix; CeCeCe; Cyofrem; Cycogan; Manipulator; Terbine

EINECS No. 213-666-4

RTECS No. BP 5250000

Uses Plant growth regulator.

Physical properties

M. Pt. 245°C (decomp.) **Volatility** v.p. 0.75 mmHg at 20°C

Solubility Water: >1 kg l⁻¹ at 20°C. Organic solvents: acetone, chloroform, ethanol

Occupational exposure

Supply classification harmful

Risk phrases Harmful in contact with skin and if swallowed (R21/22)

Safety phrases Keep out of reach of children (if sold to general public) – Wear suitable protective clothing and gloves (S2, S36/37)

Ecotoxicity

Fish toxicity

LC₅₀ (72 hr) mirror carp >1000 mg l⁻¹ (1).

LC₅₀ (96 hr) rainbow trout >1000 mg l⁻¹ (1).

Invertebrate toxicity

EC₅₀ (48 hr) *Daphnia* sp. 17 mg l⁻¹ (1).

LC₅₀ (96 hr) fiddler crab ≥1000 mg l⁻¹ (1).

LC₅₀ (96 hr) shrimp 804 mg l⁻¹ (1).

LC₅₀ (96 hr) oyster 67 mg l⁻¹ (1).

Non-toxic to bees (1).

Environmental fate

Degradation studies

In soil, rapidly degraded by microbial action (1).

Has no effect on soil microflora or fauna (1).

Mammalian & avian toxicity

Acute data

LD₅₀ oral pheasant 261 mg kg⁻¹ (1).

LD₅₀ oral chicken 920 mg kg⁻¹ (1).

LD₅₀ oral mouse 54 mg kg⁻¹ (2).

LC₅₀ (4 hr) inhalation rat >5.2 g m⁻³ air (1).

LD₅₀ dermal rabbit 232 mg kg⁻¹ (3).

LD₅₀ intravenous mouse 7 mg kg⁻¹ (4).

LD_{Lo} humans 10 mg kg⁻¹; at these levels automatic nervous system effects such as respiratory depression have been reported (4).

Sub-acute and sub-chronic data

Gavage rat (97 day) unspecified concentration $6 \times \text{wk}^{-1}$. Chlormequat chloride was tolerated well at doses not exceeding $6 \text{ mg kg}^{-1} \text{ day}^{-1}$. Slight damage to internal organs was found in some animals treated with $18 \text{ mg kg}^{-1} \text{ day}^{-1}$. High doses (up to $162 \text{ mg kg}^{-1} \text{ day}^{-1}$) produced a diffuse fatty degeneration of the liver and haemorrhagic pulmonary inflammation. There was no accumulation in the body (5).

Carcinogenicity and chronic effects

Oral rat (108 wk) 1500 or 3000 ppm or oral mouse (102 wk) 500 or 2000 ppm. No tumours occurred that could be associated with the compound (6).

No-observed-effect levels (2 yr) for rats 50, ♂ mice 336, ♀ mice 23 mg kg^{-1} body weight (1).

Metabolism and toxicokinetics

Following oral administration to goats, 97% was eliminated within 24 hr, principally as the unchanged substance (1).

Metabolically inert in rats. Absorption was very rapid, followed by elimination in urine. Small amounts were eliminated via respiratory gases and in the faeces (7,8).

Genotoxicity

At concentrations of 3.2 to 7.9% and pH 6.8 it showed no significant mutation effect whereas at the same concentrations and pH 9 it caused mutations in a valine-sensitive strain of *Escherichia coli* (9).

Did not induce mutagenesis in *Drosophila melanogaster* after abdominal injection or in *Klebsiella pneumoniae* or *Citrobacter freundii* (10).

Other effects

Any other adverse effects

$0\text{--}10^{-3} \text{ M}$ chlormequat chloride had no effect on *in vitro* hepatocytes, mitochondria, and microsomes isolated from ♂ rats (11).

Legislation

Included in Schedule 6 (Release into Land: Prescribed Substances) of Statutory Instrument No. 472, 1991 (12).

Limited under EC Directive on Drinking Water Quality 80/778/EEC. Pesticides: maximum admissible concentration $0.1 \mu\text{g l}^{-1}$ (13).

Tolerable daily intake (TDI), humans $50 \mu\text{g kg}^{-1}$ (14).

WHO Toxicity Class III (15).

EPA Toxicity Class III (1).

Other comments

Soaking gladiolus corms in 25 ppm gibberellic acid and 10,000 ppm chlormequat induced earlier blooming of gladiolus. Spraying before flowering (4-5 leaf stage) induced earlier flowering and enhanced corm and cormel formation (16).

Hygroscopic.

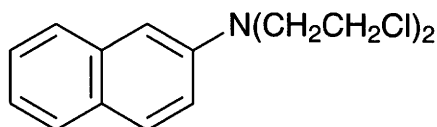
Metabolic pathways reviewed (17).

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c142 chlornaphazine



C₁₄H₁₅Cl₂N

Mol. Wt. 268.19

CAS Registry No. 494-03-1

Synonyms *N,N*-bis(2-chloroethyl)-2-naphthylamine; dichloroethyl-naphthylamine; 2-naphthylamine mustard; Chlornaftina; Erysan

EINECS No. 207-785-0

RTECS No. QM 2450000

Uses Antineoplastic agent, used in treatment of leukaemia and Hodgkin's disease.

Physical properties

M. Pt. 54-56°C **B. Pt.** 210°C at 5 mmHg

Solubility Water: <1 g l⁻¹ at 22°C. Organic solvents: acetone, dimethyl sulfoxide, ethanol

Mammalian & avian toxicity

Acute data

LD₅₀ intraperitoneal rat 1090 mg kg⁻¹ (1).

Sub-acute and sub-chronic data

Oral mice 5 g kg⁻¹ single dose in corn oil caused occasional death during four days post-exposure but median level was not established. Depression of erythropoiesis was observed in mice (2).

Carcinogenicity and chronic effects

Sufficient evidence for carcinogenicity to humans, limited evidence for carcinogenicity to animals, IARC classification group 1 (3).

In long-term rodent carcinogenicity studies chlornaphazine induced lung tumours in test animals. Primary site of induction in humans is the bladder (4).

Among 61 patients with polycythaemia vera treated with chlornaphazine in 1954-1962 and followed until 1974, 8 developed invasive carcinoma of the bladder, 5 developed papillary carcinomas of the bladder and 8 had abnormal urinary cytology. The invasive carcinomas were seen in 4/5 patients treated with a cumulative dose of 200 g or more, in 2/15 patients given 100-199 g, in 1/10 patients given 50-99 g and in 1/31 patients given less than 50 g. No non-causal explanation could be suggested (5).

Genotoxicity

Salmonella typhimurium TA98, TA1538 without metabolic activation negative, with metabolic activation positive (6).

Salmonella typhimurium TA98, TA100, TA1535, TA1537, TA1538 with metabolic activation positive (2).

In vitro Chinese hamster lung cells clastogenic (2).

Induced chromosome aberrations in Chinese hamster ovary cells *in vitro* (7).

Increased sex-linked recessive lethal mutations and chromosome aberrations in *Drosophila melanogaster* (8).

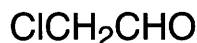
Other comments

Reviews on experimental toxicology and human health effects listed (9).

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C143 chloroacetaldehyde



$\text{C}_2\text{H}_3\text{ClO}$

Mol. Wt. 78.50

CAS Registry No. 107-20-0

Synonyms chloroacetaldehyde monomer; 2-chloroacetaldehyde; 2-chloroethanal; monochloroacetaldehyde

EINECS No. 203-472-8

RTECS No. AB 2450000

Uses Intermediate in the manufacture of 2-aminothiazole. Used to remove bark from tree trunks.

Physical properties

M. Pt. -16.3°C **B. Pt.** 85-86°C **Flash point** 53°C **Volatility** v.p. 100 mmHg at 45°C

Solubility Organic solvents: diethyl ether, ethanol

Occupational exposure

FR-VLE 1 ppm (3 mg m⁻³)

UK-STEL 1 ppm (3.3 mg m⁻³)

US-STEL ceiling limit 1 ppm (3.2 mg m⁻³)

UN No. 2232 **HAZCHEM Code** 2XE **Conveyance classification** toxic substance

Ecotoxicity

Fish toxicity

Chloroacetaldehyde (1-100 $\mu\text{mol l}^{-1}$) toxicity to fertilised zebra fish eggs, from 8-cell stage continuously to hatching, was studied. No-effect level 3 $\mu\text{mol l}^{-1}$, LC_{50} 13.8 $\mu\text{mol l}^{-1}$, LC_{100} 60 $\mu\text{mol l}^{-1}$ (1).

Invertebrate toxicity

IC_{50} *Tetrahymena pyriformis* 10 mg l^{-1} (flask technique), 3 mg l^{-1} (microplate technique) (2).

Mammalian & avian toxicity

Acute data

LD_{50} oral mouse 69 mg kg^{-1} (3).

LD_{50} dermal rabbit 224 mg kg^{-1} (3).

LD_{50} intraperitoneal rat 6 mg kg^{-1} (3).

Sub-acute and sub-chronic data

♂ Sprague-Dawley rats injected with $\geq 0.5\%$ aqueous solution $3 \times \text{wk}^{-1}$ for 12 wk, 5/8 animals in the highest dose group died. The sub-acute LD_{50} was estimated as 3 mg kg^{-1} (3).

Carcinogenicity and chronic effects

In an initiation-promotion experiment with mice, no increase in the incidence of benign or malignant skin tumours was observed (4).

Irritancy

A 40% solution represents a serious hazard to eye and corrosion potential to skin. Inhalation of 5 ppm produced eye and nasal irritation in experimental animals (species unspecified) (5).

Dermal rabbit (duration and concentration unspecified) pure material caused severe and extensive tissue damage. A 0.03% solution caused definite but reversible eye irritation in rabbits, while more concentrated solutions caused extensive eye damage (3).

Sensitisation

Sensitisation potential negative in five guinea pigs using a 0.002% solution (3).

Genotoxicity

Salmonella typhimurium TA100, TA1530, TA1535 with and without metabolic activation negative (6-9).

Induced 8-azaguanine- and ouabain-resistant mutations in Chinese hamster V79 cells in a dose-dependent manner (10).

Exposure of several *trp*-auxotrophic *Escherichia coli* strains, carrying base-pair substitutions, increased the mutation frequency to tryptophan prototropy (11).

Drastically inhibited DNA synthesis in animal cells at 785-1570 $\mu\text{g l}^{-1}$; the inhibitory effect was directly upon DNA synthesis (12,13).

Other effects

Any other adverse effects

Experiments with isolated rat hepatocytes indicate that chloroacetaldehyde-induced hepatocyte toxicity involves reversible thiol protein adduct formation, mitochondrial toxicity and lipid peroxidation (14).

Intraperitoneal rats (30 consecutive days) unspecified concentration caused 67% mortality. Treated rats gained weight more slowly than controls (3).

Other comments

Metabolite of vinyl chloride and of chloroethanol. Rearrangement product of chloroethylene oxide.

Metabolism and genotoxicity reviewed (15).

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C144 2-chloroacetamide



$\text{C}_2\text{H}_4\text{ClNO}$

Mol. Wt. 93.51

CAS Registry No. 79-07-2

Synonyms α -chloroacetamide; 2-chloroethanamide; chloroacetamide

EINECS No. 201-174-2

RTECS No. AB 5075000

Physical properties

M. Pt. 116-118°C (1) B. Pt. 225°C (decomp.)

Solubility Organic solvents: ethanol

Mammalian & avian toxicity

Acute data

LD₅₀ oral rat 70 mg kg⁻¹ (1).

LD₅₀ intraperitoneal mouse 100 mg kg⁻¹ (2).

Sub-acute and sub-chronic data

3-6 hr following intraperitoneal administration of 75 mg kg⁻¹ 2-chloroacetamide to rats, mid-zonal and peripheral lesions developed in the liver parenchyma and lipid peroxidation was enhanced (3).

Sensitisation

Predictive skin sensitisation tests showed that 2-chloroacetamide has skin sensitisation potential (>5% sensitisation index) (4).

2-Chloroacetamide has been declared unsafe for use as a cosmetic ingredient (5).

Genotoxicity

Salmonella typhimurium TA100 with and without metabolic activation negative (5).

Klebsiella pneumoniae fluctuation test, mutagenic activity found (6).

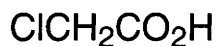
Other comments

Toxicity to humans and laboratory animals has been reviewed (7).

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c145 chloroacetic acid



$\text{C}_2\text{H}_3\text{ClO}_2$

Mol. Wt. 94.50

CAS Registry No. 79-11-8

Synonyms α -chloroacetic acid; chloroethanoic acid; monochloroacetic acid; monochloroethanoic acid; Atlas Somon; Croptex Steel

EINECS No. 201-178-4

RTECS No. AF 8575000

Uses Herbicide. Manufacture of dyestuffs and organic chemicals. Preservative. Bacteriostat.

Physical properties

M. Pt. 62-64°C **B. Pt.** 189°C **Flash point** 126°C **Specific gravity** 1.58 at 20°C with respect to water at 20°C

Volatility v.p. 1 mmHg at 43°C ; v.den. 3.26

Solubility Organic solvents: benzene, chloroform, diethyl ether, ethanol

Occupational exposure

SE-LEVL 1 ppm (4 mg m⁻³)

SE-STEL 2 ppm (8 mg m⁻³)

UK-LTEL 0.3 ppm (1.2 mg m⁻³)

UN No. 1751 (solid)

UN No. 1750 (solution)

UN No. 3250 (molten) **HAZCHEM Code** 2X **Conveyance classification** toxic substance, corrosive

Supply classification toxic, dangerous for the environment

Risk phrases Toxic if swallowed – Causes burns – Very toxic to aquatic organisms (R25, R34, R50)

Safety phrases Keep locked up and out of the reach of children (if sold to general public) – Do not breathe vapour – Wear suitable gloves – In case of accident or if you feel unwell, seek medical advice immediately (show label where possible) – Avoid release to the environment. Refer to special instructions/safety data sheet (S1/2, S23, S37, S45, S61)

Ecotoxicity

Fish toxicity

IC₅₀ *Tetrahymena pyriformis* 83 mg l⁻¹ (flask technique), 16 mg l⁻¹ (microplate technique) (1).

Environmental fate

Nitrification inhibition

Does not inhibit nitrifying bacteria at 100 mg l⁻¹ (2).

Degradation studies

Degraded by sewage microorganisms but the rate of degradation is much slower than that of acetic acid (3).

Mammalian & avian toxicity

Acute data

LD₅₀ oral rat, mouse 55, 165 mg kg⁻¹, respectively (4-6).

LD₅₀ subcutaneous rat 5 mg kg⁻¹ (7).

Sub-acute and sub-chronic data

Gavage B6C3F1 mice (5 days wk⁻¹ for 13 wk) no-observable-effect level 100 mg kg⁻¹ in water (8).

Rats were given 180 mg kg⁻¹ day⁻¹ in drinking water for 90 days. Variable degrees of alteration occurred in the lung and liver. Testes were atrophic with few spermatocytes and no mature spermatozoa. Focal vacuolation and gliosis were present in the forebrain and brainstem (9).

Carcinogenicity and chronic effects

In a 580-day study, 2 mg chloroacetic acid in 0.1 ml acetone was applied to the skin of 50 mice 3 × wk⁻¹. No carcinomas were observed (10).

In a 580-day test, 50 mice were given 0.5 mg chloroacetic acid in 0.05 ml tricapylin subcutaneously 1 × wk⁻¹ for the duration of the experiment. Sarcomas were observed in three mice but this was not considered significant (10).

Metabolism and toxicokinetics

Following administration of ¹⁴C-labelled chloroacetic acid to rats, 82-88% of the radioactivity was found in the urine and 8% in the expired air over a three-day period. The major urinary metabolites were S-carboxymethyl-L-cysteine and thiodiacetic acid; glycolic acid was a minor metabolite (11).

Tracer studies showed that chloroacetic acid and its metabolites accumulate in hydrophilic tissues at early stages of metabolism and in lipophilic tissues later (12).

Irritancy

Dermal rabbit 0.05% solution caused irritation (6).

The solid or solution severely irritated or burned the eyes and caused severe burns to skin (species unspecified) (13).

Genotoxicity

Drosophila melanogaster sex-linked recessive lethal assay, negative results following feeding and equivocal results after injection (14).

Chloroacetic acid did not induce strand breaks in rodent liver (a tissue in which they induce tumours), in rodent hepatocytes in primary culture, or in a human lymphoblastic leukaemia cell line (15).

Salmonella typhimurium TA98, TA100, TA1535 with and without metabolic activation negative (16-18).

Does not induce 8-azaguanine- and ouabain-resistant mutations in Chinese hamster V79 cells (19).

In vitro Chinese hamster ovary cells with and without metabolic activation, chromosomal aberration and sister chromatid exchange negative (20).

Salmonella typhimurium TA100 Ames fluctuation test negative (21).

Escherichia coli PQ 37 SOS chromotest negative (21).

Other effects

Any other adverse effects

Chronic inhalation guinea pigs, rats 5.8 or 20.8 mg m⁻³, respectively, caused decreased oxygen uptake and rectal temperature, haemoglobinaemia and inflammatory changes in the respiratory organs (6).

0.75 mM Chloroacetic acid was toxic to ♂ BALB/s mouse hepatocytes (5 hr *in vitro*) incubation (22).

Legislation

Limited under EC Directive on Drinking Water Quality 80/778/EEC. Pesticides: maximum admissible concentration 0.1 µg l⁻¹ (23).
WHO Toxicity Class III (24).

Other comments

Experimental toxicology and human health effects reviewed (25).

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c146 chloroacetone



C₃H₅ClO

Mol. Wt. 92.52

CAS Registry No. 78-95-5

Synonyms acetonyl chloride; 1-chloro-2-propanone; 1-chloro-2-oxopropane; 1-chloro-2-ketopropane; monochloroacetone

EINECS No. 201-161-1

RTECS No. UC 0700000

Uses Tear gas component for police and military use. Manufacture of couplers for colour photography. Enzyme inactivator. Intermediate in the manufacture of perfumes, antioxidants and drugs. Insecticide formulations. Photopolymerisation of vinyl compounds. Catalyst in tetraethyllead production. Selective solvent for separating diolefins.

Physical properties

M. Pt. -44.5°C B. Pt. 119.7°C Flash point 27°C Specific gravity 1.123 at 25°C with respect to water at 4°C
Solubility Water: 1 g in 10 g. Organic solvents: chloroform, diethyl ether, miscible ethanol

Occupational exposure

US-STEL ceiling limit 1 ppm (3.8 mg m⁻³)

UN No. 1695 HAZCHEM Code 2WE Conveyance classification toxic substance

Ecotoxicity

Fish toxicity

LC₅₀ (14 day) guppy 0.7 mg l⁻¹ (1).

Environmental fate

Abiotic removal

Undergoes hydrolysis, releasing hydrochloric acid, which is responsible for its lachrymatory effect (2).

Mammalian & avian toxicity

Acute data

LD₅₀ oral rat, mouse 100-127 mg kg⁻¹ (2).

LC₅₀ (1 hr) inhalation rat 226 ppm (3).

LC_{Lo} (10 min) inhalation human 605 ppm (4).

LD₅₀ dermal rabbit 141 mg kg⁻¹ (3).

LD₅₀ intraperitoneal rat 80 mg kg⁻¹ (5).

LD₅₀ intraperitoneal mouse 92 mg kg⁻¹ (5).

Acute symptoms after intraperitoneal injection to rats include inhibition of central nervous system, especially respiratory depression, and local irritation of tissues (5).

Carcinogenicity and chronic effects

Dermal albino mice (1 yr) 0.2 ml (in 0.3% acetone) induced papillomas (6,7).

Dermal application to stock mice in 183 days had no tumorigenic effects, but 24 applications to albino mice of 0.2 ml of 0.3% in acetone resulted in 44/19 papillomas compared to 10/20 in controls (8).

Applied topically to SENCAR mice at 50 mg kg⁻¹ in 2 ml ethanol 6 × over 2 wk period did not initiate skin tumours (9).

Metabolism and toxicokinetics

♂ F344 rats received 58 mg kg⁻¹ by gavage. 4-6% of the administered dose was excreted in the bile within 6 hr after dosing. Two major metabolites were identified: 1-(S-glutathionyl)-2-propanone and 1-(S-glutathioyl)-2-cyanopropane in the ratio of ~1:2. These data are indirect evidence that chloroacetone is metabolised via an epoxide intermediate (1-cyano-1-methyloxirane) and catalysed via the cytochrome P450 enzyme system (10).

Irritancy

Reported to be lachrymatory at concentrations of 5-8 ppm (species unspecified) (11).

Genotoxicity

Salmonella typhimurium TA98, TA100 with and without metabolic activation negative (12,13).

Drosophila melanogaster sex chromosome loss and nondisjunction positive (14).

Other effects

Other adverse effects (human)

When used as a war gas, a concentration of 2.3 mg l⁻¹ (605 ppm) was found to be lethal after 10 min and 0.1 mg l⁻¹ (26 ppm) was intolerable after one min exposure. The effect was irritation of the upper respiratory tract and a

burning sensation on exposed skin. Most serious effects, such as pulmonary oedema, did not occur at the low irritating concentration. Even small amounts in the eyes were reported to cause permanent damage (15).

Legislation

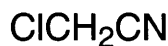
Limited under EC Directive Relating to Drinking Water Quality 80/778/EEC. Organochlorine compounds: guide level $1 \mu\text{g l}^{-1}$ (16).

Included in Schedule 6 (Release into Land: Prescribed Substances) of Statutory Instrument No. 472, 1991 (17).

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c147 chloroacetonitrile



$\text{C}_2\text{H}_2\text{ClN}$

Mol. Wt. 75.50

CAS Registry No. 107-14-2

Synonyms chloromethyl cyanide

EINECS No. 203-467-0

RTECS No. AL 8225000

Uses Analytical reagent. Intermediate in synthetic chemistry. Has been used as a fumigant.

Physical properties

B. Pt. $124\text{--}126^\circ\text{C}$ (1) Flash point 47°C Specific gravity 1.193 at 20°C Partition coefficient $\log P_{\text{ow}}$ 0.23

Volatility v.p. 8.0 mmHg at 20°C ; v.den. 3.0

Solubility Organic solvents: diethyl ether, ethanol

Occupational exposure

UN No. 2668 HAZCHEM Code 2W Conveyance classification toxic substance, danger of fire (flammable liquid)

Supply classification toxic

Risk phrases Toxic by inhalation, in contact with skin and if swallowed (R23/24/25)

Safety phrases Keep locked up and out of the reach of children (if sold to general public) – In case of accident or if you feel unwell, seek medical advice immediately (show label where possible) (S1/2, S45)

Mammalian & avian toxicity

Acute data

LD₅₀ oral mouse, rat 136, 220 mg kg⁻¹, respectively (2).

LC_{Lo} (4 hr) inhalation rat 250 ppm (3).

LD₅₀ intraperitoneal mouse 100 mg kg⁻¹ (4).

Carcinogenicity and chronic effects

Inadequate evidence for carcinogenicity to animals, not classifiable as to its carcinogenicity to humans, IARC classification group 3 (5).

No skin tumours occurred when groups of 40 ♀ Sencar mice were given topical applications of 800 mg kg⁻¹ chloroacetonitrile in 0.2 ml acetone 3 × wk⁻¹ for 24 wk (6).

40 ♀ mice, 10-wk-old, were given 10 mg kg⁻¹ chloroacetonitrile in 10% Emulphor by oral gavage, 3 × wk⁻¹ for 6 wk. At the end of the study the number of animals with lung tumours and the average number of tumours per animal were 9/28 survivors and 0.43 compared with 3/31 and 0.1 for controls (7).

Teratogenicity and reproductive effects

No effect on pregnancy, pup survival or growth after birth was observed in rats administered chloroacetonitrile by gavage at 55 mg kg⁻¹ daily on gestation days 7-21. There was a significant decrease in maternal weight gain and the litter weight at birth was significantly lower than in controls (8).

Metabolism and toxicokinetics

Rats given 57 mg kg⁻¹ chloroacetonitrile dissolved in tricaprylin by gavage excreted 14.2% of the dose in urine as thiocyanate within 24 hr (9).

Chloroacetonitrile is metabolised to hydrogen cyanide by mouse hepatic microsomal fractions (2).

Irritancy

Dermal rabbit (24 hr) 14 mg caused mild irritation (3).

Genotoxicity

Salmonella typhimurium TA98, TA100, TA1535, TA1537 and TA1538 with and without metabolic activation negative (5).

Sister chromatid exchange was induced in one study using Chinese hamster ovary cells (5).

DNA strand breaks were weakly induced using a human lymphoblast cell line (10).

In mice dosed for five days, neither micronuclei nor abnormal sperm morphology was induced (5,11).

Other comments

Toxicology studies of the potential carcinogenic and mutagenic hazards associated with drinking water, including volatile organic compounds and by-products of chlorination reviewed (12).

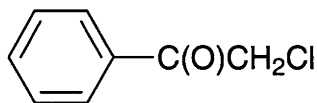
Reacts *in vitro* with calf thymus DNA, alkylating the guanine moiety to form a 7-(cyanomethyl)guanine adduct (13).

References

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9. Pereira, M. et al *J. Toxicol. Environ. Health* 1984, **13**, 633.
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c148 2-chloroacetophenone



C₈H₇ClO

Mol. Wt. 154.60

CAS Registry No. 532-27-4

Synonyms 2-chloro-1-phenylethanone; phenacyl chloride; α -chloroacetophenone; MACE; CN; phenyl chloromethyl ketone

EINECS No. 218-397-6

RTECS No. AM 6300000

Uses Tear gas preparations. Soil pesticide.

Physical properties

M. Pt. 54°C **B. Pt.** 244-245°C **Flash point** 88°C **Specific gravity** 1.188 **Volatility** v.p. 5.4×10^{-3} mmHg
Solubility Organic solvents: benzene, diethyl ether, ethanol

Occupational exposure

FR-VME 0.05 ppm (0.4 mg m⁻³)

UK-LTEL 0.05 ppm (0.32 mg m⁻³)

US-TWA 0.05 ppm (0.32 mg m⁻³)

UN No. 1697 (chloroacetophenone) **Conveyance classification** toxic substance

Mammalian & avian toxicity

Acute data

LD₅₀ oral rat, guinea pig 127, 158 mg kg⁻¹, respectively (1).

LD₅₀ intravenous, intraperitoneal rat 36, 41 mg kg⁻¹, respectively (1).

LC_{Lo} (20 min) inhalation human 159 mg m⁻³ (2).

Carcinogenicity and chronic effects

Rats and mice were exposed to 2-chloroacetophenone vapour 6 hr day⁻¹, 5 day wk⁻¹ for 103 wk. There was no evidence for carcinogenicity in ♂ rats exposed at 1 or 2 mg m⁻³ or in mice exposed at 2 or 4 mg m⁻³ (3).

Irritancy

Dermal rat (6 hr) 12% solution caused moderate irritation (1).

TC_{Lo} (3 min) inhalation human 93 mg m⁻³ severe eye irritation (4).

Rabbits' eyes were contaminated by 2-chloroacetophenone in solution (1-10% in PEG 300), as a solid (0.1 to 5 mg) and as aerosols (15 min exposure to 360-719 mg m⁻³). In solution, it caused marked and persistent inflammatory effects. Corneal damage was marked and persistent with 5 and 10% solutions; the lowest concentrations causing just detectable keratitis in a small proportion of animals was 2%. The solid was even more damaging to the eye

than similar amounts in solution. Aerosols did not damage the eye but irritation of lids and conjunctivitis was marked and persistent (5).

Sensitisation

Caused contact sensitisation or delayed hypersensitivity in guinea pigs by either topical or intradermal administration (6).

Other effects

Any other adverse effects

Signs of toxicity in rats, mice and guinea pigs include lachrymation, salivation, lethargy and laboured breathing (4). Inhalation mice (15 min) 0.469 mg l⁻¹ did not induce any significant change on migration inhibition factor and bactericidal activity of alveolar macrophages (7).

Inhalation mice (5 or 10 days) 87.6 mg m⁻³, 15 min day⁻¹. A significant decrease in body weight gain and decrease in spleen to body weight ratio were observed along with histological changes in lung, liver and kidneys. A toxic response was shown by biochemical indicators, but the only consistent change was an increase in blood glucose (8). Inhalation rat (1 hr) 60.26 mg m⁻³ caused damage evident up to the 30th day post-exposure. During exposure the following effects were observed: necrobiosis, attenuation of bronchiolar epithelium, oedema in the airways and also in the lumen of alveoli, leading to substantial changes in the histoarchitecture of the lung (9).

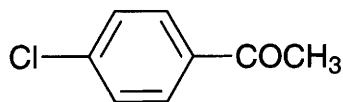
Other comments

Detected in water samples by GLC/MS qualitatively. Toxicity reviewed (10,11).

References

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c149 4'-chloroacetophenone



C₈H₇ClO

Mol. Wt. 154.60

CAS Registry No. 99-91-2

Synonyms 1-(4-chlorophenyl)ethanone

EINECS No. 202-800-7

RTECS No. KM 5600000

Uses Hair perming component.

Physical properties

M. Pt. 20°C **B. Pt.** 233°C (1) **Flash point** 90°C **Specific gravity** 1.192 at 20°C with respect to water at 4°C
Volatility v.p. 0.012 mmHg at 0°C
Solubility Organic solvents: miscible with diethyl ether, ethanol

Mammalian & avian toxicity

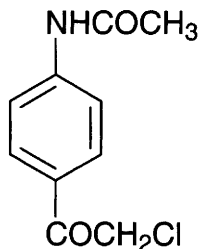
Acute data

LD₅₀ oral mouse 1200 mg kg⁻¹ (2).
LC_{Lo} (1 min) inhalation human 1 mg m⁻³ (3).
LD₅₀ intraperitoneal mouse 100 mg kg⁻¹ (4).

References

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3. Sollman, T. (Ed.) *Manual of Therapeutics and Toxicology* 8th ed., 1957, W. B. Sanders, Philadelphia, USA.
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c150 4-(chloroacetyl)acetanilide



C₁₀H₁₀ClNO₂

Mol. Wt. 211.65

CAS Registry No. 140-49-8

Synonyms *p*-acetamidophenacyl chloride; *p*-(acetylamino)phenacyl chloride; acetamide, *N*-[4-(chloroacetyl)phenyl]-

EINECS No. 205-416-8

RTECS No. AE 1050000

Uses Dyestuff intermediate.

Physical properties

M. Pt. 212°C
Solubility Organic solvents: benzene, diethyl ether

Mammalian & avian toxicity

Acute data

LD₅₀ oral mouse, rat 1470, 2150 mg kg⁻¹, respectively (1).

Carcinogenicity and chronic effects

4-(Chloroacetyl)acetanilide is not carcinogenic when administered in the diet to ♂ and ♀ rats and mice. The high

and low dietary concentrations used were 2000 and 1000 ppm for rats, and 10,000 and 5000 ppm for mice. Doses were administered for 87 wk of a 102-wk period for rats and for 90 wk of a 105-wk period for mice (1).

Genotoxicity

Salmonella typhimurium TA98, TA1537 without metabolic activation positive (2).

References

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c151 chloroacetyl chloride



$\text{C}_2\text{H}_2\text{Cl}_2\text{O}$

Mol. Wt. 112.94

CAS Registry No. 79-04-9

Synonyms chloroacetic acid chloride; chloracetic chloride; monochloroacetyl chloride

EINECS No. 200-171-6

RTECS No. AO 6475000

Uses Acylation reagent. Used in the manufacture of chloroacetophenone.

Physical properties

M. Pt. -22°C B. Pt. $105\text{--}106^\circ\text{C}$ (1) **Specific gravity** 1.418 **Volatility** v.p. 20 mmHg at 21°C

Solubility Water: (decomp.). Organic solvents: acetone

Occupational exposure

FR-VME 0.05 ppm (0.2 mg m^{-3})

US-TWA 0.05 ppm (0.23 mg m^{-3})

US-STEL 0.15 ppm (0.69 mg m^{-3})

UN No. 1752 **HAZCHEM Code** 4WE **Conveyance classification** toxic substance, corrosive

Supply classification corrosive

Risk phrases Causes burns – Irritating to the respiratory system (R34, R37)

Safety phrases Keep locked up and out of the reach of children (if sold to general public) – Keep container in a well ventilated place – In case of contact with eyes, rinse immediately with plenty of water and seek medical advice – In case of accident or if you feel unwell, seek medical advice immediately (show label where possible) (S1/2, S9, S26, S45)

Mammalian & avian toxicity

Acute data

LD₅₀ oral rat 120 mg kg^{-1} (2).

LC₅₀ (4 hr) inhalation rat 1000 ppm (3).

LD₅₀ dermal rat 662 mg kg^{-1} (4).

LD₅₀ intravenous mouse 32 mg kg^{-1} (5).

Irritancy

The vapour is a severe irritant to all parts of the respiratory system (species unspecified) (6,7).

The vapour is an irritant to skin and eyes; liquid may produce skin blisters and burns in eyes (3,6).

Genotoxicity

Chloroacetyl chloride induced neither chromosomal aberrations nor sister chromatid exchange in *in vitro* tests using a Chinese hamster cell line (8).

Other effects

Other adverse effects (human)

Fatalities have resulted from exposure to chloroacetyl chloride. One incident was due to massive skin contact which caused cardiorespiratory arrest within a few minutes. Other data indicate that exposure may promote ventricular arrhythmias (9).

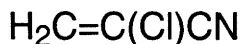
Any other adverse effects

Systemic effects indicated liver damage, carbohydrate and lipid metabolic disorders (3).

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c152 2-chloroacrylonitrile



$\text{C}_3\text{H}_2\text{ClN}$

Mol. Wt. 87.51

CAS Registry No. 920-37-6

Synonyms α -chloroacrylonitrile; 2-propenenitrile, 2-chloro-

EINECS No. 213-055-2

RTECS No. AT 5525000

Uses In the production of synthetic fibres, elastomers and plastics.

Physical properties

M. Pt. -65°C B. Pt. $88-89^\circ\text{C}$ Flash point 6°C Specific gravity 1.096

Mammalian & avian toxicity

Acute data

LD_{50} intravenous mouse 100 mg kg^{-1} (1).

Teratogenicity and reproductive effects

Inhalation Sprague-Dawley ♀ rats (6 hr day $^{-1}$, days 6-20 of gestation) 1-12 ppm. Maternal toxicity was observed, but no significant embryonal or foetal toxicity up to 12 ppm (2).

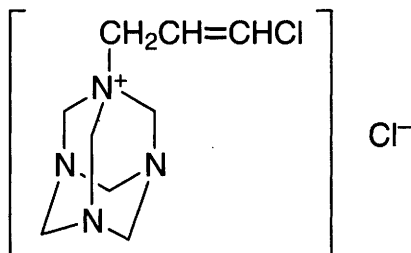
Genotoxicity

Salmonella typhimurium TA100 positive with metabolic activation, equivocal without (3).

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C153 N-(3-chloroallyl)hexaminium chloride



C₉H₁₆Cl₂N₄

Mol. Wt. 251.16

CAS Registry No. 4080-31-3

Synonyms 1-(3-chloroallyl)-3,5,7-triaza-1-azoniaadamantane chloride; Dowcil 200

EINECS No. 223-805-0

RTECS No. XX 8450000

Uses Antimicrobial agent. Preservative in cosmetic formulations. Latex paints. Used in floor cements, adhesives, inks and starches.

Physical properties

Solubility Water: >10 mg ml⁻¹ at 21°C. Organic solvents: ethanol

Environmental fate

Degradation studies

Biodegradable at 125 and 250 ppm in activated sludge; higher concentrations killed the sludge microorganisms (1).

Mammalian & avian toxicity

Acute data

LD₅₀ oral chick 2800 mg kg⁻¹ (2).

LD₅₀ oral ♂ rat, guinea pig 940, 1070 mg kg⁻¹, respectively (2).

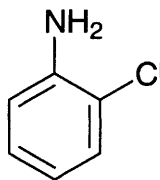
Irritancy

Undiluted material is slightly irritating to the eye. Not absorbed in toxic amounts through rabbit skin when applied for 21 days as a 20% aqueous solution (3).

References

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C154 2-chloroaniline



C_6H_6ClN

Mol. Wt. 127.57

CAS Registry No. 95-51-2

Synonyms 1-amino-2-chlorobenzene; *o*-chloroaniline; *o*-chloraniline; *o*-aminochlorobenzene; Fast Yellow GC Base; 2-chlorobenzenamine

EINECS No. 202-426-4

RTECS No. BX 0525000

Uses Dyestuff.

Physical properties

M. Pt. $-2^{\circ}C$ **B. Pt.** $208.8^{\circ}C$ **Flash point** $97^{\circ}C$ **Specific gravity** 1.213 at $20^{\circ}C$ with respect to water at $4^{\circ}C$

Partition coefficient $\log P_{ow}$ 1.90

Solubility Organic solvents: soluble in most organic solvents

Occupational exposure

UN No. 2018 (solid)

UN No. 2019 (liquid) **HAZCHEM Code** 2X **Conveyance classification** toxic substance

Supply classification toxic

Supply classification dangerous for the environment

Risk phrases Toxic by inhalation, in contact with skin and if swallowed – Danger of cumulative effects – Very toxic to aquatic organisms, may cause long-term adverse effects in the aquatic environment (R23/24/25, R33, R50/53)

Safety phrases Keep locked up and out of the reach of children (if sold to general public) – After contact with skin, wash immediately with plenty of water – Wear suitable protective clothing and gloves – In case of accident or if you feel unwell, seek medical advice immediately (show label where possible) – This material and/or its container must be disposed of as hazardous waste – Avoid release to the environment. Refer to special instructions/safety data sheet (S1/2, S28, S36/37, S45, S60, S61)

Ecotoxicity

Fish toxicity

LC_{50} (96 hr) zebrafish $41 \mu g l^{-1}$ semi-static at $26.5^{\circ}C$ (1).

Guppies (96 hr, static system) biotransformed 2-chloroaniline into 2-chloroacetanilide. This acetylation reaction was shown to be reversible (2).

Toxicity to other species

EC_{50} (7 and 14 days) lettuce *Lactuca sativa* $>32 \mu g g^{-1}$ in soil (3).

EC_{50} (16 – 21 days) lettuce *Lactuca sativa* $31 mg l^{-1}$ in nutrient solution (3).

Bioaccumulation

Non-accumulative or low accumulative (4).

Bioconcentration factor for zebrafish (exposed under static conditions to $0.2 \mu g l^{-1}$) 15.3 (1).

Bioconcentration factor (24-336 hr exposure) for carp exposed to 16.1 and $0.83 \mu g l^{-1}$ under continuous flow-through conditions, 2.0 and 3.7, respectively. Whole-body excretion rate constant $0.19 hr^{-1}$ (5).

Environmental fate

Anaerobic effects

2-Chloroaniline was more toxic to acetoclastic methanogens than to ethanol-degrading methanogens in anaerobic culture (6).

Degradation studies

Biodegradable (4).

Aerobacter sp. 500 mg l⁻¹ incubated with parent compound at 30°C degraded in 60 hr, mutant strain caused 100% ring disruption in 18 hr (7).

Decomposition by soil microflora >64 days (8).

Adapted bench scale activated sludge, fill and draw operations at 20°C, product was used as sole carbon source, 98% COD removal (16.7 mg COD g⁻¹ dry inoculum hr⁻¹) (9).

Warburg respirometer adapted bench scale activated sludge, fill and draw operations from mixed domestic and industrial treatment plant, 22-41% depletion, 20 mg l⁻¹, 6 hr, 25°C (10).

The degradation of a mixture of 13 chloroaromatic compounds including 2-chloroaniline was studied in soil slurries by a mixed culture of *Pseudomonas acidovorans* strain BN3.1, *P. rushlandii* strain FRB2, *P. cepacia* strain JH230 and *P. aeruginosa* strain RHO1. Around 70% of the organically bound chlorine was eliminated in 25 days from soil with a carbon content of 8% when 2-3 × 10⁵ cells g⁻¹ were added to the slurries (11).

Abiotic removal

In a 10-16 wk study, strong sorption occurred and very low degradation of 2-chloroaniline was observed (12).

Mammalian & avian toxicity

Acute data

LD₅₀ oral redwing blackbird 100-562 mg kg⁻¹ (13).

LD₅₀ oral starling >1000 mg kg⁻¹ (13).

LD₅₀ oral Japanese quail >100 mg kg⁻¹ (13).

LD₅₀ oral mouse 256 mg kg⁻¹ (14).

LD₅₀ dermal cat 222 mg kg⁻¹ (14).

Irritancy

Causes skin irritation in mice (15).

Genotoxicity

Salmonella typhimurium TA92, TA94, TA98, TA100, TA1535, TA1537 with and without metabolic activation negative (16,17).

Other effects

Any other adverse effects

In rats, 2-chloroaniline administered intraperitoneally decreased urine volume, elevated the blood urea nitrogen concentration and depressed basal and lactate-stimulated *p*-aminohippurate accumulation by renal cortical slices at 1.0 mmol kg⁻¹ (18).

Male Fischer 344 rats injected intraperitoneally with 1.0 or 1.25 mmol kg⁻¹ 2-chloroaniline suffered oliguria, diminished kidney weight, tubular casts and decreased renal cortical slice accumulation of organic anions. Blood urea nitrogen levels increased, plasma ALT/GPT activities were elevated and altered hepatic morphology in the centrilobular region was seen (19).

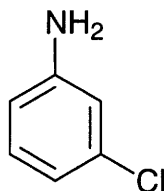
Other comments

Hazardous properties reviewed (20).

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c155 3-chloroaniline



C_6H_6ClN

Mol. Wt. 127.57

CAS Registry No. 108-42-9

Synonyms *m*-chloroaniline; 3-chlorophenylamine; 1-amino-3-chlorobenzene; *m*-aminochlorobenzene; 3-chlorobenzeneamine; Orange GC Base

EINECS No. 203-581-0

RTECS No. BX 0350000

Uses Intermediate for azo dyestuffs and pigments, pharmaceuticals, insecticides and agricultural chemicals.

Physical properties

M. Pt. -10.4°C **B. Pt.** 229.8°C **Flash point** 123°C **Specific gravity** 1.216 at 20°C with respect to water at 4°C
Partition coefficient log P_{ow} 1.88 **Volatility** v.p. 1 mmHg at 63.5°C ; v.den. 4.41
Solubility Organic solvents: soluble in most organic solvents

Occupational exposure

UN No. 2019 (liquid)

UN No. 2018 (solid) **HAZCHEM Code** 2X **Conveyance classification** toxic substance
Supply classification toxic

Risk phrases Toxic by inhalation, in contact with skin and if swallowed – Danger of cumulative effects (R23/24/25, R33)

Safety phrases Keep locked up and out of the reach of children (if sold to general public) – After contact with skin, wash immediately with plenty of water – Wear suitable protective clothing and gloves – In case of accident or if you feel unwell, seek medical advice immediately (show label where possible) (S1/2, S28, S36/37, S45)

Ecotoxicity

Fish toxicity

LC₅₀ (96 hr) zebrafish 147 µm l⁻¹ semi-static at 26.5°C (1).

Guppies (96 hr, static system) biotransformed 3-chloroaniline into 3-chloroacetanilide. This acetylation reaction was shown to be reversible (2).

Toxicity to other species

EC₅₀ (7 and 14 days) lettuce *Lactuca sativa* 17 and 15 µg g⁻¹, respectively, in soil (3).

EC₅₀ (16-21 days) lettuce *Lactuca sativa* 5.9 mg l⁻¹ in nutrient solution (3).

Bioaccumulation

Bioconcentration factor (24-336 hr exposure) for carp exposed to 14.7 and 0.67 µg l⁻¹ under continuous flow-through conditions, 0.8 and 2.2, respectively. Whole-body excretion rate constant 0.21 hr⁻¹ (4).

Bioconcentration factor for zebrafish (exposed under static conditions to 0.2 µg l⁻¹) 11.5 (1).

Environmental fate

Anaerobic effects

3-Chloroaniline was more toxic to acetoclastic methanogens than to ethanol-degrading methanogens in anaerobic culture (5).

Degradation studies

Biodegradable (6).

Biodegradation rates using adapted bench scale activated sludge, fill and draw operations at 20°C, product as sole carbon source, 97.2% COD removal (6.2 mg COD g⁻¹ dry inoculum hr⁻¹) (7).

Aerobacter sp. 500 mg l⁻¹ incubated with parent compound caused 100% ring disruption in 68 hr, while mutant strains caused 100% ring disruption in 16 hr (8).

Decomposition period by unspecified soil microflora >64 days (9).

Warburg respirometer, activated sludge from mixed domestic and industrial treatment plant, 14% depletion, 20 mg l⁻¹, 6 hr, 25°C (10).

The degradation of a mixture of 13 chloroaromatic compounds including 3-chloroaniline was studied in soil slurries by a mixed culture of *Pseudomonas acidovorans* strain BN3.1, *P. rushlandii* strain FRB2, *P. cepacia* strain JH230 and *P. aeruginosa* strain RHO1. Around 70% of the organically bound chlorine was eliminated in 25 days from soil with a carbon content of 8% when 2-3 × 10⁵ cells g⁻¹ were added to the slurries (11).

Abiotic removal

In a 10-16 wk study the degradation rate was 12-17%; >7% was adsorbed onto soil (12).

Mammalian & avian toxicity

Acute data

LD₅₀ oral redwing blackbird 133 mg kg⁻¹ (13).

LD₅₀ oral starling >1000 mg kg⁻¹ (13).

LD₅₀ oral Japanese quail 422 mg kg⁻¹ (13).

LD₅₀ oral rat, mouse 256, 334 mg kg⁻¹, respectively (14,15).

LD₅₀ dermal cat 223 mg kg⁻¹ (15).

Metabolism and toxicokinetics

After oral administration to rats, hydroxylation of the benzene ring, partial acetylation of the amino group, and conjugation of the phenolic compounds with glucuronic and sulfuric acids occur (16).

Genotoxicity

Salmonella typhimurium TA92, TA94, TA98, TA100, TA1535, TA1537 with and without metabolic activation negative (17).

Legislation

Maximum permissible concentration in domestic water in the former USSR 0.2 mg l⁻¹. No-effect level determined for domestic water in the former USSR from mammalian toxicity tests 0.01 mg kg⁻¹ (18).

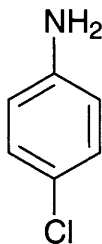
Other comments

Reviews on toxicity and hazards listed (19).

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19. *ECETOC Technical Report No. 71* 1996, European Centre for Ecotoxicology and Toxicology of Chemicals, 4 Avenue E. Van Nieuwenhuysse (Bte 6), B-1160 Brussels, Belgium

c156 4-chloroaniline



C₆H₆ClN

Mol. Wt. 127.57

CAS Registry No. 106-47-8

Synonyms 1-amino-4-chlorobenzene; benzenamine, 4-chloro-; 4-chlorophenylamine; *p*-chloroaniline; 4-chlorobenzeneamine

EINECS No. 203-401-0

RTECS No. BX 0700000

Uses Used as a dyestuffs intermediate and in the manufacture of pharmaceuticals and agricultural chemicals.

Physical properties

M. Pt. 72°C **B. Pt.** 232°C **Flash point** >104°C **Specific gravity** 1.427 at 19°C with respect to water at 4°C
Partition coefficient $\log P_{ow}$ 1.83 **Volatility** v.p. 0.015 mmHg at 20°C ; v.den. 4.41
Solubility Water: 1 mg ml⁻¹ at 21°C. Organic solvents: acetone, diethyl ether, dimethyl sulfoxide, ethanol

Occupational exposure

UN No. 2018 (solid)

UN No. 2019 (liquid) **HAZCHEM Code** 2X **Conveyance classification** toxic substance

Supply classification toxic

Supply classification dangerous for the environment

Risk phrases Toxic by inhalation, in contact with skin and if swallowed – Danger of cumulative effects – Very toxic to aquatic organisms, may cause long-term adverse effects in the aquatic environment (R23/24/25, R33, R50/53)

Safety phrases Keep locked up and out of the reach of children (if sold to general public) – After contact with skin, wash immediately with plenty of water – Wear suitable protective clothing and gloves – In case of accident or if you feel unwell, seek medical advice immediately (show label where possible) – This material and/or its container must be disposed of as hazardous waste – Avoid release to the environment. Refer to special instructions/safety data sheet (S1/2, S28, S36/37, S45, S60, S61)

Ecotoxicity

Fish toxicity

LC₅₀ (96 hr) fathead minnow, rainbow trout 12-14 mg l⁻¹ (1).

LC₅₀ (96 hr) zebrafish 270 µm l⁻¹ semi-static bioassay at 26.5°C (2).

Guppies (96 hr) biotransformed 4-chloroaniline into 4-chloroacetanilide. This acetylation reaction was shown to be reversible (3).

Microinjection of ≥12.5 ng 4-chloroaniline into zebrafish eggs caused ultrastructural changes in both liver and kidney in a dose- and time-dependent fashion (4).

N-Acetylation is the dominant route of *in vivo* metabolism of 4-chloroaniline in rice fish (5).

Invertebrate toxicity

EC₅₀ (48 hr) *Daphnia magna* <10 mg l⁻¹ (6).

Bioaccumulation

Bioconcentration factor for zebrafish (exposed under static conditions to 0.2 µg l⁻¹) 8.1 (2).

Bioconcentration factor (24-336 hr exposure) for carp exposed to 10.4 and 0.3 µg l⁻¹ under continuous flow-through conditions, 0.8 and 1.7, respectively. Whole-body excretion rate constant 0.16 hr⁻¹ (7).

Environmental fate

Anaerobic effects

4-Chloroaniline was more toxic to acetoclastic methanogens than to ethanol-degrading methanogens in anaerobic cultures (8).

Degradation studies

Biodegradation rates using adapted bench scale activated sludge at 20°C, product as sole carbon source, 96.5% COD removal (5.7 mg COD g⁻¹ dry inoculum hr⁻¹) (8).

Aerobacter sp. 500 mg l⁻¹ incubated with parent compound at 30°C caused 100% ring disruption in 59 hr (9).

Decomposition period by an unspecified soil microflora >64 days (10).

Warburg respirometer, activated sludge from mixed domestic and industrial treatment plant, 9-34% depletion, 20 mg l⁻¹, 6 hr, 25°C (11).

In the closed-bottle test, 4-chloroaniline remained highly resistant to biodegradation after 10 days incubation time.

In the simulated activated sludge process, ≈ 97% is bioeliminated after 10-16 days adaptation time (12).

4-Chloroaniline is converted into 4'-chloroacetanilide and 4'-chloropropionaldehyde by soil bacteria, e.g. *Bacillus*

firmus; when the concentration in the culture medium is increased to 3.2 mg ml⁻¹, 7-chloro-2-amino-3H-phenoxazin-3-one is also formed (13).

After 16 wk incubation of labelled 4-chloroaniline with four types of soil at 1 ppm, 80-85% of the label was still present in the soil and only 2-4.5% was extractable (14).

Pseudomonas cepacia, which was isolated from soil, degrades 4-chloroaniline (15).

The degradation of a mixture of 13 chloroaromatic compounds including 4-chloroaniline was studied in soil slurries by a mixed culture of *Pseudomonas acidovorans* strain BN3.1, *P. rushlandii* strain FRB2, *P. cepacia* strain JH230 and *P. aeruginosa* strain RHO1. Around 70% of the organically bound chlorine was eliminated in 25 days from soil with a carbon content of 8% when 2-3 × 10⁵ cells g⁻¹ were added to the slurries (16).

Mammalian & avian toxicity

Acute data

LD₅₀ oral redwing blackbird 100-562 mg kg⁻¹ (17).

LD₅₀ oral starling >1000 mg kg⁻¹ (17).

LD₅₀ oral rat 310 mg kg⁻¹ (18).

LD₅₀ dermal cat 239 mg kg⁻¹ (19).

LD₅₀ intraperitoneal rat 420 mg kg⁻¹ (20).

Inhalation human (1 min) 8 ppm caused severe toxic effects, including methaemoglobinaemia and cyanosis (21).

Sub-acute and sub-chronic data

4-Chloroaniline hydrochloride administered by gavage to groups of 10 rats and 10 mice of each sex for 13 wk. Doses of 0-80 mg kg⁻¹ day⁻¹ for rats and 0-120 mg kg⁻¹ day⁻¹ for mice. No treatment-related effects on organ weights were observed at autopsy except for a dose-related increase in spleen weight. The proportion of haemoglobin in the form of metHb was increased in treated animals and resulted in a secondary anaemia, the severity of which was dose related (22).

Carcinogenicity and chronic effects

4-Chloroaniline was administered in feed for 78 wk to ♂ and ♀ rats and mice at 500 and 250 ppm for rats and 5000 and 2500 ppm for mice. The only neoplastic lesions observed that might be related to the administration were mesenchymal tumours in the spleens of ♂ rats and haemangiomatous tumours in mice. Sufficient evidence was not found to establish the carcinogenicity of 4-chloroaniline to rats and mice (23).

Groups of 50 rats and 50 mice of each sex were given by gavage 4-chloroaniline hydrochloride in deionised water at doses of 0-18 mg kg⁻¹ (rats) or 0-30 mg kg⁻¹ (mice) 5 days wk⁻¹ for 103 wk. In general, body weights and survival were unaffected. Sarcomas of the spleen occurred in ♂ rats, their incidence being 38/50 in the high-dose group. It was concluded that 4-chloroaniline is carcinogenic in ♂ rats and ♂ mice; there is equivocal evidence for ♀ rats and no evidence in ♀ mice (24).

Teratogenicity and reproductive effects

Rats exposed to vapour (10 wk) 0-450 ppm; no effects on fertility observed (21).

Metabolism and toxicokinetics

♂ Sprague-Dawley rats were dosed intraperitoneally with 100 mg kg⁻¹ 4-chloroaniline. The following metabolites were found in the urine 24 hr after dosing: 2,4-dichloroaniline, 2-amino-5-chlorophenol, 4-chloroacetanilide, 4-chloro-2-hydroxyacetanilide, *p*-chloro-oxanilic acid, and unchanged 4-chloroaniline. The same metabolic pathway appeared to be used in both humans and rats (25).

Irritancy

Dermal rabbit (24 hr) 500 mg caused mild irritation and 0.25 mg instilled into rabbit eye for 24 hr caused severe irritation (26).

Genotoxicity

Salmonella typhimurium TA98, TA100 with and without metabolic activation negative (27).

In the spot test, 4-chloroaniline showed no mutagenic effects on the five *Salmonella typhimurium* strains studied, but in the plate incorporation test TA98 showed a significant response with metabolic activation (28).

Aspergillus nidulans without metabolic activation positive (26).

Saccharomyces cerevisiae negative (29).

Caused chromosome aberrations in cultured human lymphocytes (30).

Other effects

Other adverse effects (human)

In humans, absorption through skin can cause methaemoglobinaemia, haematuria, haemorrhagic cystitis (31).

Legislation

Maximum permissible concentration in domestic water in the former USSR 0.2 mg l⁻¹. No-effect level for domestic water in the former USSR from mammalian toxicity tests was 0.01 mg kg⁻¹ (32).

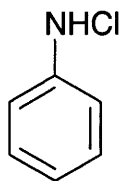
Other comments

Genotoxicity reviewed (33).

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C157 *N*-chloroaniline



C_6H_6ClN

Mol. Wt. 127.57

CAS Registry No. 24613-03-4

Synonyms *N*-chlorobenzenamine; phenylchloramine

Occupational exposure

Supply classification toxic

Supply classification dangerous for the environment

Risk phrases Toxic by inhalation, in contact with skin and if swallowed – Danger of cumulative effects – Very toxic to aquatic organisms, may cause long-term adverse effects in the aquatic environment (R23/24/25, R33, R50/53)

Safety phrases Keep locked up and out of the reach of children (if sold to general public) – After contact with skin, wash immediately with plenty of water – Wear suitable protective clothing and gloves – In case of accident or if you feel unwell, seek medical advice immediately (show label where possible) – This material and/or its container must be disposed of as hazardous waste – Avoid release to the environment. Refer to special instructions/safety data sheet (S1/2, S28, S36/37, S45, S60, S61)

Legislation

Limited under EC Directive on Drinking Water Quality 80/778/EEC. Organochlorine compounds: guide level $1 \mu\text{g l}^{-1}$ (1).

Included in Schedule 6 (Release into Land: Prescribed Substances) of Statutory Instrument No. 472, 1991 (2).

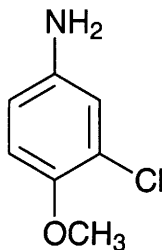
Other comments

A rapidly formed chlorination product of aniline. Decomposes rapidly in water to form acetic acid, NH_3 , CO_2 and Cl^- or, depending on pH, pyruvic acid, NH_3 and Cl^- . $t_{1/2}$ at pH 5-9 is 46 min at 25°C (3).

References

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c158 3-chloro-*p*-anisidine



C_7H_8ClNO

Mol. Wt. 157.60

CAS Registry No. 5345-54-0

Synonyms 3-chloroanisidine; benzenamine, 3-chloro-4-methoxy-; 3-chloro-4-methoxyaniline; 2-chloro-4-aminoanisole; 3-chloro-4-methoxybenzenamine

EINECS No. 226-298-4

RTECS No. BZ 6260000

Uses Dyestuff intermediate.

Physical properties

M. Pt. 50-55°C (90% pure) (1) Flash point >110°C

Occupational exposure

UN No. 2233 HAZCHEM Code 2Z Conveyance classification toxic substance

Mammalian & avian toxicity

Acute data

LD₅₀ oral rat, mouse 550, 650 mg kg⁻¹, respectively (2).

LD₅₀ intraperitoneal rat, mouse 510, 670 mg kg⁻¹, respectively (2).

Irritancy

Instillation into rabbits' eyes caused severe conjunctivitis followed by an epithelial keratitis. Application to rabbit skin caused mild irritation (2).

500 mg dermal rabbit (24 hr) and 100 mg instilled into rabbits' eyes caused mild irritant effects (2).

Sensitisation

Sensitises guinea pig skin (2).

Legislation

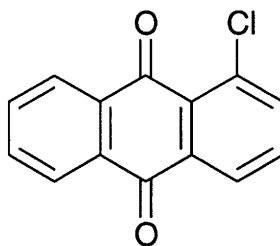
Limited under EC Directive on Drinking Water Quality 80/778/EEC. Organochlorine compounds: guide level 1 µg l⁻¹ (3).

Included in Schedule 6 (Release into Land: Prescribed Substances) of Statutory Instrument No. 472, 1991 (4).

References

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3. *EC Directive Relating to the Quality of Water Intended for Human Consumption* 1982, 80/778/EEC, Office for Official Publications of the European Communities, 2 rue Mercier, L-2985 Luxembourg.
4. *S. I. 1991 No. 472 The Environmental Protection (Prescribed Processes and Substances) Regulations* 1991, HMSO, London, UK

C159 1-chloroanthraquinone



$C_{14}H_7ClO_2$

Mol. Wt. 242.66

CAS Registry No. 82-44-0

Synonyms 1-chloro-9,10-anthraquinone; α -anthraquinone, 1-chloro-; 1-chloro-9,10-anthracenedione

EINECS No. 201-421-4

RTECS No. CB 6150000

Physical properties

M. Pt. 159-160°C

Ecotoxicity

Bioaccumulation

Non-accumulative or low accumulative (1).

Environmental fate

Degradation studies

Confirmed non-biodegradable (1).

Mammalian & avian toxicity

Acute data

LD₅₀ intravenous mouse 56 mg kg⁻¹ (2).

Irritancy

Dermal rabbit (24 hr) 500 mg caused mild irritation and 100 mg applied to rabbit eye caused severe irritation (3).

Genotoxicity

Salmonella typhimurium TA100, TA1537 with and without metabolic activation negative (4).

Weak dose-independent toxic effects were observed in cultured human lymphocytes using the sister chromatid exchange test. Metabolic activation caused a mild unsystematic enhancement of the toxic effects (5).

Does not pose a genetic risk for humans (5).

Other effects

Any other adverse effects

1-Chloroanthraquinone was an effective laxative when administered orally at 100-200 mg kg⁻¹ to mice and at 200-400 mg kg⁻¹ to rats (6).

UC₅₀ (concentration of chemical required to cause 50% uncoupling of oxidative phosphorylation) 125 μ M in the rat liver mitochondrial toxicity test (7).

Legislation

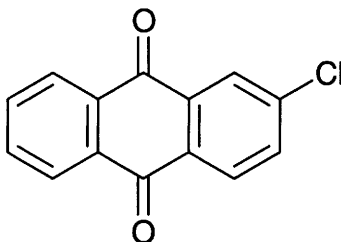
Limited under EC Directive on Drinking Water Quality 80/778/EEC. Organochlorine compounds: guide level $1 \mu\text{g l}^{-1}$ (8).

Included in Schedule 6 (Release into Land: Prescribed Substances) of Statutory Instrument No. 472, 1991 (9).

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c160 2-chloroanthraquinone



$\text{C}_{14}\text{H}_7\text{ClO}_2$

Mol. Wt. 242.66

CAS Registry No. 131-09-9

Synonyms 9,10-anthracenedione, 2-chloro-; 2-chloro-9,10-anthracenedione; anthraquinone, 2-chloro-

EINECS No. 205-010-0

RTECS No. CB 6151000

Physical properties

M. Pt. 211°C

Ecotoxicity

Bioaccumulation

Non-accumulative or low accumulative (1).

Mammalian & avian toxicity

Acute data

LD_{50} oral redwing blackbird, starling 316 mg kg^{-1} (2).

LD_{50} intraperitoneal rat 4310 mg kg^{-1} (3).

Genotoxicity

Salmonella typhimurium TA100, TA1537 with and without metabolic activation negative (4).

Legislation

Limited under EC Directive on Drinking Water Quality 80/778/EEC. Organochlorine compounds: guide level $1 \mu\text{g l}^{-1}$ (5).

Included in Schedule 6 (Release into Land: Prescribed Substances) of Statutory Instrument No. 472, 1991 (6).

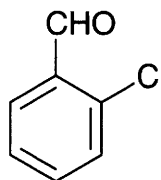
Other comments

Physico-chemical properties, human health effects, experimental toxicology, exposure levels (workplace and environment), epidemiology and environmental effects reviewed (7).

References

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c161 2-chlorobenzaldehyde



$\text{C}_7\text{H}_5\text{ClO}$

Mol. Wt. 140.57

CAS Registry No. 89-98-5

Synonyms *o*-chlorobenzaldehyde; benzaldehyde, *o*-chloro-; *o*-chlorobenzenecarboxaldehyde

EINECS No. 201-956-3

RTECS No. CU 5075000

Physical properties

M. Pt. $10-11.5^\circ\text{C}$ B. Pt. $209-215^\circ\text{C}$ Flash point 87°C Specific gravity 1.248

Occupational exposure

Supply classification corrosive

Risk phrases Causes burns (R34)

Safety phrases Keep locked up and out of the reach of children (if sold to general public) – In case of contact with eyes, rinse immediately with plenty of water and seek medical advice – In case of accident or if you feel unwell, seek medical advice immediately (show label where possible) (S1/2, S26, S45)

Ecotoxicity

Fish toxicity

LC_{50} (12, 24, 48 hr) rainbow trout 5.2, 3.6, 2.8 mg l^{-1} , respectively (1).

Environmental fate

Degradation studies

Euglena gracilis Z transforms 2-chlorobenzaldehyde to 2-chlorobenzyl alcohol (2).

Dunaliella tertiolecta transforms 2-chlorobenzaldehyde to 2-chlorobenzyl alcohol within 1 day (3).

Mammalian & avian toxicity

Acute data

LD₅₀ intraperitoneal mouse 10 mg kg⁻¹ (4).

LD₅₀ intravenous rabbit 8.5 mg kg⁻¹ (5).

Metabolism and toxicokinetics

Intraperitoneal rat 6.8-7.6% of dose was excreted as mercapturic acid in the urine (6,7).

After intravenous, intraperitoneal administration of radiolabelled 2-chlorobenzaldehyde to rats, the plasma radioactivity declined rapidly over a 24 hr period. After cutaneous administration (75 µl kg⁻¹) a slow skin penetration occurred but no evidence for skin toxicity or storage was found. The primary urinary metabolite detected was 2-chlorohippuric acid (8).

Genotoxicity

Saccharomyces cerevisiae D7 negative (9).

Salmonella typhimurium TA97, TA98, TA100, TA1535, TA1537 with and without metabolic activation negative (10).

Salmonella typhimurium TA1535/pSK1002 *umu*-test with and without metabolic activation negative (11).

Legislation

Limited under EC Directive on Drinking Water Quality 80/778/EEC. Organochlorine compounds: guide level 1 µg l⁻¹ (12).

Included in Schedule 6 (Release into Land: Prescribed Substances) of Statutory Instrument No. 472, 1991 (13).

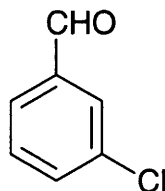
Other comments

Human health effects, experimental toxicology, exposure levels, workplace experience, environmental effects, epidemiology and physico-chemical properties reviewed (14,15).

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C162 3-chlorobenzaldehyde



C_7H_5ClO

Mol. Wt. 140.57

CAS Registry No. 587-04-2

Synonyms *m*-chlorobenzaldehyde; benzaldehyde, 3-chloro-

EINECS No. 209-596-9

Physical properties

M. Pt. 17-18°C B. Pt. 213-214°C Flash point 88°C Specific gravity 1.241

Environmental fate

Degradation studies

Euglena gracilis Z transforms 3-chlorobenzaldehyde to 3-chlorobenzyl alcohol as the major product and 3-chlorobenzoic acid as the minor product. Over time, the concentration of the alcohol decreases and the acid gradually predominates (1).

Dunaliella tertiolecta transforms 3-chlorobenzaldehyde to 3-chlorobenzyl alcohol within one day (2).

Mammalian & avian toxicity

Metabolism and toxicokinetics

After intraperitoneal administration to rats, 1.1% of the initial dose was excreted in the urine as benzylmercapturonic acid (3).

Genotoxicity

Salmonella typhimurium TA1535/pSK1002 *umu*-test with and without metabolic activation negative (4).

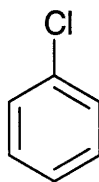
Legislation

Limited under EC Directive on Drinking Water Quality 80/778/EEC. Organochlorine compounds: guide level 1 $\mu\text{g l}^{-1}$ (5).

Included in Schedule 6 (Release into Land: Prescribed Substances) of Statutory Instrument No. 472, 1991 (6).

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C₆H₅Cl

Mol. Wt. 112.56

CAS Registry No. 108-90-7

Synonyms phenyl chloride; monochlorobenzene; benzene chloride; Abluton T30

EINECS No. 203-628-5

RTECS No. CZ 0175000

Uses Paint solvent. Manufacture of dyestuffs, herbicides and pesticides. Heat-transfer medium.

Physical properties

M. Pt. -45°C B. Pt. 131-132°C Flash point 41°C (closed cup) Specific gravity 1.104 at 20°C with respect to water at 4°C Partition coefficient log P_{ow} 2.84 Volatility v.p. 8.8 mmHg at 20°C; v.den. 3.88

Solubility Water: 295 mg l⁻¹ at 25°C. Organic solvents: benzene, carbon disulfide, carbon tetrachloride, chloroform, diethyl ether, ethanol

Occupational exposure

DE-MAK 10 ppm (47 mg m⁻³)

FR-VME 10 ppm

JP-OEL 10 ppm (46 mg m⁻³)UK-LTEL 50 ppm (234 mg m⁻³)US-TWA 10 ppm (46 mg m⁻³)

UN No. 1134 HAZCHEM Code 2Y Conveyance classification flammable liquid

Supply classification harmful

Supply classification dangerous for the environment

Risk phrases Flammable – Harmful by inhalation – Toxic to aquatic organisms, may cause long-term adverse effects in the aquatic environment (R10, R20, R51/53)

Safety phrases Keep out of reach of children (if sold to general public) – Avoid contact with skin and eyes – Avoid release to the environment. Refer to special instructions/safety data sheet (S2, S24/25, S61)

Ecotoxicity

Fish toxicity

LC₅₀ (24-96 hr) bluegill sunfish, goldfish, guppy, fathead minnow 24-73 mg l⁻¹ (1).LC₅₀ (96 hr) fathead minnow 7.7 mg l⁻¹ (2).

Invertebrate toxicity

Toxicity threshold (cell multiplication inhibition test) *Pseudomonas putida* 17 mg l⁻¹ (3), *Scenedesmus quadricauda*, *Entosiphon sulcatum* >390 mg l⁻¹ (4), *Uronema parduczi* >392 mg l⁻¹ (4), *Microcystis aeruginosa* 120 mg l⁻¹ (4), *Daphnia magna* 2.5 mg l⁻¹ reduced fertility by 50% (5).

LC₅₀ (2-day contact test) earthworm, *Eisenia foetida* 0.11 mg kg⁻¹ (6).

Toxicity to other species

EC₅₀ (the concentration of chlorobenzene required to produce 50% reduction in growth) (7 and 14 days static, 16-21 days semi-static test) lettuce *Lactuca sativa* 1000 and >1000 µg g⁻¹ soil and 9.3 mg l⁻¹ solution, respectively (7).

Environmental fate

Nitrification inhibition

No inhibition of NH_3 oxidation by *Nitrosomonas* sp. at concentrations of 100 mg l^{-1} chlorobenzene (8).

Degradation studies

BOD_5 0.03 standard dilute sewage, COD 0.41, ThOD $2.06 \text{ mg l}^{-1} \text{ O}_2$, respectively (9).

The soil mycobacterium *Mycobacterium vaccae* strain JOB-5 catabolises chlorobenzene to 4-chlorophenol (10). Chlorobenzene was degraded by indigenous soil microbial populations incubated at 27°C in slurries of 29% (w/w) suspended solids within one month (11).

Abiotic removal

Evaporation rate relative to *n*-butylacetate which has been assigned a value of 1 at 25°C is 1.15 (12).

Mammalian & avian toxicity

Acute data

LD_{50} oral mouse 250 mg kg^{-1} (13).

LD_{50} intraperitoneal mouse 515 mg kg^{-1} (14).

Carcinogenicity and chronic effects

National Toxicology Program tested chlorobenzene in rat, mouse via oral gavage. Designated non-carcinogen in ♀ rat, ♀ and ♂ mouse. Equivocal in ♂ rat (15).

Gavage rats, mice (103 wk) 120 mg kg^{-1} , evidence for liver adenoma in ♂ rats equivocal (16).

Evidence for carcinogenicity in rats; target organ is the liver (17).

Teratogenicity and reproductive effects

Inhalation of 590 ppm, 6 hr day^{-1} on days 6-15 gestation, not embryotoxic or teratogenic in rats. Slightly delayed skeletal development and maternal toxicity was reported in a subsequent study at the same dose (18).

Inhalation of 590 ppm, 6 hr day^{-1} on days 6-18 gestation caused visceral malformations (not dose-related) in rabbits. A subsequent study at the same dose reported no malformations (19).

Metabolism and toxicokinetics

After intraperitoneal injection into rats, 4-chlorocatechol, 2-, 3- and 4-chlorophenol and 4-chlorophenylmercapturonic acid were identified as metabolites in the urine (19).

Concentrations of metabolites of chlorobenzene (4-chlorocatechol, 2-, 3- and 4-chlorophenol) in the urine of four men exposed to chlorobenzene in the manufacture of dye intermediates were measured. A linear correlation was found between exposure to chlorobenzene and urinary concentrations of 4-chlorocatechol and 4-chlorophenol (20).

Genotoxicity

Saccharomyces cerevisiae gene conversion and mitotic recombination positive (21).

Salmonella typhimurium TA98, TA190, TA1535, TA1537, TA1538, with and without metabolic activation negative (22,23).

Salmonella typhimurium TA1535/pSK1002 *umu*-test with and without metabolic activation negative (24).

Significant positive response in the L-5178Y tk⁺/tk⁻ mouse lymphoma cell forward mutation assay (25).

Streptomyces griseus strain H69 point mutation assay and strain FS2 frameshift mutation assay, without metabolic activation, negative (26).

Drosophila melanogaster induction of sex-linked recessive lethal mutations negative (27).

Chinese hamster ovary cells, chromosomal aberrations with or without metabolic activation negative, sister chromatid exchange with metabolic activation positive, without metabolic activation negative (28).

In vivo mouse bone marrow micronucleus test negative (29).

Other effects

Other adverse effects (human)

Moderately toxic to humans. Irritant to eyes and nose. Inhalation in humans caused narcosis, paralysis, headache, dizziness, cyanosis, liver and kidney disorders. Some rare cases of methaemoglobinaemia. Concentrations of 400 ppm inhaled for 1 hr caused severe toxic effects (30).

Legislation

Limited under EC Directive on Drinking Water Quality 80/778/EEC. Organochlorine compounds: guide level $1 \mu\text{g l}^{-1}$ (31).

Included in Schedule 6 (Release into Land: Prescribed Substances) of Statutory Instrument No. 472, 1991 (32).

The former USSR: maximum admissible concentration air 50 mg m^{-3} , maximum admissible concentration water 0.02 mg l^{-1} , maximum admissible concentration fisheries $1 \mu\text{g l}^{-1}$ (33).

Other comments

Investigated as a component of leachate from waste sites (34).

Toxicity of mixtures of organic chemicals to activated sludge microorganisms investigated (35,36).

Quantitative structure-activity relationship of toxicity in several organisms reviewed (37).

Toxicity and hazards reviewed (38).

Review of toxicity and health hazards (39-42).

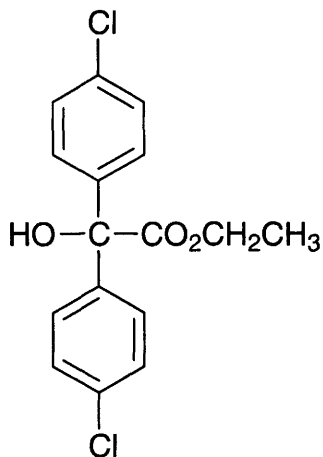
Included in List 1 Council Directive 76/464/EEC. Chlorobenzene may persist in water. Produces hydrogen chloride and phosgene when burnt, hence inhalation of fumes is hazardous.

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c164 chlorobenzilate



C₁₆H₁₄Cl₂O₃

Mol. Wt. 325.19

CAS Registry No. 510-15-6

Synonyms 4,4'-dichlorobenzidic acid, ethyl ester; benz-*o*-chlor; chlorobenzylate; ethyl 4,4'-dichlorobenzilate; ethyl *p,p*-dichlorobenzilate; ethyl 2-hydroxy-2,2-bis(4-chlorophenyl)acetate; Benzilan

EINECS No. 208-110-2

RTECS No. DD 2275000

Uses Superseded acaricide.

Physical properties

M. Pt. 35-37°C **B. Pt.** 156-158°C **Specific gravity** 1.28 at 20°C with respect to water at 4°C

Volatility v.p. 2.2×10^{-6} mmHg at 20°C

Solubility Water: slightly soluble. Organic solvents: soluble in most organic solvents

Occupational exposure

Supply classification harmful

Risk phrases Harmful if swallowed (R22)

Safety phrases Keep out of reach of children (if sold to general public) (S2)

Ecotoxicity

Fish toxicity

LC₅₀ (96 hr) rainbow trout, bluegill sunfish 0.6, 1.8 mg l⁻¹, respectively (1).

Invertebrate toxicity

Non-toxic to bees (1).

Environmental fate

Nitrification inhibition

When applied to soils at 0.25-1.0 ppm and incubated in the laboratory for 16 wk, no effect on nitrification capacity (2).

Mammalian & avian toxicity

Acute data

LD₅₀ oral redwing blackbird 100 mg kg⁻¹ (3).

LD₅₀ oral rat 1040-1220 mg kg⁻¹ (4).

LD₅₀ oral hamster 700 mg kg⁻¹ (5).

Sub-acute and sub-chronic data

Dogs tolerated daily doses of 64.1 mg kg⁻¹ for 35 wk without signs of toxicity or gross or microscopic pathology (6).

Carcinogenicity and chronic effects

No adequate data for carcinogenicity to humans, limited evidence for carcinogenicity to animals, IARC classification group 3 (7).

The National Toxicology Program tested rats and mice via feed. Equivocal evidence of carcinogenicity in ♂ and ♀ rats, positive evidence of carcinogenicity in ♂ and ♀ mice (8).

Oral rat, mouse (78 wk) 0.3 and 0.8%, respectively, via feed induced liver carcinomas (9).

Malignant neoplasms at all sites were increased in chlorobenzilate-treated ♂ or ♀ rats (10,11).

Metabolism and toxicokinetics

Rapidly excreted in the urine of rats and no significant storage in tissues (6).

Metabolised by rat liver preparations; principal metabolite *p*-chlorobenzoic acid (12).

Irritancy

Dermal rabbit (24 hr) 125 mg caused mild irritation and 25 mg instilled into rabbit eye caused moderate irritation (13).

Genotoxicity

Salmonella typhimurium TA98, TA100, TA1535, TA1537, TA1538 with and without metabolic activation negative (13).

Escherichia coli WP2 hcr negative (14).

Significant response in the L-5178Y tk+ /tk- mouse lymphoma cell forward mutation assay (15).

Escherichia coli Microscreen prophage lambda-induction assay with metabolic activation equivocal, without metabolic activation positive (16).

Other effects

Other adverse effects (human)

A patient developed toxic encephalopathy after exposure to chlorobenzilate mist with associated clinical and EEG abnormalities (17).

Any other adverse effects

Incubation of isolated rat hepatocytes, mitochondria and microsomes with 10⁻³ M chlorobenzilate resulted in decreased cell viability and depletion of cellular ATP content until cell death (18).

Legislation

Limited under EC Directive on Drinking Water Quality 80/778/EEC. Organochlorine compounds: guide level 1 µg l⁻¹ (19).

Included in Schedule 6 (Release into Land: Prescribed Substances) of Statutory Instrument No. 472, 1991 (20).
WHO Toxicity Class III (21).
EPA Toxicity Class III (1).

Other comments

Tested for carcinogenicity in male F344 rats as one of a mixture of pesticides, each at the acceptable daily intake level for humans. The results support the safety factor (usually 100) currently used to evaluate the quantitative pesticide risk to humans (22).

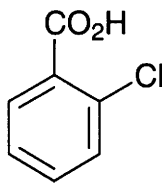
Health hazards reviewed (23).

Reviews on physico-chemical properties, human health effects, exposure levels, experimental toxicology, workplace experience, epidemiology and environmental effects listed (24).

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C165 2-chlorobenzoic acid



C₇H₅ClO₂

Mol. Wt. 156.57

CAS Registry No. 118-91-2

Synonyms *o*-chlorobenzoic acid; 2-CBA

EINECS No. 204-285-4

RTECS No. DG 4976000

Uses Preservative for glues, paints. Intermediate in the preparation of fungicides and dyestuffs.

Physical properties

M. Pt. 142°C B. Pt. sublimes Specific gravity 1.544 at 20°C with respect to water at 4°C

Partition coefficient log P_{ow} 1.98

Solubility Water: 2100 mg l⁻¹ at 25°C. Organic solvents: miscible with diethyl ether, ethanol

Ecotoxicity

Bioaccumulation

Non-accumulative or low accumulative (1).

Environmental fate

Degradation studies

2-Chlorobenzoic acid is utilised by anaerobic denitrifying cultures from river sediments under denitrifying conditions (2).

Decomposition period by soil microflora >64 days (3).

A strain of *Pseudomonas cepacia* isolated from soil caused complete degradation with the formation of chlorine (4).

Lag period for degradation at 16 mg l⁻¹, pH 7.3 and 30°C by waste water was >25 days, and in aqueous soil suspensions 7-14 days (4).

Pseudomonas sp. strain CPE2 converts 2-chlorobenzoic acid into catechol via a reaction utilising molecular oxygen and exogenous reduced nicotinamide adenine dinucleotide (5).

Pseudomonas stutzeri oxidises 2-chlorobenzoic acid to 2-chloropyrocatechol (6).

2-Chlorobenzoic acid disappeared from soil columns inoculated with *Pseudomonas stutzeri* within eight days (7).

The concentration of 2-chlorobenzoic acid not substantially inhibiting *Pseudomonas stutzeri* strain KS25 (able to utilise the acid as sole carbon and energy source) was 0.25-0.5 g l⁻¹ (8).

Mammalian & avian toxicity

Acute data

LD₅₀ oral rat 6460 mg kg⁻¹ (9).

LD₅₀ intraperitoneal rat 2300 mg kg⁻¹ (10).

Genotoxicity

Salmonella typhimurium TA97, TA98, TA100, TA1535, TA1537 with and without metabolic activation negative (11).

Salmonella typhimurium TA1535/pSK1002 *umu*-test with and without metabolic activation negative (12).

Legislation

Limited under EC Directive on Drinking Water Quality 80/778/EEC. Organochlorine compounds: guide level 1 µg l⁻¹ (13).

Included in Schedule 6 (Release into Land: Prescribed Substances) of Statutory Instrument No. 472, 1991 (14).

Other comments

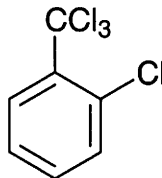
2-Chlorobenzoic acid is found bound to marine and riverine humic substances (15).

Reviews on human health effects, epidemiology, workplace experience and experimental toxicology listed (16).

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C166 2-chlorobenzotrichloride



C₇H₄Cl₄

Mol. Wt. 229.92

CAS Registry No. 2136-89-2

Synonyms o-chlorobenzotrichloride; α,α,α,2-tetrachlorotoluene; o,α,α,α-tetrachlorotoluene; 1-chloro-2-(trichloromethyl)benzene

EINECS No. 218-377-7

Uses Vulcanisation accelerator.

Physical properties

M. Pt. 29-31°C **B. Pt.** 260-264°C **Flash point** 98°C **Specific gravity** 1.508 at 20°C with respect to water at 4°C
Solubility Organic solvents: acetone, diethyl ether

Occupational exposure

UN No. 2238 HAZCHEM Code 3  Conveyance classification flammable liquid

Legislation

Limited under EC Directive on Drinking Water Quality 80/778/EEC. Organochlorine compounds: guide level $1 \mu\text{g l}^{-1}$ (1).

Included in Schedule 6 (Release into Land: Prescribed Substances) of Statutory Instrument No. 472, 1991 (2).

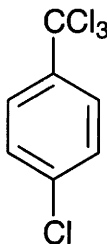
Other comments

Human health effects, experimental toxicology, epidemiology and physico-chemical properties reviewed (3).

References

1. EC Directive Relating to the Quality of Water Intended for Human Consumption 1982, 80/778/EEC, Office for Official Publications of the European Communities, 2 rue Mercier, L-2985, Luxembourg.
2. S. I. 1991 No. 472 The Environmental Protection (Prescribed Processes and Substances) Regulations 1991, HMSO, London, UK.
3. BG Chemie Toxicological Evaluations 1992, 3, Springer-Verlag, Postfach 311340, D-10643 Berlin, Germany

c167 4-chlorobenzotrichloride



$\text{C}_7\text{H}_4\text{Cl}_4$

Mol. Wt. 229.92

CAS Registry No. 5216-25-1

Synonyms *p*-chlorobenzotrichloride; $\alpha,\alpha,\alpha,4$ -tetrachlorotoluene; *p*- α,α,α -tetrachlorotoluene; 1-chloro-4-(trichloromethyl)benzene; α,α,α -trichloro-4-chlorotoluene

EINECS No. 226-009-1

RTECS No. XT 8580000

Uses Veterinary anthelmintic.

Physical properties

B. Pt. 245°C **Flash point** $>110^\circ\text{C}$ **Specific gravity** 1.495 at 20°C with respect to water at 4°C

Solubility Organic solvents: diethyl ether

Occupational exposure

UN No. 2238 HAZCHEM Code 3  Conveyance classification flammable liquid

Mammalian & avian toxicity

Acute data

LD_{50} gastric administration mouse, rat 700, 1350 mg kg^{-1} , respectively (1).

LC_{50} (duration unspecified) inhalation rat, mouse 125 mg m^{-3} (1).

LC_{Lo} (duration unspecified) inhalation rat, mouse 22.4 mg m^{-3} (1).

Carcinogenicity and chronic effects

Oral gavage ♀ mice (17.5 wk) 0.05-2 µl twice wkly. High-dose animals had tumours of skin, mammary and salivary glands. Lymphomas on thymus developed in 30% of animals receiving high doses. Stomach cancer developed in <25% in each group. Lung cancer was seen in all groups (2).

Metabolism and toxicokinetics

Rats administered single 1.5 mg kg⁻¹ oral dose of ¹⁴C-labelled compound. Within 4-6 days 87% of administered ¹⁴C excreted in urine and 9% in faeces. Major urinary metabolite 4-chlorohippuric acid representing 78% of applied dose. Whereas ~65% of the faecal ¹⁴C residues were not extractable with organic solvents, free 4-chlorobenzoic acid and α,α',4,4'-tetrachlorostilbene contributed 10% and 8% respectively of the faecal ¹⁴C. The metabolic production of α,α',4,4'-tetrachlorostilbene appears to occur by a novel metabolic pathway (3).

Irritancy

Extremely destructive to tissues of mucous membranes, upper respiratory tract, eyes and skin (4).

Legislation

Limited under EC Directive on Drinking Water Quality 80/778/EEC. Organochlorine compounds: guide level 1 µg l⁻¹ (5).

Included in Schedule 6 (Release into Land: Prescribed Substances) of Statutory Instrument No. 472, 1991 (6).

Other comments

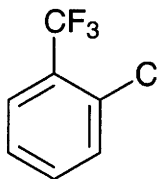
Reviews on human health effects, experimental toxicology, epidemiology, physico-chemical properties, exposure levels, environmental effects and workplace experience listed (7).

Lachrymatory.

References

1. Khalepo, A. I. et al *Gig. Tr. Prof. Zabol.* 1984, 6, 41-43 (Russ.) (*Chem. Abstr.* 101, 124312b).
2. Fakuda, K. et al *Proc. Jpn. Assoc. Ind. Health* 1979, 330-331.
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4. Lenga, R. E. *Sigma-Aldrich Library of Chemical Safety Data* 2nd ed., 1988, 745, Sigma-Aldrich, Milwaukee, USA.
5. *EC Directive Relating to the Quality of Water Intended for Human Consumption* 1982, 80/778/EEC, Office for Official Publications of the European Communities, 2 rue Mercier, L-2985 Luxembourg.
6. *S. I. 1991 No. 472 The Environmental Protection (Prescribed Processes and Substances) Regulations* 1991, HMSO, London, UK.
7. *ECETOC Technical Report No. 71* 1996, European Centre for Ecotoxicology and Toxicology of Chemicals, 4 Avenue E. Van Nieuwenhuyse (Bte 6), B-1160 Brussels, Belgium

c168 2-chlorobenzotrifluoride



C₇H₄ClF₃

Mol. Wt. 180.56

CAS Registry No. 88-16-4

Synonyms 2-chloro-α,α,α-trifluorotoluene; 1-chloro-2-(trifluoromethyl)benzene; o-chlorobenzotrifluoride; o-chloro-α,α,α-trifluorotoluene; 2-(trifluoromethyl)chlorobenzene

EINECS No. 201-805-1

Uses Lubricant additive. Intermediate in the production of dyestuffs and herbicides.

Physical properties

M. Pt. -6°C B. Pt. 152°C Flash point 58°C Specific gravity 1.379 at 20°C with respect to water at 4°C
Solubility Organic solvents: chloroform

Occupational exposure

UN No. 2234 HAZCHEM Code 2M Conveyance classification flammable liquid

Mammalian & avian toxicity

Sub-acute and sub-chronic data

Oral rat (3 months) 500 mg kg⁻¹ no toxic effects reported (1).

Metabolism and toxicokinetics

Following oral administration to the rat with radio-labelled compound, 3-4% of radioactivity was excreted in faeces and 14-15% in urine during one 4-day test period. Major urinary metabolites were glucuronides of dihydroxybenzotrifluoride and 4-chloro-3-hydrobenzotrifluoride (each 3-4% of applied dose), with minor amounts of mercapturic acid conjugate of 2-chlorobenzotrifluoride (2).

Irritancy

High concentrations are extremely destructive to the mucous membranes of the upper respiratory tract, eyes and skin (3).

Genotoxicity

Salmonella typhimurium TA97, TA98, TA100, TA1535, TA1537, TA1538 with and without metabolic activation negative (4,5).

Bacillus subtilis recE4, DNA damage negative (4).

Saccharomyces cerevisiae 6117 with and without metabolic activation gene conversion and mitotic crossing-over short-term tests negative (4).

Legislation

Limited under EC Directive on Drinking Water Quality 80/778/EEC. Organochlorine compounds: guide level 1 µg l⁻¹ (6).

Included in Schedule 6 (Release into Land: Prescribed Substances) of Statutory Instrument No. 472, 1991 (7).

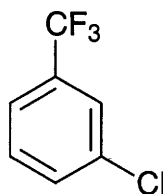
Other comments

Human health effects, experimental toxicology, epidemiology and physico-chemical properties reviewed (8).

References

1. Lilly Research Laboratories 1983, EPA 40-8452058 (Hazardous Substances Data Bank, US National Library of Medicine).
2. Zoecon Corp. 1982, EPA 40-8352054 (Hazardous Substances Data Bank, US National Library of Medicine).
3. Lenga, R. E. *Sigma-Aldrich Library of Chemical Safety Data* 2nd ed., 1988, 745, Sigma-Aldrich, Milwaukee, USA.
4. Mazza, G. et al *Farmaco, Ed. Prat.* 1986, **41**(7), 215-225 (*Chem. Abstr.* **105**, 92763p).
5. Zeiger, E. et al *Environ. Mol. Mutagen.* 1992, **19**(Suppl. 21), 2-141.
6. *EC Directive Relating to the Quality of Water Intended for Human Consumption* 1982, 80/778/EEC, Office for Official Publications of the European Communities, 2 rue Mercier, L-2985 Luxembourg.
7. S. I. 1991 No. 472 *The Environmental Protection (Prescribed Processes and Substances) Regulations* 1991, HMSO, London, UK.
8. *BG Chemie Toxicological Evaluations* 1992, 3, Springer-Verlag, Postfach 311340, D-10643 Berlin, Germany

c169 3-chlorobenzotrifluoride



$C_7H_4ClF_3$

Mol. Wt. 180.56

CAS Registry No. 98-15-7

Synonyms 3-chloro- α,α,α -trifluorotoluene; 1-chloro-3-(trifluoromethyl)benzene; *m*-chlorobenzotrifluoride; *m*-chloro- α,α,α -trifluorotoluene; 3-(trifluoromethyl)chlorobenzene

EINECS No. 202-642-9

Physical properties

M. Pt. -56°C B. Pt. $137\text{--}138^{\circ}\text{C}$ Flash point 38°C Specific gravity 1.331 at 20°C with respect to water at 4°C

Occupational exposure

UN No. 2234 HAZCHEM Code 2 $\frac{+}{-}$ Conveyance classification flammable liquid

Mammalian & avian toxicity

Irritancy

High concentrations are extremely destructive to the mucous membranes of the upper respiratory tract, eyes and skin (1).

Genotoxicity

Salmonella typhimurium TA97, TA98, TA100, TA1535, TA1537, TA1538 with and without metabolic activation negative (2,3).

Bacillus subtilis recE4 DNA damage negative (2).

Saccharomyces cerevisiae 6117 with and without metabolic activation gene conversion and mitotic crossing-over short-term tests negative (2).

Legislation

Limited under EC Directive on Drinking Water Quality 80/778/EEC. Organochlorine compounds: guide level $1\text{ }\mu\text{g l}^{-1}$ (4).

Included in Schedule 6 (Release into Land: Prescribed Substances) of Statutory Instrument No. 472, 1991 (5).

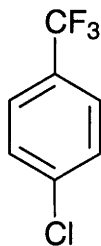
Other comments

Human health effects, experimental toxicology, epidemiology and physico-chemical properties reviewed (6).

References

1. Lenga, R. E. *Sigma-Aldrich Library of Safety Data* 2nd ed. 1988, 745, Sigma-Aldrich, Milwaukee, USA.
2. Mazza, G. et al *Farmaco, Ed. Prat.* 1986, **41**(7), 215-225 (*Chem. Abstr.* 105, 92763p).
3. Zeiger, E. et al *Environ. Mol. Mutagen.* 1992, **19**(Suppl. 21), 2-141.
4. EC Directive Relating to the Quality of Water Intended for Human Consumption 1982, 80/778/EEC, Office for Official Publications of the European Communities, 2 rue Mercier, L-2985 Luxembourg.
5. S. I. 1991 No. 472 *The Environmental Protection (Prescribed Processes and Substances) Regulations* 1991, HMSO, London, UK.
6. BG Chemie *Toxicological Evaluations* 1992, 3, Springer-Verlag, Postfach 311340, D-10643 Berlin, Germany

c170 4-chlorobenzotrifluoride



C₇H₄ClF₃

Mol. Wt. 180.56

CAS Registry No. 98-56-6

Synonyms 4-chloro- α,α,α -trifluorotoluene; 1-chloro-4-(trifluoromethyl)benzene; *p*-chlorobenzotrifluoride; *p*-chloro- α,α,α -trifluorotoluene; 4-(trifluoromethyl)chlorobenzene

EINECS No. 202-681-1

RTECS No. XS 9145000

Uses Intermediate in the synthesis of dinitroaniline and diphenyl ether herbicides from 4-chlorotoluene. Intermediate in dyestuffs synthesis.

Physical properties

M. Pt. -36°C **B. Pt.** 136-138°C **Flash point** 47°C **Specific gravity** 1.353 at 20°C with respect to water at 4°C

Solubility Water: <1 mg l⁻¹ at 23°C. Organic solvents: acetone, dimethyl sulfoxide, ethanol

Occupational exposure

UN No. 2234 HAZCHEM Code 2 $\frac{+}{-}$ Conveyance classification flammable liquid

Mammalian & avian toxicity

Acute data

LD₅₀ oral mouse, rat 11.5, 13 g kg⁻¹, respectively (1,2).

LC₅₀ (duration unspecified) inhalation rat, mouse 20, 22 g m⁻³, respectively (2).

Sub-acute and sub-chronic data

Inhalation exposure of rats to 4-chlorobenzotrifluoride (13 wk, 0-250 ppm) did not significantly alter V_{max} or k_m values for the metabolism of the compound to its 3-hydroxy derivative, viz. V_{max} 1038 nmol hr⁻¹ kg⁻¹ body weight, k_m 65.7 μ mol l⁻¹ (3).

Inhalation Sprague-Dawley rats (90 days) 0-250 ppm. A significant increase in liver weight and liver microsome cytochrome P450 content was seen in ♀ rats dosed with 250 ppm. Neither parameters were significantly increased in ♂s under the same conditions. No-observed-effect level 50 ppm (4).

Inhalation Sprague-Dawley rats (13 wk) 0-150 ppm, 6 hr day⁻¹, 5 days wk⁻¹. No untoward observations during the exposure or during weekly clinical evaluations. Body weight was not affected and there were no effects on the nervous system. A possible, but minimal, decrease in food consumption (6% in the 250 ppm group) was observed during the first few weeks of exposure. Both ♂s and ♀s of the 250 ppm group suffered an 11% increase in relative liver weights which correlated with the centrilobular hypertrophy seen microscopically. After a 13 wk recovery period there was no sign of centrilobular hypertrophy in any of the dosed groups. After 13 wk of inhalation (whole body exposure) a single nose-only exposure showed the levels of 4-chlorobenzotrifluoride to increase twofold in the brain, kidney, liver, lungs, muscle, fat and blood. The level in the fat did not decay during the 24 hr post-exposure period (5).

The threshold of toxicity to rats exposed 24 hr day⁻¹ for 4 months was 9.42 mg m⁻³ (6).

In rats exposed to 20.5-440 mg m⁻³ for 3-120 days, changes were observed in haematocrit values, blood haemoglobin concentration, lactose dehydrogenase and cholinesterase activities, erythrocyte and leucocyte counts. The toxicity mainly affects blood and the central nervous system (2).

Gavage B6C3F1 mice and F344 rats 10-1000 and 50-1000 mg kg⁻¹, respectively, in corn oil daily for 14 days. 4-Chlorobenzotrifluoride accumulated in the ♂ rat kidney, and dose-dependent toxic nephropathy was seen at ≥50 mg kg⁻¹. Both ♂ and ♀ rats developed hepatocellular hypertrophy and cytoplasmic vacuolation of the adrenal cortex. No tissue bioaccumulation was found in ♂ or ♀ mice, but hepatocellular hypertrophy and cholestasis occurred at doses of 400 and 1000 mg kg⁻¹ (7).

Metabolism and toxicokinetics

Rats administered a single 1 mg kg⁻¹ oral dose of ¹⁴C-labelled compound. 3-4% of ¹⁴C excreted in faeces and 14-15% in urine. Major urinary metabolites were dihydroxybenzotrifluoride glucuronide and 4-chloro-3-hydroxybenzotrifluoride glucuronide (each representing 3-4% of applied ¹⁴C) as well as minor amounts of 4-chlorobenzotrifluoride mercapturic acid conjugate. 62-82% of applied chemical rapidly expired as CO₂. Levels of ¹⁴C-labelled residues in tissues were low. Small amount in rat carcass four days after dosage (≈1% applied dose) occurred as unmetabolised compound predominantly in fat (8).

Genotoxicity

Salmonella typhimurium TA98, TA100, TA1535, TA1537, TA1538 with and without metabolic activation negative (9).
Bacillus subtilis recE4 DNA damage negative (9).
Saccharomyces cerevisiae 6117 with and without metabolic activation gene conversion and mitotic crossing-over short-term tests negative (9).

Legislation

Limited under EC Directive on Drinking Water Quality 80/778/EEC. Organochlorine compounds: guide level 1 µg l⁻¹ (10).
Included in Schedule 6 (Release into Land: Prescribed Substances) of Statutory Instrument No. 472, 1992 (11).

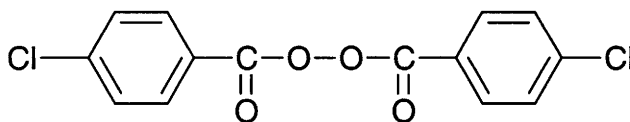
Other comments

The National Toxicology Program tested rats and mice via gavage, short-term toxicity study report available (12).
Studies of olfactory detection by volunteers gave a one-time maximum tolerance level of 0.1 mg m⁻³ (6).
Reviews on physico-chemical properties, human health effects, exposure levels, workplace experience, environmental effects, epidemiology and experimental toxicology listed (13).

References

1. Khalepo, A. I. et al *Gig. Tr. Prof. Zabol.* 1984, **5**, 49-51 (Russ.) (*Chem. Abstr.* **101**, 67234b).
2. Charyev, O. G. et al *Gig. Sanit.* 1985, **7**, 26-28 (Russ.) (*Chem. Abstr.* **103**, 99931j).
3. Knaak, J. B. et al *Inhalation Toxicol.* 1998, **10**(1), 65-85.
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10. *EC Directive Relating to the Quality of Water Intended for Human Consumption* 1982, 80/778/EEC, Office for Official Publications of the European Communities, 2 rue Mercier, L-2985 Luxembourg.
11. *S. I. 1991 No. 472 The Environmental Protection (Prescribed Processes and Substances) Regulations* 1991, HMSO, London, UK.
12. *National Toxicology Program Research and Testing Division* April 1997, Report No. TOX-14, NIEHS, Research Triangle Park, NC, USA.
13. *ECETOC Technical Report No. 71* 1996, European Centre for Ecotoxicology and Toxicology of Chemicals, 4 Avenue E. Van Nieuwenhuysse (Bte 6), B-1160 Brussels, Belgium

c171 4-chlorobenzoyl peroxide



$C_{14}H_8Cl_2O_4$

Mol. Wt. 311.12

CAS Registry No. 94-17-7

Synonyms bis(4-chlorobenzoyl) peroxide; *p*-chlorobenzoyl peroxide; di-(4-chlorobenzoyl) peroxide

EINECS No. 202-310-3

RTECS No. SD 7875000

Uses Bleaching agent. Polymerisation catalyst. Vulcanising agent.

Physical properties

M. Pt. 137-138°C

Occupational exposure

UN No. 2113 (maximum 75% with water)

UN No. 2114 (maximum 52% as paste)

UN No. 2115 (maximum concentration 52% in solution)

Mammalian & avian toxicity

Acute data

LD_{Lo} intraperitoneal mouse 500 mg kg⁻¹ (1).

Legislation

Limited under EC Directive on Drinking Water Quality 80/778/EEC. Organochlorine compounds: guide level 1 µg l⁻¹ (2).

Included in Schedule 6 (Release into Land: Prescribed Substances) of Statutory Instrument No. 472, 1991 (3).

Other comments

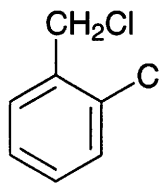
Reviews on human health effects and experimental toxicology listed (4).

Strong oxidising agent. Explosion hazard over 38°C. Will ignite on contact with organic materials.

References

1. *Summary Tables of Biological Tests* Natl. Res. Council Chem. Biol. Coord. Centre (Natl. Acad. Sci. Library), Washington, DC, USA.
2. *EC Directive Relating to the Quality of Water Intended for Human Consumption* 1982, 80/778/EEC, Office for Official Publications of the European Communities, 2 rue Mercier, L-2985 Luxembourg.
3. *S.I. 1991 No. 472 The Environmental Protection (Prescribed Processes and Substances) Regulations* 1991, HMSO, London, UK.
4. *ECETOC Technical Report No. 71* 1996, European Centre for Ecotoxicology and Toxicology of Chemicals, 4 Avenue E. Van Nieuwenhuysse (Bte 6), B-1160 Brussels, Belgium

c172 2-chlorobenzyl chloride



$C_7H_6Cl_2$

Mol. Wt. 161.03

CAS Registry No. 611-19-8

Synonyms α ,2-dichlorotoluene; *o*, α -dichlorotoluene; 1-chloro-2-(chloromethyl)benzene; *o*-chlorobenzyl chloride; Urushiol

EINECS No. 210-258-8

RTECS No. CZ 0195000

Uses Intermediate for pharmaceuticals and dyestuffs.

Physical properties

M. Pt. -17°C **B. Pt.** $213\text{--}214^{\circ}\text{C}$ **Flash point** 82°C **Specific gravity** 1.274 at 20°C with respect to water at 4°C

Solubility Organic solvents: acetic acid, benzene, carbon disulfide

Occupational exposure

UN No. 2235 HAZCHEM Code 2X Conveyance classification toxic substance

Ecotoxicity

Fish toxicity

In 24-hr toxicity tests exposure to ≥ 5 ppm mixture of 2- and 4-chlorobenzyl chloride caused death in brook trout in 6 hr; sickness in bluegill sunfish and goldfish within 1 hr. Test conditions: temperature 30°C ; pH 7; dissolved oxygen 7.5 ppm; total hardness (soap method) 300 ppm; alkalinity 310 ppm (methyl orange); free carbon dioxide 5 ppm (1).

Mammalian & avian toxicity

Irritancy

Extremely destructive to tissues of the mucous membranes, upper respiratory tract, eyes and skin (2).

Sensitisation

Intraperitoneal guinea pigs of $0.01\text{ mg } 2 \times \text{wk}^{-1}$ for 12 wk followed by dermal challenge 2 wk later with a 20% solution caused sensitisation. Cross-sensitisation to 2,4-dinitrobenzyl chloride reported (3).

Other effects

Any other adverse effects

RD_{50} (the concentration of chemical required to produce a 50% reduction in respiratory rate) σ Swiss-Webster mice 4.9 ppm (4).

Inhibits growth of *Saccharomyces cerevisiae* and lowers the contents of sterols and fatty acids. Inhibition considerably alleviated by presence of sterols such as ergosterol, cholesterol and unsaturated fatty acids such as oleate and linoleate (5).

Legislation

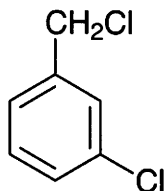
Limited under EC Directive on Drinking Water Quality 80/778/EEC. Organochlorine compounds: guide level $1\text{ }\mu\text{g l}^{-1}$ (6).

Included in Schedule 6 (Release into Land: Prescribed Substances) of Statutory Instrument No. 472, 1991 (7).

References

1. Hollis, E. H. et al *The Toxicity of 1,085 Chemicals to Fish, Part 2* 1987, 58, EPA 560/6-87-002, Washington, DC, USA.
2. Lenga, R. E. *Sigma-Aldrich Library of Chemical Safety Data* 2nd ed. 1988, 750, Sigma-Aldrich, Milwaukee, USA.
3. Landsteiner, K. et al *J. Exp. Med.* 1936, **64**, 625-639.
4. Dudek, B. R. et al *J. Toxicol. Environ. Health* 1992, **37**(4), 511-518.
5. Ariga, N. et al *J. Biochem. (Tokyo)* 1980, **88**(1), 97-102 (*Chem. Abstr.* **93**, 89343e).
6. *EC Directive Relating to the Quality of Water Intended for Human Consumption* 1982, 80/778/EEC, Office for Official Publications of the European Communities, 2 rue Mercier, L-2985 Luxembourg.
7. *S. I.* 1991 No. 472 *The Environmental Protection (Prescribed Processes and Substances) Regulations* 1991, HMSO, London, UK

c173 3-chlorobenzyl chloride



C₇H₆Cl₂

Mol. Wt. 161.03

CAS Registry No. 620-20-2

Synonyms α ,3-dichlorotoluene; *m*, α -dichlorotoluene; 1-chloro-3-(chloromethyl)benzene;
m-chlorobenzyl chloride

EINECS No. 210-629-4

Physical properties

B. Pt. 215-216°C **Flash point** 98°C **Specific gravity** 1.270 at 20°C with respect to water at 4°C
Solubility Organic solvents: ethanol

Occupational exposure

UN No. 2235 **HAZCHEM Code** 2X **Conveyance classification** toxic substance

Environmental fate

Degradation studies

Degraded by *Pseudomonas* sp. (1).

Mammalian & avian toxicity

Irritancy

Lachrymator.

Extremely destructive to tissues of the mucous membranes, upper respiratory tract, eyes and skin (2).

Other effects

Any other adverse effects

RD₅₀ (the concentration of chemical required to produce a 50% reduction in respiratory rate) σ Swiss-Webster mice 13 ppm (3).

Legislation

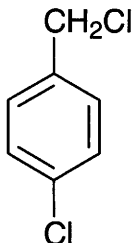
Limited under EC Directive on Drinking Water Quality 80/778/EEC. Organochlorine compounds: guide level 1 µg l⁻¹ (4).

Included in Schedule 6 (Release into Land: Prescribed Substances) of Statutory Instrument No. 472, 1991 (5).

References

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3. Dudek, B. R. et al *J. Toxicol. Environ. Health* 1992, 37(4), 511-518.
4. *EC Directive Relating to the Quality of Water Intended for Human Consumption* 1982, 80/778/EEC, Office for Official Publications of the European Communities, 2 rue Mercier, L-2985 Luxembourg.
5. S. I. 1991 No. 472 *The Environmental Protection (Prescribed Processes and Substances) Regulations* 1991, HMSO, London, UK

c174 4-chlorobenzyl chloride



C₇H₆Cl₂

Mol. Wt. 161.03

CAS Registry No. 104-83-6

Synonyms *p*-chlorobenzyl chloride; *p*, α -dichlorotoluene; α ,4-dichlorotoluene;
1-chloro-4-(chloromethyl)benzene

EINECS No. 203-242-7

RTECS No. XT 0720000

Uses Gas chromatography analysis.

Physical properties

M. Pt. 28-30°C **B. Pt.** 223°C **Flash point** 97°C **Specific gravity** 1.270-1.280 at 25°C with respect to water at 15°C **Partition coefficient** log P_{ow} 3.42

Solubility Organic solvents: carbon tetrachloride

Occupational exposure

UN No. 2235 HAZCHEM Code 2X **Conveyance classification** toxic substance

Ecotoxicity

Fish toxicity

In 24-hr toxicity tests a 5 mg l⁻¹ mixture of 2- and 4-chlorobenzyl chloride caused death to brook trout in 6 hr and sickness in bluegill sunfish and goldfish within 1 hr (1).

Environmental fate

Degradation studies

Degraded by *Pseudomonas* sp. (2).

Mammalian & avian toxicity

Acute data

LD₅₀ oral rat, mouse, guinea pig 1075-5625 mg kg⁻¹ (3).

Teratogenicity and reproductive effects

Administration during days 1-19 of pregnancy caused embryo-lethal effects in rodents (3).

Metabolism and toxicokinetics

In rabbits the principal products excreted after administration were *N*-acetyl-S-(*p*-chlorophenyl)-L-cysteine, 4-chlorohippuric acid and 4-chlorobenzoic acid; little or no conjugation with glucuronic acid or sulfuric acid occurred (4).

Irritancy

Extremely destructive to tissues of the mucous membranes, upper respiratory tract, eyes and skin (5).

Sensitisation

Showed no sensitisation effect on guinea pig skin (3).

Genotoxicity

Salmonella typhimurium TA100 without metabolic activation negative (6).

Other effects

Any other adverse effects

EC₅₀ cytotoxicity to rat hepatocytes *in vitro* 0.17 mM. Lipid peroxidation was shown to be involved in cytotoxicity (7).

Concentration of chemical required to produce 50% reduction in respiratory rate ♂ Swiss-Webster mice 14 ppm (8).

Legislation

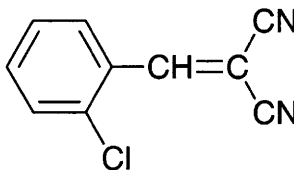
Limited under EC Directive on Drinking Water Quality 80/778/EEC. Organochlorine compounds: guide level 1 µg l⁻¹ (9).

Included in Schedule 6 (Release into Land: Prescribed Substances) of Statutory Instrument No. 472, 1991 (10).

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10. S. I. 1991 No. 472 *The Environmental Protection (Prescribed Processes and Substances) Regulations* 1991, HMSO, London, UK

c175 2-chlorobenzylidenemalononitrile



$C_{10}H_5ClN_2$

Mol. Wt. 188.62

CAS Registry No. 2698-41-1

Synonyms α -(*o*-chlorobenzylidene)malononitrile; [(2-chlorophenyl)methylene]propanedinitrile; *o*-chlorobenzalmalononitrile; β,β -dicyano-*o*-chlorostyrene; CS; OCBM

EINECS No. 220-278-9

Uses Lachrymatory chemical warfare agent. Used in riot control.

Physical properties

M. Pt. 95-96°C **B. Pt.** 310-315°C

Solubility Water: 1-5 mg ml⁻¹. Organic solvents: acetone, benzene, dimethyl sulfoxide, dioxane, ethyl acetate, methylene chloride

Occupational exposure

FR-VLE 0.05 ppm (0.4 mg m⁻³)

US-STEL ceiling limit 0.05 ppm (0.39 mg m⁻³)

Ecotoxicity

Fish toxicity

LC₅₀ (24 hr) rainbow trout 0.45 mg l⁻¹ (1).

Environmental fate

Abiotic removal

Hydrolyses in water to give 2-chlorobenzaldehyde and malononitrile (2).

Mammalian & avian toxicity

Acute data

LD₅₀ oral rabbit, rat, mouse 143, 282 mg kg⁻¹, respectively (3-5).

LC_{Lo} (45 min) inhalation rat 1806 mg m⁻³ (5).

LC_{Lo} (20 min) inhalation mouse 2753 mg m⁻³ (5).

LC_{Lo} (10 min) inhalation rabbit 1800 mg m⁻³ (5).

LD₅₀ intraperitoneal mouse, rat 32, 48 mg kg⁻¹, respectively (6,7).

Sub-acute and sub-chronic data

No clinical abnormalities noted in seven σ human volunteers exposed to concentrations of 1-13 mg m⁻³ over a 15-day period, except for a rising value of the thymol turbidity value in one volunteer. None of the volunteers developed tolerance during ten exposures (8).

Daily exposure of dogs for 1 min, 5 days wk⁻¹ to 680 mg m⁻³ had no apparent effect (9).

Carcinogenicity and chronic effects

The National Toxicology Program tested rats and mice via inhalation. No evidence of carcinogenic activity in σ or f rats or mice (10).

Teratogenicity and reproductive effects

No teratogenicity or foetotoxicity reported in rats and rabbits exposed to 6, 20 or 60 mg m⁻³ for 5 min on days 6-15 and 6-18 of pregnancy, respectively, or in rats following intraperitoneal injection of 20 mg kg⁻¹ on days 6, 8, 10, 12 or 14 of pregnancy (7,11).

Metabolism and toxicokinetics

Blood and urine tests after intraperitoneal injection to mice of half LD₅₀ dose and relatively high aerosol dose of 20 g min⁻¹ demonstrate the formation of cyanide. However in humans, the severity of irritant effects would be likely to preclude an absorbed dose sufficiently high to produce toxic amounts of cyanide in the body (12).

t_{1/2} cats blood 5.5 sec (13).

When administered intravenously or intragastrically to rats, 44-100% of the dose was eliminated in the urine. The principal urinary metabolites were 2-chlorohippuric acid, 1-O-(2-chlorobenzyl)glucuronic acid, S-(2-chlorobenzyl)cysteine and 2-chlorobenzoic acid (14).

When administered intravenously to rabbits, it was biotransformed mainly in the blood, giving 2-chlorobenzaldehyde, malononitrile and o-chlorobenzylmalononitrile (15).

Irritancy

Application of 20-30 mg under a watch glass to skin of human volunteers for 1 hr produced faint erythema and transient irritation (16).

Sensitisation

Significant human skin sensitising potential affecting arms and neck reported from industrial exposure (17).

Genotoxicity

Salmonella typhimurium TA97, TA98, TA100, TA102, TA104 with and without metabolic activation negative (18). Induced micronuclei and mutants resistant to 6-thioguanidine in V79 Chinese hamster cells, but did not elicit DNA synthesis (19).

Other effects

Other adverse effects (human)

Caused intense eye and skin irritation, with coughing, difficulty in breathing, chest tightness, running nose, dizziness, nausea and vomiting. Median incapacitating effects range from 10-20 mg m⁻³ with onset of incapacitation ≈20 sec after exposure. Duration of effects may persist for 5-10 min following removal of the affected individual to fresh air (20).

Any other adverse effects

RD₅₀ (concentration associated with 50% decrease in respiratory rate) 0.52 ppm (≈4 mg m⁻³) (21).

Legislation

Limited under EC Directive on Drinking Water Quality 80/778/EEC. Organochlorine compounds: guide level 1 µg l⁻¹ (22).

Included in Schedule 6 (Release into Land: Prescribed Substances) of Statutory Instrument No. 472, 1991 (23).

Other comments

A ceiling limit of 0.05 ppm (≈0.4 mg m⁻³) recommended to prevent acute effects from handling (24).

Hazards reviewed (25).

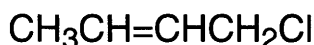
Human health effects, experimental toxicology, physico-chemical properties, epidemiology, exposure levels and workplace experience reviewed (26,27).

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c176 1-chloro-2-butene



C₄H₇Cl

Mol. Wt. 90.55

CAS Registry No. 591-97-9

Synonyms 2-butenyl chloride; α -chloro—butylene; crotyl chloride; γ -methylallyl chloride; γ -methallyl chloride

EINECS No. 209-739-5

RTECS No. EM 4264000

Physical properties

B. Pt. 84.8°C (*trans*), 84.1°C (*cis*) **Flash point** -5°C (*trans*) **Specific gravity** 0.9295 (*trans*), 0.9246 (*cis*) at 20°C with respect to water at 4°C **Partition coefficient** log P_{ow} 2.05

Ecotoxicity

Fish toxicity

LC₅₀ (96 hr) guppy 6 mg l⁻¹ (1).

Mammalian & avian toxicity

Acute data

LD₅₀ oral mouse, rat 460-530 mg kg⁻¹ (2).

Irritancy

Reported to cause irritation to eyes and respiratory passages (species unspecified) (3).

Genotoxicity

Salmonella typhimurium TA100 with and without metabolic activation positive (4).

In vitro human HeLa cells induced unscheduled DNA synthesis (5).

Legislation

Limited under EC Directive on Drinking Water Quality 80/778/EEC. Organochlorine compounds: guide level 1 µg l⁻¹ (6).

Included in Schedule 6 (Release into Land: Prescribed Substances) of Statutory Instrument No. 472, 1991 (7).

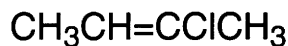
Other comments

Strategy for the rapid screening of the genotoxic activities of allylic compounds proposed. The most significant factors for genotoxicity are the leaving groups and halogen substituents. Alkyl substituents increase the direct genotoxicity while decreasing the indirect activity (via acrolein) (8).

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c177 2-chloro-2-butene



C₄H₇Cl

Mol. Wt. 90.55

CAS Registry No. 4461-41-0

Synonyms 2-chlorobutene

EINECS No. 224-719-6

RTECS No. EM 4265000

Uses Preparation of chlorophene.

Physical properties

B. Pt. 62-67°C Flash point -19°C Specific gravity 0.926 at 20°C

Mammalian & avian toxicity

Acute data

LC_{Lo} (15 min) inhalation mouse 48,800 ppm (1).

Irritancy

Vapour or mist irritating to the eyes, mucous membranes and upper respiratory tract (species unspecified) (2).

Genotoxicity

Salmonella typhimurium TA100 without metabolic activation negative; with metabolic activation positive (3).

Legislation

Limited under EC Directive on Drinking Water Quality 80/778/EEC. Organochlorine compounds: guide level 1 µg l⁻¹ (4).

Included in Schedule 6 (Release into Land: Prescribed Substances) of Statutory Instrument No. 472, 1991 (5).

Other comments

Mixture of *cis*- and *trans*-forms. Lachrymatory.

References

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5. S. I. 1991 No. 472 *The Environmental Protection (Prescribed Processes and Substances) Regulations* 1991, HMSO, London, UK

c178 3-chloro-1-butene



C₄H₇Cl

Mol. Wt. 90.55

CAS Registry No. 563-52-0

Synonyms 2-chloro-3-butene; γ-chloro—butylene; α-methallyl chloride

EINECS No. 209-252-8

RTECS No. EM 4261000

Physical properties

B. Pt. 64–65°C Flash point –20°C Specific gravity 0.8978 at 20°C with respect to water at 4°C

Partition coefficient log P_{ow} 1.93

Solubility Organic solvents: acetone, chloroform, diethyl ether

Ecotoxicity

Fish toxicity

LC₅₀ (96 hr) guppy 6.1 mg l⁻¹ (1).

Genotoxicity

Salmonella typhimurium TA100 with and without metabolic activation positive (2).

Induced unscheduled DNA synthesis in human HeLa cell line (3).

Legislation

Limited under EC Directive on Drinking Water Quality 80/778/EEC. Organochlorine compounds: guide level $1 \mu\text{g l}^{-1}$ (4).
Included in Schedule 6 (Release into Land: Prescribed Substances) of Statutory Instrument No. 472, 1991 (5).

Other comments

Occurs as an impurity in chlorophene. Lachrymatory.

References

1. Hermans, J. et al *Toxicol. Environ. Chem.* 1985, 9(3), 219-236.
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c179 4-chloro-1-butene



$\text{C}_4\text{H}_7\text{Cl}$

Mol. Wt. 90.55

CAS Registry No. 927-73-1

Synonyms 3-butenyl chloride; 1-chloro-3-butene

EINECS No. 213-160-3

Physical properties

B. Pt. 75°C at 773 mmHg Specific gravity 1.4233 at 20°C with respect to water at 4°C

Solubility Organic solvents: chloroform, diethyl ether

Genotoxicity

Salmonella typhimurium TA100 with and without metabolic activation negative (1).

Legislation

Limited under EC Directive on Drinking Water Quality 80/778/EEC. Organochlorine compounds: guide level $1 \mu\text{g l}^{-1}$ (2).
Included in Schedule 6 (Release into Land: Prescribed Substances) of Statutory Instrument No. 472, 1991 (3).

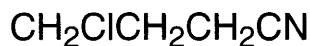
Other comments

Occurs as water and air pollutant (4).

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c180 4-chlorobutyronitrile



$\text{C}_4\text{H}_6\text{ClN}$

Mol. Wt. 103.55

CAS Registry No. 628-20-6

Synonyms 4-chlorobutanenitrile; γ -chlorobutyronitrile; butanenitrile, 4-chloro-

EINECS No. 211-031-6

RTECS No. ET 9020000

Uses Preparation of the neuroregulator γ -aminobutyric acid (GABA).

Physical properties

B. Pt. 196-197°C **Flash point** 85°C **Specific gravity** 1.158 at 20°C with respect to water at 4°C

Solubility Organic solvents: diethyl ether, ethanol.

Mammalian & avian toxicity

Acute data

LD_{50} oral mouse 53 mg kg^{-1} (1).

Metabolism and toxicokinetics

Liberates cyanide both *in vivo* and *in vitro* (species unspecified) (1).

Irritancy

Vapour or mist irritated eyes, mucous membranes and upper respiratory tract (species unspecified) (2).

Legislation

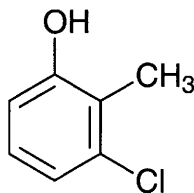
Limited under EC Directive on Drinking Water Quality 80/778/EEC. Organochlorine compounds: guide level 1 $\mu\text{g l}^{-1}$ (3).

Included in Schedule 6 (Release into Land: Prescribed Substances) of Statutory Instrument No. 472, 1991 (4).

References

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c181 3-chloro-o-cresol



$\text{C}_7\text{H}_7\text{ClO}$

Mol. Wt. 142.58

CAS Registry No. 3260-87-5

Synonyms 3-chloro-2-methylphenol

EINECS No. 221-861-0

Physical properties

M. Pt. 86-87°C B. Pt. 225°C

Solubility Organic solvents: benzene, diethyl ether, ethanol

Occupational exposure

UN No. 2669 HAZCHEM Code 2X Conveyance classification toxic substance

Ecotoxicity

Fish toxicity

LC₅₀ brown trout 1-2 mg l⁻¹ (1).

Genotoxicity

Salmonella typhimurium TA98, TA100, TA1535, TA1537 with or without metabolic activation negative (2).

Legislation

Limited under EC Directive on Drinking Water Quality 80/778/EEC. Organochlorine compounds: guide level 1 µg l⁻¹ (3).

Included in Schedule 6 (Release into Land: Prescribed Substances) of Statutory Instrument No. 472, 1991, (4).

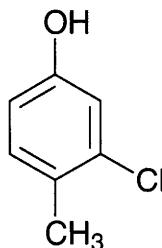
Other comments

Exhibits inhibitory activity against a variety of microorganisms (5).

References

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c182 3-chloro-*p*-cresol



C₇H₇ClO

Mol. Wt. 142.58

CAS Registry No. 615-62-3

Synonyms 3-chloro-4-methylphenol

EINECS No. 210-439-1

Physical properties

M. Pt. 55°C B. Pt. 228°C

Occupational exposure

UN No. 2669 HAZCHEM Code 2X Conveyance classification toxic substance

Legislation

Limited under EC Directive on Drinking Water Quality 80/778/EEC. Organochlorine compounds: guide level 1 µg l⁻¹ (1).

Included in Schedule 6 (Release into Land: Prescribed Substances) of Statutory Instrument No. 472, 1991 (2).

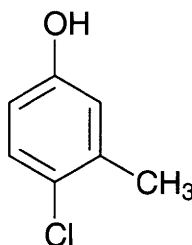
Other comments

Synergistic herbicidal effect with 3,4-dichloropropionanilide. Especially effective in rice paddies (3).

References

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c183 4-chloro-*m*-cresol



C₇H₇ClO

Mol. Wt. 142.58

CAS Registry No. 59-50-7

Synonyms 4-chloro-3-methylphenol; *p*-chloro-*m*-cresol; chlorocresol; 6-chloro-3-hydroxytoluene; 4-chloro-1-hydroxy-3-methylbenzene; PCMC

EINECS No. 200-431-6

RTECS No. GO 7100000

Uses Antiseptic. Preservative for glues, gums, inks, paints, textiles and leather goods.

Physical properties

M. Pt. 65-68°C (99% pure) (1) B. Pt. 235°C Partition coefficient log P_{ow} 3.10

Solubility Water: 3.8 g l⁻¹ at 20°C. Organic solvents: acetone, benzene, chloroform, diethyl ether, ethanol, terpenes

Occupational exposure

SE-LEVL 3 mg m⁻³

SE-STEL 6 mg m⁻³

UN No. 2669 HAZCHEM Code 2X Conveyance classification toxic substance

Supply classification harmful

Supply classification dangerous for the environment

Risk phrases Harmful in contact with skin and if swallowed – Risk of serious damage to eyes – May cause sensitisation by skin contact – Very toxic to aquatic organisms (R21/22, R41, R43, R50)

Safety phrases Keep out of reach of children (if sold to general public) – In case of contact with eyes, rinse immediately with plenty of water and seek medical advice – Wear suitable protective clothing, gloves and eye/face protection – Avoid release to the environment. Refer to special instructions/safety data sheet (S2, S26, S36/37/39, S61)

Ecotoxicity

Fish toxicity

LC₅₀ (96 hr) fathead minnow 0.01-0.1 mg l⁻¹ in static bioassay (2).

LC₅₀ (24, 48, 72 and 96 hr) fathead minnow 13.3, 11.4, 9.21 and 7.56 mg l⁻¹, respectively (3).

Invertebrate toxicity

No-observed-effect level (NOEL) for *Daphnia magna* 1.3 mg l⁻¹. At higher concentrations significant effects on reproductive rate observed (4).

Toxicity to other species

EC₅₀ (the concentration of chemical required to produce 50% reduction in growth) lettuce *Lactuca sativa* (7 and 14 day static tests) >32, <100 µg g⁻¹ soil, (16-21 days semi-static test) 2.3 mg l⁻¹ nutrient solution (5).

Environmental fate

Nitrification inhibition

Inhibition of nitrification in sewage treatment works occurs at a threshold concentration 4.0 mg l⁻¹ (6).

Degradation studies

In a 32-day study on the effect of 12.7 µg l⁻¹ on anaerobic sludge, 90-95% and 55-60% degradation occurred in active and sterile sludge, respectively, after 16 days (7).

After 3 wk of adaptation at 20 mg l⁻¹ at 22°C, 30% degradation when product is sole carbon source, 100% degradation with synthetic sewage under aerobic conditions (8).

Pseudomonas putida EKII is able to metabolise 4-chloro-*m*-cresol as the sole carbon and energy source (9).

Abiotic removal

Adsorption capacity of activated carbon 124 mg g⁻¹ (10).

Mammalian & avian toxicity

Acute data

LD₅₀ oral redwing blackbird >113 mg kg⁻¹ (11).

LD₅₀ oral rat 1830 mg kg⁻¹ (12).

LD₅₀ intravenous mouse 70 mg kg⁻¹ (13).

LD₅₀ subcutaneous mouse, rat 200, 400 mg kg⁻¹, respectively (13).

Sub-acute and sub-chronic data

A significant decrease in body weight has been reported in a 28-day sub-acute study using ♂ and ♀ rats dosed with 400 mg kg⁻¹ day⁻¹ (route unspecified) (13).

Metabolism and toxicokinetics

Conjugation with glucuronic acid and sulfate. Excreted in urine mainly as conjugates with very little being excreted unchanged (species unspecified) (14).

Genotoxicity

Salmonella typhimurium TA98, TA100, TA1535, TA1537 with and without metabolic activation negative (15).

Escherichia coli strain PQ37 SOS DNA repair test without metabolic activation positive (16).

Legislation

Limited under EC Directive on Drinking Water Quality 80/778/EEC. Organochlorine compounds: guide level 1 µg l⁻¹ (17).

Included in Schedule 6 (Release into Land: Prescribed Substances) of Statutory Instrument No. 472, 1991 (18).

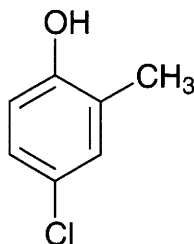
Other comments

Reviews on physico-chemical properties, human health effects, exposure levels, workplace experience, environmental effects, experimental toxicology and epidemiology listed (19).

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c184 4-chloro-o-cresol



C₇H₇ClO

Mol. Wt. 142.58

CAS Registry No. 1570-64-5

Synonyms 4-chloro-2-methylphenol

EINECS No. 216-381-3

RTECS No. GO 7120000

Uses Additive tracer for resist plasma etching. Disinfectant. Manufacture of the herbicide 4-chloro-2-methylphenoxyacetic acid (MCPA).

Physical properties

M. Pt. 45-48°C B. Pt. 220-225°C Flash point >110°C Partition coefficient $\log K_{ow}$ 2.78
Solubility Organic solvents: petroleum ether

Occupational exposure

UN No. 2669 HAZCHEM Code 2X Conveyance classification toxic substance

Supply classification harmful

Risk phrases Harmful in contact with skin and if swallowed – Irritating to the skin (R21/22, R38)

Safety phrases In case of contact with eyes, rinse immediately with plenty of water and seek medical advice –
After contact with skin, wash immediately with plenty of water (S26, S28)

Ecotoxicity

Fish toxicity

LC₅₀ (24 hr) sea trout 2.1 mg l⁻¹ static bioassay. Sea trout exposed to 0.5 ppm were histologically normal. Trout exposed to 1-1.5 ppm had histological changes in liver, kidney and gills (1).

Toxicity to other species

EC₅₀ phytotoxicity to *Lactuca sativa* in soil (7 and 14 days) >32 and <100 µg g⁻¹ and in nutrient solution (16-21 days) 4.0 mg l⁻¹ (2).

Environmental fate

Degradation studies

t_{1/2} in sandy clay and silty clay soils 19-23 days (3).

Abiotic removal

Vapour phase degraded in the atmosphere by reaction with photochemically produced hydroxyl radicals.

Estimated t_{1/2} 1.25 days (4).

Exposure to low ozone doses. Products formed were not biodegradable (5).

Mammalian & avian toxicity

Acute data

LD₅₀ oral rat, mouse 1190, 1320 mg kg⁻¹, respectively (6,7).

LD₅₀ intraperitoneal rat 794 mg kg⁻¹ (6).

Irritancy

Irritating to skin, eyes, mucous membranes and upper respiratory tract (species unspecified) (8).

Genotoxicity

Salmonella typhimurium TA98, TA100, TA1535, TA1537 with and without metabolic activation negative (9).

Salmonella typhimurium TA97, TA104 with metabolic activation positive (10).

Other effects

Any other adverse effects

Decreased the rate of respiration of isolated rat liver mitochondria by inhibiting the NAD-dependent dehydrogenases (11).

Legislation

Limited under EC Directive on Drinking Water Quality 80/778/EEC. Organochlorine compounds: guide level 1 µg l⁻¹ (12).

Included in Schedule 6 (Release into Land: Prescribed Substances) of Statutory Instrument No. 472, 1991 (13).

Other comments

Exhibits fungicidal activity (14).

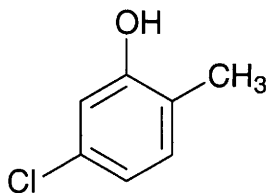
Reviews on experimental toxicology and human health effects listed (15).

Impurity in technical grade MCPA. Metabolite of MCPA.

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c185 5-chloro-o-cresol



C₇H₇ClO

Mol. Wt. 142.58

CAS Registry No. 5306-98-9

Synonyms 5-chloro-2-methylphenol; 3-chloro-6-methylphenol

EINECS No. 226-160-3

Physical properties

M. Pt. 73-74°C **B. Pt.** 160-165°C at 2-3 mmHg

Occupational exposure

UN No. 2669 **HAZCHEM Code** 2X **Conveyance classification** toxic substance

Genotoxicity

Salmonella typhimurium TA98, TA100, TA1535, TA1537 with and without metabolic activation negative (1).

Legislation

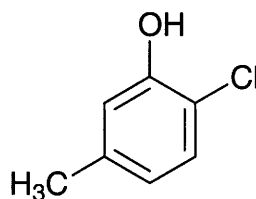
Limited under EC Directive on Drinking Water Quality 80/778/EEC. Organochlorine compounds: guide level $1 \mu\text{g l}^{-1}$ (2).

Included in Schedule 6 (Release into Land: Prescribed Substances) of Statutory Instrument No. 472, 1991 (3).

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C186 6-chloro-*m*-cresol



$\text{C}_7\text{H}_7\text{ClO}$

Mol. Wt. 142.58

CAS Registry No. 615-74-7

Synonyms 2-chloro-5-methylphenol; 6-chloro-3-methylphenol

EINECS No. 210-444-9

RTECS No. SK 4930000

Physical properties

M. Pt. 46°C B. Pt. 196°C Flash point 81°C Specific gravity 1.215 at 20°C with respect to water at 4°C

Solubility Organic solvents: ethanol

Occupational exposure

UN No. 2669 HAZCHEM Code 2X Conveyance classification toxic substance

Legislation

Limited under EC Directive on Drinking Water Quality 80/778/EEC. Organochlorine compounds: guide level $1 \mu\text{g l}^{-1}$ (1).

Included in Schedule 6 (Release into Land: Prescribed Substances) of Statutory Instrument No. 472, 1991 (2).

Other comments

Hazards reviewed (3).

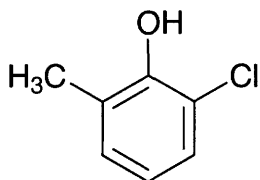
A QSAR equation expressing toxicity of phenols against *Tetrahymena pyriformis* as a non-linear function of their hydrophobicity and acidity has been developed (4).

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c187 6-chloro-o-cresol



C₇H₇ClO

Mol. Wt. 142.58

CAS Registry No. 87-64-9

Synonyms 6-chloro-2-methylphenol; 2-chloro-6-methylphenol

EINECS No. 201-760-8

RTECS No. GO 7120100

Physical properties

M. Pt. 1-2°C **B. Pt.** 188-189°C at 740 mmHg

Solubility Organic solvents: diethyl ether

Occupational exposure

UN No. 2669 **HAZCHEM Code** 2X **Conveyance classification** toxic substance

Mammalian & avian toxicity

Acute data

LD₅₀ oral mouse 710 mg kg⁻¹ (1).

Legislation

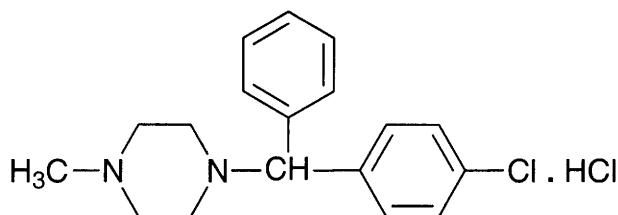
Limited under EC Directive on Drinking Water Quality 80/778/EEC. Organochlorine compounds: guide level 1 µg l⁻¹ (2).

Included in Schedule 6 (Release into Land: Prescribed Substances) of Statutory Instrument No. 472, 1991 (3).

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C188 chlorocyclizine hydrochloride



C₁₈H₂₂Cl₂N₂

Mol. Wt. 337.29

CAS Registry No. 14362-31-3

Synonyms piperazine, 1-[(4-chlorophenyl)phenylmethyl]-4-methyl-, hydrochloride

EINECS No. 238-335-1

RTECS No. TL 2200000

Uses Antihistamine.

Physical properties

M. Pt. 216-216.5°C

Solubility Organic solvents: ethanol

Mammalian & avian toxicity

Acute data

LD₅₀ oral mouse 300 mg kg⁻¹ (1).

LD₅₀ intraperitoneal mouse 137 mg kg⁻¹ (2).

Teratogenicity and reproductive effects

Chlorocyclizine (60 or 80 mg kg⁻¹ day⁻¹ by oral gavage on days 12-16 of gestation) given to pregnant rats induced hydronephrosis and hydro-ureter in 37% of foetuses and undescended testes in 55% of the ♂ at the lower dose, whereas at the higher dose only 4% were hydronephrotic although 100% of the ♂ were cryptorchid (3).

Hydrocephalus, hydronephrosis, undescended testes and cleft palate occurred at the highest incidences when chlorocyclizine was given late to pregnant rats (days 13-16) (4).

Chlorocyclizine and its active metabolite norchlorcyclizine produced cleft palate only when given on days 12-14 of embryonic development in pregnant rats (5).

Metabolism and toxicokinetics

Within 4 hr after administration of chlorocyclizine to rats, high concentrations of norchlorcyclizine were found in various tissues (6).

Legislation

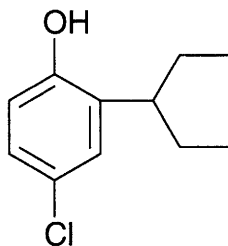
Limited under EC Directive on Drinking Water Quality 80/778/EEC. Organochlorine compounds: guide level 1 µg l⁻¹ (7).

Included in Schedule 6 (Release into Land: Prescribed Substances) of Statutory Instrument No. 472, 1991 (8).

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c189 4-chloro-2-cyclopentylphenol



$C_{11}H_{13}ClO$

Mol. Wt. 196.68

CAS Registry No. 13347-42-7

Synonyms 2-cyclopentyl-4-chlorophenol

EINECS No. 236-395-3

RTECS No. SK 3675000

Uses Used in the formulation of disinfectants.

Physical properties

B. Pt. 181-185°C

Mammalian & avian toxicity

Acute data

LD_{Lo} oral rat, rabbit 420 mg l⁻¹ (1).

LD₅₀ dermal rabbit 850 mg kg⁻¹ (1).

Irritancy

Dermal human (duration unspecified) 25 mg caused mild irritation and 100 mg instilled into rabbit eye caused severe irritation (1).

Legislation

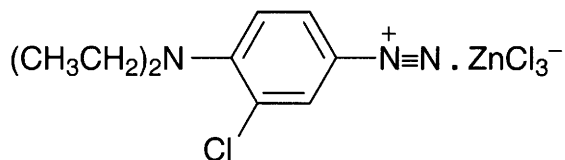
Limited under EC Directive on Drinking Water Quality 80/778/EEC. Organochlorine compounds: guide level 1 µg l⁻¹ (2).

Included in Schedule 6 (Release into Land: Prescribed Substances) of Statutory Instrument No. 472, 1991 (3).

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c190 3-chloro-4-diethylaminobenzenediazonium trichlorozincate



$\text{C}_{10}\text{H}_{13}\text{Cl}_4\text{N}_3\text{Zn}$

Mol. Wt. 382.43

CAS Registry No. 15557-00-3; 36356-20-4

Synonyms zinc chloride 3-chloro-4-diethylaminobenzenediazonium chloride (1:1) complex

EINECS No. 239-609-3

Uses Halography. Thermal recording sheets. Epoxy coatings. Light-sensitive compositions. Photodiazotype processes. Used in diazo copying compositions and in lithographic printing plates.

Other effects

Any other adverse effects

Actinomyces antibioticus (thiamine deficient) 100-1000 mg l⁻¹ positive (1).

Actinomyces streptomycini positive (high toxicity; sporulation stimulated) (2).

Actinomyces griseus 5-250 mg l⁻¹ positive (3).

Legislation

Limited under EC Directive on Drinking Water Quality 80/778/EEC. Organochlorine compounds: guide level 1 µg l⁻¹ (4).

Included in Schedule 6 (Release into Land: Prescribed Substances) of Statutory Instrument No. 472, 1991 (5).

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c191 1-chloro-1,1-difluoroethane



$\text{C}_2\text{H}_3\text{ClF}_2$

Mol. Wt. 100.50

CAS Registry No. 75-68-3

Synonyms chlorodifluoroethane; 1,1-difluoro-1-chloroethane; α-chloroethylidene fluoride

EINECS No. 200-891-8

RTECS No. KH 7650000

Uses Aerosol propellant. Blowing agent for polymers. Solvent. Working fluid for heat pumps. Refrigerant.

Physical properties

M. Pt. -131°C to -130.8°C **B. Pt.** -10°C to -9.2°C **Volatility** v.p. 1103 mmHg at 0°C

Solubility Water: 9.18×10^3 mg l⁻¹ at 25°C. Organic solvents: benzoate esters, benzyl acetate, dicumylmethane, oleic acid, phthalate esters

Occupational exposure

DE-MAK 1000 ppm (4200 mg m⁻³)

Environmental fate

Abiotic removal

Undergoes photolysis. Stratospheric lifetime estimated to be a few decades (1).

Mammalian & avian toxicity

Acute data

LC₅₀ (2 hr) inhalation mouse 1514 g m⁻³ (2).

LC₅₀ (½ hr) inhalation (AP) mouse 1228 g m⁻³ (3).

LC₅₀ (2 hr) inhalation mouse 1760 g m⁻³ (4).

LC₅₀ (4 hr) inhalation rat 2050 g m⁻³ (4).

Sub-acute and sub-chronic data

Inhalation rats (4 wk) 500-600 mg l⁻¹, 14 hr day⁻¹, 6 days wk⁻¹ caused a 2.32% decrease in iodine uptake, and hypofunction in thyroid and central nervous system. Long-term exposure gives opposite effects (2).

Inhalation mice (10 min) 25% by vol (anaesthetic dose) caused convulsions on recovery (5).

Carcinogenicity and chronic effects

Groups of 110 rats of each sex were exposed by whole-body inhalation to 0, 1000, 10,000 and 20,000 ppm for 6 hr day⁻¹, 5 days wk⁻¹ for 104 wk. No toxicologically significant effects were observed in behaviour, appearance, growth, clinical pathology or gross and microscopic pathology (6).

Teratogenicity and reproductive effects

Inhalation rats (15 wk) 20,000 ppm, 6 hr day⁻¹, 5 days wk⁻¹, no effect on male reproduction was found (6).

Metabolism and toxicokinetics

Inhalation Fischer 344 and Sprague-Dawley rats (2 hr) 1.0% (v/v) air atm. Chlorodifluoroacetic acid was excreted in urine; no volatile metabolites were detected in tissue samples (7).

Evidence was obtained that incubation of rat liver microsomes with ca. 1% 1-chloro-1,1-difluoroethane resulted in dechlorination (8).

Irritancy

Chronic inhalation rats, positive pulmonary irritant (9).

Genotoxicity

Salmonella typhimurium TA100, TA1535 with metabolic activation positive (10).

In vitro hamster kidney fibroblasts BHK21 with metabolic activation positive (10).

Inhalation ♂ rat (13 wk) 20,000 ppm, 6 hr day⁻¹, 5 day wk⁻¹ bone marrow cytogenic studies negative (6).

Other effects

Any other adverse effects

LC_{Lo} inhalation mice (duration unspecified) 60% by vol, no cardiac arrhythmias observed (11).

LC_{Lo} inhalation dogs 5% by vol sensitised the heart to arrhythmias by epinephrine (12).

Inhalation rhesus monkey (duration unspecified) caused hypotension and respiratory stimulation (13).

Caused hypertension in dogs when administered at a concentration of 20%. There was accompanying tachycardia, an increase in pulmonary resistance and a decrease in pulmonary compliance (14).

Legislation

Included in Schedule 4 (Release into Air: Prescribed Substances) Statutory Instrument No. 472, 1991 (15).

Other comments

Experimental toxicology and human health effects reviewed (16,17).

Colourless, flammable gas.

Air pollutant, which may have an effect on atmospheric ozone and the greenhouse effect (18,19).

Ozone depletion potential $\approx 0.05 \times$ that of CFC-11 (CCl_3F). Global warming potential ≈ 0.33 that of CFC-11.

Calculated atmospheric global lifetime 19-25 yr (1D model), 15.1-28 yr (2D model) (20).

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c192 chlorodifluoromethane



CHClF₂

Mol. Wt. 86.47

CAS Registry No. 75-45-6

Synonyms difluorochloromethane; monochlorodifluoromethane; R22; Korform 22; Genetron 22

EINECS No. 200-871-9

RTECS No. PA 6390000

Uses Refrigerant. Aerosol propellant. Low-temperature solvent. Component of fluorocarbon resins such as tetrafluoroethylene polymers.

Physical properties

M. Pt. -146°C **B. Pt.** -40.8°C **Specific gravity** 1.4909 at -69°C

Solubility Organic solvents: acetone, chloroform, diethyl ether

Occupational exposure

DE-MAK 500 ppm (1800 mg m⁻³)

FR-VME 1000 ppm (3500 mg m⁻³)

JP-OEL 1000 ppm (3500 mg m⁻³)

SE-LEVL 500 ppm (1800 mg m⁻³)

UK-LTEL 1000 ppm (3590 mg m⁻³)

US-TWA 1000 ppm (3540 mg m⁻³)

SE-STEL 750 ppm (2500 mg m⁻³)

UN No. 1018 HAZCHEM Code 2RE Conveyance classification non-flammable non-toxic gas

Mammalian & avian toxicity

Acute data

LC₅₀ (20 min) inhalation mouse 28 pph (1).

Sub-acute and sub-chronic data

In rats and guinea pigs exposure to 75,000-100,000 ppm (duration unspecified) produced excitation and changes in equilibrium. Narcosis occurred at 200,000 ppm and death at 300,000 ppm (2).

Carcinogenicity and chronic effects

Inadequate evidence for carcinogenicity to humans, limited evidence for carcinogenicity to animals, IARC classification group 3 (3,4).

Administration by inhalation at 5000, 1000 and 0 ppm, 4 hr day⁻¹, 5 days wk⁻¹ to rats and mice for 104 and 78 wk, respectively, failed to show any carcinogenic effects (5).

Did not induce tumours in rats dosed 300 mg kg⁻¹ by gavage in corn oil 5 days wk⁻¹ for 1 yr (6).

Metabolism and toxicokinetics

Male human volunteers were exposed (4 hr) to 327 or 1833 mg m⁻³ atmospheric concentrations of chlorodifluoromethane. The results indicated that, following inhalation, the compound was poorly absorbed and rapidly eliminated from the body, and that it was unlikely to have been metabolised to a significant extent (7).

Genotoxicity

Salmonella typhimurium TA100, TA1535 with and without metabolic activation positive (6,8).

In vivo mouse bone marrow micronucleus test negative (8).

Other effects

Any other adverse effects

In humans, produced cardiac arrhythmias or arrest under circumstances where an abnormally large amount of adrenaline is secreted endogenously. High atmospheric levels of Freon 22 produce stimulation and then depression of the central nervous system, and finally asphyxiation (9).

Legislation

Maximum permissible concentration in domestic water in the former USSR 10 mg l⁻¹ (10).

Included in Schedule 4 (Release into Air: Prescribed Substances) Statutory Instrument No. 472, 1991 (11).

Other comments

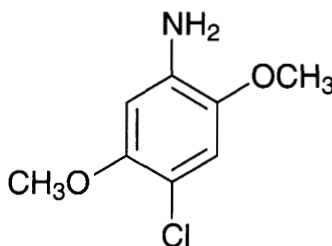
Indirect long-term effects on living systems due to depletion of ozone layer and enhancement of UVB radiation (9). Human health effects, experimental toxicology, environmental effects, ecotoxicology, exposure levels, epidemiology and workplace experience reviewed (12-14).

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C193 4-chloro-2,5-dimethoxyaniline



$C_8H_{10}ClNO_2$

Mol. Wt. 187.63

CAS Registry No. 6358-64-1

Synonyms 2,5-dimethoxy-4-chloroaniline; 4-chloro-2,5-dimethoxybenzenamine

EINECS No. 228-782-0

RTECS No. BX 1225000

Mammalian & avian toxicity

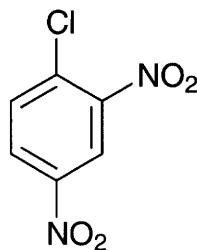
Acute data

LD₅₀ oral redwing blackbird and starling >100 mg kg⁻¹ (1).

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C194 1-chloro-2,4-dinitrobenzene



$C_6H_3ClN_2O_4$

Mol. Wt. 202.55

CAS Registry No. 97-00-7

Synonyms 2,4-dinitrochlorobenzene; 4-chloro-1,3-dinitrobenzene; 6-chloro-1,3-dinitrobenzene; chlorodinitrobenzene; DNCB

EINECS No. 202-551-4

RTECS No. CZ 0525000

Uses Immunostimulant in the treatment of leprosy and some forms of cancer. Treatment for alopecia and warts. Possibly active in the treatment of AIDS. Used in the determination of pyridine compounds. Manufacture of azo-dyestuffs, fungicides, rubber chemicals and explosives.

Physical properties

M. Pt. 53-54°C **B. Pt.** 315°C **Flash point** 195°C (closed cup) **Specific gravity** 1.687 at 22°C

Volatility v.den. 6.98

Solubility Water: 8 mg l⁻¹ at 15°C. Organic solvents: benzene, carbon disulfide, diethyl ether, ethanol

Occupational exposure

UN No. 1577 **HAZCHEM Code** 2W **Conveyance classification** toxic substance

Supply classification toxic

Supply classification dangerous for the environment

Risk phrases Toxic by inhalation, in contact with skin and if swallowed – Danger of cumulative effects – Very toxic to aquatic organisms, may cause long-term adverse effects in the aquatic environment (R23/24/25, R33, R50/53)

Safety phrases Keep locked up and out of the reach of children (if sold to general public) – After contact with skin, wash immediately with plenty of water – Wear suitable gloves – In case of accident or if you feel unwell, seek medical advice immediately (show label where possible) – This material and/or its container must be disposed of as hazardous waste – Avoid release to the environment. Refer to special instructions/safety data sheet (S1/2, S28, S37, S45, S60, S61)

Ecotoxicity

Fish toxicity

Loss of equilibrium was observed in steelhead trout exposed to 5 mg l⁻¹ within 1-2 hr and death occurred within 2-3 hr (1).

Invertebrate toxicity

EC₅₀ (5-30 min) *Photobacterium phosphoreum* 3.52 ppm Microtox test (2).

Environmental fate

Degradation studies

100 mg l⁻¹ in activated sludge for a 2-wk incubation period. No biodegradation occurred (3).

Abiotic removal

Vapour phase was degraded in the atmosphere by reaction with photochemically produced hydroxyl radicals, $t_{1/2}$ 2 yr (3).

Mammalian & avian toxicity

Acute data

LD₅₀ oral rat 1070 mg kg⁻¹ (4).

LD₅₀ dermal rabbit 130 mg kg⁻¹ (4).

LD₅₀ intraperitoneal rat 280 mg kg⁻¹ (5).

Sub-acute and sub-chronic data

Intragastric rats (30 day) 78 mg kg⁻¹ day⁻¹ caused the aerobic and anaerobic metabolic rate of carbohydrates and concentrations of ATP and creatine phosphate in the brain and liver to increase (6).

Carcinogenicity and chronic effects

Administered in the diet, it was inactive in long-term toxicity and carcinogenicity tests on ♂ rats and ♂ and ♀ mice (dose unspecified) (7).

Teratogenicity and reproductive effects

Increased post-implantation mortality and decreased weight and length of surviving foetuses have been reported in rats following inhalation during pregnancy (dose and duration unspecified) (8).

Metabolism and toxicokinetics

Rapidly absorbed by the skin (9).

Conjugation with glutathione leads to the formation of *N*-acetylcysteine derivatives (10).

Irritancy

Dermal rabbit (24 hr) 2 mg produced severe irritation, and (24 hr) 50 µg instilled into rabbit eye produced severe irritation (11).

A primary skin irritant and causes severe allergic dermatitis in humans (12-15).

Sensitisation

Reported to be a sensitising agent, inducing allergic contact dermatitis. A greater response was observed in women (16).

Skin sensitivity was reported to be enhanced in women taking a combined oestrogen-progesterone oral contraceptive Neogynon or intramuscular injections of Depoprovera, but lower in those using the sequential pill Serial (17).

Reported to be responsible for an outbreak of occupational dermatitis in a rubber tyre factory (18).

Genotoxicity

Salmonella typhimurium TA98, TA100, TA1538 with and without metabolic activation positive (19-21).

Other effects

Other adverse effects (human)

Eye contact may cause colour vision disturbances (22).

Human platelets were reported to be time- and dose-dependently depleted of intracellular glutathione.

Glutathione peroxidase activity was also inhibited (concentration unspecified) (23).

Any other adverse effects

The median toxic concentration (TC₅₀) of 1-chloro-2,4-dinitrobenzene (CDNB) to murine P388D1 macrophages *in vitro* was 63±6 µM. Reduced glutathione ethyl mono- and di-esters were potent antidotes with EC₅₀'s to the TC₅₀ of 3.6±0.6 mM and 603±0.2 µM, respectively (24).

Glutathione *S*-transferase (GST) activities in the liver cytosolic fraction of ♂ C57BL/6 mice fed a diet containing either 0.3 or 0.5% ursodeoxycholic acid (UDCA) were significantly increased. Survival rates (24 hr) after an oral challenge of 3.5 mg kg⁻¹ CDNB were significantly higher ($P < 0.05$) in UDCA-fed groups compared with the

control group. It is likely that the reduction in systemic toxicity of CDNB was the result of the increase in GST activity caused by UDCA feeding (25).

Legislation

Included in Schedule 6 (Release into Land: Prescribed Substances) of Statutory Instrument No. 472, 1991 (26).
Limited under EC Directive on Drinking Water Quality 80/778/EEC. Organochlorine compounds: guide level 1 µg l⁻¹ (27).

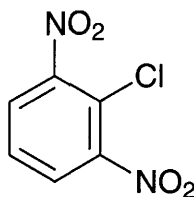
Other comments

Has been shown to cross-react with chloramphenicol (28).
Reviews on experimental toxicology and human health effects listed (29).

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C195 2-chloro-1,3-dinitrobenzene



$C_6H_3ClN_2O_4$

Mol. Wt. 202.55

CAS Registry No. 606-21-3

Synonyms 1,3-dinitro-2-chlorobenzene

EINECS No. 247-109-1

RTECS No. CZ 0490000

Uses Immunotherapy.

Physical properties

M. Pt. 86-87°C B. Pt. 315°C Specific gravity 1.6867 at 16.5°C with respect to water at 4°C

Solubility Organic solvents: benzene, diethyl ether, ethanol

Occupational exposure

UN No. 1577 HAZCHEM Code 2W Conveyance classification toxic substance

Supply classification toxic

Supply classification dangerous for the environment

Risk phrases Toxic by inhalation, in contact with skin and if swallowed – Danger of cumulative effects – Very toxic to aquatic organisms, may cause long-term adverse effects in the aquatic environment (R23/24/25, R33, R50/53)

Safety phrases Keep locked up and out of the reach of children (if sold to general public) – After contact with skin, wash immediately with plenty of water – Wear suitable gloves – In case of accident or if you feel unwell, seek medical advice immediately (show label where possible) – This material and/or its container must be disposed of as hazardous waste – Avoid release to the environment. Refer to special instructions/safety data sheet (S1/2, S28, S37, S45, S60, S61)

Mammalian & avian toxicity

Acute data

LD₅₀ oral rat 300 mg kg⁻¹ (1).

Genotoxicity

Salmonella typhimurium TA98, TA100, TA1538 without metabolic activation positive (2).

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C₂H₅Cl

Mol. Wt. 64.51

CAS Registry No. 75-00-3

Synonyms ethyl chloride; chloroethyl; hydrochloric ether; monochloroethane; muriatic ether

EINECS No. 200-830-5

RTECS No. KH 7525000

Uses Alkylating agent. Anaesthetic. Blowing agent. Solvent. Working fluid for compression heat pumps.
 Manufacture of tetraethyllead.

Physical properties

M. Pt. -139°C B. Pt. 12.3°C Flash point -50°C Specific gravity 0.8978 at 20°C with respect to water at 4°C

Partition coefficient log P_{ow} 1.43 Volatility v.p. 1000 mmHg at 20°C ; v.den. 2.22

Solubility Water: 5.74 g l⁻¹ at 20°C. Organic solvents: *tert*-butyl methyl ether, diethyl ether, ethanol

Occupational exposure

FR-VME 1000 ppm (2600 mg m⁻³)

JP-OEL 100 ppm (260 mg m⁻³)

SE-LEVL 500 ppm (1300 mg m⁻³)

SE-STEL 700 ppm (1900 mg m⁻³)

UK-LTEL 1000 ppm (2700 mg m⁻³)

UK-STEL 1250 ppm (3380 mg m⁻³)

US-TWA 100 ppm (264 mg m⁻³)

UN No. 1037 HAZCHEM Code 2WE Conveyance classification flammable gas

Supply classification extremely flammable

Supply classification harmful

Risk phrases Extremely flammable – Possible risk of irreversible effects – Harmful to aquatic organisms, may cause long-term adverse effects in the aquatic environment (R12, R40, R52/53)

Safety phrases Keep out of reach of children (if sold to general public) – Keep container in a well ventilated place

– Keep away from sources of ignition – No smoking – Take precautionary measures against static discharges –

Wear suitable protective clothing and gloves – Avoid release to the environment. Refer to special instructions/safety data sheet (S2, S9, S16, S33, S36/37, S61)

Ecotoxicity

Bioaccumulation

Calculated bioconcentration factor range 0.67-0.86 indicating that the potential for environmental accumulation is low (1).

Environmental fate

Abiotic removal

Evaporation of 1 mg l⁻¹ in still air from water of average depth 6.5 cm, t_{1/2} 21 min. 90% evaporation after 79 min (2).

Reaction with photochemically produced hydroxyl radicals in the atmosphere t_{1/2} (calc.) ≈40 day. This value indicates that <1% will eventually diffuse above the ozone layer where it will be destroyed by photolysis (3).

Hydrolysis in water at 25°C, t_{1/2} 38 day (estimated), ethanol and hydrochloric acid were the hydrolysis products identified (4).

Adsorption and retention

Estimated K_{oc} 33-143 indicated that chloroethane will not adsorb to soil and sediments (1).

Mammalian & avian toxicity

Acute data

LC₅₀ (2 hr) inhalation rat 152 g m⁻³. Signs of toxicity included anaesthesia, liver congestion, haemorrhage and lung oedema (5).

Sub-acute and sub-chronic data

Inhalation mouse 0.66, 3.3 or 13 g m⁻³ for 23 hr day⁻¹ for 11 consecutive days. The high dose caused increased liver weights (6).

Carcinogenicity and chronic effects

No adequate data for evidence of carcinogenicity to humans, limited evidence for carcinogenicity to animals, IARC classification group 3 (7).

Inhalation mouse 39,600 mg m⁻³, 6 hr day⁻¹ for 5 day wk⁻¹ for 100 wk. Carcinomas of the uterus occurred in 0/49 ♀ controls and 43/50 treated ♀ mice, and the carcinomas in many ♀ mice metastasised to a variety of organs. Primary hepatocellular tumours occurred in 3/49 ♀ controls and 8/48 treated ♀ mice. The incidence of liver tumours in treated ♂ mice was not increased. In ♂ mice alveolar/bronchiolar adenomas occurred in 3/50 controls and 8/48 treated mice. There was no increase in the incidence of these tumours in treated ♀ mice (8).

Inhalation rat 39,600 mg m⁻³, 6 hr day⁻¹ for 5 day wk⁻¹ for 102 wk. Skin tumours occurred in 4/50 control ♂ and 9/50 treated ♂ rats. Brain glial-cell tumours occurred in 3/50 ♀ rats compared to 0/50 controls (8).

Metabolism and toxicokinetics

In humans, the serum/gas partition coefficient (K_D at 25°C) is 2.3 (9).

Undergoes <0.5% dechlorination when incubated with rat hepatic microsomal fractions in the presence of NADPH and oxygen (10).

Sensitisation

Has been reported to cause allergic contact dermatitis (11).

Genotoxicity

Salmonella typhimurium TA98, TA110, TA1535 with and without metabolic activation positive (8).

In vitro BALB/C3T3 mouse cells unscheduled DNA synthesis negative (12).

Other effects

Other adverse effects (human)

Deaths that occurred under anaesthesia at very high concentrations were caused by respiratory depression (13).

Can cause frostbite through rapid evaporation on skin contact with liquified gas direct from a cylinder (14).

Inhalation human, anaesthetic concentration ~4% (15).

Any other adverse effects

Inhalation rat, mouse (6 hr) 11-26 g m⁻³ resulted in decreased non-protein sulphhydryl concentrations in the liver (16).

Legislation

Organic solvents are included in Schedule 6 (Release into Land: Prescribed Substances) of Statutory Instrument No. 472, 1991 (17).

Other comments

In flue gases of waste incinerator plants, emissions from industrial processes and from landfill gas emissions.

Residues have been identified in drinking water, soil, sediments, aquatic species and in human milk (7-21).

Physical properties, use, exposure, carcinogenicity, mammalian toxicity, genotoxicity and metabolism reviewed (7,15,22,23).

Environmental fate reviewed (21).

Toxicity reviews cited (24).

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c197 2-chloroethanol



$\text{C}_2\text{H}_5\text{ClO}$

Mol. Wt. 80.51

CAS Registry No. 107-07-3

Synonyms β -chloroethyl alcohol; glycol chlorohydrin; ethylene chlorohydrin; ethylene glycol, chlorohydrin; glycol monochlorohydrin; 2-monochloroethanol

EINECS No. 203-459-7

RTECS No. KK 0875000

Uses Solvent. Organic intermediate.

Occurrence Vinyl chloride metabolite.

Physical properties

M. Pt. -89°C (1) **B. Pt.** 129°C (1) **Flash point** 60°C (1) **Specific gravity** 1.197 at 20°C with respect to water at 4°C **Volatility** v.p. 4.9 mmHg at 20°C ; v.den. 2.78

Occupational exposure

DE-MAK 1 ppm (3.3 mg m^{-3})

FR-VLE 1 ppm (3 mg m^{-3})

SE-CEIL 1 ppm (3.5 mg m^{-3})

UK-STEL 1 ppm (3.4 mg m⁻³)

US-STEL ceiling limit 1 ppm (3.3 mg m⁻³)

UN No. 1135 HAZCHEM Code 2W Conveyance classification toxic substance, danger of fire (flammable liquid)

Supply classification very toxic

Risk phrases Very toxic by inhalation, in contact with skin and if swallowed (R26/27/28)

Safety phrases Keep locked up and out of the reach of children (if sold to general public) – Keep container tightly closed and in a well ventilated place – After contact with skin, wash immediately with plenty of water – In case of accident or if you feel unwell, seek medical advice immediately (show label where possible) (S1/2, S7/9, S28, S45)

Environmental fate

Degradation studies

Resistant to degradation by activated sludge (2).

Degradation of 2-chloroethanol by *Pseudomonas putida* US2 results in proton release. Complete degradation of the compound under batch, repeated batch, and continuous culture methods is prevented by decreasing pH at concentrations of the compound >25 nM (3).

Mammalian & avian toxicity

Acute data

LD₅₀ oral rat, guinea pig 71-110 mg kg⁻¹ (4).

LC₅₀ (duration unspecified) inhalation rat 290 mg m⁻³ (5).

LD₅₀ dermal mouse 18 mg kg⁻¹ (6).

LD₅₀ intraperitoneal rat 58 mg kg⁻¹ (4).

LD₅₀ subcutaneous rat 84 mg kg⁻¹ (7).

Acute poisoning in a 24-yr-old human subject caused severe functional shifts in the central nervous system, respiratory and cardiovascular centres, resulting in collapse, hypoxia of the organs, disruption of the excretory function of the kidneys and the detoxifying function of the liver (8).

Sub-acute and sub-chronic data

In 13-wk studies (route unspecified), mortality was observed in ♂ and ♀ rats receiving >250 mg kg⁻¹ day⁻¹ and in ♂ and ♀ mice receiving >20 mg kg⁻¹ day⁻¹ (9).

Administration of 6.4 mg kg⁻¹ day⁻¹ intraperitoneally for 1 month or of 12.8 mg kg⁻¹ 3 × wk⁻¹ for 3 months had no adverse effect on rats (10).

Oral ♂ Sprague-Dawley rats (60 days) 500 ppm (in drinking water) were sacrificed on day 61. Body weights were significantly reduced compared with controls. Low serum cholesterol (88% of control), reduced hepatic alcohol dehydrogenase activity (33% of control), significant increases in serum IgG, IgM, and IgA, and lymphatic interstitial infiltration of the lungs were observed. Sub-chronic exposure caused hepatic injury with hypergammaglobulinaemia (11).

Carcinogenicity and chronic effects

In a 104-wk study using dermal application, no evidence of carcinogenicity was found in rats given 50 or 100 mg kg⁻¹ day⁻¹ or in mice given 7.5 or 15 mg kg⁻¹ day⁻¹ (9).

No evidence for carcinogenicity was found in experiments where 2-chloroethanol was administered subcutaneously to ♀ mice or intragastrically to rats (12).

Teratogenicity and reproductive effects

2-Chloroethanol administered intragastrically to pregnant mice on days 6-16 of gestation at 100 mg kg⁻¹ produced a significant reduction in maternal weight gain and a decrease in foetal body weight and liver weight. A lower dose of 50 mg kg⁻¹ had no consistent effect and a higher dose of 150 mg kg⁻¹ was maternally lethal.

Administration in drinking water at doses of 16, 43, 77 or 227 mg kg⁻¹ did not produce any adverse effects in maternal or foetal body weight, viability or foetal anatomical development (13).

No evidence was observed for a foetotoxic or teratogenic effect when administered to New Zealand white rabbits on days 6-14 of gestation (dose and duration unspecified) (14).

Intravenous administration of 60 or 120 mg kg⁻¹ day⁻¹ 2-chlorethanol in 5% dextrose to mice in a volume of 1 ml kg⁻¹ on days 4-6, 6-8, 8-10 and 10-12 of gestation. Evidence of embryotoxicity in the low-dose group was observed only following exposure on days 8-10 of gestation, a treatment which decreased average foetal body weight. The high dose was embryotoxic and produced a reduction in average foetal body weight for each exposure period (15).

Metabolism and toxicokinetics

Excretion and tissue distribution were studied in rats following single oral administration of 5 and 50 mg kg⁻¹. At both dose levels two metabolites, thiodiacetic acid and thionylodiacetic acid, were detected. Excretion occurred in approximately equal amounts at the lower dose, whereas the thiodiacetic acid predominated in urine ~70% at the high dose (16).

Irritancy

Dermal rabbit (2 hr) 200 mg caused mild irritation and 33 mg instilled into rabbit eye caused moderate irritation (17).

Genotoxicity

Salmonella typhimurium TA100, TA1530, TA1535 with and without metabolic activation positive (9,16).

Did not induce sex-linked recessive lethal mutations in *Drosophila melanogaster* (9,18).

L-5178Y tk⁺/tk⁻ mouse lymphoma cell forward mutation assay without metabolic activation negative, with metabolic activation positive (19).

Escherichia coli prophage-induction assay with and without metabolic activation positive (20).

Gavage rats administered a single or two successive doses equal to one-half the LD₅₀ and killed at various times after dosing exhibited no signs indicative of genotoxic activity as measured by frequency of both micronucleated polychromatic erythrocytes in the bone marrow and micronucleated hepatocytes (after partial hepatectomy), of *in vivo* – *in vitro* induction of DNA fragmentation, and of unscheduled DNA synthesis in hepatocyte primary cultures (21).

Other comments

Reviews on human health effects, experimental toxicology, physico-chemical properties, epidemiology and workplace experience listed (22).

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c198 2-chloroethyl chloroformate



$\text{C}_3\text{H}_4\text{Cl}_2\text{O}_2$

Mol. Wt. 142.97

CAS Registry No. 627-11-2

Synonyms 2-chloroethyl chlorocarbonate; 2-chloroethyl carbonochloridate; (2-chloroethoxy)carbonyl chloride; β -chloroethyl chloroformate

EINECS No. 210-982-4

RTECS No. LQ 5950000

Uses Chemical intermediate. Cross-linking agent for cellulose.

Physical properties

B. Pt. 155-157°C **Flash point** 70°C (closed cup) **Specific gravity** 1.3847 at 20°C with respect to water at 4°C

Mammalian & avian toxicity

Acute data

LC_{Lo} (10 min) inhalation mouse 200 mg m^{-3} (1).

Legislation

Limited under EC Directive on Drinking Water Quality 80/778/EEC. Organochlorine compounds: guide level 1 $\mu\text{g l}^{-1}$ (2).

Included in Schedule 6 (Release into Land: Prescribed Substances) of Statutory Instrument No.472, 1991 (3).

Other comments

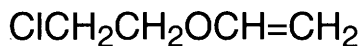
Pollutant in tap and natural waters (4).

Corrosive. Lachrymator.

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c199 2-chloroethyl vinyl ether



$\text{C}_4\text{H}_7\text{ClO}$

Mol. Wt. 106.55

CAS Registry No. 110-75-8

Synonyms (2-chloroethoxy)ethene; β -chloroethyl vinyl ether; vinyl 2-chloroethyl ether; vinyl β -chloroethyl ether; 2-vinyloxyethyl chloride; RCRA waste number U042

EINECS No. 203-799-6

RTECS No. KN 6300000

Uses Manufacturing intermediate for anaesthetics, sedatives, cellulose ethers and esters. Polymer and copolymer intermediate. Plant regulator.

Physical properties

M. Pt. -70.3°C **B. Pt.** 109°C at 740 mmHg **Flash point** 16°C (closed cup) **Specific gravity** 1.0525 at 15°C with respect to water at 15°C **Partition coefficient** $\log P_{ow}$ 1.28 (calc.) (1) **Volatility** v.p. 27 mmHg at 20°C **Solubility** Water: 3 mg l^{-1} at 25°C

Ecotoxicity

Fish toxicity

LC_{50} (24-96 hr) bluegill sunfish 452, 350 mg l^{-1} , respectively (2,3).

Invertebrate toxicity

LC_{50} (48 hr) contact *Eisenia foetida* 33 $\mu\text{g cm}^{-2}$ (1).

LC_{50} (14 days) adsorbed on soil *Eisenia foetida* 740 mg kg^{-1} (1).

Bioaccumulation

Average bioconcentration factor 2.5; calculated for weighted average 3.0% lipids for consumed fish and shellfish (4).

Environmental fate

Degradation studies

BOD_7 incubated with 5 ppm, 75-76% degradation in original culture. First subculture BOD_7 10 ppm O_2 , 52-68% degradation. Second and third subculture BOD_7 5 and 10 ppm O_2 , respectively; both showed 100% degradation (4).

Abiotic removal

Chlorination in water-treatment plants may introduce chloride substituent at either carbon α to the ether linkage. The product may be decomposed by water (4).

Adsorption and retention

Atmospheric $t_{1/2}$ 30 min. Maximum $t_{1/2}$ water 6 months. Some adsorption occurred on humic materials (4).

Mammalian & avian toxicity

Acute data

LD_{50} oral rat 250 mg kg^{-1} (1,5).

LC_{Lo} (4 hr) inhalation rat 250 ppm (6).

LD_{50} dermal rabbit 3350 mg kg^{-1} (5).

Irritancy

Primary skin irritation score Draize test 1 (no reaction undiluted material) in rabbits. Dermal rabbit 525 mg caused severe irritation and 500 mg instilled into rabbit eye caused irritation (7).

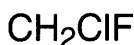
Other comments

Readily hydrolysed by alkaline waters. Water and air pollutant (8-10).

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c200 chlorofluoromethane



CH₂ClF

Mol. Wt. 68.48

CAS Registry No. 593-70-4

Synonyms fluorochloromethane; HCF₃ 31; Freon 31; R31; FC31

EINECS No. 209-803-2

RTECS No. PA 6408000

Uses Blowing agent. Refrigerant. Alkylating agent.

Physical properties

M. Pt. -133°C B. Pt. -9.1°C

Solubility Organic solvents: chloroform

Environmental fate

Abiotic removal

Reaction with photochemically produced hydroxyl radicals in the atmosphere, estimated $t_{1/2}$ 1.6 yr (1).

Mammalian & avian toxicity

Sub-acute and sub-chronic data

Inhalation rat 28,000 mg m⁻³ 6 hr day⁻¹ 5 days wk⁻¹ for 2 wk caused damage to the kidneys, adrenal glands, testes, epididymis and haematopoietic tissues (2).

Inhalation rat, monkey (4 hr) 28,000 and 56,000 mg m⁻³, respectively, caused central nervous system depression in both species. 50% of the monkeys died as a result of exposure (3).

Inhalation monkey, 14,000 mg m⁻³ 6 hr day⁻¹ for 19-20 days, 5/8 animals died with severe epistaxis and 5 had centrilobular to diffuse hepatic swelling (3).

Carcinogenicity and chronic effects

No adequate data on carcinogenicity to humans, limited evidence for carcinogenicity to animals, IARC classification group 3 (4).

Gavage rat (125 wk) 300 mg kg⁻¹ day⁻¹ 5 days wk⁻¹ for 52 wk. All treated ♂ rats died by 100 wk and ♀ by 108 wk.

The incidence of malignant forestomach and stomach neoplasms was 67/72 treated animals compared to 2/208 in controls (5).

Teratogenicity and reproductive effects

Inhalation rat 2800 mg m⁻³ 6 hr day⁻¹ on days 6-15 of gestation, cervical ribs were found in 8/208 fetuses of exposed dams (3).

Inhalation ♂ rat and monkey, 2800 or 14,000 mg m⁻³ 6 hr day⁻¹ for 20 days. ♂ rats in the high-dose group exhibited slight hypospermatogenesis. After 65 exposures to 2800 mg m⁻³ over 13 wk, rats exhibited hypospermatogenesis which was not reversed during a 4-wk recovery period (3).

Metabolism and toxicokinetics

Metabolised *in vitro* to carbon monoxide by Aroclor-induced rat hepatic microsomes, and to formaldehyde by rat hepatic cytosolic fractions in the presence of glutathione (6).

Genotoxicity

Salmonella typhimurium TA100, TA1535 with and without metabolic activation positive (5,6).

In vitro Chinese hamster ovary cells, induction of 6-thioguanine-resistant mutants, with and without metabolic activation positive (7).

In vivo mouse bone marrow no cytogenic or dominant lethal effect was observed (3).

Other comments

Potential for stratospheric ozone depletion reviewed (8).

Physical properties, occurrence, carcinogenicity, mammalian toxicity and mutagenicity reviewed (9,10).

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c201 chloroform



CHCl₃

Mol. Wt. 119.38

CAS Registry No. 67-66-3

Synonyms formyl trichloride; methyl trichloride; methane trichloride; methenyl trichloride; trichloroform

EINECS No. 200-663-8

RTECS No. FS 9100000

Uses Anaesthetic. Chemical intermediate in the synthesis of the refrigerant fluorocarbon 22. Intermediate in the production of tetrafluoroethylene and PTFE. Laboratory and industrial solvent. Extractant.

Physical properties

M. Pt. -63.5°C **B. Pt.** 61-62°C **Flash point** none **Specific gravity** 1.488 at 20°C with respect to water at 4°C
Partition coefficient log P_{ow} 1.97 at 20°C **Volatility** v.p. 160 mmHg at 20°C ; v.den. 4.12

Solubility Water: 8000 mg l⁻¹ at 20°C. Organic solvents: acetone, benzene, carbon disulfide, carbon tetrachloride, diethyl ether, ethanol, petroleum ether

Occupational exposure

DE-MAK 10 ppm (50 mg m⁻³)

FR-VME 5 ppm (25 mg m⁻³)

FR-VLE 50 ppm (250 mg m⁻³)

JP-OEL 10 ppm (49 mg m⁻³)

SE-LEVL 2 ppm (10 mg m⁻³)

SE-STEEL 5 ppm (25 mg m⁻³)

UK-LTEL 2 ppm (9.9 mg m⁻³)

US-TWA 10 ppm (49 mg m⁻³)

UN No. 1888 **HAZCHEM Code** 2Z **Conveyance classification** toxic substance

Supply classification harmful

Risk phrases Harmful if swallowed – Irritating to the skin – Possible risk of irreversible effects – Harmful: danger of serious damage to health by prolonged exposure through inhalation and if swallowed (R22, R38, R40, R48/20/22)

Safety phrases Restricted to professional users – Keep out of reach of children (if sold to general public) – Wear suitable protective clothing and gloves (S2, S36/37)

Ecotoxicity

Fish toxicity

LC₅₀ goldfish 92 mg l⁻¹ (1).

LC₅₀ guppy 102 ppm (2).

Invertebrate toxicity

EC₅₀ (24 hr) *Daphnia magna* 290 mg l⁻¹ (1).

EC₁₀ (24 hr) *Haematococcus pluvialis* 440 mg l⁻¹ (1).

Cell multiplication inhibition test *Pseudomonas putida* 125 mg l⁻¹ (1).

Cell multiplication inhibition test *Scenedesmus quadricauda* 1100 mg l⁻¹, *Entosiphon sulcatum* >6560 mg l⁻¹ (3).

Bioaccumulation

Anguilla anguilla liver 474 ng g⁻¹ (3).

Gadus virens stomach 51 ng g⁻¹ (3).

Pecten maximus gill 1046 ng g⁻¹ (3).

Environmental fate

Nitrification inhibition

75% inhibition of ammonia oxidation by activated sludge at 18 mg l⁻¹ (4).

No inhibition of nitrifying bacteria at 50 mg l⁻¹ (4).

Degradation studies

Resting cells of *Methylosinus trichosporium* OB-3b grown in the absence of copper salts oxidised chloroform to CO₂ t_{1/2} 38 min. Methane monooxygenase is the responsible enzyme (5).

Abiotic removal

Volatilisation measured t_{1/2} 18-25 min (in still air at 25°C and average water depth of 6.5 cm) initial concentration in aqueous solution 1 ppm (6).

Evaporation from water at 25°C of a 1 ppm solution 50% after 18-25 min; 90% after 62-83 min (7).

Mammalian & avian toxicity

Acute data

LD₅₀ oral rat 1000 mg kg⁻¹. 14-day-old rats were found to be twice as susceptible as adults and mice were more susceptible than rats (8).

LD₅₀ oral rat 908 mg kg⁻¹ (9).

LC_{Lo} (4 hr) inhalation rat 8000 ppm (10).

LD₅₀ intraperitoneal mouse 1480 mg kg⁻¹ (11).

Acute doses of 10,000-15,000 ppm cause anaesthesia, while doses of 15,000-18,000 ppm may be fatal, causing respiratory paralysis or cardiac arrest (12).

♂ Sprague-Dawley rats were administered a single non-lethal dose of 3 mmol kg⁻¹ chloroform intraperitoneally. Chloroform-induced reduction of renal concentrating ability was most pronounced at 21-24 hr after injection. Interference with proximal tubular secretion was maximal at 8 hr and with reabsorption during the first 24 hr (with recovery during the second day). Tubular damage appears to be the primary event leading to further manifestations of renal dysfunction (13).

LD_{Lo} (causing death within 3 days) intratracheal ♂ Sprague-Dawley rats 90 mg kg⁻¹ (14).

Oral ♂ Wistar rats administered 0.31 and 1.25 mmol kg⁻¹ suffered arrhythmogenic and negative chronotropic and dromotropic effects. Atrioventricular conduction time and the intraventricular extension time were increased, a slight shortening of the repolarisation velocity was observed, myocardial contractility was depressed and the heart was sensitised to the arrhythmogenic effects of epinephrine (15).

Sub-acute and sub-chronic data

Repeated inhalation exposure in humans leads to kidney and particularly liver damage. Damage localised in these tissues, metabolites binding covalently to cellular macromolecules. Ethanol ingestion may potentiate the toxicity of chloroform vapour (8).

The maximum concentration tolerated by animals for prolonged exposure with slight symptoms is 2000-2500 ppm. Chronic exposure may lead to severe toxemia and damage to the liver, heart and kidneys (16).

Inhalation ♀ B6C3F1 mice and ♂ F-344 rats 0-300 ppm chloroform (6 hr day⁻¹ for 7 days), necropsied on day 8. Mice exposed to 100-300 ppm exhibited centrilobular hepatocyte necrosis and severe vacuolar degeneration of midzonal and periportal hepatocytes. The kidneys of mice exposed to 300 ppm were affected; half of the proximal tubules were lined by regenerating epithelium. In rats exposed to 300 ppm, mild centrilobular vacuolation of the liver and 25-50% of kidney proximal tubules lined with regenerating epithelium were observed. Exposure to 10 ppm and above caused nasal lesions in rats but no nasal lesions were seen in mice exposed to up to 300 ppm chloroform (17,18).

Inhalation ♀ B6C3F1 mice and F-344 rats (6 hr day⁻¹ for 7 days) 0-300 ppm chloroform resulted in concentration-dependent lesions in the nasal passages of rats, and to a lesser degree in mice. The no-observed-effect level for the responses ranged from 3 to 100 ppm (19).

Dose-response relationships were determined for the induction of cytolethality and regenerative cell proliferation in the target organs for chloroform (liver, kidney, and nasal passages) administered by gavage to ♀ F-344 rats (0-400 mg kg⁻¹ day⁻¹) for 4 consecutive days, or for 5 days week⁻¹ for 3 weeks (20).

Inhalation BDF1 mice (13 wk) 0-90 ppm 6 hr day⁻¹, 5 days wk⁻¹. No-observed-adverse-effect level for nephrotoxicity, cell proliferation, and cancer 5 ppm (21).

Carcinogenicity and chronic effects

Inadequate evidence for carcinogenicity to humans, sufficient evidence for carcinogenicity to animals, IARC classification group 2B (22).

Carcinogenic to rats and mice, malignant kidney tumours observed in ♂ rats, thyroid tumours in ♀ rats and hepatomas and hepatocellular carcinomas in mice. Suspected as a long-term carcinogen in man (23,24).

Produced benign and malignant tumours of the liver and kidney following oral gavage in rodents (24,25).

Administration in drinking water to ♀ mice did not increase the incidence of liver tumours (26).

Administration to rats by gavage or in drinking water increased the incidences of kidney and thyroid tumours (25,27).

A significant increase in the incidence of neoplasms in mice was observed at concentrations of 250 mg kg⁻¹ but not at 15 mg kg⁻¹ administered via a probe, i.e. carcinogenic activity is seen only at concentrations which exceed normal levels (28).

Prolonged administration as an anaesthetic may lead to such serious effects as profound toxemia and damage to the liver, heart and kidneys; prolonged inhalation causes paralysis accompanied by cardiac respiratory failure and finally death (8,29).

Teratogenicity and reproductive effects

TC_{Lo} (7 hr) inhalation rat 30 ppm. Affected fertility and caused developmental abnormalities of the musculoskeletal system when administered during days 6-15 gestation (30).

Teratogenic to rats and mice and highly foetotoxic in inhalation experiments with rats (31-34).

Metabolism and toxicokinetics

The C-H bond of chloroform is oxidised to produce trichloromethanol, which spontaneously dehydrochlorinates to yield phosgene (28).

Undergoes considerable biotransformation in man with the formation of CO₂ and HCl. 43% of a single dose is eliminated unchanged in expired air within 8 hr and 50% is found as exhaled CO₂ in the same period. <0.01% of the dose was found in 8 hr urine samples (35).

Chloroform is highly lipid-soluble and tends to accumulate in adipose tissue (36).

The nephrotoxic metabolite of chloroform is produced within the kidney and the hepatotoxic metabolite in the liver (37).

Phospholipase A2 activation may be part of the chain of causality leading from initial bioactivation to ultimate cell death in rat hepatocytes (38).

Studies indicate that enzyme induction and toxicokinetics resulting from the oral administration of chloroform to rats differ from those resulting from both intraperitoneal and inhalation administration. This is because of a first-pass metabolism unique to oral administration (39).

Irritancy

Dermal rabbit (24 hr) 500 mg caused mild irritation and 148 mg instilled into rabbit eye caused moderate irritation (22).

Dermal rabbit (24 hr) 10 mg caused mild irritation (10).

20 mg instilled into rabbit eye caused moderate irritation within 24 hr (40).

Genotoxicity

Chloroform did not induce mutation or DNA damage in bacteria (41).

Showed direct or indirect DNA damaging potential in the liquid *Bacillus subtilis* microsome rec-assay (42).

Escherichia coli K-12 DNA repair host-mediated (mouse) assay negative (43).

Salmonella typhimurium TA98, TA100, TA1535, TA1537, TA1538 with and without metabolic activation negative (44).

Induced DNA damage but not mutation, aneuploidy, mitotic recombination or gene conversion in *Saccharomyces cerevisiae*. Gene mutation, mitotic recombination and conversion were induced in *Saccharomyces cerevisiae* under conditions in which endogenous levels of cytochrome P450 were induced (41).

Drosophila melanogaster W/W⁺ eye mosaic assay negative (45).

Induced chromosome aberrations *in vivo* in rat bone marrow cells (46). No adequate data available on the genetic and related effects of chloroform in humans (41).

Other effects

Other adverse effects (human)

In humans inhalation of chloroform causes drowsiness, giddiness, headache, nausea and unconsciousness (12). Anaesthetists, occupationally exposed to chloroform vapour in the late 19th and early 20th centuries had higher death rates from all malignant neoplasms and from tumours of the digestive organs than anaesthetists several decades later (47).

In vitro human epithelial cell (McCoy) (72 hr) CT₅₀ value (the minimum chloroform concentration inducing morphological changes in 50% of cells or 50% cell death and/or 50-100% increase in LDH release compared to controls) 20.65 mM (48).

Job-exposure matrices (for years 1920-1980) for six individual chlorinated aliphatic hydrocarbons and for the general class of organic solvents were applied to data from a case-control study of brain cancer among white men. Exposure to chloroform showed little indication of an association with brain cancer (49).

Any other adverse effects

Ascites sarcoma BP8 growth inhibition test, IC_{50} $5.03 \pm 0.62 \mu\text{M}$ (50).

In vitro rat hepatocyte (24 hr) and bovine kidney (MDBK) (72 hr) cytotoxicity CT_{50} values (the minimum chloroform concentration inducing morphological changes in 50% of cells or 50% cell death and/or 50-100% increase in LDH release compared to controls) 6.198 and 8.677 mM, respectively (48).

Cell viability began to decrease 30 min after incubation of isolated rat hepatocytes with 100 or 1000 ppm chloroform. Aspartate transaminase leakage increased 60 min after incubation with 1 or 10 ppm and alanine transaminase leakage increased after exposure to 100 or 1000 ppm at 60 min and 30 min, respectively. The data indicated that the toxic effect of chloroform was dose- and time-dependent. The degree of GSH depletion correlated with increased cytotoxicity and decreased glutathione peroxidase activity due to chloroform (51).

Rats orally administered $3.35 \text{ mmol kg}^{-1}$ showed a decrease in hepatic glutathione content after 3 hr, followed by an increase from 6 hr and complete recovery at 48 hr. Plasma alanine aminotransferase and aspartate aminotransferase activities increased 6 hr after treatment, reaching a maximum at 24 hr. Levels were still abnormal at 72 hr. The livers of the treated rats showed little or no morphological changes (52).

Legislation

In the UK compensation is available via Industrial Injuries Benefit for cases of liver and kidney damage caused by exposure to chloroform. In the USA the EPA has banned chloroform due to positive carcinogenic studies in mice. No link to bladder cancer resulting from chloroform in drinking water has been proven. Included in Schedule 2 Statutory Instrument No. 2286, 1989 (53).

Limited under EC Directive on Drinking Water Quality. Organochlorines: guide level $1 \mu\text{g l}^{-1}$. Haloform concentrations must be as low as possible (54).

Included in Schedule 6 (Release into Land: Prescribed Substances) of Statutory Instrument No. 472, 1991 (55).

Other comments

Administration of dichloro- or trichloro-acetic acid (0.92 and $2.45 \text{ mmol kg}^{-1}$, respectively, by gavage, three times over 24 hr) increased the toxicity of an intraperitoneal injection (0.75 mg kg^{-1} administered 3 hr after the last gavage dose) in ♀ but not in ♂ rats (56).

Toxicology, metabolism, teratogenicity, mutagenicity and carcinogenicity reviewed (57-59).

Reproductive toxicology reviewed (60).

Discontinued as anaesthetic due to its toxicity.

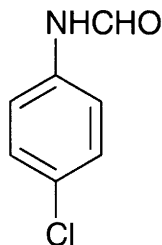
Found in chlorinated drinking water.

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C202 4-chloroformanilide



C_7H_6ClNO

Mol. Wt. 155.58

CAS Registry No. 2617-79-0

Synonyms *N*-(4-chlorophenyl)formamide

RTECS No. LQ 4666000

Physical properties

M. Pt. 102-103.5°C

Mammalian & avian toxicity

Acute data

LD₅₀ oral rat, mouse 800 mg kg⁻¹ (1).

Other comments

Limited under EC Directive on Drinking Water Quality 80/778/EEC. Organochlorine compounds: guide level 1 µg l⁻¹ (2).

Included in Schedule 6 (Release into Land: Prescribed Substances) of Statutory Instrument No.472, 1991 (3).

Formed in soils from chloroaniline degradation. Diflubenzuron metabolite.

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C203 4-chloro-3-hydroxybutanenitrile



C_4H_6ClNO

Mol. Wt. 119.55

CAS Registry No. 105-33-9

EINECS No. 203-287-2

Uses Catalyst, prepomatic of L-carotene (1).

Legislation

Limited under EC Directive on Drinking Water Quality 80/778/EEC. Organochlorine compounds: guide level 1 µg l⁻¹ (2).

Included in Schedule 6 (Release into Land: Prescribed Substances) of Statutory Instrument No. 472, 1991 (3).

Other comments

Found in water samples (4).

Oral contraceptive for ♂ rats, when fed at 5 mg day⁻¹ for 7 wk prevented pregnancy in mated ♀ after 1 wk (5).

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C204 2-chloro-*N*-(hydroxymethyl)acetamide



C₃H₆ClNO₂

Mol. Wt. 123.54

CAS Registry No. 2832-19-1

Synonyms *N*-methylol-2-chloroacetamide; α-chloro-*N*-(hydroxymethyl)acetamide; *N*-(hydroxymethyl)-2-chloroacetamide; *N*-methylolchloracetamide

EINECS No. 220-598-9

RTECS No. AB 5733000

Uses Biocide in paints and fibres. Preservative in cosmetics. Used in cooling lubricants. Chemical intermediate.

Physical properties

M. Pt. 100-105°C Specific gravity 1.05

Ecotoxicity

Invertebrate toxicity

LC₅₀ (24-96 hr) brown shrimp and *Agonis* sp. >10,000 mg l⁻¹ (1).

Environmental fate

Degradation studies

> 90% degradation in 6 days with 0 day adaption 16% COD day⁻¹ (2).

Mammalian & avian toxicity

Acute data

LD₅₀ intravenous mouse 180 mg kg⁻¹ (3).

Sensitisation

174 patients were investigated in two occupational dermatological clinics (with patch tests, a cutting fluid series and their own cutting fluids). 43% showed allergic reactions which were thought to be relevant to their dermatitis.

In 44% of the patients, the final diagnosis was thought to be multifactorial, emphasising endogenous, irritant and allergic factors that often contribute to the aetiology of occupational dermatitis (4).

Genotoxicity

Salmonella typhimurium TA98, TA100 with and without metabolic activation negative (5).

In vitro human lymphocytes weakly clastogenic (5).

In vivo mouse bone marrow micronucleus test. Intraperitoneal positive, oral negative (5).

Legislation

Limited under EC Directive on Drinking Water Quality 80/778/EEC. Organochlorine compounds: guide level 1 µg l⁻¹ (6).

Other comments

Only commercially available in solution. Slow hydrolysis occurs *in vitro* and the [carbonyl ¹⁴C] substance interacts covalently with calf-thymus DNA, which may cause it to be a direct acting carcinogen in rodents (5).

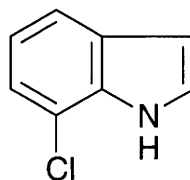
The importance of *N*-nitrosamines, pre-stages of nitrosamine formation, and the significance of mineral oil and further additives in cooling lubricants is discussed with regard to their cancer-causing effect (7).

Lachrymator.

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C205 7-chloroindole



C₈H₆ClN

Mol. Wt. 151.60

CAS Registry No. 53924-05-3

Synonyms 1*H*-indole, 7-chloro-

EINECS No. 258-865-7

Uses Drug intermediate.

Physical properties

M. Pt. 58-58.5°C B. Pt. 86-88°C at 5 mmHg

Legislation

Limited under EC Directive on Drinking Water Quality 80/778/EEC. Organochlorine compounds: guide level $1 \mu\text{g l}^{-1}$ (1).

Included in Schedule 6 (Release into Land: Prescribed Substances) of Statutory Instrument No. 472, 1991 (2).

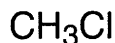
Other comments

Formed enzymatically by the chlorination of indole by *Pseudomonas pyrocinia* (3).

References

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3. Wiesner, W. et al *FEBS Lett.* 1986, **209**(2), 321-324

c206 chloromethane



CH_3Cl

Mol. Wt. 50.49

CAS Registry No. 74-87-3

Synonyms methyl chloride

EINECS No. 200-817-4

RTECS No. PA 6300000

Uses Formerly used as a local anaesthetic. Refrigerant.

Physical properties

M. Pt. -97.7°C B. Pt. -24°C Flash point -50°C Specific gravity 0.915 Volatility v.p. $3.8 \times 10^3 \text{ mmHg}$ at 20°C ; v.den. 1.78

Solubility Water: 303 ml gas/100 ml at 20°C . Organic solvents: miscible with chloroform, diethyl ether, glacial acetic acid; soluble in ethanol

Occupational exposure

DE-MAK 50 ppm (100 mg m^{-3})

FR-VME 50 ppm (105 mg m^{-3})

JP-OEL 50 ppm (100 mg m^{-3})

SE-LEVL 10 ppm (20 mg m^{-3})

UK-LTEL 50 ppm (105 mg m^{-3})

US-TWA 50 ppm (103 mg m^{-3})

FR-VLE 100 ppm (210 mg m^{-3})

SE-STEL 20 ppm (40 mg m^{-3})

UK-STEL 100 ppm (210 mg m^{-3})

US-STEL 100 ppm (207 mg m^{-3})

UN No. 1063 HAZCHEM Code 2WE Conveyance classification flammable gas

Supply classification extremely flammable, harmful

Risk phrases Extremely flammable – Possible risk of irreversible effects – Harmful: danger of serious damage to health by prolonged exposure through inhalation (R12, R40, R48/20)

Safety phrases Keep out of reach of children (if sold to general public) – Keep container in a well ventilated place – Keep away from sources of ignition – No smoking – Take precautionary measures against static discharges (S2, S9, S16, S33)

Ecotoxicity

Fish toxicity

LC₅₀ (96 hr) inland silverside, bluegill sunfish 270, 550 ppm static bioassay at 23°C, synthetic seawater and freshwater, respectively (1,2).

Invertebrate toxicity

Cell multiplication inhibition test *Entosiphon sulcatum* 8000 mg l⁻¹, *Pseudomonas putida* 500 mg l⁻¹, *Microcystis aeruginosa* 550 mg l⁻¹, *Scenedesmus quadricauda* 1450 mg l⁻¹ (3-6).

Environmental fate

Degradation studies

Resting cells of *Methylosinus trichosporium* OB-3b grown in the absence of copper salts rapidly oxidise chloromethane, t_{1/2} 9.4 min with a cell density of 0.1 g ml⁻¹. Methane monooxygenase is the responsible enzyme (7).

Abiotic removal

Evaporation from water at 25°C, 50% after 27 min, 90% after 91 min (initial concentration 1 ppm solute) (5,6).

Mammalian & avian toxicity

Acute data

LD₅₀ oral rat 1800 mg kg⁻¹ (8).

LC₅₀ (6 hr) inhalation mouse 2200 ppm (9).

LC₅₀ (30 min) inhalation rat 15,200 mg m⁻³ (10).

LC₅₀ (7 hr) inhalation mouse 3150 ppm (11).

Carcinogenicity and chronic effects

Inadequate evidence for carcinogenicity to humans, limited evidence for carcinogenicity to animals, IARC classification group 3 (9,12).

Teratogenicity and reproductive effects

TC_{Lo} (6 hr) inhalation ♂ rat 3000 ppm effects on fertility (13).

Chloromethane inhalation exposure in pregnant rats was not teratogenic at concentrations which elicited maternal and foetal toxicity. In pregnant mice, chloromethane was severely toxic to dams following four or more days exposure to 1500 ppm in air. Chloromethane at 500, but not 100 ppm, was teratogenic in mice leading to a malformation of the heart (14).

Irritancy

Slight irritant (species not specified) (1).

Genotoxicity

Salmonella typhimurium TA1535 without metabolic activation positive (15,16).

In vitro human lymphocyte gene mutation and sister chromatid exchange positive (15,17).

In an established human lymphoblast line, a 3-hr treatment with 0-5% chloromethane resulted in a dose-related increase in mutant fraction at the thymidine kinase locus and induction of sister chromatid exchange. No increase in DNA damage was detected in the lymphoblasts at concentrations shown to be mutagenic (17).

Other effects

Other adverse effects (human)

Inhalation human systemic effects include convulsions, nausea or vomiting and unspecified effects on the eyes. Slight narcotic action. Exposures to high concentrations cause dizziness, convulsions and coma. May lead to death (18).

Can cause liver, kidney and central nervous system damage (1).

Legislation

Limited under EC Directive on Drinking Water Quality 80/778/EEC. Organochlorine compounds: guide level $1 \mu\text{g l}^{-1}$ (19).

Included in Schedule 4 (Release into Air: Prescribed Substances) of Statutory Instrument No. 472, 1991 (20).

Other comments

Induced chromosomal aberrations in plants (21).

The dechlorination of MeCl, with tetrahydrofolate as the Me acceptor, by cell extracts of the strictly anaerobic homoacetogen strain MC occurred at the rate of $c. 20 \text{ nmol min}^{-1} \text{ mg}^{-1}$ cell protein (22).

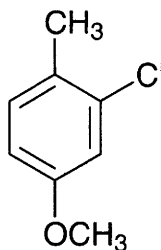
Very dangerous fire hazard when exposed to heat, flame or powerful oxidisers. Moderate explosion hazard when exposed to flame and sparks (23).

Reproductive and genotoxic, neurotoxic, behavioural, neurological and toxic effects reviewed (24-26).

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C207 3-chloro-4-methylanisole



C_8H_9ClO

Mol. Wt. 156.61

CAS Registry No. 54788-38-4

Synonyms 2-chloro-4-methoxy-1-methylbenzene; 2-chloro-4-methoxytoluene

Uses Chemical intermediate.

Physical properties

B. Pt. 212°C

Legislation

Limited under EC Directive on Drinking Water Quality 80/778/EEC. Organochlorine compounds: guide level 1 $\mu g\ l^{-1}$ (1).

Included in Schedule 6 (Release into Land: Prescribed Substances) of Statutory Instrument No. 472, 1991 (2).

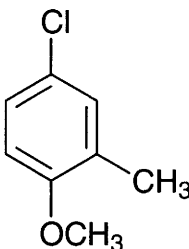
Other comments

Preparation reported in 1907 (3).

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C208 4-chloro-2-methylanisole



C_8H_9ClO

Mol. Wt. 156.61

CAS Registry No. 3260-85-3

Synonyms 1-chloro-4-methoxy-3-methylbenzene; 3-chloro-6-methoxytoluene; 4-chloro-2-methylphenol methyl ether

EINECS No. 221-860-5

Physical properties

B. Pt. 213-215°C

Legislation

Limited under EC Directive on Drinking Water Quality 80/778/EEC. Organochlorine compounds: guide level 1 µg l⁻¹ (1).

Included in Schedule 6 (Release into Land: Prescribed Substances) of Statutory Instrument No. 472, 1991 (2).

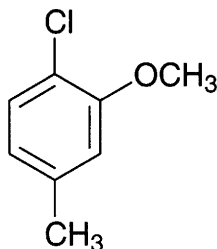
Other comments

Photochemical degradation product of the pesticide (4-chloro-2-methylphenoxy)acetic acid (3).

References

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c209 6-chloro-3-methylanisole



C₈H₉ClO

Mol. Wt. 156.61

CAS Registry No. 73909-16-7

Synonyms 1-chloro-2-methoxy-4-methylbenzene; 4-chloro-3-methoxytoluene; 2-chloro-5-methylphenol methyl ether

RTECS No. XS 9070000

Physical properties

M. Pt. 185°C B. Pt. 106-108°C at 3 mmHg

Mammalian & avian toxicity

Acute data

LD₅₀ intravenous mouse 180 mg kg⁻¹ (1).

Legislation

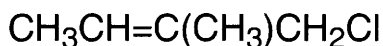
Limited under EC Directive on Drinking Water Quality 80/778/EEC. Organochlorine compounds: guide level 1 µg l⁻¹ (2).

Included in Schedule 6 (Release into Land: Prescribed Substances) of Statutory Instrument No. 472, 1991 (3).

References

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2. EC Directive Relating to the Quality of Water Intended for Human Consumption 1982, 80/778/EEC, Office for Official Publications of the European Communities, 2 rue Mercier, L-2985 Luxembourg.
3. S. I. 1991 No 472 The Environmental Protection (Prescribed Processes and Substances) Regulations 1991, HMSO, London, UK

c210 1-chloro-2-methyl-2-butene



$\text{C}_5\text{H}_9\text{Cl}$

Mol. Wt. 104.58

CAS Registry No. 13417-43-1

Synonyms 1-chloro-2-methylbut-2-ene

RTECS No. EM 4298000

Physical properties

B. Pt. 110°C Specific gravity 0.9327 at 20°C with respect to water at 4°C

Solubility Organic solvents: acetone, diethyl ether, ethanol

Genotoxicity

Salmonella typhimurium TA100 without metabolic activation positive (1).

Legislation

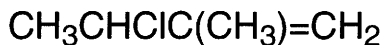
Limited under EC Directive on Drinking Water Quality 80/778/EEC. Organochlorine compounds: guide level 1 µg l⁻¹ (2).

Included in Schedule 6 (Release into Land: Prescribed Substances) of Statutory Instrument No. 472, 1991 (3).

References

1. Neudecker, T. et al *Biochem. Pharmacol.* 1980, **29**, 2611-2617.
2. EC Directive Relating to the Quality of Water Intended for Human Consumption 1982, 80/778/EEC, Office for Official Publications of the European Communities, 2 rue Mercier, L-2985 Luxembourg.
3. S. I. 1991 No. 472 The Environmental Protection (Prescribed Processes and Substances) Regulations 1991, HMSO, London, UK

c211 3-chloro-2-methyl-1-butene



$\text{C}_5\text{H}_9\text{Cl}$

Mol. Wt. 104.58

CAS Registry No. 5166-35-8

Synonyms 3-chloro-2-methylbut-1-ene

RTECS No. EM 4297200

Physical properties

B. Pt. 94°C

Solubility Organic solvents: chloroform, diethyl ether

Environmental fate

Abiotic removal

Removed from water by coagulation with alum and by granular activated carbon (1).

Genotoxicity

Salmonella typhimurium TA100 without metabolic activation positive (2).

Legislation

Limited under EC Directive on Drinking Water Quality 80/778/EEC. Organochlorine compounds: guide level 1 µg l⁻¹ (3).

Included in Schedule 6 (Release into Land: Prescribed Substances) of Statutory Instrument No. 472, 1991 (4).

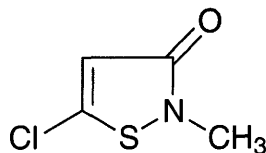
Other comments

Formed by chlorination of humic acid. Isolated from water and soil (1).

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3. *EC Directive Relating to the Quality of Drinking Water Intended for Human Consumption* 1982, 80/778/EEC, Office for Official Publications of the European Communities, 2 rue Mercier, L-2985 Luxembourg.
4. S. I. 1991 No. 472 *The Environmental Protection (Prescribed Processes and Substances) Regulations* 1991, HMSO, London, UK

c212 5-chloro-2-methyl-4-isothiazolinone



C₄H₄ClNOS

Mol. Wt. 149.60

CAS Registry No. 26172-55-4

Synonyms 5-chloro-2-methyl-4-isothiazolin-3-one; 5243-K-CG; 3(2*H*)-isothiazolone, 5-chloro-2-methyl-; Kathon CG

EINECS No. 247-500-7

RTECS No. NX 8156850

Uses Antimicrobial agent for metalworking fluids. Antifouling agent. Pesticide. Preservative for cosmetics. Antimicrobial and slimicide for paper mills, cooling tower waters and oil drilling muds. Antistatic agent in photographic film.

Physical properties

M. Pt. 54-55°C

Occupational exposure

DE-MAK 0.05 mg m⁻³ (for 3:1 mixture with CAS No. 2682-20-4)

Environmental fate

Carbonaceous inhibition

ID (28 day) *Pseudomonas aeruginosa* 781-6250 µg l⁻¹ (1).

Degradation studies

Evaluation of the effect of alkaline decomposition of biocides on the efficacy against microorganisms in cooling tower model. Parameters controlled included temperature, pH, concentration, blowdown rate, recirculation rate and lighting. The hardness of water could be significant in reducing the rate of decomposition in highly alkaline waters (2).

Mammalian & avian toxicity

Acute data

LD₅₀ oral rat, mouse 53-60 mg kg⁻¹ (3).

Inhalation rat (13 hr) 0.037 mg m⁻³ no adverse effects reported (4).

Sub-acute and sub-chronic data

Oral rat, mouse (5 day) 12 ml kg⁻¹ day⁻¹ (aqueous solution) containing 15 mg kg⁻¹ active ingredient (0.18 mg kg⁻¹) caused decreased motor activity, decreased respiration, and ataxia (3).

Carcinogenicity and chronic effects

Dermal skin painting mice (30 months) 25 µl of 400 ppm solution 3 × wk⁻¹, 5% of animals developed skin cancer (5).

Metabolism and toxicokinetics

Degraded sequentially to form *N*-methyl malonic acid, malonamic acid, malonic acid, *N*-methyl glyoxylamide, ethylene glycol, acetic and formic acids (species unspecified) (6).

Single dermal dose (24 hr) 2000 ppm; ~50% absorbed, 50% still associated at the site of application. Percutaneous absorption not affected by concentration (500-4000 ppm) (6).

Intravenous rat 0.8 mg kg⁻¹ dose sequestered by cellular fraction of blood, elimination is biphasic, more concentrated in kidney than in liver. After 96 hr ~70% excreted (urine 31%, faeces 35%, other 4%) (6).

Percutaneous rat (24 hr) 4000 ppm in 0.2 ml or 4 × 1000 ppm in 0.2 ml, systemic absorption ~12.9% of dose after 24 hr. Higher concentrations give higher systemic absorption, more excretion and more in tissues and less in skin application site. Elimination from dermal site is monophasic, t_{1/2} 13 days. Elimination from blood is biphasic, first component complete by 4 days, with t_{1/2} 2-3 days, second component t_{1/2} 17 days. Elimination from plasma, testes is monophasic, t_{1/2} 4.0, 8.6 days, respectively. Main elimination route for percutaneous dose is via urine; faecal excretion accounts for <4% of dose (6).

Irritancy

Inhalation rat (13 hr) 0.124 mg m⁻³ caused mild mucous membrane irritation (4).

Sensitisation

Contact sensitizer in guinea pigs. Moderate erythema observed in 33-50% of animals tested. Lower sensitivity if formaldehyde is applied during induction (7).

In vitro lymphocyte responses were evaluated in 18 patients with dermatitis and positive patch tests to 200 ppm of a combination of 5-chloro-2-methyl-4-isothiazolinone and 2-methylisothiazolinone. The lymphocyte proliferation to isothiazolinones indicates the presence of memory cells in the patient blood and confirms the immunological reaction to the inducing agent (8).

Guinea pig maximisation test 5-chloro-2-methyl-4-isothiazolinone strong sensitizer (9).

Genotoxicity

Salmonella typhimurium TA98, TA100 with and without metabolic activation positive (as Kathon) (10).

In vitro *Escherichia coli* WP2 *uvr* A(p) with metabolic activation positive (11).

Legislation

Limited under EC Directive on Drinking Water Quality 80/778/EEC. Pesticides: maximum admissible concentration $0.1 \mu\text{g l}^{-1}$ (12).

Included in Schedule 6 (Release into Land: Prescribed Substances) of Statutory Instrument No. 472, 1991 (13).

Other comments

Unstable as free base, shelf-lives are markedly extended by the formation of adducts with calcium chloride (6).

Allergenic effects of paint preservatives containing 5-chloro-2-methyl-4-isothiazolinone reviewed.

Recommended that this compound not be used as preservatives in water-based paints (14).

Properties and cosmetic uses reviewed (15,16).

The effectiveness of biocides to control biofouling was tested in model systems (17,18).

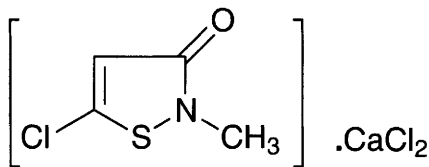
The chemical characteristics, health risks, and environmental effects (fish toxicity, biodegradability and bioaccumulation) of additives used in paper manufacture are given (19).

Recommended that Kathon CG undergoes further testing to assure the safety of products containing the compound in the light of its skin sensitising activity and bacterial mutagenicity (20).

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C213 5-chloro-2-methyl-4-isothiazolinone calcium chloride complex



C₄H₄CaCl₃NOS

Mol. Wt. 260.58

CAS Registry No. 55965-85-0

Synonyms calcium chloride 5-chloro-2-methyl-3(2*H*)-isothiazolone (1:1) complex

Uses Microbiocide.

Ecotoxicity

Bioaccumulation

Bioconcentration factor (49 day) bluegill sunfish 22-27 (whole fish minus viscera), 157-300 (viscera) (1).

Bioconcentration factor (43 day) bluegill sunfish 30 (whole fish minus viscera), 204 (viscera) (1).

Environmental fate

Degradation studies

Aerobic, activated sludge 80-100% degradation, with co-metabolism (2).

No residual toxicity to *Bacillus subtilis* (2).

Degradation in river water is concentration-dependent. At 0.1 ppm, 21 days, 2.98%; 1 ppm, 21 days, 1.84% degradation to carbon dioxide (3).

(24-day build-up) activated sludge: 53% as effluent, 20% as carbon dioxide after 50 days (3).

(48 hr) 48% drop in concentration on UV exposure in pond water, pH 8 (3).

Degradation products detected using activated sludge, in river water, by hydrolysis and photolysis include malonamic acid, acetic acid, formic acid, *N*-methylmalonamic acid, ethylene glycol, and urea (4).

Abiotic removal

No degradation occurs in aqueous solution under aerobic and anaerobic conditions (3).

Adsorption and retention

Soils leach 24-75% over 8 wk. Adsorption on river silt 1 and 10 ppm initial concentration was 5 and 8%, respectively, after 24 hr. Absorption by river plants: duckweed, *Salvine* 20-42 hr (4).

Mammalian & avian toxicity

Metabolism and toxicokinetics

Oral rats (3 days) ♂ [♀] % excretion in faeces, urine, CO₂, tissues, residues 52[56], 37[36], 0.4[1.5], 1.7[1.8], 7.9[2.7]%, respectively (4).

Major metabolites detected in rat urine after oral challenge were *N*-methylmalonamic acid (30-38%) and urea (7-9%) (5).

Legislation

Limited under EC Directive on Drinking Water Quality 80/778/EEC. Organochlorine compounds: guide level 1 µg l⁻¹ (6).

Included in Schedule 6 (Release into Land: Prescribed Substances) of Statutory Instrument No. 472, 1991 (7).

Other comments

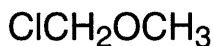
Allergic effects of paint preservatives containing 5-chloro-2-methyl-4-isothiazolinone reviewed. Recommended that this compounds is not used as preservatives in water-based paints (8).

The chemical characteristics, health risks and environmental effects (fish toxicity, biodegradability and bioaccumulation) of additives used in paper manufacture are given (9).
Other 5-chloro-2-methyl-4-isothiazolone compounds complexed with indeterminate amounts of calcium chloride are CAS RN 77716-89-3 and CAS RN 57373-19-0.

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C214 chloromethyl methyl ether



C₂H₅ClO

Mol. Wt. 80.51

CAS Registry No. 107-30-2

Synonyms chlorodimethyl ether; dimethyl ether, chloro; methyl chloromethyl ether; methane, chloromethoxy-

EINECS No. 203-480-1

RTECS No. KN 6650000

Uses In the preparation of ion-exchange resins. Synthesis of chloromethylated compounds.

Physical properties

M. Pt. -103.5°C **B. Pt.** 55-57°C **Flash point** <23°C **Specific gravity** 1.0625 at 20°C with respect to water at 4°C **Volatility** v.p. 260 mmHg at 20°C

Occupational exposure

UN No. 1239 **HAZCHEM Code** 3WE **Conveyance classification** flammable liquid

Supply classification highly flammable, toxic

Risk phrases May cause cancer – Highly flammable – Harmful by inhalation, in contact with skin and if swallowed (R45, R11, R20/21/22)

Safety phrases Restricted to professional users – Avoid exposure – obtain special instruction before use – In case of accident or if you feel unwell, seek medical advice immediately (show label where possible) (S53, S45)

Environmental fate

Abiotic removal

Hydrolyses in water with $t_{1/2}$ of <1 sec (1).

Mammalian & avian toxicity

Acute data

LD₅₀ oral rat 817 mg kg⁻¹ (2).

LC₅₀ (2 hr) inhalation mouse 1030 mg m⁻³ (3).

LC₅₀ (7 hr) inhalation hamster 65 ppm (4).

Sub-acute and sub-chronic data

LC₅₀ (14 day) inhalation rat, rabbit 55 ppm and 65 ppm, respectively, for 7 hr day⁻¹ caused congestion, oedema and haemorrhage in the respiratory tract in all animals (5).

Carcinogenicity and chronic effects

Sufficient evidence for carcinogenicity to humans and animals, IARC classification group 1 (6).

Dermal mouse (325 days) 0.1 ml of 2% solution in benzene administered 3 × wk⁻¹; animals were observed for a total of 540 days. No tumours were reported but the compound was active as an initiator. 1 mg in 0.1 ml benzene followed by a promoting treatment (0.025 mg mixed phorbol esters in 0.1 ml acetone), resulted in five mice developing papillomas, one of which progressed to a carcinoma. Controls given a single dose of chloromethyl methyl ether followed by no treatment or acetone developed no tumours (7,8).

Inhalation mouse (6 hr day⁻¹, 5 days wk⁻¹, 21 wk) 25 animals exhibited lung tumours (9).

Genotoxicity

Salmonella typhimurium TA98 with metabolic activation positive (10).

Chloromethyl methyl ether enhanced virus-induced transformation of Syrian hamster embryo cells (11).

Caused gene mutation in prokaryotes (12).

Other effects

Other adverse effects (human)

During a 5-yr period 111 chloromethyl methyl ether workers were studied and four cases of lung cancer were diagnosed (13).

An industrial study of 2857 workers at a chemical plant using chloromethyl ethers between 1948 and 1971 found that 737 had been exposed to chloromethyl ethers and the mortality from cancer of the respiratory tract was significantly greater in exposed workers (14).

Reports from five countries on studies undertaken in the period 1955-1984 cited 87 persons dying from respiratory cancer out of a workforce of 3024 (15).

A slight increase in the incidence of chromosomal aberrations was observed in peripheral lymphocytes of workers exposed to chloromethyl methyl ether in the preparation of ion-exchange resins (16).

Legislation

Covered in the UK by the Control of Carcinogenic Substances, Control of Substances Hazardous to Health Regulations 1988 (17).

Included in Schedule 6 (Release into Land: Prescribed Substances) of Statutory Instrument No. 472, 1991 (18).

Other comments

Commercial chloromethyl methyl ether usually contains, as an impurity, 1-7% of bis-chloromethyl ether, a proven carcinogen (18).

Toxicology and human health effects reviewed (19,20).

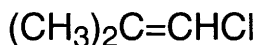
Incidence of lung cancer in workers exposed to chloromethyl methyl ether in anion-exchange resin manufacture reviewed (21).

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c215 1-chloro-2-methylpropene



C₄H₇Cl

Mol. Wt. 90.55

CAS Registry No. 513-37-1

Synonyms dimethylvinyl chloride; 1-propene, 1-chloro-2-methyl-; α-chloroisobutylene; β,β-dimethylvinyl chloride; isocrotyl chloride

EINECS No. 208-158-4

RTECS No. UC 8045000

Uses Intermediate in organic synthesis.

Physical properties

B. Pt. 68.1°C Specific gravity 0.9186 at 20°C with respect to water at 4°C

Ecotoxicity

Invertebrate toxicity

EC₅₀ (30 min) *Photobacterium phosphoreum* 16.9 mg l⁻¹ Microtox test (1).

Mammalian & avian toxicity

Acute data

LD_{Lo} (10 min) inhalation mouse >181 g m⁻³ (2).

Sub-acute and sub-chronic data

Oral rat (2 wk) negative results in carcinogenicity test based on forestomach cell proliferation (3).

Mouse, rat (13 wk) 250 and 500 mg kg⁻¹ caused histopathological changes in intestine, bone marrow, hepatocytes and testes of rats; lymphopoietic cells, liver, pancreas, ovary, testes and spleen of mice (4).

Carcinogenicity and chronic effects

National Toxicology Program tested rats and mice via gavage (2 yr) at 100 and 200 mg kg⁻¹ 5 day wk⁻¹. Clear evidence of carcinogenicity was found in both sexes of both species. There was an increased incidence of neoplasms in nasal cavity, oral cavity, oesophagus and forestomach in ♂ and ♀ rats. In both sexes of mice there was an increased incidence of squamous cell neoplasms of forestomach and in ♂ an increase in squamous cell carcinomas in preputial glands (5).

Classified as a genotoxic carcinogen in both rats and mice inducing tumours (unspecified) at one or more sites in both species (6).

Metabolism and toxicokinetics

Metabolism can be effected by rat liver microsomes. Cytochrome P₄₅₀ catalysed aliphatic hydroxylation has been shown to be stereo-selective, and reactive electrophilic aldehydic species have been proposed as hidden metabolites (7).

An oral dose to rats or mice of 150 mg resulted in 25% of compound being eliminated as CO₂ within 24 hr. 30% was eliminated in urine of rats and 5% in the urine of mice. Daily multi-dosing had little effect on metabolism. Metabolites included 2-amino-6-methyl-4-thio-5-heptene-1,7-dioic acid and *N*-acetyl derivatives (8).

Genotoxicity

Salmonella typhimurium TA98, TA1537 with and without metabolic activation negative (9).

Salmonella typhimurium TA1535 without metabolic activation equivocal; TA100 with metabolic activation positive (10).

In vitro Chinese hamster ovary cells with and without metabolic activation sister chromatid exchanges positive, chromosomal aberrations negative (11).

Legislation

Limited under EC Directive on Drinking Water Quality 80/778/EEC. Chlorides: guide level 25 mg l⁻¹ (12).

Other comments

Included in a database covering aquatic environmental toxicity (13).

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c216 3-chloro-2-methylpropene



C₄H₇Cl

Mol. Wt. 90.55

CAS Registry No. 563-47-3

Synonyms 3-chloro-2-methyl-1-propene; 3-chloro-2-methylprop-1-ene; methallyl chloride; 2-methallyl chloride; β-methallyl chloride; γ-chloroisobutylene; 3-chloroisobutene; isobutenyl chloride

EINECS No. 209-251-2

RTECS No. UC 8050000

Uses Intermediate in the synthesis of polymers, pharmaceuticals and pesticides. Insecticide. Fumigant.

Physical properties

M. Pt. -80°C **B. Pt.** 71-72°C **Flash point** -19.4°C (closed cup) **Specific gravity** 0.9165 at 20°C with respect to water at 4°C **Partition coefficient** log P_{ow} 1.849 (1) **Volatility** v.p. 101.7 mmHg at 20°C ; v.den. 3.12
Solubility Water: <1 mg ml⁻¹ at 22°C. Organic solvents: acetone, chloroform, diethyl ether, dimethyl sulfoxide, ethanol

Occupational exposure

UN No. 2554 **HAZCHEM Code** 2WE **Conveyance classification** flammable liquid

Supply classification highly flammable

Supply classification corrosive

Supply classification dangerous for the environment

Risk phrases Highly flammable – Harmful by inhalation and if swallowed – Causes burns – May cause sensitisation by skin contact – Toxic to aquatic organisms, may cause long-term adverse effects in the aquatic environment (R11, R20/22, R34, R43, R51/53)

Safety phrases Keep out of reach of children (if sold to general public) – Keep container in a well ventilated place – Keep away from sources of ignition – No smoking – Do not empty into drains – In case of contact with eyes, rinse immediately with plenty of water and seek medical advice – Wear suitable protective clothing, gloves and eye/face protection – In case of accident or if you feel unwell, seek medical advice immediately (show label where possible) – Avoid release to the environment. Refer to special instructions/safety data sheet (S2, S9, S16, S29, S26, S36/37/39, S45, S61)

Ecotoxicity

Fish toxicity

LC₅₀ (24 hr) goldfish 14 mg l⁻¹ (2).

Invertebrate toxicity

EC₅₀ (5, 15, 30 min) *Photobacterium phosphoreum* 154 ppm Microtox test (3).

Mammalian & avian toxicity

Acute data

LD₅₀ oral rat 676 mg kg⁻¹ (4).

LC₅₀ (30 min) inhalation rat, mouse 34, 57 mg l⁻¹, respectively (5).

Lowest lethal concentration inhalation human (10 min) 22,000 ppm (6).

Sub-acute and sub-chronic data

In 13-wk gavage studies 50-100% mortality occurred in groups of ♂ and ♀ rats receiving 400 mg kg⁻¹. ♂ rats receiving 300 mg kg⁻¹ day⁻¹ and ♂ and ♀ mice receiving 500-1250 mg kg⁻¹ day⁻¹ had inflammation and necrosis of the liver. Necrosis of cortical tubules of the kidney was also detected in mice (7).

Rats were administered 0, 40 or 60 mg kg⁻¹ day⁻¹ for 14 days (route unspecified). Body weight changes were observed in ♀ at the high dose, an increase in the incidence of minor renal changes at the high dose, and increased incidence of gastric lesions, severe irritative changes in the stomach and focal erosion of the cardiac mucosa with moderate hyperkeratosis and acanthosis in the forestomach in both treated groups were observed. No effects were observed in maternal mortality and testes weights and morphology (8).

Carcinogenicity and chronic effects

Gavage rats (2 yr) ≥50 mg kg⁻¹ and mice ≥200 mg kg⁻¹ 5 day wk⁻¹ for 103 wk. Evidence of carcinogenicity was shown by the increased incidences of squamous cell neoplasms in the forestomach of ♂ and ♀ rats and mice (7). Gavage administration (dose unspecified) caused forestomach neoplasms in rats and mice. Neoplasms of the oral and nasal cavities were observed in rats but not in mice (9).

Metabolism and toxicokinetics

Following oral administration to rats and mice at a dose of 150 mg kg⁻¹ rats exhaled ~10% as carbon dioxide. In rats 24 hr after dosing 7% was expired unchanged, and 58% excreted in the urine unchanged. A mercapturic acid metabolite was also identified in urine of rats and mice (9).

Irritancy

Irritating to the skin, eyes and mucous membranes (species unspecified) (10).

Genotoxicity

Salmonella typhimurium TA98, TA100, TA1535, TA1537, TA1538 with and without metabolic activation negative (11,12).

In vitro mouse lymphoma L5178 tk⁺/tk⁻ forward mutation assay without metabolic activation positive (13).

In vitro Chinese hamster ovary cells without metabolic activation induced chromosomal aberrations and sister chromatid exchanges (14).

Induced unscheduled DNA synthesis in HeLa cells (15).

Induced a marginal dose-dependent increase in morphological transformation with added metabolic activation in the BALB/3T3 mouse cell line but not in the absence of metabolic activation (16).

Mouse bone marrow micronucleus test negative (17).

Drosophila interchromosomal mitotic recombination assay positive (18).

Drosophila melanogaster sex-linked recessive lethal assay positive, reciprocal translocation test negative (19).

Aspergillus nidulans diploid strain P1 mitotic chromosome malsegregation assay negative (20).

Other effects

Any other adverse effects

Sub-chronic oral exposure to rats caused histological and enzymatic changes in the intestine and liver but these alterations were not of pathological significance (duration and concentration unspecified) (4).

Legislation

Included in Schedule 6 (Release into Land: Prescribed Substances) of Statutory Instrument No. 472, 1991 (21).

Limited under EC Directive on Drinking Water Quality 80/778/EEC. Pesticides: maximum admissible concentration 0.1 µg l⁻¹ (22).

Other comments

Isolated from water and sediments.

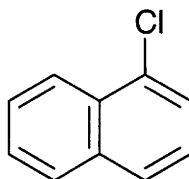
Reviews on experimental toxicology and human health effects listed (23).

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c217 1-chloronaphthalene



C₁₀H₇Cl

Mol. Wt. 162.62

CAS Registry No. 90-13-1

Synonyms α -chloronaphthalene; α -chlornaphthalene; α -naphthyl chloride

EINECS No. 201-967-3

RTECS No. QJ 2100000

Uses Immersion liquid in the microscopic determination of refractive index of crystals. Solvent for oils, fats, DDT. The major component of Halowax 1031.

Physical properties

M. Pt. -2.5°C **B. Pt.** 259°C **Flash point** 121°C **Specific gravity** 1.194 at 20°C with respect to water at 4°C

Partition coefficient $\log P_{ow}$ 3.90

Solubility Organic solvents: benzene, ethanol, petroleum ether

Occupational exposure

SE-LEVL 0.2 mg m⁻³

SE-STEL 0.6 mg m⁻³

Ecotoxicity

Toxicity to other species

LD₅₀ frog, *Rana esculenta* 900 mg kg⁻¹ (1).

Bioaccumulation

Non-accumulative or low accumulative (2).

Mammalian & avian toxicity

Acute data

LD₅₀ oral mouse, rat 1090, 1540 mg kg⁻¹, respectively (3,4).

LD₅₀ oral guinea pig 2000 mg kg⁻¹ (5).

Metabolism and toxicokinetics

4-Chloro-1-naphthol was a major metabolite in the urine after retrocarotid injection into pigs (6,7).

Genotoxicity

Salmonella typhimurium TA98, TA100 with or without metabolic activation negative (8).

Other effects

Any other adverse effects

EC₅₀ *in vitro* mitochondrial respiration inhibition test 3.8 ppm (23.4 µM) (9).

Legislation

Limited under EC Directive on Drinking Water Quality 80/778/EEC. Organochlorine compounds: guide level 1 µg l⁻¹ (10).

Included in Schedule 6 (Release into Land: Prescribed Substances) of Statutory Instrument No. 472, 1991 (11).

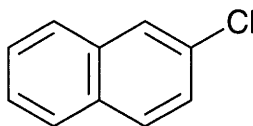
Other comments

A quantitative structure-activity relationship between the sublethal toxicity to marine mussels (*Mytilus edulis*) of organic chemicals and their solubility in water has been developed (12).

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c218 2-chloronaphthalene



C₁₀H₇Cl

Mol. Wt. 162.62

CAS Registry No. 91-58-7

Synonyms β-chloronaphthalene; β-naphthyl chloride

EINECS No. 202-079-9

RTECS No. QJ 2275000

Uses A component of Halowax 1031.

Physical properties

M. Pt. 59.5°C **B. Pt.** 256°C **Partition coefficient** log P_{ow} 3.98

Solubility Organic solvents: benzene, chloroform, diethyl ether, ethanol

Occupational exposure

SE-LEVL 0.2 mg m⁻³

SE-STEL 0.6 mg m⁻³

Mammalian & avian toxicity

Acute data

LD₅₀ oral rat 2080 mg kg⁻¹ (1).

LD₅₀ oral mouse 886 mg kg⁻¹ (1).

Metabolism and toxicokinetics

3-Chloro-2-naphthol was a major metabolite in urine after retrocarotid administration of 2-chloronaphthalene to pigs (2,3).

Legislation

Limited under EC Directive on Drinking Water Quality 80/778/EEC. Organochlorine compounds: guide level 1 µg l⁻¹ (4).

Included in Schedule 6 (Release into Land: Prescribed Substances) of Statutory Instrument No. 472, 1991 (5).

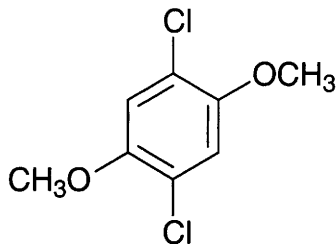
Other comments

A quantitative structure-activity equation has been developed for the bioconcentration in fish of organic chemicals and their *n*-octanol/water partition coefficients (6).

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c219 chloroneb



C₈H₈Cl₂O₂

Mol. Wt. 207.06

CAS Registry No. 2675-77-6

Synonyms 1,4-dichloro-2,5-dimethoxybenzene

EINECS No. 220-222-3

RTECS No. CZ 4750000

Uses Superseded systemic fungicide.

Physical properties

M. Pt. 133-135°C **B. Pt.** 268°C **Volatility** v.p. 3×10^{-3} mmHg at 25°C

Solubility Water: 8 mg l⁻¹ at 25°C. Organic solvents: acetone, dichloromethane, dimethyl formamide, dimethyl sulfoxide, ethanol, xylene

Ecotoxicity

Fish toxicity

LC₅₀ (8 hr) bluegill sunfish >4200 mg l⁻¹ (1).

Environmental fate

Degradation studies

Subject to microbial decomposition in soil under moist conditions (1).

Mammalian & avian toxicity

Acute data

LD₅₀ oral mallard duck, Japanese quail >5000 mg kg⁻¹ (1).

LD₅₀ oral starling, redwing blackbird >100 mg kg⁻¹ (2).

LD₅₀ oral rat >11 g kg⁻¹ (3).

LD₅₀ dermal rabbit >5000 mg kg⁻¹ (1).

Carcinogenicity and chronic effects

Oral rat (2 yr) 2500 mg kg⁻¹ diet, reduced growth and food consumption were the only observed effects (1).

Metabolism and toxicokinetics

2,5-Dichloro-4-methoxyphenol was isolated as the only metabolite in the urine of dogs, rats and cows maintained on chloroneb-containing diets. It was present both in the free form and as conjugates (4).

Irritancy

Dermal guinea pig (duration unspecified) 50% aqueous suspension caused no irritation (5).

Sensitisation

Dermal guinea pig (duration unspecified) 50% aqueous suspension caused no sensitisation (5).

Genotoxicity

Salmonella typhimurium TA98, TA100, TA1535, TA1537, TA1538 with and without metabolic activation negative (6).

Did not induce sex-linked recessive lethal mutations in meiotic and post-meiotic germ cell stages of ♂ *Drosophila melanogaster* (7).

Aspergillus nidulans sex chromosome loss and nondisjunction positive (8).

Legislation

Limited under EC Directive on Drinking Water Quality 80/778/EEC. Pesticides: maximum admissible concentration 0.1 µg l⁻¹ (9).

Included in Schedule 6 (Release into Land: Prescribed Substances) of Statutory Instrument No. 472, 1991 (10).

WHO Toxicity Class Table 5 (11).

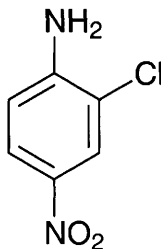
EPA Toxicity Class IV (1).

References

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c220 2-chloro-4-nitroaniline



C₆H₅ClN₂O₂

Mol. Wt. 172.57

CAS Registry No. 121-87-9

Synonyms 1-amino-2-chloro-4-nitrobenzene; *o*-chloro-*p*-nitroaniline; 4-nitro-2-chloroaniline; 2-chloro-4-nitrobenzenamine

EINECS No. 204-502-2

RTECS No. BX 1400000

Uses Preparation of dyestuffs.

Physical properties

M. Pt. 109°C

Solubility Organic solvents: benzene, carbon disulfide, diethyl ether, ethanol

Occupational exposure

UN No. 2237 HAZCHEM Code 2Z Conveyance classification toxic substance

Supply classification toxic

Supply classification dangerous for the environment

Risk phrases Harmful if swallowed – Toxic to aquatic organisms, may cause long-term adverse effects in the aquatic environment (R22, R51/53)

Safety phrases Keep out of reach of children (if sold to general public) – Do not breathe dust – Avoid contact with the skin – Avoid release to the environment. Refer to special instructions/safety data sheet (S2, S22, S24, S61)

Ecotoxicity

Fish toxicity

Exposure to 10 mg l⁻¹ caused loss of equilibrium to stickleback in 6-8 hr and death in 16-24 hr. Steelhead trout and sockeye salmon exposed to 10 mg l⁻¹ died within 2-3 hr (1).

Mammalian & avian toxicity

Acute data

LD₅₀ oral mouse, rat 1250, 6430 mg kg⁻¹, respectively (2).

LD_{Lo} intraperitoneal mouse 500 mg kg⁻¹ (3).

LD_{Lo} intravenous mouse 50 mg kg⁻¹ (4).

Sub-acute and sub-chronic data

Oral rats (30 day) at concentrations of 0.1 to 0.2 of the LD₅₀ caused transformation of haemoglobin into methaemoglobin, nitrosylhaemoglobin and sulphaemoglobin in addition to a decrease in oxyhaemoglobin. However the total level of haemoglobin remained unchanged (5).

Teratogenicity and reproductive effects

Gavage B6C3F₁ mice (13 wk) 300, 600, 1200 mg kg⁻¹, F344 rats (13 wk) 200, 400, 800 mg kg⁻¹ caused decreased body weight and sperm motility in ♂ mice and decreased body weight, epididymis, cauda epididymis and increased testes weight in rats (6).

Irritancy

Irritant to eyes, skin, mucous membranes and upper respiratory tract (species unspecified) (7).

Genotoxicity

Salmonella typhimurium TA100 with metabolic activation negative; TA98, TA1538 with metabolic activation positive (8).

Escherichia coli WP2uvrA/pKM positive (9).

In vitro rat hepatocytes DNA repair negative (8).

Legislation

Limited under EC Directive on Drinking Water Quality 80/778/EEC. Organochlorine compounds: guide level 1 µg l⁻¹ (10).

Included in Schedule 6 (Release into Land: Prescribed Substances) of Statutory Instrument No. 472, 1991 (11).

Other comments

Environmental degradation product of niclosamide (2',5-dichloro-4'-salicylanilide) (12).

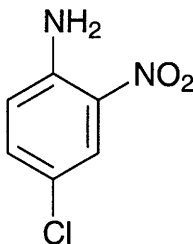
A quantitative structure-activity relationship for the genotoxicity of substituted nitrobenzenes in the chromosome aberrations test in *in vitro* human peripheral lymphocytes has been developed (13).

Reviews on experimental toxicology and human health effects listed (14).

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c221 4-chloro-2-nitroaniline



$C_6H_5ClN_2O_2$

Mol. Wt. 172.57

CAS Registry No. 89-63-4

Synonyms 4-chloro-2-nitrobenzenamine; *p*-chloro-*o*-nitroaniline

EINECS No. 201-925-4

RTECS No. BX 1575000

Uses Preparation of dyestuffs.

Physical properties

M. Pt. 117-119°C (99% pure) (1)

Solubility Organic solvents: acetic acid, diethyl ether, ethanol, methanol

Occupational exposure

UN No. 2237 HAZCHEM Code 2Z Conveyance classification toxic substance

Supply classification very toxic

Risk phrases Very toxic by inhalation, in contact with skin and if swallowed – Danger of cumulative effects (R26/27/28, R33)

Safety phrases Keep locked up and out of the reach of children (if sold to general public) – After contact with skin, wash immediately with plenty of water – Wear suitable protective clothing and gloves – In case of accident or if you feel unwell, seek medical advice immediately (show label where possible) (S1/2, S28, S36/37, S45)

Ecotoxicity

Invertebrate toxicity

EC₅₀ (24, 48 hr) *Daphnia magna* 3.7, 3.2 mg l⁻¹, respectively (2).

EC₅₀ (30 min) *Photobacterium phosphoreum* 19.8 ppm Microtox test (3).

Bioaccumulation

Non-accumulative or low accumulative (4).

Environmental fate

Degradation studies

A theoretical BOD was found to be <30% over a 2-wk incubation period using the Japanese MITI test and a non-acclimated sewage inoculum. Classified as being non-biodegradable in the MITI test (5).

Abiotic removal

Degraded in the atmosphere by reaction with photochemically produced hydroxyl radicals. $t_{1/2} \approx 18$ hr (6).

Mammalian & avian toxicity

Acute data

LD₅₀ oral rat, mouse 400-800 mg kg⁻¹ (7).

LD₅₀ intraperitoneal rat, mouse 200 mg kg⁻¹ (6).

LD₅₀ intravenous mouse 63 mg kg⁻¹ (8).

Teratogenicity and reproductive effects

Gavage B6C3F₁ mice (13 wk) 300, 600, 1200 mg kg⁻¹, F344 rats (13 wk) 200, 400, 800 mg kg⁻¹ caused decreased body weight and sperm motility in ♂ mice and decreased body weight, epididymis, cauda epididymis and increased testes weight in rats (9).

Irritancy

Irritant to eyes and skin (species unspecified) (10).

Genotoxicity

In vitro Chinese hamster ovary cells with and without metabolic activation, induction of chromosomal aberrations and sister chromatid exchange positive (11).

Salmonella typhimurium TA1535/pSK1002 *umu*-test with and without metabolic activation negative (12).

Legislation

Limited under EC Directive on Drinking Water Quality 80/778/EEC. Organochlorine compounds: guide level 1 µg l⁻¹ (13).

Included in Schedule 6 (Release into Land: Prescribed Substances) of Statutory Instrument No. 472, 1991 (14).

Other comments

Residues have been detected in wastewater effluent and incineration effluents.

Reviews on toxicology and human health effects listed (15).

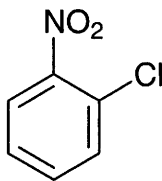
In vitro toxicity assessment of substituted phenols and anilines reviewed (16).

Toxicity of phenols and anilines in different test systems (bacteria, yeasts, algae, plant protoplasts and *Daphnia*) reviewed (17).

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c222 2-chloronitrobenzene



$C_6H_4ClNO_2$

Mol. Wt. 157.56

CAS Registry No. 88-73-3

Synonyms 1-chloro-2-nitrobenzene; o-chloronitrobenzene; o-nitrochlorobenzene; chloro-o-nitrobenzene

EINECS No. 201-854-9

RTECS No. CZ 0875000

Uses Intermediate in dyestuff synthesis.

Physical properties

M. Pt. 32-33°C **B. Pt.** 245-246°C **Flash point** 123°C **Specific gravity** 1.368 at 22°C with respect to water at 4°C **Partition coefficient** $\log P_{ow}$ 2.24 **Volatility** v.p. 3.0×10^{-2} mmHg at 20°C

Solubility Water: <0.1 mg ml^{-1} at 22°C. Organic solvents: acetone, benzene, diethyl ether, ethanol, methanol, pyridine, toluene

Occupational exposure

UN No. 1578 HAZCHEM Code 2X Conveyance classification toxic substance

Ecotoxicity

Fish toxicity

LC₅₀ (96 hr) bluegill sunfish 1.2 mg l^{-1} static bioassay (1).

LC₅₀ (96 hr) inland silverside 0.55 mg l^{-1} static bioassay (1).

LC₅₀ (14 day) guppy 30 mg l^{-1} (2).

Invertebrate toxicity

EC₅₀ (24 hr) *Daphnia magna* 12 mg l^{-1} (3).

EC₅₀ (15 min) *Photobacterium phosphoreum* 4.5 mg l^{-1} Microtox test (4).

EC₅₀ (96 hr) *Chlorella pyrenoidosa* 6.8 mg l^{-1} (5).

Toxicity to other species

EC₅₀ (the concentration of chemical required to produce 50% reduction in growth) lettuce *Lactuca sativa* (7 and 14 day static tests) 5.0 and 5.4 $\mu g\ g^{-1}$ soil, respectively, (16-21 day semi-static test) 1.8 mg l^{-1} nutrient solution (6).

Bioaccumulation

The Japanese MITI test indicates a bioconcentration factor of <100 (7).

Environmental fate

Degradation studies

Decomposition period by soil microflora >64 days (8).

In river water seeded with sewage, a concentration of 21 mg l^{-1} was not appreciably degraded in 175 days (9).

Confirmed non-biodegradable (10).

Abiotic removal

Undergoes photodegradation in water following first-order reaction kinetics. An increase in pH of the water increases degradation rates whereas an increase in fulvic acid concentration decreases degradation rates (11).

A reduction of chloronitrobenzenes in water, from 1.9 mg l^{-1} to <30 $\mu g\ l^{-1}$, was achieved by the application of 8 mg l^{-1} ozone and 3 mg l^{-1} hydrogen peroxide with a 20 min contact time (12).

Removal from groundwater with granular activated carbon was reported (13).

In the atmosphere vapour phase is predicted to react with photochemically generated hydroxyl radicals with an estimated $t_{1/2}$ of 2 days at 25°C. Chloronitrophenols may be formed (14).

Adsorption and retention

Minimal adsorption to river sediment (15).

Mammalian & avian toxicity

Acute data

LD₅₀ oral mouse, rabbit, rat 135, 280, 288 mg kg⁻¹, respectively (16,17).

Sub-acute and sub-chronic data

Inhalation F344/N rats and B6C3F1 mice (6 hr day⁻¹, 5 days wk⁻¹ for 13 wk) 0, 1.1, 2.3, 4.5, 9 or 18 ppm. The mean body weights of exposed animals were not affected; in rats, methaemoglobinaemia occurred leading to a regenerative anaemia and a variety of tissue changes secondary to the oxidative erythrocyte injury. Morphological changes to erythrocytes included Heinz bodies, poikilocytes and polychromasia. In rats, serum alanine aminotransferase and sorbitol dehydrogenase activities and bile acid concentration were increased. In mice, hepatocellular necrosis and chronic inflammation occurred. Lesions were also observed in the kidney, spleen and bone marrow. Hyperplasia of the nasal cavity epithelium was observed in rats. A no-observed-adverse-effect level for histopathological injury in mice was determined as 4.5 ppm (18).

Carcinogenicity and chronic effects

♂ Rats were dosed with 500 and 1000 mg kg⁻¹ in the diet for 13 and 12 months, respectively. There was an increase in multiple tumours in rats fed the lower dose; in addition, ♂ and ♀ mice fed 1500 and 3000 mg kg⁻¹ for 10 months showed an increase in liver tumours (17).

Metabolism and toxicokinetics

Metabolised in rabbit to yield: *N*-acetyl-*S*-(*o*-nitrophenyl)-*L*-cysteine, *o*-chloroaniline, 2-chloro-3-nitrophenol, 3-chloro-2-nitrophenol, 3-chloro-4-nitrophenol and 4-chloro-3-nitrophenol (19).

Irritancy

Irritant to eyes, skin and respiratory tract (species unspecified) (20).

Genotoxicity

Salmonella typhimurium TA98, TA100, TA1537, TA1538 without metabolic activation negative (21,22).

Chloronitrobenzenes were mutagenic in Ames test when incubated with both norharman (CAS RN 244-63-3) and metabolic activation. Mutagenic induction by norharman was strong with the *o*-isomers, weak with the *p*-isomers, and not observed with the *m*-isomers (22).

Escherichia coli PQ37 (SOS chromotest) with and without metabolic activation negative (23).

Salmonella typhimurium TA1535/pSK1002 *umu*-test with and without metabolic activation negative (24).

Legislation

Limited under EC Directive on Drinking Water Quality 80/778/EEC. Organochlorine compounds: guide level 1 µg l⁻¹ (25).

Included in Schedule 6 (Release into Land: Prescribed Substances) of Statutory Instrument No. 472, 1991 (26).

Maximum permissible concentration in domestic water in the former USSR 0.05 mg l⁻¹ (27).

Other comments

A quantitative structure-activity relationship has been developed for the acute toxicity of nitroaromatic compounds to carp (*Cyprinus carpio*) (28).

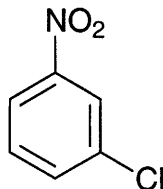
Reviews on physico-chemical properties, human health effects, exposure levels, workplace experience, environmental effects, experimental toxicology and epidemiology listed (29).

Found as trace contaminant in water, sediments and soil, and in fish.

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c223 3-chloronitrobenzene



$C_6H_4ClNO_2$

Mol. Wt. 157.56

CAS Registry No. 121-73-3

Synonyms 1-chloro-3-nitrobenzene; *m*-chloronitrobenzene; *m*-nitrochlorobenzene; chloro-*m*-nitrobenzene

EINECS No. 204-496-1

RTECS No. CZ 0940000

Uses In preparation of the dyestuff intermediate 2,2'-dichlorobenzidine.

Physical properties

M. Pt. 46°C **B. Pt.** 235-236°C **Flash point** 103°C **Specific gravity** 1.534 at 20°C with respect to water at 4°C
Partition coefficient $\log P_{ow}$ 2.41-2.46
Solubility Organic solvents: acetone, benzene, carbon disulfide, chloroform, diethyl ether, ethanol, glacial acetic acid

Occupational exposure

UN No. 1578 **HAZCHEM Code** 2X **Conveyance classification** toxic substance

Ecotoxicity

Fish toxicity

Non-toxic to brown trout, bluegill sunfish, yellow perch, and goldfish exposed to 5 ppm for 24 hr (1).

LC₅₀ (96 hr) guppy 20 mg l⁻¹ (2).

LC₅₀ (96 hr) bluegill sunfish 1.2 mg l⁻¹ (3).

LC₅₀ (96 hr) fathead minnow 18 mg l⁻¹ (4).

Invertebrate toxicity

EC₅₀ (48 hr) *Daphnia magna* 26 mg l⁻¹ (2).

EC₅₀ for algal growth 3.6 mg l⁻¹ (2).

EC₅₀ (15 min) *Photobacterium phosphoreum* 1.08 ppm Microtox test (5).

Toxicity to other species

EC₅₀ (the concentration of chemical required to produce 50% reduction in growth) lettuce *Lactuca sativa* (7 and 14 day static tests) 12 µg g⁻¹ soil, (16-21 day semi-static test) 4.6 mg l⁻¹ nutrient solution (6).

Bioaccumulation

Bioconcentration by *Cyprinus carpio* follows first-order kinetics. A significant correlation between bioconcentration and *n*-octanol/water partition coefficient reported (7).

Environmental fate

Degradation studies

Decomposition period by soil microflora >64 days (8).

Mammalian & avian toxicity

Acute data

LD₅₀ oral mouse, rat 390, 470 mg kg⁻¹, respectively (9,10).

Metabolism and toxicokinetics

Metabolism in isolated rat hepatocytes found the major metabolite to be 3-chloroaniline (31% of added substrate in 90 min); smaller amounts of 3-chloroaniline-*N*-glucuronide (7%) and 3-chloroacetanilide (17%) were formed (11).

Irritancy

Dermal rabbit (4 hr) 0.5 g caused no erythema or oedema (12).

Genotoxicity

Salmonella typhimurium TA98, TA100, TA1535, TA1537, TA1538 with and without metabolic activation negative (13,14).

Escherichia coli (SOS chromotest) with and without metabolic activation negative (14).

Salmonella typhimurium TA1535/pSK1002 *umu*-test with and without metabolic activation negative (15).

Other effects

Any other adverse effects

When administered by inhalation to rats daily for up to 98 days showed threshold concentration of $8 \mu\text{g m}^{-3}$ in regard to adverse effects on the central nervous system (16).

A potent methaemoglobin former when absorbed through the skin (10).

Legislation

Limited under EC Directive on Drinking Water Quality 80/778/EEC. Organochlorine compounds: guide level $1 \mu\text{g l}^{-1}$ (17).

Included in Schedule 6 (Release into Land: Prescribed Substances) of Statutory Instrument No. 472, 1991 (18).

Other comments

Formed in small quantities during chlorination of water when air and nitrobenzene are present (19).

A quantitative structure-activity relationship has been developed for the acute toxicity of nitroaromatic compounds to carp (*Cyprinus carpio*) (20).

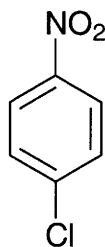
Reviews on human health effects, experimental toxicology, environmental effects, ecotoxicology, exposure levels and workplace experience listed (21).

The dust is the main source of toxicity in industrial environments.

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C224 4-chloronitrobenzene



$C_6H_4ClNO_2$

Mol. Wt. 157.56

CAS Registry No. 100-00-5

Synonyms 1-chloro-4-nitrobenzene; *p*-chloronitrobenzene; *p*-nitrochlorobenzene; 4-chloro-1-nitrobenzene

EINECS No. 202-809-6

RTECS No. CZ 1050000

Uses Used in the manufacture of dyestuffs, insecticides, and in rubber industries.

Physical properties

M. Pt. 83°C **B. Pt.** 242°C **Flash point** >110°C **Specific gravity** 1.520 at 20°C with respect to water at 4°C

Partition coefficient $\log P_{ow}$ 2.39-2.41 **Volatility** v.den. 5.44

Solubility Organic solvents: carbon disulfide, diethyl ether, ethanol

Occupational exposure

JP-OEL 0.1 ppm (0.64 mg m⁻³)

UK-LTEL 1 mg m⁻³

UK-STEL 2 mg m⁻³

US-TWA 0.1 ppm (0.64 mg m⁻³)

UN No. 1578 **HAZCHEM Code** 2X **Conveyance classification** toxic substance

Supply classification toxic, dangerous for the environment

Risk phrases Toxic by inhalation, in contact with skin and if swallowed – Danger of cumulative effects – Toxic to aquatic organisms, may cause long-term adverse effects in the aquatic environment (R23/24/25, R33, R51/53)

Safety phrases Keep locked up and out of the reach of children (if sold to general public) – After contact with skin, wash immediately with plenty of water – Wear suitable gloves – In case of accident or if you feel unwell, seek medical advice immediately (show label where possible) – Avoid release to the environment. Refer to special instructions/safety data sheet (S1/2, S28, S37, S45, S61)

Ecotoxicity

Fish toxicity

Non-toxic to brown trout, bluegill sunfish, yellow perch and goldfish exposed to 5 ppm for 24 hr (1).

LC₅₀ (96 hr) guppy 13 mg l⁻¹ (2).

LC₅₀ (48 hr) carp 0.22 mmol l⁻¹ (3).

Invertebrate toxicity

EC₅₀ (48 hr) *Daphnia magna* 8.9 mg l⁻¹ (2).

EC₅₀ for algal growth 5.5 mg l⁻¹ (2).

Bioaccumulation

Calculated bioconcentration factor 39 (2).

Non-accumulative or low accumulative (4).

Environmental fate

Nitrification inhibition

Ammonia oxidation by *Nitrosomonas* sp. not inhibited at 100 mg l⁻¹ (5).

Degradation studies

Concentrations of $<0.05 \text{ mg l}^{-1}$ in wastewater are reported to be completely degraded under anaerobic conditions (6).

Biodegradation period by soil microflora >64 days (7).

Some soil micro-organisms (*Arthrobacter simplex* and *Streptomyces* spp.) have been shown to be able to grow in the presence of 100 mg l^{-1} at $25\text{--}30^\circ\text{C}$. It is thought that these organisms slowly break down this isomer under aerobic conditions (8).

Mammalian & avian toxicity

Acute data

LD₅₀ oral rat, mouse 420, 650 mg kg^{-1} , respectively (9,10).

LD₅₀ dermal rat 16 g kg^{-1} (9).

LD₅₀ intraperitoneal rat 420 mg kg^{-1} (9).

Sub-acute and sub-chronic data

Groups of 10 ♂ and 10 ♀ rats were exposed to 4-chloronitrobenzene vaporised from a solution in ethylene glycol monomethyl ether at 0, 5, 15 and 45 mg m^{-3} for 6 hr day^{-1} , 5 days wk^{-1} for 4 wk. No significant toxicological effects were exhibited other than those of methaemoglobinaemia, anaemia and splenic changes associated with nitroaromatics (11).

F344/N rats and B6C3F1 mice were exposed to 0, 1.5, 3, 6, 12 and 24 ppm by whole-body inhalation for 6 hr day^{-1} , 5 days wk^{-1} , for 13 weeks. No treatment-related mortalities occurred, and no changes in body weight gain were seen. In rats, inhalation exposure caused methaemoglobinaemia, leading to a regenerative anaemia and secondary tissue changes. Alterations of erythrocyte morphology, such as Heinz bodies, poikilocytes and polychromasia were seen. Increased serum activities of alanine aminotransferase and sorbitol dehydrogenase and increased bile acid concentrations were observed. Microscopic liver changes took place in both rats and mice, such as haemosiderin deposition in Kupffer cells, hepatocytomegaly (only in mice) and cytoplasmic basophilia (only in rats). Lesions were also observed in the spleen, bone marrow and kidney tubules. In rats, lesions unrelated to haematotoxicity included hyaline droplet nephropathy and degeneration of the testis (in ♂ rats), and inflammation of the Harderian gland. In mice, hyperplasia of the forestomach epithelium was seen; the no-observed-adverse-effect level for histopathological injury in mice was 6 ppm (12).

Carcinogenicity and chronic effects

No increase in incidence of tumours when ♂ rats were dosed 500 and 1000 mg kg^{-1} for 13 and 12 months, respectively. ♂ and ♀ mice fed 3000 and 6000 mg kg^{-1} showed a significant increase in vascular tumours at the high dose. There was a significant increase in liver tumours in ♂ mice but this only occurred at the low dose (13).

Metabolism and toxicokinetics

Single doses of 30, 100 or 333 mg kg^{-1} given intraperitoneally to ♂ Sprague-Dawley rats were excreted mostly in the urine ($\sim 2/3$ of the administered dose). Of the five urinary metabolites measured, *N*-acetyl-S-(4-nitrophenyl)-L-cysteine comprised $\sim 1/2$ of the total amount excreted; this proportion was constant over a wide dose-range, as a result of the linear metabolism process in the dose-range studied (14).

The urinary excretion of five metabolites of 4-chloronitrobenzene in six human subjects following accidental exposure was studied. The proportion of the total amount of the metabolites and the mean residence time in the six patients, respectively, were 12.2% and 6.7 days for 2-chloro-5-nitrophenol, 48.0% and 7.0 days for *N*-acetyl-S-(4-nitrophenyl)-L-cysteine, 1.2% and 3.7 days for 2,4-dichloroaniline, 29.9% and 10.0 days for 4-chloroaniline, and 8.7% and 6.0 days for 2-amino-5-chlorophenol (15).

Genotoxicity

Salmonella typhimurium TA98, TA100 with and without metabolic activation negative; TA98 with metabolic activation and norharman weakly positive (16).

Escherichia coli PQ37 (SOS chromotest) with and without metabolic activation negative (17).

Salmonella typhimurium TA1535/pSK1002 (*umu*-test) with and without metabolic activation negative (18).

Legislation

Limited under EC Directive on Drinking Water Quality 80/778/EEC. Organochlorine compounds: guide level 1 µg l⁻¹ (19).

Included in Schedule 6 (Release into Land: Prescribed Substances) of Statutory Instrument No. 472, 1991 (20).

Other comments

The National Toxicology Program tested rats and mice via inhalation. The short-term toxicity report is available (21).

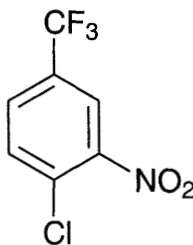
A QSAR study found that the toxicity of nitrobenzenes to river bacteria and to *Photobacterium phosphoreum* is controlled mainly by electronic factors (22).

Reviews on physico-chemical properties, human health effects, experimental toxicology, exposure levels, epidemiology and environmental effects listed (23).

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c225 4-chloro-3-nitrobenzotrifluoride



$C_7H_3ClF_3NO_2$

Mol. Wt. 225.55

CAS Registry No. 121-17-5

Synonyms 3-nitro-4-chlorobenzotrifluoride; 4-chloro-3-nitro- α,α,α -trifluorotoluene; 3-nitro-4-chloro- α,α,α -trifluorotoluene

EINECS No. 204-451-6

RTECS No. XS 9140000

Physical properties

B. Pt. 222°C Flash point 101°C Specific gravity 1.511

Occupational exposure

UN No. 2307 HAZCHEM Code 2X Conveyance classification toxic substance

Mammalian & avian toxicity

Acute data

LD₅₀ oral mouse, rat 400, 1075 mg kg⁻¹, respectively (1).

References

1. *Gig. Sanit.* 1982, 47(3), 88

c226 1-chloro-1-nitroethane



$C_2H_4ClNO_2$

Mol. Wt. 109.51

CAS Registry No. 598-92-5

Synonyms 1-nitro-1-chloroethane

RTECS No. KH 7875000

Physical properties

M. Pt. 1°C B. Pt. 124°C Flash point 56°C Specific gravity 1.3

Mammalian & avian toxicity

Acute data

LD₅₀ oral mouse 185 mg kg⁻¹ (1).

LC₅₀ (3 hr) inhalation mouse 21 mg l⁻¹ (1).
LD₅₀ subcutaneous mouse 185 mg kg⁻¹ (1).
LD₅₀ intraperitoneal mouse 560 mg kg⁻¹ (2).

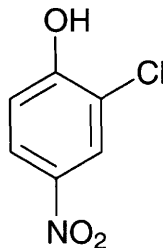
Legislation

Limited under EC Directive on Drinking Water Quality 80/778/EEC. Organochlorine compounds: guide level 1 µg l⁻¹ (3).
Included in Schedule 6 (Release into Land: Prescribed Substances) of Statutory Instrument No. 472, 1991 (4).

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C227 2-chloro-4-nitrophenol



C₆H₄ClNO₃

Mol. Wt. 173.56

CAS Registry No. 619-08-9

Synonyms 4-chloro-2-nitrophenol

EINECS No. 210-578-8

RTECS No. SK 5075000

Uses Fungicide.

Physical properties

M. Pt. 111°C

Solubility Organic solvents: benzene, chloroform, diethyl ether, ethanol

Ecotoxicity

Fish toxicity

Rainbow trout and white sucker exposed for 24 hr to 2 mg l⁻¹ showed no adverse effects (1).

Threespine stickleback and rainbow trout exposed for 24 hr to 10 mg l⁻¹ showed no adverse effects (2).

Environmental fate

Degradation studies

As sole carbon source in bench scale activated sludge fill and draw operations at 20°C, 71.5% COD removal at a rate of 5.3 mg COD g⁻¹ dry inoculum hr⁻¹ (3).

Biodegradable (4).

Mammalian & avian toxicity

Acute data

LD₅₀ oral rat 900 mg kg⁻¹ (5).

LD₅₀ intraperitoneal mouse 80 mg kg⁻¹ (6).

Genotoxicity

Salmonella typhimurium TA1535/pSK1002 (*umu*-test) with metabolic activation negative, without metabolic activation positive (7).

Legislation

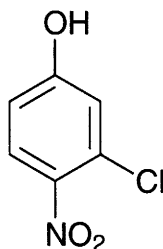
Limited under EC Directive on Drinking Water Quality 80/778/EEC. Pesticides: maximum admissible concentration 0.1 µg l⁻¹ (8).

Included in Schedule 6 (Release into Land: Prescribed Substances) of Statutory Instrument No. 472, 1991 (9).

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9. S. I. 1991 No. 472 *The Environmental Protection (Prescribed Processes and Substances) Regulations* 1991, HMSO, London, UK

c228 3-chloro-4-nitrophenol



C₆H₄ClNO₃

Mol. Wt. 173.56

CAS Registry No. 491-11-2

Synonyms 2-chloro-4-hydroxynitrobenzene; 4-nitro-3-chlorophenol

EINECS No. 207-730-0

RTECS No. SK 5250000

Physical properties

M. Pt. 121-122°C

Solubility Organic solvents: benzene, ethanol

Ecotoxicity

Fish toxicity

Rainbow trout and white sucker exposed to 3 mg l⁻¹ for 24 hr showed no adverse effects (1).

Threespine stickleback and rainbow trout exposed to 5 mg l⁻¹ for 24 hr showed no adverse effects (2).

Mammalian & avian toxicity

Acute data

LD_{Lo} intraperitoneal mouse 125 mg kg⁻¹ (3).

Legislation

Limited under EC Directive on Drinking Water Quality 80/778/EEC. Phenols: maximum admissible concentration 0.5 µg l⁻¹ (4).

Included in Schedule 6 (Release into Land: Prescribed Substances) of Statutory Instrument No. 472, 1991 (5).

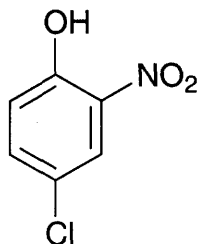
Other comments

A metabolite of organophosphorus pesticides (6).

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c229 4-chloro-2-nitrophenol



C₆H₄ClNO₂

Mol. Wt. 173.56

CAS Registry No. 89-64-5

Synonyms 4-chloro-*o*-nitrophenol; 2-nitro-4-chlorophenol

EINECS No. 201-927-5

Uses Increases shelf life of thermosetting vinyl ester resins.

Physical properties

M. Pt. 85-87°C B. Pt. 235-236°C Specific gravity 1.534 at 20°C with respect to water at 4°C

Partition coefficient log P_{ow} 2.46 (1)

Ecotoxicity

Fish toxicity

Rainbow trout and white sucker exposed to 4 mg l⁻¹ for 24 hr showed no adverse effects (2).

Threespine stickleback exposed to 10 mg l⁻¹ suffered loss of equilibrium and death within 8-12 hr. No effect was observed in rainbow trout after 24 hr (3).

Environmental fate

Degradation studies

Enterobacter cloacae (50 hr incubation) converted 4-chloro-2-nitrophenol into 4-chloro-2-aminophenol (8.1%) and 4-chloro-2-acetoaminophenol (16%) under anaerobic conditions. *Alcaligenes* sp. further degraded the reduction product 4-chloro-2-aminophenol under aerobic conditions (4).

Pseudomonas sp. N31 used 4-chloro-2-nitrophenol as a source of nitrogen, eliminating nitrite and accumulating 4-chlorocatechol. Other strains utilising 4-chloro-2-nitrophenol as a sole source of carbon or nitrogen included *Pseudomonas* sp. B13 and *Alcaligenes eutrophus* JMP 134 (5).

Decomposition period by soil microflora >64 days (6).

Mammalian & avian toxicity

Irritancy

Skin, eye, mucous membrane and upper respiratory tract irritant (species unspecified) (7).

Genotoxicity

Salmonella typhimurium TA1535/pSK1002 (*umu*-test) with and without metabolic activation negative (8).

Legislation

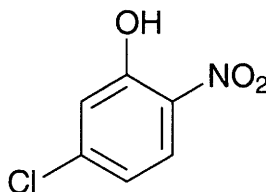
Limited under EC Directive on Drinking Water Quality 80/778/EEC. Phenols: maximum admissible concentration 0.5 µg l⁻¹ (9).

Included in Schedule 6 (Release into Land: Prescribed Substances) of Statutory Instrument No. 472, 1991 (10).

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C230 5-chloro-2-nitrophenol



$C_6H_4ClNO_3$

Mol. Wt. 173.56

CAS Registry No. 611-07-4

Synonyms 3-chloro-6-nitrophenol; 2-nitro-5-chlorophenol

EINECS No. 210-249-9

Physical properties

M. Pt. 42-43°C

Solubility Organic solvents: acetic acid, diethyl ether, ethanol

Ecotoxicity

Fish toxicity

Rainbow trout and white sucker exposed to 0.5 mg l⁻¹ for 24 hr showed no adverse effects (1).

Threespine stickleback and rainbow trout exposed to 10 mg l⁻¹ for 24 hr showed no adverse effects (2).

LC₁₀₀ larvae of sea lamprey 3 mg l⁻¹ (3).

Legislation

Limited under EC Directive on Drinking Water Quality 80/778/EEC. Phenols: maximum admissible concentration 0.5 µg l⁻¹ (4).

Included in Schedule 6 (Release into Land: Prescribed Substances) of Statutory Instrument No. 472, 1991 (5).

Other comments

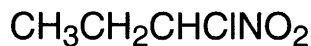
Quantitative structure activity relationship (QSAR) toxicity evaluation and data obtained on eight species of freshwater fish were compared for 110 phenol compounds including 5-chloro-2-nitrophenol. Overall the experimental results and QSAR evaluations were consistent (6).

Hydroxylation of 2,4-difluoronitrobenzene with sodium hydroxide in aqueous dioxane containing a phase transfer catalyst gave 5-fluoro-2-nitrophenol. During vacuum distillation of 5-fluoro-2-nitrophenol on a 20:1 scale an explosion and fire occurred. Thermal analysis of crude 5-fluoro-2-nitrophenol demonstrated that it is capable of undergoing highly exothermic decomposition. It is recommended that the large-scale preparation and purification of 5-fluoro-2-nitrophenol and, by analogy, 5-chloro-2-nitrophenol should not be attempted (7).

References

1. McPhee, C. et al *Fish Toxicity Screening Data* 1989, Part 1, USEPA 560/6-89-001.
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5. S. I. 1991 No. 472 *The Environmental Protection (Prescribed Processes and Substances) Regulations* 1991, HMSO, London, UK.
6. Lipnick, R. L. et al *ASTM Spec. Tech. Publ.* 1985, **891**, 153-176.
7. Robinson, N. *Chem. Br.* 1987, **23**(9), 837

C231 1-chloro-1-nitropropane



$\text{C}_3\text{H}_6\text{ClNO}_2$

Mol. Wt. 123.54

CAS Registry No. 600-25-9

Synonyms 1-nitro-1-chloropropane

EINECS No. 209-990-0

RTECS No. TX 5075000

Uses Manufacture of adhesives and pesticides.

Physical properties

B. Pt. 139-143°C Specific gravity 1.21 at 20°C with respect to water at 20°C

Volatility v.p. 5.8 mmHg at 25°C

Solubility Water: 6 mg l⁻¹ at 20°C. Organic solvents: chloroform, diethyl ether, ethanol

Occupational exposure

FR-VME 2 ppm (10 mg m⁻³)

US-TWA 2 ppm (10 mg m⁻³)

Supply classification harmful

Risk phrases Harmful by inhalation and if swallowed (R20/22)

Safety phrases Keep out of reach of children (if sold to general public) (S2)

Mammalian & avian toxicity

Acute data

LD₅₀ oral mouse 510 mg kg⁻¹ (1).

LC₅₀ (3 hr) inhalation mouse 66 g m⁻³ (1).

LD₅₀ subcutaneous mouse 165 mg kg⁻¹ (1).

Caused pulmonary oedema and death to rabbit and guinea pig within 48 hr following exposure to high concentrations (concentrations unspecified). Chief site of injury was the lungs, although damage was also observed in the heart muscle, liver and kidneys (2).

Genotoxicity

Salmonella typhimurium TA98, TA100 with and without metabolic activation positive (3).

Legislation

Included in Schedule 6 (Release into Land: Prescribed Substances) of Statutory Instrument No. 472, 1991 (4).

Limited under EC Directive on Drinking Water Quality 80/778/EEC. Organochlorine compounds: guide level 1 µg l⁻¹ (5).

Other comments

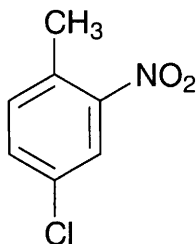
Reviews on physico-chemical properties, human health effects, experimental toxicology, exposure levels (workplace) and epidemiology listed (6).

References

1. Neklesova, I. D. et al *Gig. Sanit.* 1969, **34**(12), 79-81 (Russ.) (*Chem. Abstr.* **72**, 64884k).
2. Clayton, D. G. et al (Ed.) *Patty's Industrial Hygiene and Toxicology* 3rd ed., 1982, 4162, John Wiley, New York, USA.
3. Zeiger, E. et al *Environ. Mol. Mutagen.* 1992, **19**(Suppl. 21), 2-141.
4. S. I. 1991 No. 472 *The Environmental (Prescribed Processes and Substances) Regulations* 1991, HMSO, London, UK.

5. EC Directive Relating to the Quality of Water Intended for Human Consumption 1982, 80/778/EEC, Office for Official Publications of the European Communities, 2 rue Mercier, L-2985 Luxembourg.
6. ECETOC Technical Report No. 71 1996, European Centre for Ecotoxicology and Toxicology of Chemicals, 4 Avenue E. Van Nieuwenhuyse (Bte 6), B-1160 Brussels, Belgium

c232 4-chloro-2-nitrotoluene



$C_7H_6ClNO_2$

Mol. Wt. 171.58

CAS Registry No. 89-59-8

Synonyms 4-chloro-1-methyl-2-nitrobenzene

EINECS No. 201-921-2

Physical properties

M. Pt. 38-39°C B. Pt. 239-240°C at 718 mmHg Flash point >110°C Specific gravity 1.2559 Partition coefficient $\log P_{ow}$ 3.05 (1)

Solubility Organic solvents: chloroform, diethyl ether, ethanol

Occupational exposure

UN No. 2433 HAZCHEM Code 2X Conveyance classification toxic substance

Ecotoxicity

Fish toxicity

LC₅₀ (14 day) guppy 6.4 mg l⁻¹ (1).

Invertebrate toxicity

EC₅₀ (48 hr) *Daphnia magna* 9.4 mg l⁻¹ (2).

EC₅₀ (96 hr) freshwater alga *Chlorella pyrenoidosa* 6.1 mg l⁻¹ (2).

EC₅₀ (15 min) *Photobacterium phosphoreum* 4.9 mg l⁻¹ (3).

EC₅₀ (0-48 hr) marine alga *Scenedesmus subspicatus* 18 mg l⁻¹ (4).

Mammalian & avian toxicity

Irritancy

Mucous membrane and upper respiratory tract irritant (species unspecified) (5).

Genotoxicity

Salmonella typhimurium TA98, TA100 with and without metabolic activation negative (6).

Salmonella typhimurium TA1535/pSK1002 (*umu*-test) with and without metabolic activation negative (7).

Other effects

Other adverse effects (human)

Absorption into the body leads to the formation of methaemoglobin which in sufficient concentrations causes cyanosis. Onset may be delayed 2-4 hr or longer (5).

Legislation

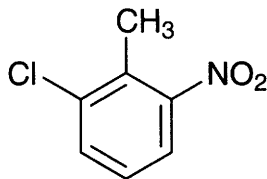
Limited under EC Directive on Drinking Water Quality 80/778/EEC. Organochlorine compounds: guide level 1 µg l⁻¹ (8).

Included in Schedule 6 (Release into Land: Prescribed Substances) of Statutory Instrument No. 472, 1991 (9).

References

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2. Deneer, J. W. et al *Aquat. Toxicol.* 1989 **15**, 83-98.
3. Kaiser, K. L. E. *Water Pollut. Res. J. Can.* 1991, **26**(3), 361-431.
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5. Lenga, R. E. *The Sigma-Aldrich Library of Chemical Safety Data* 2nd ed., 1988, **1**, 128, Sigma-Aldrich, Milwaukee, USA.
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8. *EC Directive Relating to the Quality of Water Intended for Human Consumption* 1982, 80/778/EEC, Office for Official Publications of the European Communities, 2 rue Mercier, L-2985 Luxembourg.
9. S. I. 1991 No. 472 *The Environmental Protection (Prescribed Processes and Substances) Regulations* 1991, HMSO, London, UK

c233 6-chloro-2-nitrotoluene



C₇H₆ClNO₂

Mol. Wt. 171.58

CAS Registry No. 83-42-1

Synonyms 1-chloro-2-methyl-3-nitrobenzene; 2-nitro-6-chlorotoluene; 2-chloro-6-nitrotoluene

EINECS No. 201-475-9

RTECS No. XS 9130000

Physical properties

M. Pt. 34-36°C B. Pt. 238°C Flash point 125°C Partition coefficient log P_{ow} 3.09 (1)

Solubility Organic solvents: ethanol

Occupational exposure

UN No. 2433 HAZCHEM Code 2X Conveyance classification toxic substance

Ecotoxicity

Fish toxicity

LC₅₀ guppy 30.2 µmol l⁻¹ (duration unspecified) (1).

Mammalian & avian toxicity

Acute data

LD₅₀ intravenous mouse 56 mg kg⁻¹ (2).

Genotoxicity

Salmonella typhimurium TA1535/pSK1002 (*umu*-test) with and without metabolic activation negative (3).

Other effects

Other adverse effects (human)

Absorption into the body leads to formation of methaemoglobin which in sufficient concentrations causes cyanosis. Onset may be delayed 2-4 hr or longer (4).

Legislation

Limited under EC Directive on Drinking Water Quality 80/778/EEC. Organochlorine compounds: guide level 1 µg l⁻¹ (5).

Included in Schedule 6 (Release into Land: Prescribed Substances) of Statutory Instrument No. 472, 1991 (6).

Other comments

The relationship between chemical structure and carcinogenicity was investigated in 44 chlorinated aromatic and 38 polycyclic aromatic compounds by ¹³C-NMR. As an index serving as a measure of the electronic structure which is closely related to carcinogenicity, the average ¹³C-NMR chemical shift was used. The chemical shift of carcinogenic monocyclic compounds was within the range 128-133 (7).

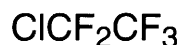
Reviews on physico-chemical properties, human health effects, experimental toxicology, exposure levels (environment) and environmental effects listed (8).

Detected in water samples (2).

References

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8. *BUA Reports* 1993, 61, Wissenschaftliche Verlagsgesellschaft/S. Hirzel-Verlag, PO Box 101 061, D-70009 Stuttgart, Germany

C234 chloropentafluoroethane



C₂ClF₅

Mol. Wt. 154.47

CAS Registry No. 76-15-3

Synonyms monochloropentafluoroethane; pentafluorochloroethane

EINECS No. 200-938-2

RTECS No. KH 7877500

Uses Refrigerant. Propellant in aerosol food preparations.

Physical properties

M. Pt. -99.4°C B. Pt. -7.9°C

Solubility Water: soluble. Organic solvents: diethyl ether, ethanol

Occupational exposure

FR-VME 1000 ppm (6320 mg m⁻³)

UK-LTEL 1000 ppm (6420 mg m⁻³)

US-TWA 1000 ppm (6320 mg m⁻³)

UN No. 1020 HAZCHEM Code 2RE Conveyance classification non-flammable non-toxic gas

Mammalian & avian toxicity

Acute data

Highest measured inhalation no-effect concentrations on single 2-hr exposure to four rats and two guinea pigs was 60% in air (1).

Sub-acute and sub-chronic data

Experimental animals exposed to concentrations of 10% in air for 90 exposures of 6 hr day⁻¹ showed no effects. The body weight and clinical conditions of rats and mice were unaffected. Rat and dog blood and urine analyses showed no effects. Dog weight gain, temperature, respiration and pulse were normal (2).

Legislation

Included in Schedule 4 (Release into Air: Prescribed Substances) of Statutory Instrument No. 472, 1991 (3).

Other comments

Reviews on physico-chemical properties, human health effects, experimental toxicology, exposure levels (workplace), epidemiology and environmental effects listed (4).

References

1. Weigand, W. *Zentralbl. Arbeitsmed. Arbeitsschutz*. 1971, **21**, 149.
2. Clayton, J. W. et al *Am. Ind. Hyg. Assoc. J.* 1966, **27**, 234.
3. S. I. 1991 No. 472 *The Environmental Protection (Prescribed Processes and Substances) Regulations* 1991, HMSO, London, UK.
4. *ECETOC Technical Report No. 71* 1996, European Centre for Ecotoxicology and Toxicology of Chemicals, 4 Avenue E. Van Nieuwenhuysse (Bte 6), B1160 Brussels, Belgium

c235 1-chloro-3-pentanone



C₅H₉ClO

Mol. Wt. 120.58

CAS Registry No. 32830-97-0

Synonyms β-chloroethyl ethyl ketone; 2-chloroethyl ethyl ketone; 1-chloropentan-3-one

EINECS No. 251-247-8

Uses Chemical reagent.

Physical properties

B. Pt. 62-64°C at 10 mmHg Flash point 51°C Specific gravity 1.042 at 20°C with respect to water at 4°C

Solubility Organic solvents: diethyl ether, ethanol

Mammalian & avian toxicity

Irritancy

Vapour or mist irritating to the eyes, mucous membranes and upper respiratory tract.
Causes skin irritation (species unspecified) (1).

Legislation

Limited under EC Directive on Drinking Water Quality 80/778/EEC. Organochlorine compounds: guide level $1 \mu\text{g l}^{-1}$ (2).

Included in Schedule 6 (Release into Land: Prescribed Substances) of Statutory Instrument No. 472, 1991 (3).

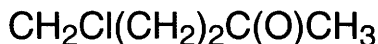
Other comments

Detected in water samples.

References

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3. S. I. 1991 No. 472 *The Environmental Protection (Prescribed Processes and Substances) Regulations* 1991, HMSO, London, UK

c236 5-chloro-2-pentanone



$\text{C}_5\text{H}_9\text{ClO}$

Mol. Wt. 120.58

CAS Registry No. 5891-21-4

Synonyms 5-chloropentan-2-one; 3-chloropropyl methyl ketone; 1-chloro-4-pentanone

EINECS No. 227-565-8

Physical properties

B. Pt. 71-72°C at 20 mmHg **Flash point** 35°C **Specific gravity** 1.057 at 20°C with respect to water at 4°C

Solubility Organic solvents: acetone, carbon tetrachloride, diethyl ether

Legislation

Limited under EC Directive on Drinking Water Quality 80/778/EEC. Organochlorine compounds: guide level $1 \mu\text{g l}^{-1}$ (1).

Included in Schedule 6 (Release into Land: Prescribed Substances) of Statutory Instrument No. 472, 1991 (2).

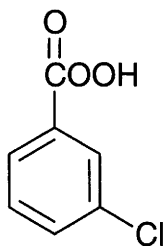
Other comments

A product of nitrophenol decomposition in water treated by chlorination (3).

References

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2. S. I. 1991 No. 472 *The Environmental Protection (Prescribed Processes and Substances) Regulations* 1991, HMSO, London, UK.
3. Vakulenko, V. F. et al *Khim. Tekhnol. Vody* 1985, 7(4), 17-21 (Russ.) (*Chem. Abstr.* 103, 183308a)

c237 3-chloroperbenzoic acid



$C_7H_5ClO_3$

Mol. Wt. 172.57

CAS Registry No. 937-14-4

Synonyms 3-chloroperoxybenzoic acid; *m*-chloroperbenzoic acid; 3-chlorobenzenecarboperoxoic acid

EINECS No. 213-322-3

RTECS No. SD 9470000

Uses Epoxidising agent.

Physical properties

M. Pt. 69-71°C

Mammalian & avian toxicity

Carcinogenicity and chronic effects

Active tumour promoter on the skin of ♀ ICR Swiss mice (1).

Genotoxicity

Salmonella typhimurium TA98, TA100 with and without metabolic activation negative (2).

Legislation

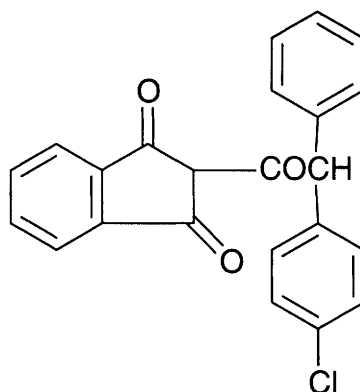
Limited under EC Directive on Drinking Water Quality 80/778/EEC. Organochlorine compounds: guide level 1 µg l⁻¹ (3).

Included in Schedule 6 (Release into Land: Prescribed Substances) of Statutory Instrument No. 472, 1991 (4).

References

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C238 chlorophacinone



$C_{23}H_{15}ClO_3$

Mol. Wt. 374.82

CAS Registry No. 3691-35-8

Synonyms 2-[2-(*p*-chlorophenyl)-2-phenylacetyl]indan-1,3-dione; 2-[(*p*-chlorophenyl)phenylacetyl]-1,3-indandione; chlorphenacome; Delta; Rozol; Topitox; Agri-bloc; Antirat; Caid; Clor; Drat

EINECS No. 223-003-0

RTECS No. NK 5335000

Uses Anticoagulant. Rodenticide.

Physical properties

M. Pt. 140°C **Specific gravity** 0.38 g cm⁻³ bulk density at 20°C **Volatility** v.p. 1×10^{-7} at 25°C

Solubility Water: 100 mg l⁻¹ at 20°C. Organic solvents: acetic acid, acetone, benzene, ethanol, ethyl acetate, methanol

Occupational exposure

Supply classification very toxic

Risk phrases Toxic by inhalation – Very toxic in contact with skin and if swallowed – Toxic: danger of serious damage to health by prolonged exposure in contact with skin and if swallowed (R23, R27/28, R48/24/25)

Safety phrases Keep locked up and out of the reach of children (if sold to general public) – Wear suitable protective clothing and gloves – In case of accident or if you feel unwell, seek medical advice immediately (show label where possible) (S1/2, S36/37, S45)

Mammalian & avian toxicity

Acute data

LD₅₀ oral redwing blackbird >100 mg kg⁻¹ (1).

LD₅₀ oral duck 0.1 mg kg⁻¹ (2).

LD₅₀ oral mouse, rat 1-2 mg kg⁻¹ (2,3).

LD₅₀ dermal rat 4.98 mg kg⁻¹ (4).

LD₁₀₀ dermal rat 5.95 mg kg⁻¹ (4).

LC₅₀ (1 hr) inhalation rat >3.0 mg l⁻¹ (5).

Genotoxicity

When administered orally to Plymouth hens at 100 mg kg⁻¹ or to cocks at 100 mg kg⁻¹ prior to mating, it caused no chromosomal aberrations in the resultant embryos (6).

Caused no chromosomal aberrations in the bone marrow of ♂ rodents (6,7).

Other effects

Other adverse effects (human)

In human volunteers given a single dose of 20 mg, blood prothrombin levels fell to 35% within 2-4 days, but recovered within 8 days without treatment (5).

Persons with blood dyscrasias, bleeding tendencies, liver or kidney diseases, ulcers of the gastro-intestinal tract, or hypertension are at increased risk from exposure (8).

Any other adverse effects

Dermal rabbit (duration unspecified) 5 mg in 2 ml liquid paraffin on skin produced only a slight reduction of prothrombin level (9).

Repeated absorption by skin and lungs may cause inhibition of prothrombin synthesis and damage to capillary permeability resulting in widespread internal haemorrhage with associated effects of nosebleed, haematoma, haematuria, widespread bruising and anaemia. Severe haemorrhaging may cause death (8).

Legislation

Limited under EC Directive on Drinking Water Quality 80/778/EEC. Pesticides: maximum admissible concentration 0.1 µg l⁻¹ (10).

Included in Schedule 6 (Release into Land: Prescribed Substances) of Statutory Instrument No. 472, 1991 (11).

WHO Toxicity Class Ia (12).

EPA Toxicity Class (technical) I, (tracking powder) II (5).

Other comments

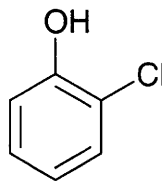
Toxicity and hazards reviewed (13).

Physico-chemical properties, human health effects, experimental toxicology, exposure levels (workplace), epidemiology and environmental effects reviewed (14).

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2. *Guide Chem. Used Crop Prot.* 1973, **6**, 112, c.f. RTECS, No. 52033.
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11. *S. I. 1991 No. 472 The Environmental Protection (Prescribed Processes and Substances) Regulations* 1991, HMSO, London, UK.
12. *The WHO Recommended Classification of Pesticides by Hazard and Guidelines to Classification* 1998-1999 WHO/PCS/98.21.
13. *Dangerous Prop. Ind. Mater. Rep.* 1993, **13**(1), 67-71.
14. *WHO/FAO Data Sheets on Pesticides* 1985, **62**, IPCS c/o WHO, 20 Avenue Appia, CH-1211 Geneva 27, Switzerland

C239 2-chlorophenol



C₆H₅ClO

Mol. Wt. 128.56

CAS Registry No. 95-57-8

Synonyms o-chlorophenol; 2-chloro-1-hydroxybenzene; 1-chloro-2-hydroxybenzene; 2-hydroxychlorobenzene

EINECS No. 202-433-2

RTECS No. SK 2625000

Uses Intermediate in organic synthesis. Dyestuffs manufacture.

Physical properties

M. Pt. 8°C B. Pt. 175-176°C Flash point 63°C Specific gravity 1.263 at 20°C with respect to water at 4°C

Partition coefficient log P_{ow} 2.15 Volatility v.p. 40 mmHg at 82°C

Solubility Water: <0.1 g in 100 g. Organic solvents: benzene, diethyl ether, ethanol

Occupational exposure

SE-LEVL 0.5 mg m⁻³

SE-STEL 1.5 mg m⁻³

UN No. 2021 (liquid)

UN No. 2020 (solid) HAZCHEM Code 2X Conveyance classification toxic substance

Supply classification harmful, dangerous for the environment

Risk phrases Harmful by inhalation, in contact with skin and if swallowed – Toxic to aquatic organisms, may cause long-term adverse effects in the aquatic environment (R20/21/22, R51/53)

Safety phrases Keep out of reach of children (if sold to general public) – After contact with skin, wash immediately with plenty of water – Avoid release to the environment. Refer to special instructions/safety data sheet (S2, S28, S61)

Ecotoxicity

Fish toxicity

LC₅₀ (24 hr) guppy, goldfish 11, 16 ppm, respectively (1).

LC₅₀ (96 hr) fathead minnow 0.10 mmol l⁻¹ (2).

Invertebrate toxicity

LC₅₀ (48 hr) earthworm *Eisenia foetida* 0.43 mg kg⁻¹ (contact test) (3).

EC₅₀ (48 hr) *Daphnia magna* 2.6 mg l⁻¹ (4).

EC₅₀ (48 hr) *Tetrahymena pyriformis* 68 mg l⁻¹ (5).

EC₅₀ (15 min) *Photobacterium phosphoreum* (Microtox test) 0.07 mmol l⁻¹ (2).

Toxicity to other species

EC₅₀ (the concentration of 2-chlorophenol required to produce 50% reduction in growth) (7 and 14 days static test, 16-21 days semi-static test) lettuce *Lactuca sativa* 52 and 43 µg g⁻¹ soil and 16 mg l⁻¹ nutrient solution, respectively (6).

Bioaccumulation

Non-accumulative or low accumulative (7).

Environmental fate

Degradation studies

Degradation by *Pseudomonas* sp. 200 mg l⁻¹ at 30°C; parent: 100% ring disruption in 52 hr; mutant: 100% ring disruption in 26 hr (8).

Completely transformed in 3 wk in anaerobic sewage sludge diluted to 10% in a mineral salts medium to produce phenol (9).

Pseudomonas putida EKII degrades *o*-substituted chlorophenols via 3-substituted catechols (10).

A consortium of anaerobic bacteria transformed *o*-substituted phenols to *m*-substituted benzoic acids under methanogenic conditions (11).

Penicillium strain Bi 7/2 metabolises 2-chlorophenol with phenol or glucose as co-substrate (12).

Under denitrifying and methanogenic conditions, chlorophenols inhibited bacterial denitrification and were stoichiometrically mineralised to CH₄ (13).

Abiotic removal

Decomposition rate in soil suspensions 14 days required for complete removal (14).

Mammalian & avian toxicity

Acute data

LD₅₀ oral redwing blackbird 113 mg kg⁻¹ (15).

LD₅₀ oral mouse, rat 345, 670 mg kg⁻¹, respectively (16,17).

LD₅₀ intraperitoneal rat 230 mg kg⁻¹ (18).

Sub-acute and sub-chronic data

Administration to rats and mice at 175 mg kg⁻¹ day⁻¹ for 14 days caused 100% lethality but at 35 mg kg⁻¹ day⁻¹ had no toxic effect (19).

Gavage Sprague-Dawley rats 13, 64, 129 or 257 mg kg⁻¹ for 10 days, or 17, 50 or 150 mg kg⁻¹ for 90 days. No treatment-related effects were seen in the 10-day study. The 90-day study found no gross or histopathological effects of treatment, but did find statistically significant differences in haematology, clinical chemistry and organ weights between treated and control rats; however, these differences were not considered to be biologically meaningful (20).

Carcinogenicity and chronic effects

Limited evidence for carcinogenicity to humans, IARC classification group 2B (21).

Genotoxicity

Salmonella typhimurium TA1535/pSK1002 with and without metabolic activation negative (22).

Disturbed spindle function (c-mitosis) in Chinese hamster lung cells *in vitro* (23).

Other effects

Any other adverse effects

EC₅₀ (the concentration of chemical causing a 50% decrease in the rate of reduction) submitochondrial particles from beef heart mitochondria 17 mg l⁻¹ (24).

Legislation

Limited under EC Directive on Drinking Water Quality 80/778/EEC. Phenols: maximum admissible concentration 0.5 µg l⁻¹ (25).

Included in Schedule 6 (Release into Land: Prescribed Substances) of Statutory Instrument No. 472, 1991 (26).

Other comments

Primary mode of action determined from acute toxicity testing of fathead minnows (27).

Mode of action determined by *in vitro* toxicity testing (28).

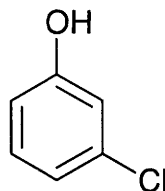
The relationship between the acute toxicity and accumulation of chlorophenols in goldfish at various pH levels, and their transport mechanism investigated (29).

Reviews on physico-chemical properties, human health effects, experimental toxicology, workplace experience, epidemiology and environmental effects listed (30).

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c240 3-chlorophenol



C₆H₅ClO

Mol. Wt. 128.56

CAS Registry No. 108-43-0

Synonyms *m*-chlorophenol; 1-chloro-3-hydroxybenzene; 3-chloro-1-hydroxybenzene; 3-hydroxychlorobenzene

EINECS No. 203-582-6

RTECS No. SK 2450000

Uses Intermediate in organic synthesis.

Physical properties

M. Pt. 33.5°C B. Pt. 214°C Flash point >110°C Specific gravity 1.245 at 45°C

Partition coefficient $\log P_{ow}$ 2.50

Solubility Water: 2.6 g l⁻¹. Organic solvents: diethyl ether, ethanol

Occupational exposure

SE-LEVL 0.5 mg m⁻³

SE-STEL 1.5 mg m⁻³

UN No. 2021 (liquid)

UN No. 2020 (solid) HAZCHEM Code 2X Conveyance classification toxic substance

Supply classification harmful, dangerous for the environment

Risk phrases Harmful by inhalation, in contact with skin and if swallowed – Toxic to aquatic organisms, may cause long-term adverse effects in the aquatic environment (R20/21/22, R51/53)

Safety phrases Keep out of reach of children (if sold to general public) – After contact with skin, wash immediately with plenty of water – Avoid release to the environment. Refer to special instructions/safety data sheet (S2, S28, S61)

Ecotoxicity

Fish toxicity

LC₅₀ (48 hr) *Ide melanote* 3 mg l⁻¹ (1).

LC₅₀ (24 hr) guppy 6.5 ppm (2).

LC₅₀ (96 hr) flounder 3.99 mg l⁻¹ (3).

Structure-activity investigations into the acute toxicity of chlorophenols to *Carassius auratus* led to the conclusion that chlorophenols (including 3-chlorophenol) are transferred from the water environment to the site of action in fish mainly by passive diffusion of their undissociated forms through various biological membranes, and that the OH group of their undissociated forms interacts with the site, resulting in the occurrence of toxicity in the fish (4).

Invertebrate toxicity

LC₅₀ (based on estimated concentrations in the soil-pore water-phase of four soil types) *Eisenia andrei* 152-315 μmol l⁻¹, *Lumbricus rubellus* 343-654 μmol l⁻¹ (5).

Bioaccumulation

Non-accumulative or low accumulative (6).

Environmental fate

Degradation studies

3-Chlorophenol was metabolised as sole substrate by phenol-grown resting cells of *Pseudomonas putida* EKII.

Growing cells degraded 3-chlorophenol only in co-metabolism with phenol (7).

Mixed bacterial cultures which degraded chlorinated benzenes, including 3-chlorophenol, were obtained by enrichment from contaminated soil samples. Chloride release and growth rates decreased with initial substrate concentrations within the range 30-250 μg l⁻¹ (8).

Laboratory soil columns were used to degrade aromatic compounds under denitrifying conditions. After an acclimation period, toluene was rapidly metabolised. Further acclimation allowed the soil microbiota to cross-adapt to degrade 3-chlorophenol (9).

Penicillium strain Bi 7/2 isolated from phenol-contaminated soil metabolises 3-chlorophenol with phenol or glucose as substrate (10).

Mammalian & avian toxicity

Acute data

LD₅₀ oral rat 570 mg kg⁻¹ (11).

Genotoxicity

Salmonella typhimurium TA1535/psK1002 umu-test strongly positive without metabolic activation (12).

Legislation

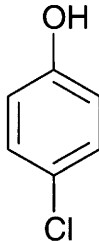
Limited under EC Directive on Drinking Water Quality 80/778/EEC. Phenols: maximum admissible concentration $0.5 \mu\text{g l}^{-1}$ ($\text{C}_6\text{H}_5\text{OH}$) (13).

Included in Schedule 6 (Release into Land: Prescribed Substances) of Statutory Instrument No. 472, 1991 (14).

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c241 4-chlorophenol



$\text{C}_6\text{H}_5\text{ClO}$

Mol. Wt. 128.56

CAS Registry No. 106-48-9

Synonyms *p*-chlorophenol; 4-hydroxychlorobenzene; 1-chloro-4-hydroxybenzene

EINECS No. 203-402-6

RTECS No. SK 2800000

Uses Intermediate in synthesis of dyestuffs and drugs. Denaturant for alcohol. Selective solvent in refining mineral oils. Antiseptic.

Physical properties

M. Pt. 43-45°C B. Pt. 220°C Flash point 115°C Specific gravity 1.306 Partition coefficient $\log P_{\text{ow}}$ 2.35

Volatility v.p. 0.10 mmHg at 20°C

Solubility Water: 27.1 g l⁻¹ at 20°C. Organic solvents: chloroform, diethyl ether, ethanol, glycerol

Occupational exposure

SE-LEVL 0.5 mg m⁻³

SE-STEL 1.5 mg m⁻³

UN No. 2021 (liquid)

UN No. 2020 (solid) **HAZCHEM Code 2X** Conveyance classification toxic substance

Supply classification harmful, dangerous for the environment

Risk phrases Harmful by inhalation, in contact with skin and if swallowed – Toxic to aquatic organisms, may cause long-term adverse effects in the aquatic environment (R20/21/22, R51/53)

Safety phrases Keep out of reach of children (if sold to general public) – After contact with skin, wash immediately with plenty of water – Avoid release to the environment. Refer to special instructions/safety data sheet (S2, S28, S61)

Ecotoxicity

Fish toxicity

LC₅₀ (96 hr) rainbow trout 1.9 mg l⁻¹ flow-through bioassay freshwater, pH 7.6-8.2, temperature 14-16°C, oxygen content 5.6-9.4 mg l⁻¹, water hardness 86 mg l⁻¹ CaCO₃ (1).

LC₅₀ (96 hr) fathead minnow 3.8-5.0 mg l⁻¹ static bioassay, freshwater at 22°C (2,3).

LC₅₀ (48, 96 hr) sheepshead minnow 5.4, 3.2 mg l⁻¹, respectively, static bioassay, seawater 1-3% salinity, 25-31°C (3,4).

Structure-activity investigations into the acute toxicity of chlorophenols to *Carassius auratus* led to the conclusion that chlorophenols (including 4-chlorophenol) are transferred from the water environment to the site of action in fish mainly by passive diffusion of their undissociated forms through various biological membranes, and that the OH group of their undissociated forms interacts with the site, resulting in the occurrence of toxicity in the fish (5). Rainbow trout fingerlings were exposed to low concentration of 4-chlorophenol in a darkened flow-through system for up to 1 hr. Levels of >30 µg l⁻¹ caused changes to ventilation rates (frequency and amplitude), swimming patterns, and general activity (6).

Bioaccumulation

Non-accumulative or low accumulative (7).

Environmental fate

Degradation studies

Degradation by *Pseudomonas* sp. 200 mg l⁻¹ at 30°C; parent: 100% ring disruption in 96 hr; mutant: 100% ring disruption in 33 hr (8).

4-Chlorophenol was investigated under denitrifying and methanogenic conditions. It was stoichiometrically mineralised to methane under methanogenic conditions and inhibited denitrification (9).

Penicillium strain Bi 7/2 isolated from phenol-contaminated soil metabolises 4-chlorophenol with phenol or glucose as co-substrate (10).

4-Chlorophenol was converted into 4-chlorocatechol under co-metabolic conditions by a mutant strain of *Azobacter* sp. GP1. Under the same conditions as the wild-type strain it accumulated 5-chloro-2-hydroxy-6-oxohexadienoic acid. The structure of this compound indicates a *meta*-proximal cleavage of 4-chlorocatechol (11).

Alcaligenes eutrophus JMP134 (pJP4) grows well on 4-chlorophenol as sole carbon source (12).

Degradation of toluene by *Mycobacterium vaccae* was inhibited by 0.2 mM 4-chlorophenol (13).

Decomposition rate in soil suspensions, nine days required for complete removal (14).

Mammalian & avian toxicity

Acute data

LD₅₀ oral redwing blackbird 113 mg kg⁻¹ (15).

LD₅₀ oral rat 670 mg kg⁻¹ (16).

LD₅₀ intraperitoneal rat 281 mg kg⁻¹ (17).

Genotoxicity

Salmonella typhimurium TA1535/pSK1002 *umu*-test with and without metabolic activation negative (18).

Legislation

Limited under EC Directive on Drinking Water Quality 80/778/EEC. Phenols: maximum admissible concentration 0.5 µg l⁻¹ (C₆H₅OH) (19).

Other comments

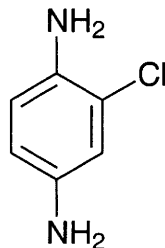
Bacterial and fish data compared (21).

Photocatalytic degradation of haloaromatic compounds using 4-chlorophenol as a model compound and titanium dioxide as photocatalyst reviewed (22).

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C242 2-chloro-*p*-phenylenediamine



C₆H₇ClN₂

Mol. Wt. 142.59

CAS Registry No. 615-66-7

Synonyms 2-chloro-1,4-phenylenediamine; 2-chloro-1,4-benzenediamine; 2-chloro-4-aminoaniline; *o*-chloro-*p*-phenylenediamine

EINECS No. 210-441-2

RTECS No. SS 8925000

Uses Oxidising agent in hair dyestuffs.

Mammalian & avian toxicity

Carcinogenicity and chronic effects

US National Cancer Institute carcinogenicity bioassay inconclusive (species unspecified) (1).

Teratogenicity and reproductive effects

Administration by gavage to rats on days 6-15 of gestation at doses of 100, 200 and 400 mg kg⁻¹ day⁻¹, maternal body weight gain was reduced by the intermediate dose. At the high dose there was an increase in resorptions and a decrease in foetal body weights. Evaluation of foetuses for gross visceral and skeletal abnormalities revealed no statistically significant differences between compound-treated and vehicle-control groups, but showed an increase in the incidence of abnormal foetuses in the group exposed to vitamin A, the positive control (2).

Irritancy

20 mg instilled into rabbit eye for 24 hr caused moderate irritation (3).

Legislation

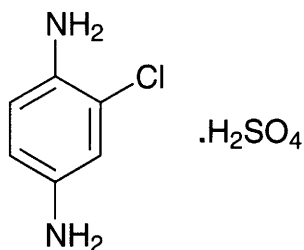
Limited under EC Directive Relating to Drinking Water Quality 80/778/EEC. Organochlorine compounds: guide level 1 µg l⁻¹ (4).

Included in Schedule 6 (Release into Land: Prescribed Substances) of Statutory Instrument No. 472, 1991 (5).

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c243 2-chloro-*p*-phenylenediamine sulfate



C₆H₉ClN₂O₄S

Mol. Wt. 240.67

CAS Registry No. 61702-44-1

Synonyms 2-chloro-1,4-phenylenediamine sulfate; 2-chloro-4-aminoaniline sulfate; 3-chloro-4-aminoaniline sulfate; 2-chloro-1,4-benzenediamine sulfate

EINECS No. 262-915-3

RTECS No. CZ 1581000

Uses Used in organic synthesis. Dyestuff intermediate.

Physical properties

M. Pt. 251-253°C

Solubility Organic solvents: dimethyl sulfoxide

Mammalian & avian toxicity

Carcinogenicity and chronic effects

In feeding experiments over 87-107 wk, no statistically significant positive association between dietary exposure and the incidence of tumours in rats was observed. In mice, no tumours occurred in statistically significantly higher incidences in treated mice than in controls. There is insufficient evidence that dietary administration causes carcinogenesis in rats or mice (1).

Although 2-chloro-*p*-phenylenediamine increased transitional cell hyperplasia of the kidney in both ♂ and ♀ rats, it had no significant neoplastic effects at the 0.15 and 0.3% levels via food (2).

Teratogenicity and reproductive effects

The compound was administered to rats on days 6-15 of gestation at doses of 100, 200 and 400 mg kg⁻¹ day⁻¹. Maternal body weight was reduced by the high and intermediate dose. Rats given the high dose showed an increase in resorptions and a decrease in foetal body weight. No significant gross, visceral or skeletal anomalies of foetuses were observed (3).

Genotoxicity

Salmonella typhimurium TA98, TA100 with and without metabolic activation positive (4).

Legislation

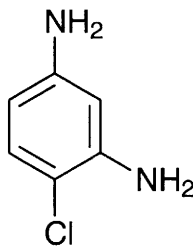
Limited under EC Directive Relating to Drinking Water Quality 80/778/EEC. Organochlorine compounds: guide level 1 µg l⁻¹ (5).

Included in Schedule 6 (Release into Land: Prescribed Substances) of Statutory Instrument No. 472, 1991 (6).

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6. *S. I.* 1991 No. 472 *The Environmental Protection (Prescribed Processes and Substances) Regulations* 1991, HMSO, London, UK

C244 4-chloro-*m*-phenylenediamine



C₆H₇ClN₂

Mol. Wt. 142.59

CAS Registry No. 5131-60-2

Synonyms 4-chloro-1,3-phenylenediamine; 4-chloro-1,3-benzenediamine; 1-chloro-2,4-diaminobenzene; 4-chlorophene-1,3-diamine; 4-chlorophenylene-1,3-diamine; *p*-chloro-*m*-phenylenediamine

EINECS No. 225-877-9

RTECS No. SS 8800000

Uses Used as a rubber processing chemical. Manufacture of dyestuffs. Oxidising colouring agent in hair dyes.

Physical properties

M. Pt. 90°C

Solubility Organic solvents: ethanol

Mammalian & avian toxicity

Acute data

Mice exposed once for 1.5 hr to vapour (concentration unspecified) showed no symptoms of acute poisoning and no fatalities occurred within 14 days (1).

Carcinogenicity and chronic effects

No adequate data on carcinogenicity to humans, inadequate evidence for carcinogenicity to animals, IARC classification group 3 (2,3).

National Toxicology Program investigated 4-chloro-*m*-phenylenediamine in rat, mouse via feed. Evidence of carcinogenicity negative in ♀ rats and ♂ mice, positive in ♂ rats and ♀ mice (4).

In dietary administration tests, results in mice were inconclusive and results in rats were not indicative of a carcinogenic effect (2).

Negative for carcinogenicity in ♀ rats and ♂ mice, tumours found in adrenal glands of ♂ rats and liver carcinomas and adenomas found in ♀ mice when administered via food (5).

Irritancy

A single application to the skin of rabbit did not produce any local irritation (1).

Genotoxicity

Salmonella typhimurium TA1535 with and without metabolic activation negative. *Escherichia coli* WP2 *uvrA* with and without metabolic activation negative (6).

Other effects

Any other adverse effects

20% and 10% depression of weight gain in rats fed 1% and mice fed 3% in diet, respectively (duration unspecified) (1).

Legislation

Permitted for use in cosmetics as oxidising agent in hair dyes only if concentration in finished product is less than 6% (calculated as the free base) (7).

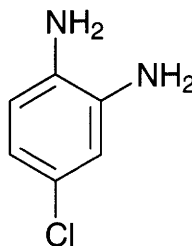
Limited under EC Directive Relating to Drinking Water Quality 80/778/EEC. Organochlorine compounds: guide level 1 µg l⁻¹ (8).

Included in Schedule 6 (Release into Land: Prescribed Substances) of Statutory Instrument No. 472, 1991 (9).

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9. S. I. 1991 No. 472 *The Environmental Protection (Prescribed Processes and Substances) Regulations* 1991, HMSO, London, UK

C245 4-chloro-*o*-phenylenediamine



C₆H₇ClN₂

Mol. Wt. 142.59

CAS Registry No. 95-83-0

Synonyms 1,2-diamino-4-chlorobenzene; 2-amino-4-chloroaniline; 4-chloro-1,2-diaminobenzene; 4-chloro-1,2-phenylenediamine; *p*-chloro-*o*-phenylenediamine; 3,4-diamino-1-chlorobenzene

EINECS No. 202-456-8

RTECS No. SS 8850000

Uses Manufacture of dyestuffs. Oxidising agent in hair colorants.

Physical properties

M. Pt. 70-73°C

Solubility Organic solvents: benzene, diethyl ether, ethanol, petroleum ether, toluene

Mammalian & avian toxicity

Carcinogenicity and chronic effects

No adequate data for carcinogenicity in humans, sufficient evidence for carcinogenicity in experimental animals, IARC classification group 2B (1,2).

The National Toxicology Program tested rats and mice via feed. Positive evidence of carcinogenicity in ♂ and ♀ of both species (3).

Hepatocellular carcinomas reported in mice after oral administration (4).

In ♂ and ♀ rats benign and malignant bladder tumours produced (4).

Liver carcinomas found in ♂ and ♀ mice when administered via food. In ♂ and ♀ rats liver adenomas and tumours in the stomach and bladder were reported following administration via food (5).

Genotoxicity

Salmonella typhimurium TA98, TA1538 without metabolic activation negative, with metabolic activation positive (6).

Escherichia coli WP2 *uvrA* with and without metabolic activation negative (6).

Elicited positive response in a DNA repair test with rat hepatocytes (7).

Other effects

Other adverse effects (human)

Absorption into the body leads to the formation of methaemoglobin which in sufficient concentration causes cyanosis. Onset may be delayed 2-4 hr or longer (8).

Any other adverse effects

25% depression of weight gain observed in both rats and mice fed 1% in diet (1).

Legislation

Permitted for use in cosmetics as oxidising agent in hair colorants only if concentration in finished product is less than 6% (calculated as the free base) (9).

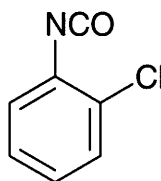
Limited under EC Directive Relating to Drinking Water Quality 80/778/EEC. Organochlorine compounds: guide level 1 µg l⁻¹ (10).

Included in Schedule 6 (Release into Land: Prescribed Substances) of Statutory Instrument No. 472, 1991 (11).

References

1. IARC Monograph 1982, **27**, 81-89.
2. IARC Monograph 1987, **Suppl. 7**, 60.
3. National Toxicology Program Research and Testing Division 1997, Report No. TR-063, NIEHS, Research Triangle Park, NC, USA.
4. Weisburger, E. K. et al *Carcinogenesis* 1980, **1**, 495-499.
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6. Dunkel, V. C. et al *Environ. Mutagen.* 1985, **7**(Suppl. 5), 1-248.
7. Yoshimi, M. et al *Mutat. Res.* 1988, **206**, 183.
8. Lenga, R. E. *The Sigma-Aldrich Library of Chemical Safety Data* 2nd ed., 1988, **1**, 837, Sigma-Aldrich, Milwaukee, USA.
9. *Official J. Eur. Commun.* 1976, **L262**, 184-185.
10. *EC Directive Relating to the Quality of Water Intended for Human Consumption* 1982, 80/778/EEC, Office for Official Publications of the European Communities, 2 rue Mercier, L-2985 Luxembourg.
11. S. I. 1991 No. 472 *The Environmental Protection (Prescribed Processes and Substances) Regulations* 1991, HMSO, London, UK

C246 2-chlorophenyl isocyanate



C₇H₄CINO

Mol. Wt. 153.57

CAS Registry No. 3320-83-0

Synonyms *o*-chlorophenyl isocyanate; 1-chloro-2-isocyanatobenzene; *o*-chlorophenylcarbonimide; isocyanic acid, *o*-chlorophenyl ester

EINECS No. 222-023-7

Physical properties

M. Pt. 30-31°C **B. Pt.** 83-84°C at 10 mmHg **Flash point** 88°C **Specific gravity** 1.273 at 20°C with respect to water at 4°C

Solubility Organic solvents: carbon tetrachloride

Occupational exposure

SE-LEVL 0.005 ppm

SE-CEIL 0.01 ppm

UK-LTEL MEL 0.02 mg m⁻³ (as NCO)

UK-STEL MEL 0.07 mg m⁻³ (as NCO)

Other effects

Any other adverse effects

Extremely destructive to tissue of the mucous membrane and upper respiratory tract, eyes and skin. Inhalation may be fatal as a result of spasm, inflammation and oedema of the larynx and bronchi, chemical pneumonitis and pulmonary oedema (species unspecified) (1).

Legislation

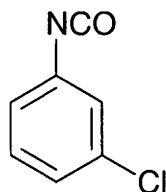
Limited under EC Directive Relating to Drinking Water Quality 80/778/EEC. Organochlorine compounds: guide level $1 \mu\text{g l}^{-1}$ (2).

Included in Schedule 6 (Release into Land: Prescribed Substances) of Statutory Instrument No. 472, 1991 (3).

References

1. Lenga R. E. *The Sigma-Aldrich Library of Chemical Safety Data* 2nd ed. 1988, 1, 839, Sigma-Aldrich, Milwaukee, USA.
2. *EC Directive Relating to the Quality of Water Intended for Human Consumption* 1982, 80/778/EEC, Office for Official Publications of the European Communities, 2 rue Mercier, L-2985 Luxembourg.
3. S. I. 1991 No. 472 *The Environmental Protection (Prescribed Processes and Substances) Regulations* 1991, HMSO, London, UK

C247 3-chlorophenyl isocyanate



$\text{C}_7\text{H}_4\text{ClNO}$

Mol. Wt. 153.57

CAS Registry No. 2909-38-8

Synonyms *m*-chlorophenyl isocyanate; 1-chloro-3-isocyanatobenzene; isocyanic acid, *m*-chlorophenyl ester

EINECS No. 220-822-5

RTECS No. NQ 8560000

Uses Production of herbicides.

Physical properties

M. Pt. -4.4°C **B. Pt.** $113\text{--}114^\circ\text{C}$ at 43 mmHg **Flash point** 86°C **Specific gravity** 1.260 at 20°C with respect to water at 4°C

Solubility Organic solvents: chloroform

Occupational exposure

SE-LEVL 0.005 ppm

SE-CEIL 0.01 ppm

UK-LTEL MEL 0.02 mg m^{-3} (as NCO)

UK-STEL MEL 0.07 mg m^{-3} (as NCO)

Mammalian & avian toxicity

Acute data

LC₅₀ inhalation (species and duration unspecified) 63 mg m^{-3} (1).

Other effects

Any other adverse effects

Extremely destructive to tissue of the mucous membrane and upper respiratory tract, eyes and skin. Inhalation may be fatal as a result of spasm, inflammation and oedema of the larynx and bronchi, chemical pneumonitis and pulmonary oedema (species and dose unspecified) (2).

Inhibits growth of Ehrlich ascites tumours in mice (3).

Legislation

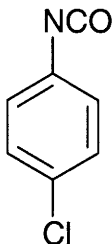
Limited under EC Directive Relating to Drinking Water Quality 80/778/EEC. Organochlorine compounds: guide level $1 \mu\text{g l}^{-1}$ (4).

Included in Schedule 6 (Release into Land: Prescribed Substances) of Statutory Instrument No. 472, 1991 (5).

References

1. Frolova, I. M. *Gig. Tr. Prof. Zabol.* 1967, 11(4), 23.
2. Lenga, R. E. *The Sigma-Aldrich Library of Chemical Safety Data* 2nd ed. 1988, 1, 839, Sigma-Aldrich, Milwaukee, USA.
3. Moss, G. E. et al *Cancer Res.* 1971, 31 (7), 937-941.
4. *EC Directive Relating to the Quality of Water Intended for Human Consumption* 1982, 80/778/EEC, Office for Official Publications of the European Communities, 2 rue Mercier, L-2985 Luxembourg.
5. S. I. 1991 No. 472 *The Environmental Protection (Prescribed Processes and Substances) Regulations* 1991, HMSO, London, UK

c248 4-chlorophenyl isocyanate



C₇H₄ClNO

Mol. Wt. 153.57

CAS Registry No. 104-12-1

Synonyms *p*-chlorophenyl isocyanate; 1-chloro-4-isocyanatobenzene; isocyanic acid, *p*-chlorophenyl ester

EINECS No. 203-176-9

RTECS No. NQ 8575000

Uses Chemical reagent. Intermediate in the synthesis of monuron herbicide.

Physical properties

M. Pt. 31°C **B. Pt.** 204°C **Flash point** 110°C **Specific gravity** 1.200 at 20°C with respect to water at 4°C

Solubility Organic solvents: ethanol

Occupational exposure

SE-LEVL 0.005 ppm

SE-CEIL 0.01 ppm

UK-LTEL MEL 0.02 mg m⁻³ (as NCO)

UK-STEL MEL 0.07 mg m⁻³ (as NCO)

Mammalian & avian toxicity

Acute data

LD₅₀ oral rat 4710 mg kg⁻¹ (1).

LD₅₀ oral mouse 530 mg kg⁻¹ (2).

LC₅₀ (duration unspecified) inhalation mouse 5.4 μg l⁻¹ (3,4).

A concentration of 1.8 μg l⁻¹ changed the rate of breathing of rabbits after 40 min inhalation (4).

Mice and rats develop tolerance to 1.2 and 1.4 μg l⁻¹, respectively (4).

Irritancy

500 mg applied to the skin of rabbits caused moderate irritation after 24 hr (1).

250 µg instilled into rabbit eye caused severe irritation after 24 hr (1).

An atmospheric concentration of 0.8 µg l⁻¹ is irritant to humans (4).

Other effects

Other adverse effects (human)

Intoxication is shown by initial irritation of the mucous membranes of the respiratory organs and eyes, dystrophic changes in the internal organs, and pulmonary adverse effects in the forms of emphysema, obliterating bronchiolitis, pyosis and oedema (2).

Legislation

A maximum permissible concentration of 0.5 µg l⁻¹ is recommended for the air of working areas (2,4).

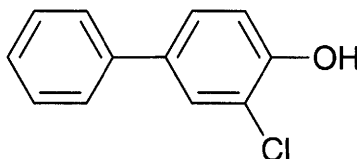
Limited under EC Directive Relating to Drinking Water Quality 80/778/EEC. Organochlorine compounds: guide level 1 µg l⁻¹ (5).

Included in Schedule 6 (Release into Land: Prescribed Substances) of Statutory Instrument No. 472, 1991 (6).

References

1. Marhold, J. V. *Sbornik Vysledku Toxikologickeho Vysetreni Latek A Pripravku* 1972, Prague, Czechoslovakia.
2. Frolova, I. M. *Gig. Tr. Prof. Zabol.* 1967, **11**, 23.
3. Frolova, I. M. *Prom. Toksikol. i Klinka Prof. Zabolevanii Khim. Etiol. Sb.* 1962, 186.
4. Frolova, I. M. *Gig. Sanit.* 1966, **31**, 108.
5. *EC Directive Relating to the Quality of Water Intended for Human Consumption* 1982, 80/778/EEC, Office for Official Publications of the European Communities, 2 rue Mercier, L-2985 Luxembourg.
6. *S. I. 1991 No. 472 The Environmental Protection (Prescribed Processes and Substances) Regulations* 1991, HMSO, London, UK

c249 2-chloro-4-phenylphenol



C₁₂H₉ClO

Mol. Wt. 204.66

CAS Registry No. 92-04-6

Synonyms 3-chloro-4-hydroxybiphenyl; 3-chloro-[1,1'-biphenyl]-4-ol; 3-chloro-4-biphenylol; 4-phenyl-2-chlorophenol

EINECS No. 202-120-0

RTECS No. DV 6650000

Uses Pesticide.

Physical properties

M. Pt. 80°C B. Pt. 322°C

Mammalian & avian toxicity

Acute data

LD₅₀ oral rat 4220 mg kg⁻¹ (1).

Irritancy

Dermal rabbit (24 hr) 500 mg caused mild irritation, and 50 µg instilled into rabbit eye caused severe irritation (1).

Legislation

Pesticide subject to registration or re-registration (2).

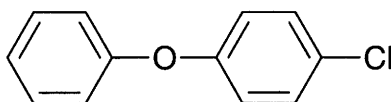
Limited under EC Directive on Drinking Water Quality 80/778/EEC. Pesticides: maximum admissible concentration 0.1 µg l⁻¹ (3).

Included in Schedule 6 (Release into Land: Prescribed Substances) of Statutory Instrument No. 472, 1991 (4).

References

1. Marhold, J. V. *Prehled Prumyslove Toxikol. Org. Latky* 1982, 72.
2. *Fed. Reg.* 1989, 54, 30848.
3. *EC Directive Relating to the Quality of Water Intended for Human Consumption* 1982, 80/778/EEC, Office for Official Publications of the European Communities, 2 rue Mercier, L-2985 Luxembourg.
4. *S. I. 1991 No. 472 The Environmental Protection (Prescribed Processes and Substances) Regulations* 1991, HMSO, London, UK

c250 4-chlorophenyl phenyl ether



C₁₂H₉ClO

Mol. Wt. 204.66

CAS Registry No. 7005-72-3

Synonyms 4-chlorodiphenyl ether; 1-chloro-4-phenoxybenzene; *p*-chlorophenyl phenyl ether

EINECS No. 230-281-7

Uses Dielectric fluid.

Physical properties

M. Pt. -8°C **B. Pt.** 161-162°C at 19 mmHg **Flash point** >110°C **Specific gravity** 1.193 at 20°C with respect to water at 4°C **Partition coefficient** log P_{ow} 4.08

Solubility Water: 3.3 mg l⁻¹ at 25°C

Ecotoxicity

Fish toxicity

LC₅₀ (96 hr) brook trout 0.73 mg l⁻¹ (1).

Bioaccumulation

Significantly bioaccumulated by fish from water. Uptake by brook trout is rapid, initially into the blood and liver before redistribution to adipose tissue and muscle (1).

Bioconcentration factor of 736 determined in rainbow trout exposed for 8-9 days (2).

Environmental fate

Degradation studies

t_{1/2} using activated sludge 4 hr (3).

Abiotic removal

Adsorption capacity of activated carbon 111 mg g⁻¹ (4).

Legislation

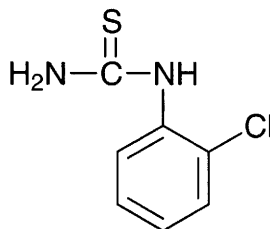
Limited under EC Directive Relating to Drinking Water Quality 80/778/EEC. Organochlorine compounds: guide level 1 µg l⁻¹ (5).

Included in Schedule 6 (Release into Land: Prescribed Substances) of Statutory Instrument No. 472, 1991 (6).

References

1. Chui, Y. C. et al *Xenobiotica* 1990, **20**, 489.
2. Gara, A. et al *Chemosphere* 1981, **10**, 365-90.
3. Callahan, M. A. et al *Water Related Environ. Fate of 129 Priority Pollutants* 1979, (Vol 2), EPA-440/4-79-029b, Washington, DC, USA.
4. *Kirk-Othmer Encyclopedia of Chemical Technology* 3rd ed., 1984, **24**, 306, John Wiley, NY, USA.
5. *EC Directive Relating to the Quality of Water Intended for Human Consumption* 1982, 80/778/EEC, Office for Official Publications of the European Communities, 2 rue Mercier, L-2985 Luxembourg.
6. S. I. 1991 No. 472 *The Environmental Protection (Prescribed Processes and Substances) Regulations* 1991, HMSO, London, UK

c251 (2-chlorophenyl)thiourea



C₇H₇ClN₂S

Mol. Wt. 186.66

CAS Registry No. 5344-82-1

Synonyms urea, 1-(*o*-chlorophenyl)-2-thio-; *N*-(2-chlorophenyl)thiourea; (*o*-chlorophenyl)thiourea; 1-(2-chlorophenyl)thiourea

EINECS No. 226-291-6

RTECS No. YS 7100000

Physical properties

M. Pt. 143-146°C **Partition coefficient** log P_{ow} 1.20 (1)

Solubility Organic solvents: benzene, ethanol

Ecotoxicity

Bioaccumulation

A bioconcentration factor of 4.8 has been estimated based on log P_{ow} value. This indicates environmental bioaccumulation is not significant (2).

Environmental fate

Abiotic removal

Reaction with photochemically produced hydroxyl radicals in the atmosphere estimated $t_{1/2}$ 4.3 hr (3).
When in a methanolic solution absorbs UV light from 290-320 nm which may result in direct photolysis (3).

Adsorption and retention

A K_{oc} of 11-107 has been estimated based on log P_{ow} value. This indicates high soil mobility (2,4).

Mammalian & avian toxicity

Acute data

LD₅₀ oral rat 4.6 mg kg⁻¹ (5).

Legislation

Included in Schedule 4 (Release into the Air: Prescribed Substances) of Statutory Instrument No. 472, 1991 (6).

References

1. GEMS; Graphical Exposure Modelling System CLOGP3 1987.
2. Lyman, W. J. et al *Handbook of Chemical Property Estimation Methods* 1982, McGraw-Hill, New York, USA.
3. Atkinson, R. *Int. J. Chem. Kinet.* 1987, **19**, 799-828.
4. Swann, R. L. et al *Res. Rev.* 1983, **85**, 16-23.
5. *J. Pharmacol. Exp. Ther.* 1947, **90**, 260.
6. S. I. 1991 No. 472 *The Environmental Protection (Prescribed Processes and Substances) Regulations* 1991, HMSO, London, UK

c252 chlorophyll

CAS Registry No. 1406-65-1

Synonyms E140

EINECS No. 215-800-7

RTECS No. FW 6420000

Uses Food, medicine and cosmetics colorant. Leather dyestuff. Sensitiser for colour film. Vulcanisation accelerator.

Occurrence The green pigment in plants, occurring in various proportions of chlorophylls a, b, c and d.

Mammalian & avian toxicity

Acute data

LD₅₀ intraperitoneal rat >100 mg kg⁻¹ (1).

LD₅₀ intravenous guinea pig 85 mg kg⁻¹ (2).

LD₅₀ intravenous mouse 285 mg kg⁻¹ (2).

Other comments

Chlorophyll undergoes transformation to phytol through the activity of chlorophyllase. It is reported that phytol may be utilised in the formation of α -tocopherol in senescing leaves (3).

Chlorophyll has been used as an external application in the treatment of wounds and ulcers. There is no clear evidence that it accelerates healing but it is considered to have a deodorant action (4).

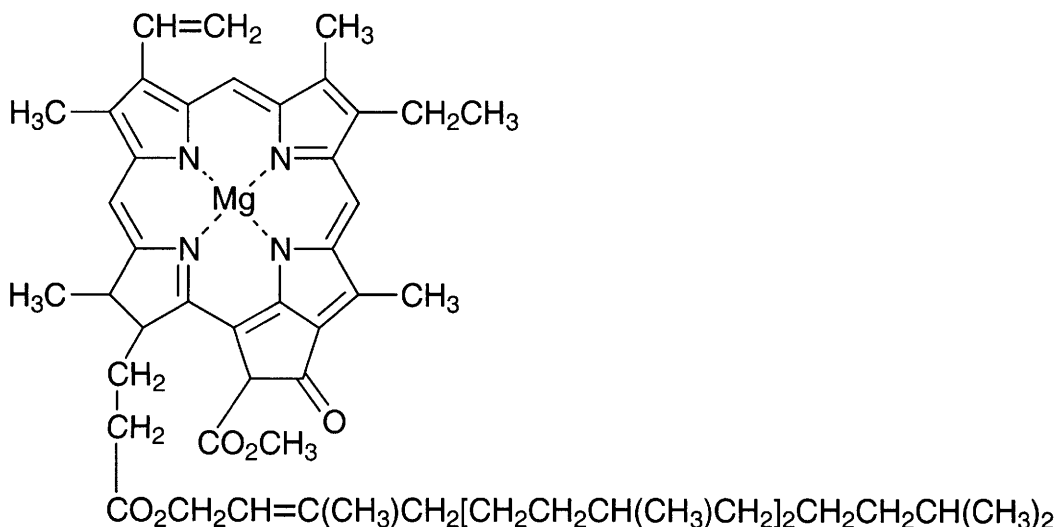
Experimental toxicology and human health effects reviewed (5).

Chlorophyll content of clover and Egyptian mallow were decreased by more than 60% by industrial air pollution at three locations in an industrial area north of Cairo (6).

References

1. *Drugs in Japan (Ethical Drugs)* 1990, 90, Japan Pharmaceutical Information Centre.
2. *Arzneim.-Forsch.* 1957, 7, 357.
3. Rise, M. et al *Plant Physiol.* 1989, 89(4), 1028-1030.
4. *Martindale: The Extra Pharmacopoeia* 31st ed., 1996, The Royal Pharmaceutical Society, London, UK.
5. *BIBRA Toxicity Profiles* 1991, British Industrial Biological Research Association, Carshalton, UK.
6. *Environ. Pollut.* 1993, 81(3), 251-255

c253 chlorophyll a



C₅₅H₇₂MgN₄O₅

Mol. Wt. 893.51

CAS Registry No. 479-61-8

EINECS No. 207-536-6

RTECS No. FW 6420000

Occurrence In higher plants and green algae, present with chlorophyll b in the approximate ratio 3:1. Also present in red algae with chlorophyll d, and in many types of marine algae with chlorophyll c.

Physical properties

M. Pt. 150-153°C (decomp.)

Solubility Organic solvents: acetone, benzene, carbon disulfide, chloroform, diethyl ether, ethanol, methanol

Other comments

Chlorophyll a was totally degraded to pheopigments in the gut of the zooplankton *Temora longicornis* within 25 min, with only a slight decrease in the total concentration of plant pigments (1).

In algae, chlorophyll a is hydrolysed to chlorophyllide through chlorophyllase activity (2).

Reported to inhibit the mutagenic activity of 4-nitro-*o*-phenylenediamine, although low concentrations may enhance its mutagenic activity (3).

Experimental toxicology and human health effects reviewed (4).

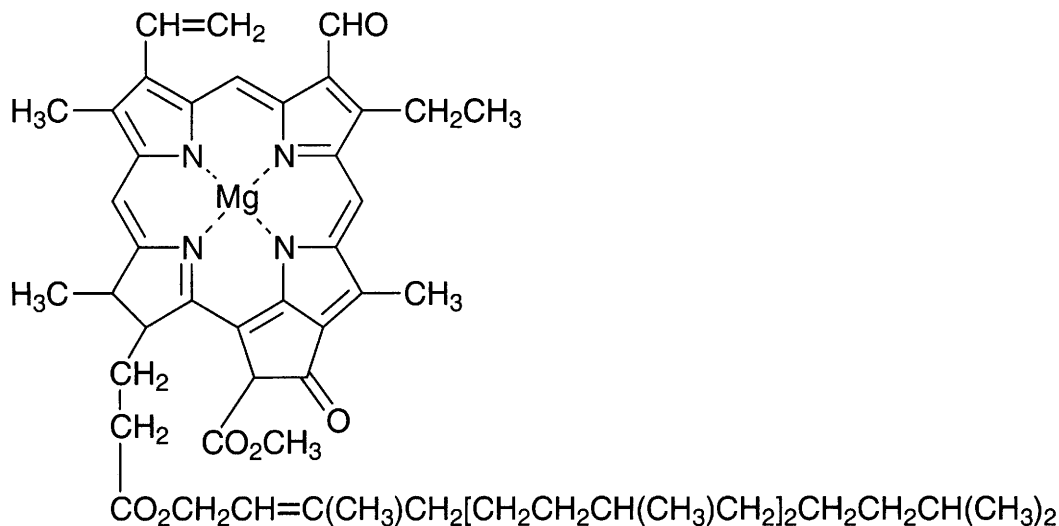
Surf-zone chlorophyll a variability at Cassino Beach, Southern Brazil, was investigated. Results indicated that mesoscale variability of chlorophyll a and accumulation of patches is primarily controlled by exogenous meteorological factors such as wind direction and velocity. Southerly onshore winds act as the main factor accumulating cells in the surf-zone at Cassino Beach (5).

The time-course development of carbon-14 specific activity of chlorophyll a in algal cultures has been investigated (6).

References

1. Pastunak, A. F. et al *Okeanologiya (Moscow)* 1987, **27**(5), 852-856 (Russ.) (*Chem. Abstr.* **107**, 233435).
2. Jeffrey, S. W. et al *Mar. Ecol.: Prog. Ser.* 1987, **35**(3), 293-304.
3. Gentile, J. M. et al *Mutat. Res.* 1991, **250**(1-2), 79-86.
4. *BIBRA Toxicity Profiles* 1991, British Industrial Biological Research Association, Carshalton, UK.
5. Oubrecht, C. et al *Estuarine, Coastal Shelf Sci.* 1995, **41**(1), 81-90.
6. Riemann, B. et al *Limnol. Oceanogr.* 1993, **38**(1), 96-111

c254 chlorophyll b



$C_{55}H_{70}MgN_4O_6$

Mol. Wt. 907.49

CAS Registry No. 519-62-0

EINECS No. 208-272-4

RTECS No. FW 6420000

Occurrence In higher plants and algae, present with chlorophyll a in the approximate ratio 1:3.

Physical properties

M. Pt. 183-185°C

Solubility Organic solvents: freely soluble in abs. ethanol, sparingly soluble in other solvents

Other comments

Pheophytin b formation identified during storage of aseptically processed spinach. Oxidation was found not to be a dominant factor in chlorophyll conversion and colour loss (1).

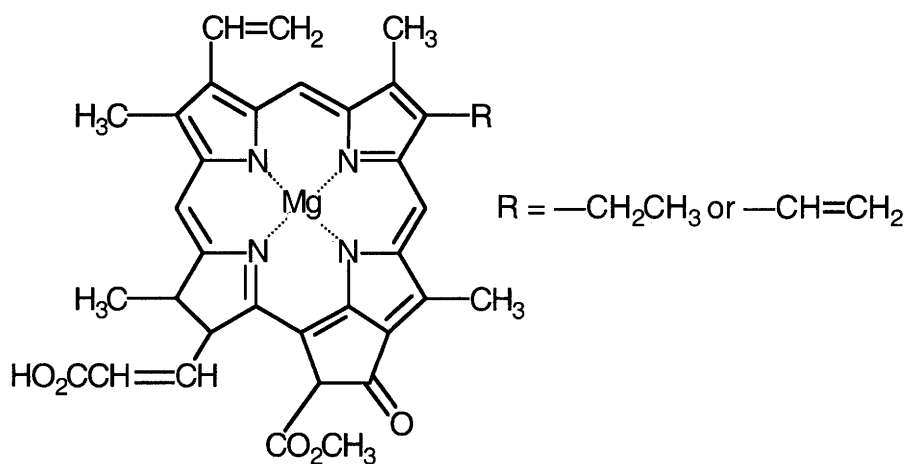
Reported to inhibit the mutagenic activity of 4-nitro-*o*-phenylenediamine, although low concentrations may enhance its mutagenic activity (2).

Experimental toxicology and human health effects reviewed (3).

References

1. Schwartz, S. J. et al *J. Food Sci.* 1991, **56**(4), 1059-1062.
2. Gentile, J. M. et al *Mutat. Res.* 1991, **250**(1-2), 79-86.
3. *BIBRA Toxicity Profiles* 1991, British Industrial Biological Research Association, Carshalton, UK

c255 chlorophyll c



$C_{35}H_{30}MgN_4O_5$

Mol. Wt. 610.95

CAS Registry No. 11003-45-5

Occurrence Found together with chlorophyll a in many types of marine algae.

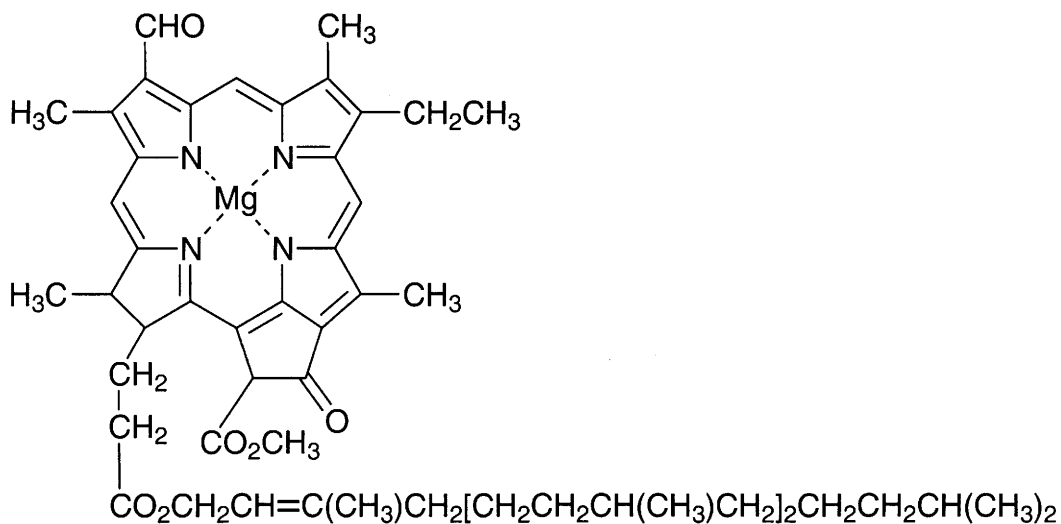
Other comments

Experimental toxicology and human health effects reviewed (1).

References

1. *BIBRA Toxicity Profiles* 1991, British Industrial Biological Research Association, Carshalton, UK

c256 chlorophyll d



C₅₄H₇₀MgN₄O₆

Mol. Wt. 895.48

CAS Registry No. 519-63-1

Occurrence Occurs in red algae with chlorophyll a.

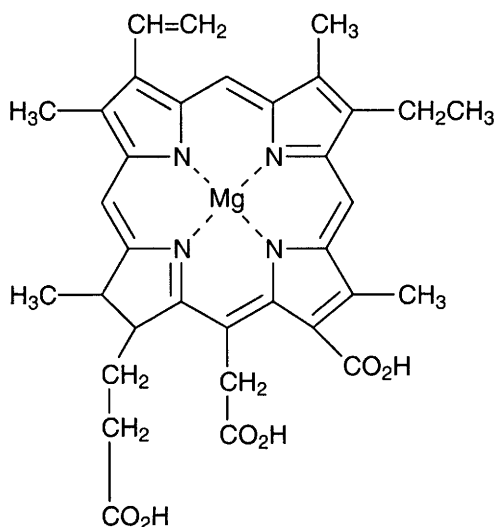
Other comments

Experimental toxicology and human health effects reviewed (1).

References

1. *BIBRA Toxicity Profiles* 1991, British Industrial Biological Research Association, Carshalton, UK

c257 chlorophyllin a



$C_{34}H_{34}MgN_4O_6$

Mol. Wt. 618.97

CAS Registry No. 15611-43-5

RTECS No. FW 6475000

Uses Colouring agent for food and medicines.

Mammalian & avian toxicity

Acute data

LD₅₀ intravenous, intraperitoneal mouse 285, 400 mg kg⁻¹, respectively (1).

LD₅₀ intravenous pig 80 mg kg⁻¹ (1).

Legislation

Acceptable daily intake as copper chlorophyllin a (acid form) 0-15 mg kg⁻¹ (2).

Other comments

Can also exist as cobalt, copper, calcium, potassium and sodium complexes. Inhibits α -amylase activity (3).

Copper complex inhibited acute or prolonged anaphylactic shock in guinea pigs (dose unspecified) (4,5).

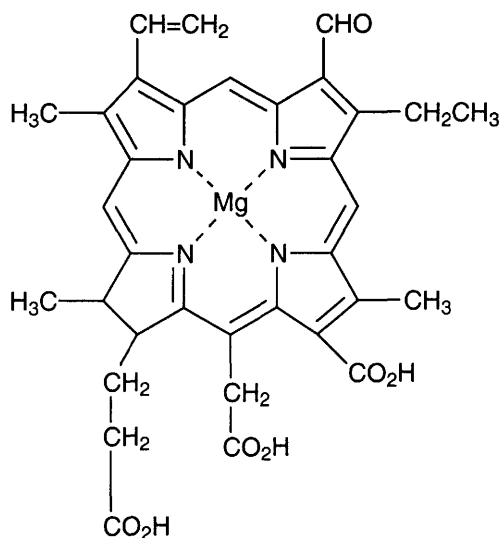
Copper and sodium complexes inhibited oxidative phosphorylation in rat mitochondria (dose unspecified) (6).

Experimental toxicology and human health effects reviewed (7).

References

1. *Arzneim.-Forsch.* 1954, 4, 19.
2. Joint FAO/WHO Expert Committee on Food Additives Report No. TRS 631-JECFA 22/20.
3. Yasunori, M. et al *Eiyo To Shokunyo* 1966, 19(3), 197-202 (Japan.) (*Chem. Abstr.* 66, 727243).
4. Freidburg, K. D. et al *Nanyn-Schmiedeburgs Arch. Pharmacol.* 1969, 265(3), 287-300 (Ger.) (*Chem. Abstr.* 72, 64820m).
5. Yamaroto, S. *Hiroshima J. Med. Sci.* 1970, 19(4), 137-149 (Japan.) (*Chem. Abstr.* 75, 74182f).
6. Lutz, F. et al *Z. Naturforsch. B* 1970, 25(5), 514-519 (Ger.) (*Chem. Abstr.* 73, 522569).
7. *BIBRA Toxicity Profiles* 1991, British Industrial Biological Research Association, Carshalton, UK.

C258 chlorophyllin b



$C_{34}H_{32}MgN_4O_7$

Mol. Wt. 614.94

CAS Registry No. 13962-39-5

Legislation

Acceptable daily intake as copper chlorophyllin b (acid form) 0-15 mg kg⁻¹ (1).

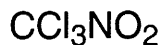
Other comments

Experimental toxicity and human health effects reviewed (2).

References

1. Joint FAO/WHO Expert Committee on Food Additives Report No. TRS 631-JECFA 22/20.
2. BIBRA Toxicity Profiles 1991, British Industrial Biological Research Association, Carshalton, UK

C259 chloropicrin



CCl_3NO_2

Mol. Wt. 164.37

CAS Registry No. 76-06-2

Synonyms trichloronitromethane; nitrochloroform; nitrotrichloromethane; Chloro-Pic; Chlorowax; Chlor-O-Pic; Chloro; Tri-Chlor

EINECS No. 200-930-9

RTECS No. PB 6300000

Uses Intermediate in organic synthesis. Dyestuff manufacture. Fumigant. Fungicide. Insecticide. Nematicide. Has been used as a tear gas.

Physical properties

M. Pt. -64°C **B. Pt.** 112°C at 757 mmHg **Specific gravity** 1.656 at 20°C with respect to water at 4°C
Partition coefficient $\log P_{ow}$ 2.09 (1) **Volatility** v.p. 17 mmHg at 20°C ; v.den. 6.69
Solubility Water: 1.62 g l⁻¹ at 25°C. Organic solvents: soluble in acetone; miscible with benzene, carbon disulfide, diethyl ether, ethanol

Occupational exposure

DE-MAK 0.1 ppm (0.68 mg m⁻³)

FR-VME 0.1 ppm (0.7 mg m⁻³)

JP-OEL 0.1 ppm (0.67 mg m⁻³)

UK-LTEL 0.1 ppm (0.68 mg m⁻³)

UK-STEL 0.3 ppm (2.1 mg m⁻³)

US-TWA 0.1 ppm (0.67 mg m⁻³)

UN No. 1580 **HAZCHEM Code** 2XE **Conveyance classification** toxic substance

Supply classification very toxic

Risk phrases Harmful if swallowed – Very toxic by inhalation – Irritating to eyes, respiratory system and skin (R22, R26, R36/37/38)

Safety phrases Keep locked up and out of the reach of children (if sold to general public) – Wear suitable protective clothing and gloves – In case of insufficient ventilation, wear suitable respiratory equipment – In case of accident or if you feel unwell, seek medical advice immediately (show label where possible) (S1/2, S36/37, S38, S45)

Ecotoxicity

Invertebrate toxicity

Toxic to earthworms (2).

Environmental fate

Degradation studies

In sandy loam soil $t_{1/2}$ 4.5 days with carbon dioxide being the terminal breakdown product. In an anaerobic aquatic/soil system chloropicrin was dehalogenated to nitromethane with $t_{1/2}$ 1.3 hr (3).

Abiotic removal

Photolytic $t_{1/2}$ in water 31.1 hr with photoproducts being carbon dioxide, biocarbonate, chloride, nitrate, and nitrite (3).

Undergoes photodegradation in surface layers of water, $t_{1/2}$ 3 days, and in atmosphere $t_{1/2}$ 20 days (4).

Removed from wastewater by treatment with an alkali metal sulfate at pH 6-14 (5).

Mammalian & avian toxicity

Acute data

LD₅₀ oral rat 250 mg kg⁻¹ (6).

LC₅₀ (4 hr) inhalation rat 6.6 ppm (7).

LC_{Lo} (20 min) inhalation human 110 ppm (8).

LC_{Lo} (10 min) inhalation human 2000 mg m⁻³ (9).

LD₅₀ intravenous guinea pig 4.2 mg kg⁻¹ (9).

Lowest irritant concentration in humans 1.3 ppm. Lowest tolerated dose inhalation (10 min) 7.5 ppm or 50 mg m⁻³ (9).

Humans can detect it in air at 0.008 mg l⁻¹. Concentrations of 0.016 mg l⁻¹ induced coughing and lachrymation, and at 0.12 mg l⁻¹ 30-60 min exposure can be fatal (10).

Sub-acute and sub-chronic data

♂ Rats were exposed by inhalation to 0.37-2.93 ppm vapour for 6 hr day⁻¹, 5 days wk⁻¹ for 13 wk. No deaths occurred during the exposure period. Exposure to 1.58 and 2.93 ppm depressed body weight increase. Treatment

at 2.93 ppm raised the red blood cell count, haematocrit and haemoglobin concentrations, and lung weight. Histological lesions were observed in the respiratory tract, major changes being degeneration and necrosis of bronchial and bronchiolar epithelia in 2.93 ppm treated rats and hypertrophy of these tissues in 1.58 ppm treated rats. No marked effect was observed on eyes, urine or serum at any concentration (11). Gavage Sprague-Dawley rats (90 day) no-observed-adverse-effect level 8 mg kg⁻¹. In 10-day studies, >10 mg kg⁻¹ caused inflammation, necrosis, acantholysis, hyperkeratosis and epithelial hyperplasia of the forestomach (12).

Carcinogenicity and chronic effects

The National Toxicology Program tested rats and mice via gavage. Evidence of carcinogenicity in ♂ and ♀ mice negative, inadequate study in ♂ and ♀ rats (13).

The bioassay of chloropicrin using Osborne-Mendel rats did not permit an evaluation of carcinogenicity because of the short survival time of dosed animals (14).

Irritancy

Potent skin irritant. Has strong lachrymatory properties. Produces increased sensitivity after frequent exposure (9).

Lachrymatory effect caused by 1 ppm in air (species unspecified) (15).

Genotoxicity

Salmonella typhimurium TA1535, TA1537, TA1538 with and without metabolic activation negative; TA100 with metabolic activation positive (16).

Escherichia coli WP2 (*hcr*) weakly positive (16).

Escherichia coli PQ37 SOS chromotest positive (17).

Drosophila sex-linked recessive lethal assay results equivocal (18).

Other effects

Other adverse effects (human)

Oral exposure may cause severe nausea, vomiting, colic and diarrhoea. Slightly higher levels of exposure can cause lachrymation, vomiting and finally bronchitis and death by pulmonary oedema (19).

Because of its reaction with thiol groups, it interferes with oxygen transport and can produce weak and irregular heart beats, recurrent asthmatic attacks and anaemia (20).

Legislation

Limited under EC Directive on Drinking Water Quality 80/778/EEC. Pesticides: maximum admissible concentration 0.1 µg l⁻¹ (21).

Included in Schedule 6 (Release into Land: Prescribed Substances) of Statutory Instrument No. 472, 1991 (22).

EPA Toxicity Class II (10).

WHO Toxicity Class Table 7 (not classified) (23).

Other comments

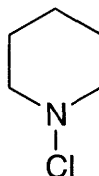
Residues have been detected in water and on food and in the air. It can be formed in drinking waters treated by chloramination (24).

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c260 1-chloropiperidine



C₅H₁₀ClN

Mol. Wt. 119.59

CAS Registry No. 2156-71-0

Synonyms N-chloropiperidine

RTECS No. TM 6468100

Uses Chlorinating agent.

Physical properties

B. Pt. 53-54°C at 29 mmHg

Mammalian & avian toxicity

Acute data

LD₅₀ intraperitoneal mouse 100 mg kg⁻¹ (1).

Genotoxicity

The genotoxicity remains to be established unequivocally (2).

The potent clastogenicity to Chinese hamster ovary cells reported (3) may be related solely to oxidative denaturation of cellular proteins induced by HOCl, a hydrolysis product (2).

Legislation

Limited under EC Directive Relating to Drinking Water Quality 80/778/EEC. Organochlorine compounds: guide level 1 µg l⁻¹ (4).

Included in Schedule 6 (Release into Land: Prescribed Substances) of Statutory Instrument No. 472, 1991 (5).

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c261 chloroplatinic acid



$\text{Cl}_6\text{H}_2\text{Pt}$

Mol. Wt. 409.81

CAS Registry No. 16941-12-1

Synonyms hexachloroplatinic acid; hydrogen hexachloroplatinate(IV); platinum chloride

EINECS No. 241-010-7

RTECS No. TP 1500000

Uses Catalyst. Dyestuff. Vulcanisation accelerator.

Physical properties

M. Pt. 60°C Specific gravity 2.430 at 20°C with respect to water at 4°C

Solubility Water: miscible. Organic solvents: ethanol

Occupational exposure

UK-LTEL MEL 0.002 mg m⁻³ (as Pt)

US-TWA 0.002 mg m⁻³ (as Pt)

UN No. 2507 HAZCHEM Code 2X Conveyance classification corrosive substance

Mammalian & avian toxicity

Acute data

LD₅₀ intravenous rat 49 mg kg⁻¹ (1).

LD₅₀ intraperitoneal mouse 61 mg kg⁻¹ (2).

LD₅₀ intraperitoneal mouse 82 mg kg⁻¹ (hexahydrate) (3).

Sensitisation

Has been reported to cause asthma and dermatitis among exposed workers (4).

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c262 chloroprene



$\text{C}_4\text{H}_5\text{Cl}$

Mol. Wt. 88.54

CAS Registry No. 126-99-8

Synonyms 2-chloro-1,3-butadiene; chlorobutadiene; β -chloroprene; Alloprenene

EINECS No. 204-818-0

RTECS No. EI 9625000

Uses Manufacture of polychloroprene elastomers.

Physical properties

M. Pt. -130°C **B. Pt.** 59.4°C **Flash point** -20°C **Specific gravity** 0.9583 at 20°C with respect to water at 4°C

Partition coefficient $\log P_{\text{ow}}$ 2.03 (1) **Volatility** v.p. 200 mmHg at 20°C ; v.den. 3.0

Solubility Water: 964 mg l^{-1} at 20°C . Organic solvents: acetone, benzene, diethyl ether

Occupational exposure

FR-VME 10 ppm (36 mg m^{-3})

SE-LEVL 1 ppm (3.5 mg m^{-3})

SE-STEL 5 ppm (18 mg m^{-3})

UK-LTEL 10 ppm (37 mg m^{-3})

US-TWA 10 ppm (36 mg m^{-3})

UN No. 1991 **HAZCHEM Code** 3WE **Conveyance classification** flammable liquid, toxic

Supply classification highly flammable, harmful

Risk phrases Highly flammable – Harmful by inhalation and if swallowed – Irritating to the eyes (R11, R20/22, R36)

Safety phrases Keep out of reach of children (if sold to general public) – Keep away from sources of ignition – No smoking (S2, S16)

Environmental fate

Abiotic removal

$t_{1/2}$ in atmosphere 1.6 hr (2).

Mammalian & avian toxicity

Acute data

LD_{50} oral rat 900 mg kg^{-1} (3).

LD_{50} oral mouse 260 mg kg^{-1} (4).

LC_{Lo} (4 hr) inhalation rat 2280 ppm (5).

LC_{100} (8 hr) inhalation mouse 600 mg m^{-3} (6).

LD_{Lo} subcutaneous rat 500 mg kg^{-1} (6).

LD_{Lo} subcutaneous mouse 1000 mg kg^{-1} (6).

LD_{Lo} intravenous rabbit 96 mg kg^{-1} (7).

Sub-acute and sub-chronic data

Symptoms observed during inhalation exposure included inflammation of the mucous membranes of the eyes and nose followed by depression of the central nervous system. In mice toxic effects have been reported after 8 hr at levels of 40-500 mg m^{-3} (6).

In rats exposure by inhalation for 6 hr day^{-1} , 5 day wk^{-1} for 4 wk resulted in a slight growth depression and behavioural effects with 1.4 g m^{-3} , and hair loss, growth retardation and morphological liver damage with 5.8 and 22.5 g m^{-3} (8).

Inhalation σ and f F344 rats and B6C3F1 mice (13 wk, 6 hr day^{-1} , 5 day wk^{-1}). In mice, exposure to 80 ppm chloroprene caused a marginal decrease in body weight gain in males and epithelial hyperplasia of the forestomach in males and females. In rats, exposure to ≥ 80 ppm chloroprene caused degeneration and metaplasia

of the olfactory epithelium and exposure to 200 ppm caused anaemia, hepatocellular necrosis, and reduced sperm motility (9).

Carcinogenicity and chronic effects

Inadequate evidence for carcinogenicity to humans and animals, IARC classification group 3 (10).

Chloroprene was tested in rats by oral administration at doses of 200 mg kg⁻¹ twice wkly for 25 wk, by subcutaneous administration of 400 mg kg⁻¹ on ten occasions over 6 months, 200 mg kg⁻¹ on 50 occasions over 6 months and by intratracheal administration of 200 mg kg⁻¹ 5 × at 20 day intervals. It was also tested by skin application in mice 50 × twice wkly for 25 wk using a 50% solution in benzene. No carcinogenic effects were found and these studies were considered to provide inadequate evidence for carcinogenicity in animals (11). Chloroprene was administered orally to pregnant rats and their offspring were treated for life by stomach tube. The total incidence of tumours was similar in treated and untreated animals (12).

The National Toxicology Program tested rats and mice via inhalation. Clear evidence of carcinogenicity in ♂ and ♀ mice and rats (13).

Teratogenicity and reproductive effects

Testicular atrophy, or reduction in the numbers and motility of sperm in rats with non-atrophied testes, occurred at inhalation exposure level of 0.15 mg m⁻³. Spermatogenesis and morphological abnormalities of sperm were observed among occupationally exposed humans (duration unspecified) (14).

Embryotoxicity was found in pregnant rats which had inhaled 0.13-53.4 mg m⁻³. The highest embryotoxic effect was observed when 4 mg m⁻³ were inhaled during the entire pregnancy, intermittently on days 1-2, 3-4 or 11-12, or given orally at a dose of 0.5 mg kg⁻¹ day⁻¹ for 14 days or on days 3-4 or 11-12. A teratogenic effect (meningoencephaloceles) was observed when administered on days 5-6, 9-10, 11-12, 13-14 and 15-16 of gestation (15).

Neither embryotoxic nor teratogenic effects were reported after exposing pregnant rats to 90.5 mg m⁻³ for 4 hr day⁻¹ from days 1-12 or from days 3-20 of gestation (16).

Genotoxicity

Salmonella typhimurium TA100, TA1530 with and without metabolic activation positive (17).

Induced sex chromosome loss and nondisjunction in *Drosophila melanogaster*, oral (3 days intermittent) 500 mg (18).

Drosophila melanogaster sex-linked recessive lethal test negative (19).

Induced dominant lethal mutations and chromosomal aberrations in bone-marrow of rats exposed to 0.14-3.6 mg m⁻³ by inhalation (14).

Reported to give negative results for the induction of sister chromatid exchanges, micronuclei and chromosomal aberrations in bone-marrow of mice exposed by inhalation (20).

A statistically significant increase in chromosome aberrations was found in the lymphocytes of five workers exposed to 2.0-2.2 mg m⁻³ chloroprene and 0.5-2.0 mg m⁻³ methyl methacrylate in air (21).

Other effects

Other adverse effects (human)

From case reports on occupational exposure, one study found an excess of lung cancer (22).

Another investigation found no excess of lung cancer or other types of cancer among workers (23).

A case of liver angiosarcoma was reported in an exposed worker (24).

Any other adverse effects

Chloroprene has been shown to induce a number of biochemical alterations in various species including inhibition of liver detoxification mechanisms, decreased activity of hepatic enzymes and glycogen content in liver and renal and splenic damage (21-26).

Legislation

Maximum permissible concentration in domestic water in the former USSR 0.1 mg l⁻¹ (27).

Limited under EC Directive on Drinking Water Quality 80/778/EEC. Organochlorine compounds: guide level 1 µg l⁻¹ (28).

Included in Schedule 6 (Release into Land: Prescribed Substances) of Statutory Instrument No. 472, 1991 (29).

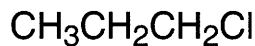
Other comments

Residues have been detected in some surface waters and in air samples.
Reviews on experimental toxicology and human health effects listed (30).
Reproductive toxicity reviewed (31).

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C263 1-chloropropane



$\text{C}_3\text{H}_7\text{Cl}$

Mol. Wt. 78.54

CAS Registry No. 540-54-5

Synonyms propyl chloride

EINECS No. 208-749-7

RTECS No. TX 4400000

Uses Anaesthetic. Antiparasiticide. Blowing agent. Solvent.

Physical properties

M. Pt. -122.8°C B. Pt. 47.2°C Flash point $<17.7^\circ\text{C}$ Specific gravity 0.890 at 20°C with respect to water at 4°C Partition coefficient $\log P_{\text{ow}}$ 2.04 Volatility v.p. 350 mmHg at 25°C

Solubility Water: 2.7 g l^{-1} at 20°C . Organic solvents: miscible with diethyl ether, ethanol

Occupational exposure

UN No. 1278 HAZCHEM Code 3ME Conveyance classification flammable liquid

Supply classification highly flammable

Supply classification harmful

Risk phrases Highly flammable – Harmful by inhalation, in contact with skin and if swallowed (R11, R20/21/22)

Safety phrases Keep out of reach of children (if sold to general public) – Keep container in a well ventilated place

– Do not empty into drains (S2, S9, S29)

Ecotoxicity

Invertebrate toxicity

EC_{50} (30 min) *Photobacterium phosphoreum* 0.06 mM (1).

Environmental fate

Degradation studies

Theoretical oxygen demand (ThOD) in activated sludge: after 6 hr 0.7% of the ThOD; after 12 hr 0.8% of ThOD; after 24 hr 1.9% of ThOD (2).

Mammalian & avian toxicity

Sub-acute and sub-chronic data

Inhalation rat (4 day) 40,000 ppm 1 hr day^{-1} slight alveolar haemorrhage of lungs and significant focal necrosis of the liver were observed (3).

Metabolism and toxicokinetics

Enzymatic dechlorination was found to occur *in vitro* using rat liver microsomes (4).

2-Hydroxypropyl mercapturic acid was found in the urine of rats injected with a 40% solution of 1-chloropropane in arachis oil (5).

Irritancy

Vapour or mist reported to be irritating to the eyes, mucous membranes and upper respiratory tract (species unspecified) (6).

Legislation

Limited under EC Directive on Drinking Water Quality 80/778/EEC. Organochlorine compounds: guide level $1 \mu\text{g l}^{-1}$ (7).

Included in Schedule 6 (Release into Land: Prescribed Substances) of Statutory Instrument No. 472, 1991 (8).

Other comments

Structural configuration/toxicity studies have been conducted on 13 chlorinated methanes, ethanes, and propanes (including 1-chloropropane). The number of chlorine atoms in the molecule contributes to the toxicity of the compound, but chemical structure has significantly more influence. Increasing the number of chlorine atoms at one carbon atom renders the compound more toxic. An α -positioned methyl group also increases toxicity (9).

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c264 2-chloropropane



$\text{C}_3\text{H}_7\text{Cl}$

Mol. Wt. 78.54

CAS Registry No. 75-29-6

Synonyms isopropyl chloride

EINECS No. 200-858-8

RTECS No. TX 4410000

Uses Solvent. Blowing Agent. Chemical intermediate. Anaesthetic.

Physical properties

M. Pt. -117°C B. Pt. 36.5°C Flash point -32°C Specific gravity 0.859 at 20°C with respect to water at 4°C
Partition coefficient $\log P_{\text{ow}}$ 1.90 Volatility v.p. 523 mmHg at 25°C
Solubility Water: 3.44 mg l^{-1} at 12.5°C . Organic solvents: miscible with diethyl ether, ethanol

Occupational exposure

UN No. 2356 HAZCHEM Code 3/M/E Conveyance classification flammable liquid

Supply classification highly flammable

Supply classification harmful

Risk phrases Highly flammable – Harmful by inhalation, in contact with skin and if swallowed (R11, R20/21/22)

Safety phrases Keep out of reach of children (if sold to general public) – Keep container in a well ventilated place
– Do not empty into drains (S2, S9, S29)

Ecotoxicity

Invertebrate toxicity

EC_{50} (30 min) *Photobacterium phosphoreum* 0.2 mM (1).

Mammalian & avian toxicity

Acute data

LD₁₀₀ oral guinea pig 10 g kg⁻¹ (2).

Sub-acute and sub-chronic data

Inhalation rat, rabbit, mouse, guinea pig, monkey (181 day) 1000 ppm, 7 hr day⁻¹, 5 day wk⁻¹ (total number of exposures 127) no adverse effects reported (2).

Metabolism and toxicokinetics

Enzymatically dechlorinated *in vitro* by rat liver microsomes (3).

Irritancy

When liquid 2-chloropropane was splashed into rabbit eyes transient irritation was reported (4).

Vapour or mist reported to be irritating to eyes, mucous membranes and upper respiratory tract (species unspecified) (5).

Genotoxicity

Salmonella typhimurium (strains unspecified) without metabolic activation positive (6).

Other effects

Other adverse effects (human)

When used as an anaesthetic in humans, it was reported to cause some histopathological changes in the liver and kidneys, vomiting and cardiac arrest (7).

Any other adverse effects

Vomiting and cardiac arrhythmia have been reported. May cause histopathological changes in the liver and kidneys (species unspecified) (2).

Legislation

Limited under EC Directive on Drinking Water Quality 80/778/EEC. Organochlorine compounds: guide level 1 µg l⁻¹ (8).

Included in Schedule 6 (Release into Land: Prescribed Substances) of Statutory Instrument No. 472, 1991 (9).

Other comments

Warning properties may be inadequate to protect against excessive repeated exposure. Several subjects did not detect 500 ppm of the vapours (2).

Structural configuration/toxicity studies have been conducted on 13 chlorinated methanes, ethanes and propanes (including 2-chloropropane). The number of chlorine atoms in the molecule contributes to the toxicity of the compound but chemical structure has significantly more influence. Increasing the number of chlorine atoms at one carbon atom renders the compound more toxic. An α-positioned methyl group also increases toxicity (10).

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C265 3-chloro-1,2-propanediol



$\text{C}_3\text{H}_7\text{ClO}_2$

Mol. Wt. 110.54

CAS Registry No. 96-24-2

Synonyms 3-chloropropane-1,2-diol; chlorohydrin; α -chlorohydrin; 3-chloropropylene glycol; epibloc; glycerin epichlorohydrin; glyceryl chloride; glyceryl α -chlorohydrin; α -monochlorohydrin

EINECS No. 202-492-4

RTECS No. TY 4025000

Uses Rodent chemosterilant. To lower the freezing point of dynamite. Manufacture of dyestuff intermediates. Solvent.

Physical properties

M. Pt. -40°C **B. Pt.** 213°C (decomp.) **Flash point** $>110^\circ\text{C}$ **Specific gravity** 1.3218 at 20°C with respect to water at 4°C **Partition coefficient** $\log P_{\text{ow}} -1.00$ (1) **Volatility** v.p. 3.75 mmHg at 25°C
Solubility Organic solvents: acetone, diethyl ether, ethanol, dimethyl sulfoxide

Occupational exposure

UN No. 2689 HAZCHEM Code 2X Conveyance classification toxic substance

Ecotoxicity

Fish toxicity

LC_{50} (24 or 48 hr) harlequin fish 2150 and 2100 ppm, respectively. Estimated lethal threshold, soft dilution water, 2070 ppm (2).

Invertebrate toxicity

EC_{50} (30 min) *Photobacterium phosphoreum* 4200 ppm, Microtox test (3).

Environmental fate

Anaerobic effects

IC_{50} (24 hr) methanogenic bacterial culture 630 mg l^{-1} (1).

Abiotic removal

Undergoes hydrolysis to give thiodiglycol (4).

Mammalian & avian toxicity

Acute data

LD_{50} oral redwing blackbird 24 mg kg^{-1} (4).

LD_{50} oral rat, mouse, quail 160-420 mg kg^{-1} (4,5).

LC_{Lo} (4 hr) inhalation rat 125 ppm (6).

LD_{50} intraperitoneal mouse 73 mg kg^{-1} (7).

Teratogenicity and reproductive effects

Oral monkey (42 day) lowest toxic dose 1260 $\text{mg kg}^{-1} \text{ day}^{-1}$, reduction of σ fertility index (8).

Oral rat (8 day) 15 $\text{mg kg}^{-1} \text{ day}^{-1}$ increased acidity of luminal fluid in seminiferous tubules, proximal caput, middle caput and proximal cauda epididymis, which may account for its infertility effects (9).

Subcutaneous σ bandicoot 50, 100, 150 mg kg^{-1} , single injection, induced selective damage to the germinal epithelium. No permanent epididymal lesions were observed even following a toxic dose (10).

Metabolism and toxicokinetics

Following intraperitoneal administration to σ rats, β -chlorolactic acid and oxalic acid were isolated from the urine (11).

Irritancy

Causes skin irritation. Vapour or mist irritating to the eyes, mucous membranes and upper respiratory tract (species unspecified) (12).

Genotoxicity

Salmonella typhimurium TA97, TA98, TA100, TA1537, TA1538 with and without metabolic activation positive (13).

In vitro mouse M2-fibroblasts induced cytotoxicity and malignant transformation (metabolic activation not stated) (14).

Drosophila melanogaster in vivo using spot test negative (15).

Other effects

Any other adverse effects

Inhibited glycolysis and the glyceraldehyde 3-phosphate dehydrogenase reaction by spermatozoa isolated from the cauda epididymis of the rhesus monkey (16).

Legislation

Limited under EC Directive on Drinking Water Quality 80/778/EEC. Pesticides: maximum admissible concentration 0.1 µg l⁻¹ (17).

Pesticides and solvents are included in Schedule 6 (Release into Land: Prescribed Substances) of Statutory Instrument No. 472, 1991 (18).

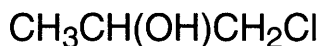
Other comments

Reviews on human health effects, experimental toxicology, physico-chemical properties listed (19).

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C266 1-chloro-2-propanol



C₃H₇ClO

Mol. Wt. 94.54

CAS Registry No. 127-00-4

Synonyms 1-chloro-2-hydroxypropane; 1-chloroisopropyl alcohol; 2-chloropropyl alcohol; propylene α -chlorohydrin; *sec*-propylene chlorohydrin

EINECS No. 204-819-6

RTECS No. UA 8942000

Uses In the preparation of propylene oxide. Intermediate in organic synthesis.

Physical properties

B. Pt. 133-134°C **Flash point** 51.7°C **Specific gravity** 1.111 at 20°C with respect to water at 4°C

Volatility v.p. 4.9 mmHg at 20°C

Solubility Water: miscible. Organic solvents: diethyl ether, dimethyl sulfoxide, ethanol

Occupational exposure

UN No. 2611 HAZCHEM Code 2W Conveyance classification toxic substance

Mammalian & avian toxicity

Acute data

LC₅₀ (4 hr) inhalation rat 1000 ppm (1).

Carcinogenicity and chronic effects

The National Toxicology Program tested mice and rats via administration in drinking water. No evidence of carcinogenicity in either species (2).

Teratogenicity and reproductive effects

Technical grade 1-chloro-2-propanol (75-76%) administered to rats via drinking water. In a 14-day dose-finding study 0.2-0.8% adversely affected weight gain and drinking. In continuous breeding protocol it had no effect on fertility or reproduction (litter size, number and days to deliver) in F₀ and F₁ generation. May adversely affect sperm morphology (3).

Metabolism and toxicokinetics

Urinary excretion and exhalation as carbon dioxide accounted for 80% of total intraperitoneal dose in rats (4).

Major urinary metabolite detected *N*-acetyl-S-(2-hydroxypropyl)cysteine, with minor metabolites β -chlorolactate and *N*-acetyl-S-(2,3-dihydroxypropyl)cysteine (5).

In rats after exposure by inhalation excreted via lungs as carbon dioxide. Metabolised via cysteine conjugates and mercapturic acids excreted in urine (4).

Irritancy

Reported to cause skin irritation. Vapour or mist irritating to the eyes, mucous membranes and upper respiratory tract (species unspecified) (6).

Genotoxicity

Salmonella typhimurium TA98, TA100, TA1535, TA1537 with and without metabolic activation positive (7).

Salmonella typhimurium TA1530 with and without metabolic activation positive (8).

Drosophila melanogaster sex-linked recessive lethal assay positive (9).

Legislation

Limited under EC Directive on Drinking Water Quality 80/778/EEC. Organochlorine compounds: guide level 1 µg l⁻¹ (10).

Included in Schedule 6 (Release into Land: Prescribed Substances) of Statutory Instrument No. 472, 1991 (11).

Other comments

Carcinogenic or teratogenic hazards to humans eating foods sterilised with propylene oxide from which chloropropanol is derived is discussed (8).

Toxicity, metabolism and carcinogenicity reviewed (12).

QSAR model to predict acute toxicity in fish (13).

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c267 2-chloropropanol



C₃H₇ClO

Mol. Wt. 94.54

CAS Registry No. 78-89-7

Synonyms 2-chloro-1-hydroxypropene; 2-chloroisopropyl alcohol; 2-chloro-1-propanol; propylene β-chlorohydrin

EINECS No. 201-154-3

RTECS No. UA 8925000

Uses Chemical intermediate.

Physical properties

B. Pt. 133-134°C **Flash point** 51°C **Specific gravity** 1.103 at 20°C with respect to water at 4°C

Solubility Organic solvents: diethyl ether, ethanol

Occupational exposure

UN No. 2611 **HAZCHEM Code** 2W **Conveyance classification** toxic substance

Mammalian & avian toxicity

Acute data

LD₅₀ oral rat 218 mg kg⁻¹ (1).

LD₅₀ oral guinea pig 720 mg kg⁻¹ (2).

LD_{Lo} (4 hr) inhalation rat 500 ppm (1).

LD₅₀ dermal rabbit 529 mg kg⁻¹ (3).

Irritancy

Dermal rabbit (duration unspecified) 500 mg (open) produced mild irritation (4).

2230 µg instilled into rabbit eye (duration unspecified) produced severe irritation (5).

Genotoxicity

Salmonella typhimurium TA100, TA1535 without metabolic activation positive (6).

Legislation

Limited under EC Directive on Drinking Water Quality 80/778/EEC. Organochlorine compounds: guide level 1 µg l⁻¹ (7).

Included in Schedule 6 (Release into Land: Prescribed Substances) of Statutory Instrument No. 472, 1991 (8).

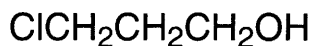
Other comments

Toxicity, metabolism, carcinogenicity and mutagenicity reviewed (9).

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c268 3-chloropropanol



C₃H₇ClO

Mol. Wt. 94.54

CAS Registry No. 627-30-5

Synonyms 1-chloro-3-hydroxypropane; 1-chloro-3-propanol; 3-chloro-1-propanol; trimethylene chlorohydrin

EINECS No. 210-992-9

RTECS No. UA 8930000

Uses Chemical intermediate.

Physical properties

B. Pt. 160-162°C **Flash point** 73°C **Specific gravity** 1.1309 at 20°C with respect to water at 4°C
Partition coefficient $\log P_{ow}$ 0.007 (1)
Solubility Water: 50-100 g l⁻¹ at 23°C. Organic solvents: carbon tetrachloride, diethyl ether, ethanol

Occupational exposure

UN No. 2849 HAZCHEM Code 2Z Conveyance classification toxic substance

Ecotoxicity

Fish toxicity
LC₅₀ (24 hr) goldfish 170 mg l⁻¹ (2).

Mammalian & avian toxicity

Acute data
LD₅₀ oral mouse 2300 mg kg⁻¹ (3).

Irritancy
Reported to cause eye and skin irritation. Vapour or mist is irritating to the eyes, mucous membranes and upper respiratory tract (species unspecified) (3).

Genotoxicity

Salmonella typhimurium TA100, TA1535, TA1538 with and without metabolic activation positive (4).
Salmonella typhimurium TA98, TA100, TA1535, TA1537 with and without metabolic activation positive (5).
Escherichia coli PQ37 with and without metabolic activation SOS chromotest negative (6).

Other effects

Other adverse effects (human)
Cytotoxicity of 3-chloropropanol was investigated using three different types of cultured cells: human leukaemia HL-60 cells 61.3% viability; mouse peritoneal macrophages 11% activity; rat liver hepatocytes 92.7% viability and 11.9% glycogenic activity (7).

Legislation

Limited under EC Directive on Drinking Water Quality 80/778/EEC. Organochlorine compounds: guide level 1 µg l⁻¹ (8).
Included in Schedule 6 (Release into Land: Prescribed Substances) of Statutory Instrument No. 472, 1991 (9).

Other comments

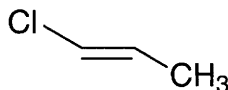
Affinity of 3-chloropropanol in biological systems described (10).
Biodegradation potential using microbial systems discussed (11).

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c269 (E)-1-chloropropene



C_3H_5Cl

Mol. Wt. 76.53

CAS Registry No. 16136-85-9

Synonyms E-1-chloro-1-propene; *trans*-1-chloro-1-propene; *trans*-1-chloropropene

RTECS No. UC 7180000

Physical properties

M. Pt. -99°C **B. Pt.** 37.4°C **Specific gravity** 0.9350 at 20°C with respect to water at 7°C

Solubility Organic solvents: acetone, benzene, chloroform, diethyl ether

Environmental fate

Abiotic removal

Evaporation from water at 25°C, initial concentration 1 ppm: 50% after 16 min; 90% after 59 min (1).

Mammalian & avian toxicity

Acute data

LC₅₀ (duration unspecified) inhalation mouse 229 mg m⁻³ (2).

Carcinogenicity and chronic effects

Intragastric intubation induced significant numbers of stomach tumours in mice (3).

Legislation

Limited under EC Directive on Drinking Water Quality 80/778/EEC. Organochlorine compounds: guide level 1 µg l⁻¹ (4).

Included in Schedules 4 and 6 (Release into Air/Land: Prescribed Substances) of Statutory Instrument No. 472, 1991 (5).

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c270 (Z)-1-chloropropene



C_3H_5Cl

Mol. Wt. 76.53

CAS Registry No. 16136-84-8

Synonyms Z-1-chloro-1-propene; cis-1-chloropropene; cis-1-chloro-1-propene

RTECS No. UC 7182000

Physical properties

M. Pt. $-134.8^{\circ}C$ B. Pt. $32.8^{\circ}C$ Specific gravity 0.9347 at $20^{\circ}C$ with respect to water at $4^{\circ}C$

Solubility Organic solvents: acetone, benzene, chloroform, diethyl ether

Environmental fate

Abiotic removal

Evaporation from water at $25^{\circ}C$, initial concentration 1 ppm: 50% after 16 min; 90% after 59 min (1).

Mammalian & avian toxicity

Acute data

LC_{50} (duration unspecified) inhalation mouse 221 mg m^{-3} (2).

Carcinogenicity and chronic effects

Intragastric intubation induced significant numbers of stomach tumours in mice (3).

Legislation

Limited under EC Directive on Drinking Water Quality 80/778/EEC. Organochlorine compounds: guide level $1 \mu g l^{-1}$ (4).

Included in Schedules 4 and 6 (Release into Air/Land: Prescribed Substances) of Statutory Instrument No. 472, 1991 (5).

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c271 2-chloropropene



C_3H_5Cl

Mol. Wt. 76.53

CAS Registry No. 557-98-2

Synonyms 2-chloro-1-propene; 2-chloroprop-1-ene

EINECS No. 209-187-5

RTECS No. UC 7200000

Uses Refrigerant. Chemical intermediate. Solvent.

Physical properties

M. Pt. -138.6°C B. Pt. 22.5-22.8°C Flash point -34°C Specific gravity 0.899 at 20°C with respect to water at 4°C

Solubility Organic solvents: acetone, benzene, chloroform, diethyl ether

Occupational exposure

UN No. 2456 HAZCHEM Code 3/E Conveyance classification flammable liquid

Environmental fate

Abiotic removal

Evaporation from water at 25°C, initial concentration 1 ppm solution: 50% after 29 min; 90% after 110 min (1).

Mammalian & avian toxicity

Acute data

LC₅₀ (duration unspecified) inhalation mouse 267 mg m⁻³ (2).

Irritancy

Reported to cause severe irritation. High concentrations are extremely destructive to tissues of the mucous membranes and upper respiratory tract (species unspecified) (3).

Genotoxicity

Did not show any direct mutagenic and alkylating properties when tested on *Salmonella typhimurium* TA100 (4).

Other effects

Other adverse effects (human)

♂ Sexual dysfunction reported following exposure (5).

Legislation

Limited under EC Directive on Drinking Water Quality 80/778/EEC. Organochlorine compounds: guide level 1 µg l⁻¹ (6).

Included in Schedules 4 and 6 (Release into Air/Land: Prescribed Substances) of Statutory Instrument No. 472, 1991 (7).

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C272 2-chloropropionic acid



$\text{C}_3\text{H}_5\text{ClO}_2$

Mol. Wt. 108.52

CAS Registry No. 598-78-7

Synonyms α -chloropropionic acid; propionic acid, α -chloro-

EINECS No. 209-952-3

RTECS No. UE 8575000

Uses Intermediate used in the agricultural, chemical and pharmaceutical industries.

Physical properties

B. Pt. 170-190°C **Flash point** 107.2°C **Specific gravity** 1.258 **Volatility** v.p. 12 mmHg at 84°C

Occupational exposure

US-TWA 0.1 ppm (0.44 mg m⁻³)

UN No. 2511 **HAZCHEM Code** 2X **Conveyance classification** corrosive substance

Supply classification corrosive

Risk phrases Harmful if swallowed – Causes severe burns (R22, R35)

Safety phrases Keep locked up and out of the reach of children (if sold to general public) – Do not breathe vapour – In case of contact with eyes, rinse immediately with plenty of water and seek medical advice – After contact with skin, wash immediately with plenty of water – Wear suitable protective clothing – In case of accident or if you feel unwell, seek medical advice immediately (show label where possible) (S1/2, S23, S26, S28, S36, S45)

Mammalian & avian toxicity

Acute data

LD₅₀ oral rat 500 mg kg⁻¹ (1).

LD₅₀ oral mouse 1670 mg kg⁻¹ (2).

LD₅₀ dermal guinea pig 1260 mg kg⁻¹ (3).

Sub-acute and sub-chronic data

Subcutaneous administration (species unspecified) (7 day) 62.5 mg kg⁻¹ day⁻¹ caused a decrease in blood lactate and pyruvate but not blood glucose concentration. Urinary oxalate was not increased. Blood ketone body concentration progressively increased after day-3 of treatment. Plasma cholesterol slowly decreased (4).

Teratogenicity and reproductive effects

Atrophy of the testes and damage to the testicular epithelium was observed in groups of ♂ rats fed 330-378 mg kg⁻¹ day⁻¹ (duration unspecified) (3).

Irritancy

Extremely destructive to tissues of the mucous membranes and upper respiratory tract, eyes and skin (species unspecified) (5).

Other effects

Other adverse effects (human)

No irritation was observed in workers exposed to the vapour at TWA concentrations up to 0.35 ppm, with exposures up to 1.95 ppm (1).

Any other adverse effects

Inhalation may be fatal as a result of spasm, inflammation and oedema of the larynx and bronchi, chemical pneumonitis and pulmonary oedema (species unspecified) (5).

Legislation

Limited under EC Directive on Drinking Water Quality 80/778/EEC. Organochlorine compounds: guide level $1 \mu\text{g l}^{-1}$ (6).

Included in Schedule 6 (Release into Land: Prescribed Substances) of Statutory Instrument No. 472, 1991 (7).

Other comments

Contaminant in the herbicide Dalapon (8).

Reviews on physico-chemical properties, human health effects, experimental toxicology, epidemiology, exposure levels, workplace experience and environmental effects listed (9).

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c273 2-chloropropionitrile



$\text{C}_3\text{H}_4\text{ClN}$

Mol. Wt. 89.52

CAS Registry No. 1617-17-0

Synonyms (\pm)-2-chloropropanenitrile

EINECS No. 216-570-0

Uses Chemical intermediate.

Physical properties

B. Pt. 120-122°C Flash point 33°C Specific gravity 1.012 at 20°C

Mammalian & avian toxicity

Irritancy

Vapour or mist reported to be irritating to the eyes, mucous membranes and upper respiratory tract (species unspecified) (1).

Legislation

Limited under EC Directive on Drinking Water Quality 80/778/EEC. Organochlorine compounds: guide level $1 \mu\text{g l}^{-1}$ (2).

Included in Schedule 6 (Release into Land: Prescribed Substances) of Statutory Instrument No. 472, 1991 (3).

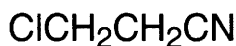
Other comments

Quantitative Structure Activity Relationship (QSAR) study suggests that duodenal ulcer can be induced by propionitrile and structurally related chemicals (4).

References

1. Lenga, R. E. *The Sigma-Aldrich Library of Chemical Safety Data* 2nd ed., 1988, 1, 848, Sigma-Aldrich, Milwaukee, USA.
2. *EC Directive Relating to the Quality of Water Intended for Human Consumption* 1982, 80/778/EEC, Office for Official Publications of the European Communities, 2 rue Mercier, L-2985 Luxembourg.
3. *S. I. 1991 No. 472 The Environmental Protection (Prescribed Processes and Substances) Regulations* 1991, HMSO, London, UK.
4. Szabo, S. et al *J. Pharmacol. Exp. Ther.* 1982, 223(1), 68-76

c274 3-chloropropionitrile



$\text{C}_3\text{H}_4\text{ClN}$

Mol. Wt. 89.52

CAS Registry No. 542-76-7

Synonyms propanenitrile, 3-chloro-; 3-chloropropanenitrile; 3-chloropropanonitrile; β -chloropropionitrile

EINECS No. 208-827-0

RTECS No. UG 1400000

Uses In pharmaceutical and polymer synthesis.

Physical properties

M. Pt. -51°C **B. Pt.** 176°C (decomp.) **Flash point** 75.5°C **Specific gravity** 1.136 at 25°C with respect to water at 4°C **Volatility** v.p. 6 mmHg at 50°C ; v.den. 3.09

Solubility Water: 2.2 ml 100 g^{-1} at 25°C . Organic solvents: miscible with acetone, benzene, carbon tetrachloride, diethyl ether, ethanol

Mammalian & avian toxicity

Acute data

LD₅₀ oral rat, mouse 9, 100 mg kg^{-1} , respectively (1).

LD₅₀ intraperitoneal mouse 100 mg kg^{-1} (2).

LD₅₀ intravenous mouse 56 mg kg^{-1} (3).

Legislation

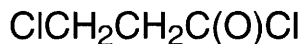
Limited under EC Directive on Drinking Water Quality 80/778/EEC. Organochlorine compounds: guide level 1 $\mu\text{g l}^{-1}$ (4).

Included in Schedules 4 and 6 (Release into Air/Land: Prescribed Substances) of Statutory Instrument No. 472, 1991 (5).

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1. Patty, F. A. (Ed.) *Patty's Industrial Hygiene and Toxicology* 2nd ed., 1962, 2, 2025, Interscience, New York, USA.
2. *NTIS Report No. AD277-689* Natl. Tech. Inf. Ser., Springfield, VA, USA.
3. *Report NX 01996* US Army Armament Research and Development Command, Chemical Systems Laboratory, NIOSH Exchange Chemicals Aberdeen Proving Ground, MD, USA.
4. *EC Directive Relating to the Quality of Water Intended for Human Consumption* 1982, 80/778/EEC, Office for Official Publications of the European Communities, 2 rue Mercier, L-2985 Luxembourg.
5. *S. I. 1991 No. 472 The Environmental Protection (Prescribed Processes and Substances) Regulations* 1991, HMSO, London, UK

c275 3-chloropropionyl chloride



$\text{C}_3\text{H}_4\text{Cl}_2\text{O}$

Mol. Wt. 126.97

CAS Registry No. 625-36-5

Synonyms 3-chloropropionyl chloride

EINECS No. 210-890-4

Uses Preparation of bacteriocides.

Physical properties

B. Pt. 143-145°C **Flash point** 61°C **Specific gravity** 1.330 at 20°C

Mammalian & avian toxicity

Irritancy

Extremely destructive to tissue of the mucous membranes and upper respiratory tract, eyes and skin (species unspecified) (1).

Other effects

Any other adverse effects

Inhalation may be fatal as a result of spasm, inflammation and oedema of the larynx and bronchi, chemical pneumonitis and pulmonary oedema (species unspecified) (1).

Legislation

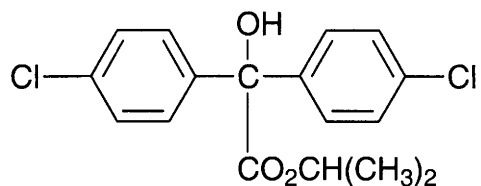
Limited under EC Directive on Drinking Water Quality 80/778/EEC. Organochlorine compounds: guide level $1 \mu\text{g l}^{-1}$ (2).

Included in Schedule 6 (Release into Land: Prescribed Substances) of Statutory Instrument No. 472, 1991 (3).

References

1. Lenga, R. E. *The Sigma-Aldrich Library of Chemical Safety Data* 2nd ed., 1988, 1, 849, Sigma-Aldrich, Milwaukee, USA.
2. *EC Directive Relating to the Quality of Water Intended for Human Consumption* 1982, 80/778/EEC, Office for Official Publications of the European Communities, 2 rue Mercier, L-2985 Luxembourg.
3. *S. I. 1991 No. 472 The Environmental Protection (Prescribed Processes and Substances) Regulations* 1991, HMSO, London, UK

C276 chloropropylate



$C_{17}H_{16}Cl_2O_3$

Mol. Wt. 339.22

CAS Registry No. 5836-10-2

Synonyms isopropyl 4,4'-dichlorobenzilate; propyl *p,p'*-dichlorobenzilate; 4-chloro- α -(4-chlorophenyl)- α -hydroxybenzene acetic acid, 1-methylethyl ester; Acarlate; Chlormite; Rospan; Rospin

EINECS No. 227-421-4

RTECS No. DD 2450000

Uses Superseded acaricide. Marine anti-fouling agent.

Physical properties

M. Pt. 73°C **B. Pt.** 148-150°C **Specific gravity** 1.35 **Volatility** v.p. 1.8×10^{-7} mmHg at 20°C

Solubility Water: 1.5 mg l⁻¹ at 20°C. Organic solvents: acetone, dichloromethane, hexane, methanol, octan-1-ol, toluene

Ecotoxicity

Fish toxicity

LC₅₀ (24-48 hr) harlequin fish, 22-20 ppm tested in standard quality soft dilution water (hardness 20 ppm CaCO₃) (1).

LC₅₀ (96 hr) bluegill sunfish, rainbow trout 0.45-0.66 mg l⁻¹ (2).

Mammalian & avian toxicity

Acute data

LD₅₀ oral redwing blackbird >100 mg kg⁻¹ (3).

LD₅₀ oral rat, mouse 5000 mg kg⁻¹ (2,4).

LD₅₀ dermal rabbit 10 g kg⁻¹ (5).

Carcinogenicity and chronic effects

In 2-yr feeding trials the no-effect level for rats was 40 mg kg⁻¹ diet and for dogs 500 mg kg⁻¹ diet (2,6).

Metabolism and toxicokinetics

When fed to cattle, more than 80% was eliminated via the urine. About 28% of the material was identified as 4,4'-dichlorobenzilic acid and 55% as conjugates. Chloropropylate was stable for up to 7 hr in rumen fluid but decomposed in the supernatant fraction of beef liver *in vitro* (7).

Irritancy

Dermal rabbit (duration unspecified) 125 mg caused mild irritation and 25 mg instilled into rabbit eye caused severe irritation (5).

Legislation

Limited under EC Directive on Drinking Water Quality 80/778/EEC. Pesticides: maximum admissible concentration in drinking water 0.1 µg l⁻¹ (8).

Included in Schedule 6 (Release into Land: Prescribed Substances) of Statutory Instrument No. 472, 1991 (9).

Other comments

Believed to be no longer manufactured, or marketed for crop protection use (10).

Residues have been detected on crops and in soil and sediments.

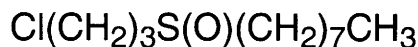
Spider mites and house flies metabolised chloropropylate to corresponding chlorine-containing analogues of benzoic acid, benzhydrol, benzophenone and benzoic acid (7).

Physico-chemical properties, human health effects, experimental toxicology and epidemiology reviewed (11).

References

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2. *The Agrochemicals Handbook* 2nd ed., 1987, The Royal Society of Chemistry, London, UK.
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c277 3-chloropropyl octyl sulfoxide



C₁₁H₂₃ClOS

Mol. Wt. 238.82

CAS Registry No. 3569-57-1

Synonyms Repellent 1207

RTECS No. WS 2800000

Mammalian & avian toxicity

Acute data

LD₅₀ oral redwing blackbird 100 mg kg⁻¹ (1).

LD₅₀ oral rat 5660 mg kg⁻¹ (2).

LD₅₀ dermal rabbit 8 mg kg⁻¹ (2).

Legislation

Included in Schedule 4 (Release into the Air: Prescribed Substances) of Statutory Instrument No. 472, 1991 (3).

References

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c278 3-chloropropyne



$\text{C}_3\text{H}_3\text{Cl}$

Mol. Wt. 74.51

CAS Registry No. 624-65-7

Synonyms 1-propyne, 3-chloro-; 2-propynyl chloride; propargyl chloride

EINECS No. 210-856-9

Uses Intermediate in organic synthesis.

Physical properties

M. Pt. -78°C **B. Pt.** 57°C **Flash point** 18°C **Specific gravity** 1.0306 at 25°C with respect to water at 4°C

Solubility Organic solvents: miscible with benzene, ethanol, diethyl ether, carbon tetrachloride, ethyl acetate

Ecotoxicity

Fish toxicity

Trout, bluegill sunfish, goldfish 5 ppm; death occurred in 8-24 hr (1).

Invertebrate toxicity

EC_{50} *Photobacterium phosphoreum* 24.7 ppm Microtox test (2).

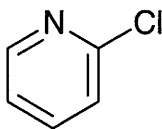
Other comments

Reviews on human health effects, experimental toxicology, and physico-chemical properties listed (3).

References

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2. Kaiser, K. L. E. et al *Water Pollut. Res. J. Can.* 1991, 26(3), 361-431.
3. *ECETOC Technical Report No. 30(4)* 1991, European Chemical Industry Ecology and Toxicology Centre, B-1160 Brussels, Belgium

c279 2-chloropyridine



$\text{C}_5\text{H}_4\text{ClN}$

Mol. Wt. 113.55

CAS Registry No. 109-09-1

Synonyms o-chloropyridine; α -chloropyridine; pyridine, 2-chloro-

EINECS No. 203-646-3

RTECS No. US 5950000

Uses Chemical synthesis.

Physical properties

B. Pt. 166°C at 714 mmHg **Flash point** 65°C **Specific gravity** 1.205 **Volatility** v.p. 1 mmHg at 30°C

Solubility Water: miscible. Organic solvents: diethyl ether, ethanol

Occupational exposure

UN No. 2822 HAZCHEM Code 2X Conveyance classification toxic substance

Ecotoxicity

Bioaccumulation

Non-accumulative or low accumulative (1).

Mammalian & avian toxicity

Acute data

LD₅₀ oral redwing blackbird, starling 1000 mg kg⁻¹ (2).

LD₅₀ oral Japanese quail 1000 mg kg⁻¹ (2).

LD₅₀ oral mouse 110 mg kg⁻¹ (3).

LC_{Lo} (4 hr) inhalation rat 100 ppm (3).

LD₅₀ dermal rabbit 64 mg kg⁻¹ (3).

LD₅₀ intraperitoneal mouse 130 mg kg⁻¹ (3).

LD₅₀ intraperitoneal rabbit 48 mg kg⁻¹ (3).

Genotoxicity

Salmonella typhimurium TA97, TA98, TA100, TA102 without metabolic activation positive (4).

Weakly active inducer of mitotic aneuploidy in *Saccharomyces cerevisiae* (5).

No cytotoxic or clastogenic activity in cultured V3 cells (6).

Legislation

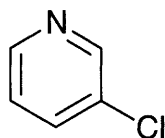
Limited under EC Directive on Drinking Water Quality 80/778/EEC. Organochlorine compounds: guide level 1 µg l⁻¹ (7).

Included in Schedule 6 (Release into Land: Prescribed Substances) of Statutory Instrument No. 472, 1991 (8).

References

1. Ministry of International Trade and Industry (MITI) Report 1984, Japan.
2. Schafer, E. W. et al *Arch. Environ. Contam. Toxicol.* 1983, **12**, 355-382.
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8. S. I. 1991 No. 472 *The Environmental Protection (Prescribed Processes and Substances) Regulations* 1991, HMSO, London, UK

C280 3-chloropyridine



C₅H₄ClN

Mol. Wt. 113.55

CAS Registry No. 626-60-8

Synonyms *m*-chloropyridine; pyridine, 3-chloro-

EINECS No. 210-955-7

RTECS No. US 6125000

Uses Chemical synthesis. Lubricating oil antiwear additive.

Physical properties

B. Pt. 148°C **Flash point** 66°C **Specific gravity** 1.194

Solubility Water: miscible

Mammalian & avian toxicity

Acute data

LD₅₀ oral redwing blackbird, starling 1000 mg kg⁻¹ (1).

LD₅₀ oral Japanese quail 750 mg kg⁻¹ (1).

LD₅₀ intraperitoneal mouse 235 mg kg⁻¹ (2).

Genotoxicity

Salmonella typhimurium TA97, TA98, TA100, TA102 with and without metabolic activation negative (3).

Cytotoxic and clastogenic in cultured V3 cells (4).

Legislation

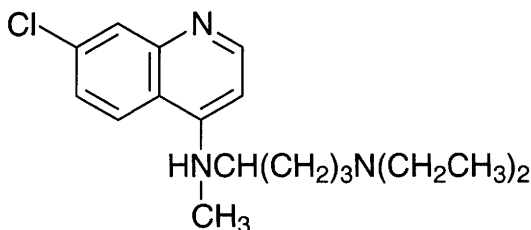
Limited under EC Directive on Drinking Water Quality 80/778/EEC. Organochlorine compounds: guide level 1 µg l⁻¹ (5).

Included in Schedule 6 (Release into Land: Prescribed Substances) of Statutory Instrument No. 472, 1991 (6).

References

1. Schafer, E. W. et al *Arch. Environ. Contam. Toxicol.* 1983, **12**, 355-382.
2. Gehring, P. J. et al *Toxicol. Appl. Pharmacol.* 1967, **11**, 361.
3. Claxton, L. D. et al *Mutat. Res.* 1987, **176**(2), 185-198.
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5. *EC Directive Relating to the Quality of Water Intended for Human Consumption* 1982, 80/778/EEC, Office for Official Publications of the European Communities, 2 rue Mercier, L-2985 Luxembourg.
6. S. I. 1991 No. 472 *The Environmental Protection (Prescribed Processes and Substances) Regulations* 1991, HMSO, London, UK

C281 chloroquine



$\text{C}_{18}\text{H}_{26}\text{ClN}_3$

Mol. Wt. 319.88

CAS Registry No. 54-05-7

Synonyms N⁴-(7-chloro-4-quinolyl)-N¹,N¹-diethyl-1,4-pentanediamine; 7-chloro-4-(diethylamino-1-methylbutylamino)quinoline; Pfizerquine

EINECS No. 200-191-2

RTECS No. UB 2360000

Uses Antimalarial. Antiamoebic. Antirheumatic. Lupus erythematosus suppressant.

Physical properties

M. Pt. 87°C

Solubility Water: very slightly soluble. Organic solvents: chloroform, ether

Mammalian & avian toxicity

Acute data

LD₅₀ oral rat 330 mg kg⁻¹ (1).

LD₅₀ oral mouse 311 mg kg⁻¹ (2).

LD₅₀ intraperitoneal rat 102 mg kg⁻¹ (3).

LD₅₀ intraperitoneal mouse 66 mg kg⁻¹ (4).

LD₅₀ subcutaneous mouse 150 mg kg⁻¹ (5).

LD₅₀ subcutaneous rabbit 75 mg kg⁻¹ (5).

LD₅₀ intramuscular mouse 71 mg kg⁻¹ (6).

LD₅₀ intravenous mouse 21.6 mg kg⁻¹ (6).

LD₅₀ intravenous rabbit 8 mg kg⁻¹ (5).

LD_{Lo} oral woman 110 mg kg⁻¹ (7).

LD_{Lo} oral man 86 mg kg⁻¹ (7).

LD_{Lo} oral human 20 mg kg⁻¹ (5).

Carcinogenicity and chronic effects

No adequate data for carcinogenicity to humans, inadequate evidence for carcinogenicity to animals, IARC classification group 3 (8).

21-day-old Osborne-Mendel rats, ♂ and ♀, were given chloroquine in diet for up to 2 yr. Inhibition of growth was severe at 800 and 1000 mg kg⁻¹ of diet but temporary at 400 mg kg⁻¹. No tumours were reported in 86 treated or in 15 control rats examined (9,10).

Teratogenicity and reproductive effects

Intragastric administration of chloroquine (700 mg kg⁻¹) to gestating rats resulted in several structural abnormalities in the developing foetuses. The incidence of hepatomegaly was increased by 30%, the liquification of visceral organs was increased by 15%, and a 9% higher incidence of cleft palate, wrist drop, clubbed foot, and brain liquification was observed compared to controls (11).

The effects of chloroquine on rat seminiferous tubular morphology have been quantified; tubular diameter and total surface area were reduced but tubular epithelial cell height was increased. The results suggest that the chloroquine has very deleterious effects on seminiferous tubules (12).

Two of 169 infants born to women who had received 300 mg chloroquine weekly throughout pregnancy had birth defects compared with 4/454 control infants whose mothers had not been exposed to antimalarials; the difference was not significant (13).

Metabolism and toxicokinetics

In man chloroquine is rapidly and almost completely absorbed from the gastro-intestinal tract when given by mouth. A mean peak plasma concentration of 76 ng ml⁻¹ was found in healthy adults 3.6 hr after administration of the equivalent of 300 mg chloroquine base by mouth (14).

About 50% of a dose of chloroquine in humans is metabolised in the liver, mainly to the *N*-dealkylated metabolite monodesethylchloroquine; smaller amounts of bisdesethylchloroquine, 7-chloro-4-aminoquinoline, and *N*-oxidation products are formed (15).

A mean of 42-47% of a dose has been reported to be excreted unchanged in the urine, and 7-12% as monodesethylchloroquine (14).

Chloroquine is avidly retained in human tissues, and, along with its metabolites, can be detected in the urine for up to five years (16).

Genotoxicity

Salmonella typhimurium, 100 µmol l⁻¹, positive (strain/metabolic activation system not specified) (17).

Salmonella typhimurium (5-5000 µg plate⁻¹) TA1537, TA1538, TA98, TA100 and *Escherichia coli* B/r WP2 uvr⁻ with and without metabolic activation, reversion test negative. *Bacillus subtilis* rec assay negative, pol assay positive (18).

Non-mutagenic (as chloroquine diphosphate) in the standard *Salmonella typhimurium* microsomal test system using strains TA1535 and TA1538; mutagenic in the fluctuation assay using TA1537, a strain which detects frameshift mutations (19).

Drosophila melanogaster adult ♂ administered chloroquine using a feeding technique; frequency of sex-linked recessive lethals increased but no induction of sex-chromosome loss in male germ cells (20).

Drosophila melanogaster zeste strain somatic mutation test positive (21).

Human lymphocytes, 100 mg l⁻¹, assay for chromosomal aberrations positive (22).

Other effects

Other adverse effects (human)

Adverse effects include headache and gastro-intestinal disturbances. Ocular toxicity is a hazard with high doses as is cardiotoxicity with large intravenous doses and rapid infusion. Chloroquine is extremely toxic in overdose (23).

Doses of 20 mg kg⁻¹ body weight are considered toxic and 30 mg kg⁻¹ may be lethal (24).

High-dose long-term therapy (more than one year) may result in retinopathy with doses exceeding 100 g and in ototoxicity (25,26).

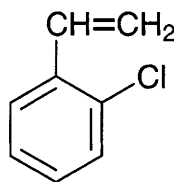
Aplastic anaemia was associated with the use of chloroquine in three patients (27).

References

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c282 2-chlorostyrene



C_8H_7Cl

Mol. Wt. 138.60

CAS Registry No. 2039-87-4

Synonyms o-chlorostyrene; 1-chloro-2-ethenylbenzene; (2-chlorophenyl)ethylene

EINECS No. 218-026-8

RTECS No. WL 4160000

Uses Manufacture of chlorostyrene polymers and polyesters.

Physical properties

M. Pt. -63.15°C **B. Pt.** 188.6°C **Flash point** 58°C **Specific gravity** 1.080 at 20°C with respect to water at 4°C

Volatility v.p. 9.6×10^{-1} mmHg at 25°C

Solubility Water: <1 g l⁻¹ at 21°C. Organic solvents: acetic acid, acetone, carbon tetrachloride, diethyl ether, ethanol

Occupational exposure

FR-VME 50 ppm (285 mg m⁻³)

US-TWA 50 ppm (283 mg m⁻³)

US-STEL 75 ppm (425 mg m⁻³)

Mammalian & avian toxicity

Acute data

LD₅₀ oral rat 5200 mg kg⁻¹ (1).

Inhalation (duration unspecified) rat, rabbit, guinea pig and dog average concentration of 100 ppm produced no adverse effects (2).

Legislation

Limited under EC Directive on Drinking Water Quality 80/778/EEC. Organochlorine compounds: guide level 1 $\mu\text{g l}^{-1}$ (3).

Included in Schedule 6 (Release into Land: Prescribed Substances) of Statutory Instrument No. 472, 1991 (4).

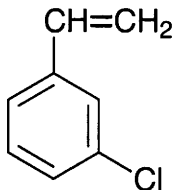
Other comments

Physico-chemical properties, human health effects, experimental toxicology, exposure levels, workplace experience and epidemiology reviewed (5).

References

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5. *ACGIH Documentation of TLVs and BEIs* 1991, ACGIH (Publication 0206), 1330 Kemper Meadow Drive, Cincinnati, Ohio 45240-1634, US

C283 3-chlorostyrene



$\text{C}_8\text{H}_7\text{Cl}$

Mol. Wt. 138.60

CAS Registry No. 2039-85-2

Synonyms *m*-chlorostyrene; 1-chloro-3-ethenylbenzene; (3-chlorophenyl)ethylene

EINECS No. 218-024-7

Physical properties

B. Pt. 57.5-57.8°C at 10mmHg Flash point 62°C Specific gravity 1.090 at 20°C with respect to water at 4°C

Partition coefficient $\log P_{\text{ow}}$ 3.58

Solubility Organic solvents: diethyl ether, ethanol

Mammalian & avian toxicity

Irritancy

May cause eye and skin irritation (species unspecified) (1).

Legislation

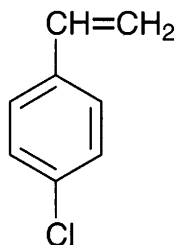
Limited under EC Directive on Drinking Water Quality 80/778/EEC. Organochlorine compounds: guide level 1 $\mu\text{g l}^{-1}$ (2).

Included in Schedule 6 (Release into Land: Prescribed Substances) of Statutory Instrument No. 472, 1991 (3).

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3. S. I. 1991 No. 472 *The Environmental Protection (Prescribed Processes and Substances) Regulations* 1991, HMSO, London, UK

C284 4-chlorostyrene



C_8H_7Cl

Mol. Wt. 138.60

CAS Registry No. 1073-67-2

Synonyms *p*-chlorostyrene; 1-chloro-4-ethenylbenzene; (4-chlorophenyl)ethylene

EINECS No. 214-028-8

Uses Manufacture of polychlorostyrene polymers and polyesters.

Physical properties

M. Pt. $-15.9^{\circ}C$ B. Pt. $192^{\circ}C$ Flash point $60^{\circ}C$ Specific gravity 1.155 at $20^{\circ}C$ with respect to water at $4^{\circ}C$

Partition coefficient $\log P_{ow}$ 3.58 Volatility v.p. 1.5 mmHg at $25^{\circ}C$

Solubility Organic solvents: acetone, benzene, carbon tetrachloride, diethyl ether, ethanol, petroleum ether

Mammalian & avian toxicity

Irritancy

May cause eye and skin irritation (species unspecified) (1).

Legislation

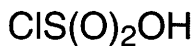
Limited under EC Directive on Drinking Water Quality 80/778/EEC. Organochlorine compounds: guide level 1 $\mu g\ l^{-1}$ (2).

Included in Schedule 6 (Release into Land: Prescribed Substances) of Statutory Instrument No. 472, 1991 (3).

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3. S. I. 1991 No. 472 *The Environmental Protection (Prescribed Processes and Substances) Regulations* 1991, HMSO, London, UK

c285 chlorosulfonic acid



ClHO_3S

Mol. Wt. 116.52

CAS Registry No. 7790-94-5

Synonyms chlorosulfuric acid; monochlorosulfuric acid; sulfuric chlorohydrin

EINECS No. 232-234-6

RTECS No. FX 5730000

Uses Manufacture of dyestuffs, pharmaceuticals, agricultural chemicals and synthetic detergents. Preparation of saccharin and sulfone compounds.

Physical properties

M. Pt. -80°C B. Pt. $151\text{--}152^\circ\text{C}$ at 755mmHg Specific gravity 1.753 at 20°C with respect to water at 4°C

Volatility v.p. 1 mmHg at 32°C

Solubility Organic solvents: dichloroethane, pyridine

Occupational exposure

UK-LTEL 1 mg m^{-3}

UN No. 1754 HAZCHEM Code 4WE Conveyance classification corrosive substance

Supply classification corrosive

Risk phrases Reacts violently with water – Causes severe burns – Irritating to the respiratory system (R14, R35, R37)

Safety phrases Keep locked up and out of the reach of children (if sold to general public) – In case of contact with eyes, rinse immediately with plenty of water and seek medical advice – In case of accident or if you feel unwell, seek medical advice immediately (show label where possible) (S1/2, S26, S45)

Environmental fate

Abiotic removal

Rapidly hydrolysed to give hydrochloric and sulfuric acid (1).

Undergoes photo-oxidation in the vapour phase by photochemically produced hydroxyl radicals (2).

Mammalian & avian toxicity

Acute data

LC₅₀ (2 hr) inhalation mouse 52.5 mg m^{-3} (3).

LC₅₀ (4 hr) inhalation rat 38.5 mg m^{-3} (3).

Irritancy

Reported to be highly irritant and corrosive to eyes, skin and mucous membranes (4).

Other effects

Other adverse effects (human)

Long-term exposure to fumes may cause erosion of the teeth followed by jaw necrosis. Bronchial irritation with chronic cough and frequent attacks of bronchial pneumonia. Gastro-intestinal disturbances were also noted (5).

Legislation

Included in Schedule 6 (Release into Land: Prescribed Substances) of Statutory Instrument No. 472, 1991 (6).

Other comments

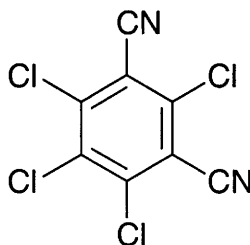
On dropping into water decomposes with explosive violence (4).

Reviews on physico-chemical properties, human health effects, experimental toxicology, exposure levels, workplace experience, epidemiology and environmental effects listed (7).

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c286 chlorothalonil



$C_8Cl_4N_2$

Mol. Wt. 265.91

CAS Registry No. 1897-45-6

Synonyms tetrachloroisophthalonitrile; 1,3-benzenedicarbonitrile, 2,4,5,6-tetrachloro-; 1,3-dicyanotetrachlorobenzene; tetrachlorometaphthalodinitrile; *m*-tetrachlorophthalodinitrile; Bravo; Daconil; Groutcide 75; Nopocide N-40-D; Nuocide; Siclor

EINECS No. 217-588-1

RTECS No. NT 2600000

Uses Fungicide. Preservative in paints and adhesives. Bactericide. Nematocide.

Physical properties

M. Pt. 250°C **B. Pt.** 350°C **Specific gravity** 1.80 at 25°C with respect to water at 4°C

Partition coefficient $\log P_{ow}$ 2.89 (1) **Volatility** v.p. <0.01 mmHg at 40°C

Solubility Water: 0.9 mg l⁻¹. Organic solvents: acetone, benzene, butane, cyclohexanone, dimethylformamide, dimethyl sulfoxide, kerosene, xylene

Occupational exposure

Supply classification harmful

Risk phrases Possible risk of irreversible effects (R40)

Safety phrases Keep out of reach of children (if sold to general public) – Wear suitable protective clothing and gloves (S2, S36/37)

Ecotoxicity

Fish toxicity

LC₅₀ (96 hr) channel catfish, rainbow trout, bluegill sunfish 44, 49, 62 ppb, respectively (1).

LC₅₀ (96 hr) channel catfish 52 µg l⁻¹. Sublethal exposure for six days resulted in acute necrosis of intestinal epithelial lining in 57% of treated catfish. No treatment-related pathological lesions were observed in liver, gills, posterior kidney, brain, spleen or heart. Catfish exposed to 13 µg l⁻¹ for 72 hr had increased tissue glutathione concentrations in liver, posterior kidney and gills suggesting a protective role of tissue GSH toward chlorothalonil exposure (2).

Metabolised *in vitro* channel catfish liver and gill by glutathione S-transferase-catalysed conjugation (3).

Invertebrate toxicity

LC₅₀ (48 hr) *Daphnia magna* 130-200 µg l⁻¹ (4).

LC₅₀ (96 hr) *Mya arenaria* 35 mg l⁻¹ (4).

LC₅₀ (96 hr) blue mussel 5.9 mg l⁻¹ (4).

A study of the effect of chlorothalonil on vesicular-arbuscular mycorrhizal (VAM) symbiosis in *Leucaena leucocephala* found that the fungicide reduced VAM colonisation of roots and completely suppressed symbiotic effectiveness in uninoculated soil. The toxic effect on the host plant was partly offset by phosphorus fertilisation. Toxicity to the VAM fungi declined over time, but was significant 12.5 wk after application of chlorothalonil (5).

Bioaccumulation

Initially accumulated by blue mussels to concentrations ~10 times greater than exposure concentrations. However, tissue concentrations returned to the same level as exposure concentrations within 96 hr (4).

Average bioconcentration factor in whole body of willow shiner (*Gnathopogon caeruleus*) and carp (*Cyprinus carpio*) 18 and 25, respectively (6).

Environmental fate

Degradation studies

Strongly inhibited bacterial degradation of cellulose in soil under aerobic and anaerobic conditions (7).

Reported to degrade more rapidly in soils with 60% water holding capacity than for 20%, 40% or 100%, while its degradation was rapid at temperatures of 25-30°C, evidently due to microbial activity (8).

Microbial degradation products identified were 2,4,5-trichloroisophthalonitrile; 2,4,6-trichloroisophthalonitrile; 2,4-dichloroisophthalonitrile; 2,5-dichloroisophthalonitrile; 4-chloroisophthalonitrile; 5-chloroisophthalonitrile; isophthalonitrile; 2,5,6-trichloro-4-hydroxyisophthalonitrile; and 2,5,6-trichloro-4-methoxyisophthalonitrile (8).

Loss was reported to be slow in still water at 15°C, with 42% remaining 75 hr after inoculation (9).

t_{1/2} 5-36 days in aerobic and anaerobic soil conditions. t_{1/2} a few hours to a few days in aerobic and anaerobic aquatic soil studies (1).

The microbial degradation of chlorothalonil in soil was enhanced by amendment with farmyard manure, due to the maintenance of a near-neutral pH value in soil (10).

Mammalian & avian toxicity

Acute data

LC₅₀ oral mallard >4640 mg kg⁻¹ (1).

LD₅₀ oral rat 10 g kg⁻¹ (10).

LC₅₀ (1 hr) inhalation rat >4.7 mg l⁻¹ air (1).

LD₅₀ dermal rabbit, rat >10 g kg⁻¹ (1,11).

LD₅₀ subcutaneous rat >5 g kg⁻¹ (12).

LD₅₀ intraperitoneal mouse 2500 mg kg⁻¹ (13).

Sub-acute and sub-chronic data

LC₅₀ (8 day) oral mallard duck and bobwhite quail >10,000 mg kg⁻¹ diet (1).

Carcinogenicity and chronic effects

Limited evidence for carcinogenicity to animals, no adequate data for evaluation of carcinogenicity to humans, IARC classification group 3 (14).

In 2-yr feeding trials, no-observed-effect levels were observed in rats, mice, dogs to be 1.8, 1.6, 3 mg kg⁻¹ body weight, respectively (1).

National Toxicology Program tested rats and mice via feed. Positive evidence of carcinogenic activity in rats, no evidence of carcinogenic activity in mice (15).

Rats were administered 10,000 mg kg⁻¹ diet for 1 wk then 5000 mg kg⁻¹ diet for a further 79 wk; a second group 20,000 mg kg⁻¹ diet for one wk followed by 10,000 mg kg⁻¹ for 79 wk. A dose-related increase in the occurrence of adenomas and adenocarcinomas of the renal tubular epithelium was observed in both sexes. In a parallel study, one group of ♂ mice was administered 10,000 mg kg⁻¹ diet for 2 wk followed by 2500 mg kg⁻¹ for 78 wk and a second group 20,000 mg kg⁻¹ for 2 wk followed by 5000 mg kg⁻¹ for 78 wk. ♀ Mice were administered 10,000 mg kg⁻¹ diet for 2 wk, 5000 mg kg⁻¹ for 10 wk and 2500 mg kg⁻¹ for 68 wk, and a second group 20,000 mg kg⁻¹ diet for 2 wk, 10,000 for 10 wk, then 5000 for 68 wk. There was no significant difference in tumour incidence compared to controls, however ♂ mice became hyperexcitable from wk-62 (16).

Teratogenicity and reproductive effects

Gavage rats (day 6-15 of gestation) 0, 25, 100 or 400 mg kg⁻¹ day⁻¹ caused no compound-related external, internal or skeletal malformations in foetuses. Doses of 400 mg kg⁻¹ day⁻¹ caused maternal toxicity with an associated slight increase in the number of early embryonic deaths (17).

Metabolism and toxicokinetics

In mammals following oral administration chlorothalonil was excreted largely unchanged although some was metabolised to the 4-hydroxy derivative (1).

Irritancy

Severe eye irritant, mild skin irritant in rabbits (1).

Sensitisation

Caused allergic side-effects in susceptible individuals. Gastro-intestinal tract and respiratory tract irritant (18). Patch testing indicated that 10-28% of 88 Japanese farmers were sensitive to chlorothalonil and other pesticides; 35 had acute dermatitis. In some cases photosensitisation was involved (19).

Highly positive reactions were also seen in 66 greenhouse workers, 51 vegetable farmers and 25 other patients with pesticide-induced dermatitis (20).

Four cases of severe, recurrent contact dermatitis were reported in workers exposed to wood preservatives containing chlorothalonil (18,21).

Genotoxicity

Salmonella typhimurium TA97, TA1535, TA1537 with or without metabolic activation negative (22,23).

Induced point mutations in *Aspergillus nidulans* biA1, methG1, meth118 strains (24).

Mutagenic in the L-5178Y tk⁺/tk⁻ mouse lymphoma forward mutation assay (25).

Did not induce mutations in silkworms nor chromosomal aberrations in hamster lung fibroblasts (details not given) (26).

Other effects

Other adverse effects (human)

A variety of health problems related to agrochemicals were reported by 95% of workers in a coffee-growing area of Kenya, where lack of protective clothing, poor handling practices and badly designed storage facilities for agrochemicals are very common (27).

A study of pesticide spraying by farmers in Indonesia found a significantly higher occurrence of neurobehavioural, respiratory and intestinal signs or symptoms of poisoning during spraying than during non-spraying seasons. 21% of spray operations resulted in three or more signs or symptoms, and various factors were significantly and independently associated with their frequency of occurrence (28).

Legislation

Limited under EC Directive on Drinking Water Quality 80/778/EEC. Pesticides: maximum admissible concentration in drinking water 0.1 µg l⁻¹ (29).

Included in Schedule 6 (Release into Land: Prescribed Substances) of Statutory Instrument No. 472, 1991 (30).

WHO Class Table 5 (31).

EPA Toxicity Class IV. ADI (human) 0.03 mg kg⁻¹, 1992 (1).

Other comments

Dermal exposure to chlorothalonil during harvesting of flowers was studied in 95 workers in carnation culture. Exposure of hands and forearms to 13-16 mg hr⁻¹ was observed; the level of exposure was directly related to the amount of dislodgeable residue of pesticide found (32).

Health risks from occupational exposure to pesticides and the regulatory response in the U.S. evaluated (33).

Non-occupational exposure of residents in two U.S. cities to 32 pesticides has been monitored and analysed (34).

Residues have been detected in water and on crops.

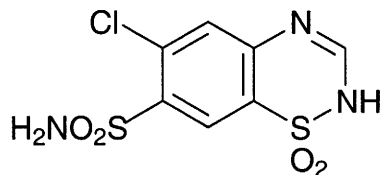
Environmental chemistry, fate and toxicology of chlorothalonil in Canadian studies reviewed (35).

Reviews on physico-chemical properties, human health effects, exposure levels, experimental toxicology, workplace experience, epidemiology and environmental effects listed (36).

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C287 chlorothiazide



C₇H₆ClN₃O₄S₂

Mol. Wt. 295.73

CAS Registry No. 58-94-6

Synonyms 6-chloro-2H-1,2,4-benzothiadiazine-7-sulfonamide 1,1-dioxide; 6-chloro-7-sulfamoyl-1,2,4-benzothiadiazine 1,1-dioxide; Chlotride; Diuril; Saluric

EINECS No. 200-404-9

RTECS No. DK 9450000

Uses Diuretic. Antihypertensive.

Physical properties

M. Pt. 342.5-343°C (decomp.)

Solubility Water: 400 mg l⁻¹. Organic solvents: acetone, dimethylformamide, dimethyl sulfoxide, ethanol, methanol, pyridine

Mammalian & avian toxicity

Acute data

LD₅₀ oral rat 10 g kg⁻¹ (1).

LD₅₀ oral mouse 8000 mg kg⁻¹ (2).

LD₅₀ intravenous rat 200 mg kg⁻¹ (3).

LD₅₀ intraperitoneal mouse 1400 mg kg⁻¹ (4).

LD₅₀ intravenous mouse 940 mg kg⁻¹ (4).

Sub-acute and sub-chronic data

Oral administration of 250 mg kg⁻¹ diet in rats (period not specified) led to intracellular alkalosis in the brain (5).

Metabolism and toxicokinetics

Estimated plasma t_{1/2} 45-120 min, although clinical effects last up to about 12 hr. Excreted unchanged in urine.

Crosses the placental barrier in humans and small amounts are reported to be found in breast milk (6).

A dose dependency on rate of absorption and urinary excretion was demonstrated by oral administration of up to 70.2 mg kg⁻¹ to rats. Absorption occurred, in decreasing order, in the jejunum, duodenum, large intestine, ileum and the stomach (7).

Genotoxicity

Salmonella typhimurium TA97, TA98, TA100, TA1535, TA1537, TA1538 with and without metabolic activation positive (8).

Other effects

Other adverse effects (human)

Two small children who ingested a total dose of 15 g between them presented with lethargy which progressed to deep coma within 12 hr. Both recovered without sequelae, and neither exhibited objective evidence of fluid or electrolyte disorder (9).

May provoke hyperglycaemia and glycosuria in diabetic and other susceptible patients. May be associated with electrolyte imbalances including hyponatraemic alkalosis, hyponatraemia and hypokalaemia (6).

Side effects of thiazide diuretics include electrolyte imbalances, anorexia, gastric irritation, nausea, vomiting,

constipation diarrhoea, dizziness, headache, photosensitivity, postural hypertension, paraesthesia, impotence, yellow vision, hypersensitivity reactions and blood disorders (6).

Any other adverse effects

Doses of up to 5 g kg⁻¹ administered to monkeys by gavage produced only transient lethargy of a moderate degree (9).

Legislation

Limited under EC Directive on Drinking Water Quality 80/778/EEC. Organochlorine compounds: guide level 1 µg l⁻¹ (10).

Included in Schedule 6 (Release into Land: Prescribed Substances) of Statutory Instrument No. 472, 1991 (11).

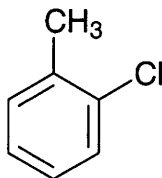
Other comments

Induced the growth of fine vellous hair, in at least a partially bald person, as a component of a topically applied formulation. Activity related to relaxation of the smooth muscles in the small blood vessels in the papilla part of connective tissue of skin supplying the hair follicle and thereby to increase blood flow to the hair matrix (12).

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C288 2-chlorotoluene



C₇H₇Cl

Mol. Wt. 126.59

CAS Registry No. 95-49-8

Synonyms o-chlorotoluene; 1-chloro-2-methylbenzene; 2-methylchlorobenzene; o-tolyl chloride; HALSO 99

EINECS No. 202-424-3

RTECS No. XS 9000000

Uses Solvent. Dyestuff intermediate. Intermediate in organic synthesis. Manufacture of pharmaceuticals and synthetic rubber compounds.

Physical properties

M. Pt. -36°C **B. Pt.** 157-159°C **Flash point** 47°C (closed cup) **Specific gravity** 1.083 at 20°C with respect to water at 4°C **Partition coefficient** $\log p_{ow}$ 3.42 **Volatility** v.p. 2.7 mmHg at 20°C
Solubility Water: 89 mg l⁻¹ at 25°C. Organic solvents: acetone, benzene, carbon tetrachloride, chloroform, diethyl ether, ethanol

Occupational exposure

FR-VME 50 ppm (250 mg m⁻³)

UK-LTEL 50 ppm (264 mg m⁻³)

US-TWA 50 ppm (259 mg m⁻³)

UN No. 2238 **HAZCHEM Code** 3 $\frac{+}{-}$ **Conveyance classification** flammable liquid

Supply classification harmful

Supply classification dangerous for the environment

Risk phrases Harmful by inhalation – Toxic to aquatic organisms, may cause long-term adverse effects in the aquatic environment (R20, R51/53)

Safety phrases Keep out of reach of children (if sold to general public) – Avoid contact with skin and eyes – Avoid release to the environment. Refer to special instructions/safety data sheet (S2, S24/25, S61)

Ecotoxicity

Fish toxicity

Not toxic to trout, bluegill sunfish, yellow perch or goldfish exposed to 5 ppm for 24 hr. Test conditions: pH 7.0; dissolved oxygen 7.5 ppm; total hardness (soap method) 300 ppm; alkalinity methyl orange 310 ppm; alkalinity phenolphthalein 0 ppm; free carbon dioxide 5 ppm; and temperature 12.8°C (1).

Invertebrate toxicity

Cell multiplication inhibition test, *Pseudomonas putida* 15 mg l⁻¹, *Scenedesmus quadricauda* >100 mg l⁻¹, *Entosiphon sulcatum* >80 mg l⁻¹ (2).

Bioaccumulation

Non-accumulative or low accumulative (3).

Environmental fate

Degradation studies

Removal from soil and polluted groundwater may be affected under aerobic conditions by motile microorganisms e.g. *Methylosinus trichosporium* (4).

Abiotic removal

$t_{1/2}$ volatilisation from water 3.4 hr. Photolytic $t_{1/2}$ reaction with hydroxyl radicals in the atmosphere 8.4 days (5).

Mammalian & avian toxicity

Acute data

LD₅₀ oral rat >1600 mg kg⁻¹ (6).

Teratogenicity and reproductive effects

Inhalation rabbits ≥ 10 mg m⁻³ caused no teratogenic effects (7).

Inhalation rats ≥ 9 mg m⁻³ caused dose-related foetal skeletal abnormalities and reduced mean foetal weight (7).

Metabolism and toxicokinetics

Following intravenous administration to rats 69-81% was excreted in urine and 14-18% expired within four days (8).

Metabolites identified as 2-chlorobenzyl alcohol glucuronide and mercapturic acid (9).

Irritancy

Dermal guinea pig (24 hr) 10 mg caused moderate irritation and 0.2 mg instilled into rabbit eye caused moderate irritation (6).

0.1 ml instilled into rabbit eye produced moderate conjunctival irritation which disappeared after 5 days (10).

Genotoxicity

Salmonella typhimurium TA98, TA100, TA1535, TA1537 with and without metabolic activation negative (11).

No significant increase in mutation was observed in the mouse lymphoma cell mutagenicity test (12).

In vitro Chinese hamster ovary cells with and without metabolic activation showed no significant increase in chromosomal damage (13).

Other effects

Any other adverse effects

Oral administration of 50-100 mg kg⁻¹ in rats produced moderate to marked weakness. Vasodilation produced at higher dose levels. Inhalation rats (6 hr) ≥73 mg l⁻¹ (14,000 ppm) caused loss of coordination, vasodilation, central nervous system depression and death (6).

Legislation

Limited under EC Directive on Drinking Water Quality 80/778/EEC. Organochlorine compounds: guide level 1 µg l⁻¹ (14).

Included in Schedule 6 (Release into Land: Prescribed Substances) of Statutory Instrument No. 472, 1991 (15).

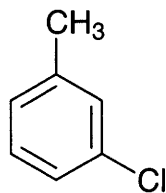
Other comments

Reviews on physico-chemical properties, human health effects, experimental toxicology, exposure levels, workplace experience, epidemiology and environmental effects listed (16).

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c289 3-chlorotoluene



C₇H₇Cl

Mol. Wt. 126.59

CAS Registry No. 108-41-8

Synonyms *m*-chlorotoluene; 1-chloro-3-methylbenzene; 3-methylchlorobenzene; *m*-tolyl chloride

EINECS No. 203-580-5

Uses Solvent. Dyestuff intermediate. Intermediate in organic synthesis.

Physical properties

M. Pt. -48°C **B. Pt.** 160-162°C **Flash point** 50°C **Specific gravity** 1.0722 at 20°C with respect to water at 4°C

Partition coefficient log *P*_{ow} 3.28 **Volatility** v.p. 9.8 mmHg at 43°C

Solubility Organic solvents: benzene, carbon tetrachloride, chloroform, diethyl ether, ethanol

Occupational exposure

UN No. 2238 HAZCHEM Code 3 $\frac{+}{-}$ Conveyance classification flammable liquid

Supply classification harmful

Supply classification dangerous for the environment

Risk phrases Harmful by inhalation – Toxic to aquatic organisms, may cause long-term adverse effects in the aquatic environment (R20, R51/53)

Safety phrases Keep out of reach of children (if sold to general public) – Avoid contact with skin and eyes – Avoid release to the environment. Refer to special instructions/safety data sheet (S2, S24/25, S61)

Ecotoxicity

Fish toxicity

LC₅₀ (7 day) guppy 18 mg l⁻¹ (1).

Mammalian & avian toxicity

Metabolism and toxicokinetics

In dogs excreted as 3-chlorohippuric acid and in rabbits excreted as 3-chlorobenzoic acid (2).

Legislation

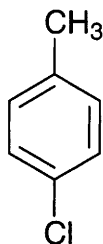
Limited under EC Directive on Drinking Water Quality 80/778/EEC. Organochlorine compounds: guide level 1 µg l⁻¹ (3).

Included in Schedule 6 (Release into Land: Prescribed Substances) of Statutory Instrument No. 472, 1991 (4).

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C290 4-chlorotoluene



C₇H₇Cl

Mol. Wt. 126.59

CAS Registry No. 106-43-4

Synonyms 1-chloro-4-methylbenzene; *p*-chlorotoluene; 4-methylchlorobenzene; *p*-tolyl chloride

EINECS No. 203-397-0

RTECS No. XS 9010000

Uses Solvent. Dyestuff intermediate. Chemical intermediate in organic synthesis.

Physical properties

M. Pt. 6-8°C **B. Pt.** 162°C **Flash point** 49°C **Specific gravity** 1.070 at 20°C with respect to water at 4°C

Partition coefficient log *P*_{ow} 3.33 **Volatility** v.p. 9.8 mmHg at 45°C

Solubility Water: 106 mg l⁻¹ at 20°C. Organic solvents: acetic acid, carbon tetrachloride, chloroform, diethyl ether, ethanol

Occupational exposure

UN No. 2238 **HAZCHEM Code** 3  **Conveyance classification** flammable liquid

Supply classification harmful

Supply classification dangerous for the environment

Risk phrases Harmful by inhalation – Toxic to aquatic organisms, may cause long-term adverse effects in the aquatic environment (R20, R51/53)

Safety phrases Keep out of reach of children (if sold to general public) – Avoid contact with skin and eyes – Avoid release to the environment. Refer to special instructions/safety data sheet (S2, S24/25, S61)

Ecotoxicity

Fish toxicity

LC₅₀ (14 day) guppy 5.9 mg l⁻¹ (1).

Bioaccumulation

Non-accumulative or low accumulative (2).

Environmental fate

Degradation studies

Metabolism by *Pseudomonas putida* to yield (+)-*cis*-4-chloro-2,3-dihydroxy-1-methylcyclohex-4,6-diene and 4-chloro-2,3-dihydroxy-1-methylbenzene. The enzymatic degradation of the former to the latter was demonstrated (3).

Abiotic removal

t_{1/2} for volatilisation from water 3.5 hr (4).

t_{1/2} for reaction with photochemically produced hydroxyl ions 8.4 days (5).

Mammalian & avian toxicity

Acute data

LD₅₀ oral mouse, rat 1900, 3600 mg kg⁻¹, respectively (6,7).

LC₅₀ (2 hr) inhalation mouse 34 g m⁻³ (8).

Metabolism and toxicokinetics

In dogs excreted as 4-chlorohippuric acid (8).

In rabbits excreted as 4-chlorobenzoic acid (9).

Intraperitoneal rat (1g kg⁻¹) resulted in peak blood and lung concentrations of 4-chlorotoluene at 4 hr, which declined to very low levels at 12 hr. 4-Chlorotoluene levels peaked in the liver and declined to low levels at 12 hr. Cytochrome P4502B1 activity in the lung and cytochrome P2B1/2B2 in the liver were significantly inhibited after 1 hr (50% and 40%, respectively) but cytochrome P4501A activity was not affected (10).

Other effects

Any other adverse effects

EC₅₀ cytotoxicity to rat hepatocytes *in vitro* 1.2 mM (11).

Legislation

Limited under EC Directive on Drinking Water Quality 80/778/EEC. Organochlorine compounds: guide level 1 µg l⁻¹ (12).

Included in Schedule 6 (Release into Land: Prescribed Substances) of Statutory Instrument No. 472, 1991 (13).

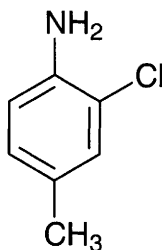
Other comments

Has been detected in water sources.

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c291 2-chloro-*p*-toluidine



C₇H₈ClN

Mol. Wt. 141.60

CAS Registry No. 615-65-6

Synonyms 2-chloro-*p*-toluidine; 2-chloro-4-methylaniline; 4-amino-3-chlorotoluene;
2-chloro-4-methylbenzenamine; *o*-chloro-*p*-toluidine

EINECS No. 210-440-7

RTECS No. XU 5110000

Uses Chemical intermediate.

Physical properties

M. Pt. 7°C B. Pt. 223-225°C Flash point 99°C Specific gravity 1.151 at 20°C with respect to water at 4°C

Occupational exposure

UN No. 2239 HAZCHEM Code 2X Conveyance classification toxic substance

Mammalian & avian toxicity

Acute data

LD₅₀ oral rat 367 mg kg⁻¹ (1).

Metabolism and toxicokinetics

Metabolites of 2-chloro-*p*-toluidine identified in rat liver microsomes by HPLC were products from side-chain C-hydroxylation (benzyl alcohols and benzaldehydes) and *N*-hydroxylation (hydroxylamines and nitroso-derivatives). Aromatic ring hydroxylation was not a major reaction pathway. A halogenated *N*-(4-aminobenzyl)-4-methylaniline (a new type of microsomal metabolite) was also detected. Azoxy, azo, and hydrazo derivatives were also formed. Benzyl alcohols and halogenated *N*-(4-aminobenzyl)-4-methylanilines were the major microsomal metabolites (2).

Irritancy

Dermal rabbit (24 hr) 2 mg caused severe irritation and 250 µg instilled into rabbit eye caused severe irritation (3).

Genotoxicity

Salmonella typhimurium TA100 with or without metabolic activation positive (4,5).

Elicited unscheduled DNA synthesis responses in a DNA repair test with rat hepatocytes (6).

Legislation

Limited under EC Directive on Drinking Water Quality 80/778/EEC. Organochlorine compounds: guide level 1 µg l⁻¹ (7).

Included in Schedule 6 (Release into Land: Prescribed Substances) of Statutory Instrument No. 472, 1991 (8).

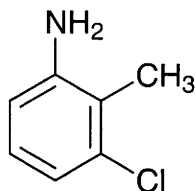
Other comments

Described as a suspected carcinogen on the basis of genotoxicity tests (5).

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c292 3-chloro-o-toluidine



C₇H₈ClN

Mol. Wt. 141.60

CAS Registry No. 87-60-5

Synonyms 1-amino-3-chloro-2-methylbenzene; 2-amino-6-chlorotoluene; 3-chloro-2-methylaniline; 3-chloro-2-methylbenzenamine; *m*-chloro-*o*-toluidine

EINECS No. 201-756-6

RTECS No. XU 4760000

Uses Chemical intermediate.

Physical properties

M. Pt. 0-2°C **B. Pt.** 245°C **Flash point** >110°C **Specific gravity** 1.185 at 20°C with respect to water at 4°C
Solubility Organic solvents: ethanol

Occupational exposure

UN No. 2239 **HAZCHEM Code** 2X **Conveyance classification** toxic substance

Mammalian & avian toxicity

Acute data

LD₅₀ oral starling 562 mg kg⁻¹ (1).
LD₅₀ oral redwing blackbird 237 mg kg⁻¹ (1).
LD₅₀ oral rat 574 mg kg⁻¹ (2).

Genotoxicity

Testicular DNA synthesis in mice was significantly depressed at 200 mg kg⁻¹ (3).

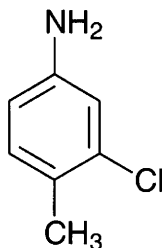
Legislation

Limited under EC Directive on Drinking Water Quality 80/778/EEC. Organochlorine compounds: guide level 1 µg l⁻¹ (4).
Included in Schedule 6 (Release into Land: Prescribed Substances) of Statutory Instrument No. 472, 1991 (5).

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5. S. I. 1991 No. 472 *The Environmental Protection (Prescribed Processes and Substances) Regulations* 1991, HMSO, London, UK

c293 3-chloro-*p*-toluidine



C₇H₈ClN

Mol. Wt. 141.60

CAS Registry No. 95-74-9

Synonyms 4-amino-2-chlorotoluene; 3-chloro-4-methylaniline; 3-chloro-4-methylbenzenamine;
m-chloro-*p*-toluidine

EINECS No. 202-446-3

RTECS No. XU 5111000

Uses Dyestuff industry. Avicide.

Physical properties

M. Pt. 26°C B. Pt. 237-238.5°C Flash point 100°C Specific gravity 1.167

Solubility Water: <1 mg ml⁻¹ at 20°C. Organic solvents: carbon tetrachloride, dimethyl sulfoxide, ethanol

Occupational exposure

UN No. 2239 HAZCHEM Code 2X Conveyance classification toxic substance

Ecotoxicity

Fish toxicity

N-Acetyl-3-chloro-*p*-toluidine was shown to be a metabolite of 3-chloro-*p*-toluidine in bluegill sunfish (1).

Invertebrate toxicity

The median threshold limit values of the hydrochloride in penaeid shrimp and blue crabs are 10.8 and 16.0 ppm, respectively. At concentrations of 25-100 ppm, shrimp jumped about vigorously, became spastic, shuddered and died. At lower concentrations, shrimp exhibited agitation, spastic behaviour, loss of equilibrium and paralysis prior to death. Crabs exhibited agitation and spastic movements similar to shrimp, followed by loss of equilibrium, turning upside down and curling leg appendages (2).

Bioaccumulation

Bluegill sunfish were continuously exposed to 0.1 µg ml⁻¹ for 28 days and steady-state concentrations were reached by day-7. Mean concentrations in the edible, non-edible, and whole-body tissues were 2.9, 12.0 and 7.5 µg g⁻¹ and calculated bioconcentration factors were 33, 150, and 88, respectively. After 28 days depuration 64% of 3-chloro-*p*-toluidine and its metabolites had been eliminated (1)

Environmental fate

Degradation studies

Degraded by soil after 72 hr to 3,3',4,4'-dichlorodimethylazobenzene and 3-chloro-4-methyl-6-(3-chloro-4-methylphenylimino)cyclohexa-2,4-dienone (3).

Pseudomonas cepacia strain CMA1, isolated from soil, utilised 3-chloro-*p*-toluidine in concentrations up to 0.2 g l⁻¹ as the sole source of carbon, nitrogen and energy (4).

Mammalian & avian toxicity

Acute data

LD₅₀ oral rat 1500 mg kg⁻¹ (5).

LD₅₀ oral mouse 316 mg kg⁻¹ (6).

LD₅₀ oral pigeon 13 mg kg⁻¹ (7).

LD₅₀ oral redwing blackbird 2.4 mg kg⁻¹ (7).

In pigeons, treatment with 25 mg kg⁻¹ in diet increased egg breakage, infertility and chick mortality (8).

LD₅₀ intraperitoneal rat 325 mg kg⁻¹ (9).

LD₅₀ intravenous rat 48 mg kg⁻¹ (9).

A lethal dose given systemically to rats or into the cerebroventricular system of cats produced death by respiratory arrest (10).

Carcinogenicity and chronic effects

National Toxicology Program investigated 3-chloro-4-toluidine in rat, mouse via feed. Designated non-carcinogenic in rat and mouse (11).

Metabolism and toxicokinetics

Following intravenous injection of ¹⁴C-labelled compound, radioactivity distributed unevenly in body. Covalent binding to kidney protein exceeded binding to liver protein where a hydroxylamine metabolite was identified (12).

Genotoxicity

Salmonella typhimurium TA98, TA100, TA1535, TA1537 with and without metabolic activation negative (13,14).

Significantly depressed testicular DNA synthesis in mice, oral administration at 200 mg kg⁻¹ (15).

Other effects

Any other adverse effects

Following intraperitoneal injection to rats, metabolic acidosis, hyperkalaemia, haematocrit, loss of plasma proteins and ascitic fluid in abdomen, skeletal muscle paralysis and fall in blood pressure observed (16).

Legislation

Limited under EC Directive on Drinking Water Quality 80/778/EEC. Organochlorine compounds: guide level 1 µg l⁻¹ (17).

Included in Schedule 6 (Release into Land: Prescribed Substances) of Statutory Instrument No. 472, 1991 (18).

Other comments

Injections into starlings caused changes in liver vacuolation and varying degrees of necrosis. Also changes in hyaline granularity of kidney cytoplasm observed (12).

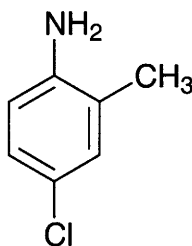
Metabolite of the herbicide chlorotoluron, found in winter wheat (19).

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c294 4-chloro-o-toluidine



C₇H₈ClN

Mol. Wt. 141.60

CAS Registry No. 95-69-2

Synonyms 2-amino-5-chlorotoluene; 4-chloro-2-methylaniline; 4-chloro-2-methylbenzenamine; 4-chloro-2-toluidine; *p*-chloro-*o*-toluidine

EINECS No. 202-441-6

RTECS No. XU 5000000

Uses Manufacture of dyestuffs and pesticides.

Physical properties

M. Pt. 29-30°C **B. Pt.** 241°C **Flash point** 99°C

Solubility Organic solvents: carbon tetrachloride, ethanol

Occupational exposure

UN No. 2239 **HAZCHEM Code** 2X **Conveyance classification** toxic substance

Environmental fate

Nitrification inhibition

Inhibits denitrification in soil (1).

Degradation studies

Resistant to degradation by activated sludge (2).

Mammalian & avian toxicity

Acute data

LD₅₀ oral redwing blackbird, starling 75->100 mg kg⁻¹ (3).

LD₅₀ oral rat 1058 mg kg⁻¹ (4).

LD_{Lo} subcutaneous cat 310 mg kg⁻¹ (5).

Intraperitoneal rats 500 mg kg⁻¹ caused 75% mortality at 24 hr (6).

Carcinogenicity and chronic effects

No adequate data on carcinogenicity to humans, sufficient evidence for carcinogenicity to animals, IARC classification group 2B (7).

Haemangiosarcomas and haemangiomas observed in mice after administration in diet after 39 wk (8).

In similar studies with rats, chromophobe adenomas of the pituitary gland were observed (8).

Metabolism and toxicokinetics

Following oral administration to rats 71% of dose was eliminated in urine and 24.5% in faeces within 72 hr (9).

After intraperitoneal administration to rats, 4-chloro-*o*-toluidine was incorporated into DNA, RNA and protein of liver (10).

Irritancy

Causes irritancy and injury to human urinary tract (11).

Genotoxicity

Salmonella typhimurium TA1535 without metabolic activation positive (12).

Salmonella typhimurium TA98 and TA100 without metabolic activation negative, with metabolic activation positive (13).

V-79 Chinese hamster cell spindle disturbance induction negative (13).

Human lymphocyte chromosome aberration and sister chromatid exchanges negative (13).

Damaged DNA of mammalian (V-79) cells (14).

Gavage mice maximal tolerated dose, mammalian spot test positive (15).

Other effects

Other adverse effects (human)

Gross haematuria and stranguria found among exposed workers (11).

The incidence of bladder cancers (7/49) in a group of workers synthesising chlorodimeform from 4-chloro-*o*-toluidine was significantly higher than that of the cancer registers of the former GDR, Saarland, and Denmark and provides evidence that 4-chloro-*o*-toluidine may be carcinogenic. Latency periods were 15-23 yr (16).

Legislation

Limited under EC Directive on Drinking Water Quality 80/778/EEC. Organochlorine compounds: guide level 1 µg l⁻¹ (17).

Included in Schedule 6 (Release into Land: Prescribed Substances) of Statutory Instrument No. 472, 1991 (18).

Other comments

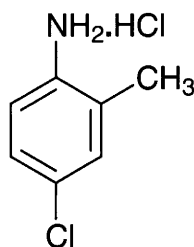
Biodegradation product of the pesticide chlorodimeform (19,20).

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c295 4-chloro-o-toluidine hydrochloride



C₇H₉Cl₂N

Mol. Wt. 178.06

CAS Registry No. 3165-93-3

Synonyms 4-chloro-2-toluidine hydrochloride; 2-amino-5-chlorotoluene hydrochloride;
4-chloro-2-methylaniline hydrochloride

EINECS No. 221-627-8

RTECS No. XU 5250000

Physical properties

Solubility Water: >100mg ml⁻¹ at 20°C

Occupational exposure

UN No. 1579 HAZCHEM Code 2X Conveyance classification toxic substance

Mammalian & avian toxicity

Acute data

LD₅₀ oral pigeon 18 mg kg⁻¹ (1).

LD₅₀ oral rat 655 mg kg⁻¹ (2).

LD₅₀ intraperitoneal mice 388 mg kg⁻¹ (3).

Carcinogenicity and chronic effects

Tested by the National Toxicology Program. 4-Chloro-o-toluidine hydrochloride was administered in feed to ♂ and ♀ rats at 1250 or 5000 ppm for 107 wk, to ♂ mice at 3750 or 15,000 ppm for 99 wk, and to ♀ mice at 1250 or 5000 ppm for 92-99 wk. It was not carcinogenic to rats but was carcinogenic to mice inducing haemangiosarcomas and haemangiomas in both ♂ and ♀ animals (4).

Legislation

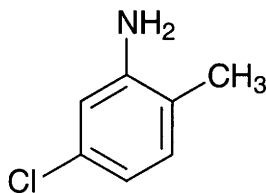
Limited under EC Directive on Drinking Water Quality 80/778/EEC. Organochlorine compounds: guide level 1 µg l⁻¹ (5).

Included in Schedule 6 (Release into Land: Prescribed Substances) of Statutory Instrument No. 472, 1991 (6).

References

1. *Toxicol. Appl. Pharmacol.* 1972, **21**, 315.
2. *Toxicol. Appl. Pharmacol.* 1971, **18**, 517.
3. *Toxicol. Appl. Pharmacol.* 1974, **29**, 135.
4. *Natl. Cancer Inst. Rep.* 1978, DHEW/PUB/NIH-79-1721, US Govt. Print. Off., Washington, DC, USA.
5. *EC Directive Relating to the Quality of Water Intended for Human Consumption* 1982, 80/778/EEC, Office for Official Publications of the European Communities, 2 rue Mercier, L-2985 Luxembourg.
6. *S. I. 1991 No. 472 The Environmental Protection (Prescribed Processes and Substances) Regulations* 1991, HMSO, London, UK

c296 5-chloro-o-toluidine



C₇H₈ClN

Mol. Wt. 141.60

CAS Registry No. 95-79-4

Synonyms 5-chloro-2-toluidine; 2-amino-4-chlorotoluene; 5-chloro-2-methylaniline; 5-chloro-2-methylbenzenamine

EINECS No. 202-452-6

RTECS No. XU 5075000

Uses Intermediate in the manufacture of dyestuffs and in organic synthesis.

Physical properties

M. Pt. 21-22°C B. Pt. 241°C Flash point 160°C

Solubility Water: <1 mg ml⁻¹ at 22°C. Organic solvents: dimethyl sulfoxide, ethanol

Occupational exposure

UN No. 2239 HAZCHEM Code 2X Conveyance classification toxic substance

Mammalian & avian toxicity

Acute data

LD₅₀ oral redwing blackbird, starling 1000-4000 mg kg⁻¹ (1).

LD₅₀ oral rat 464 mg kg⁻¹ (2).

Carcinogenicity and chronic effects

Tested by the National Toxicology Program. No evidence of carcinogenicity in ♂ and ♀ rats when administered via food. Tumours found in circulatory system of ♂ and ♀ mice when administered via food (3).

Administered in feed over 78 wk to ♂/♀ rats (5000 and 2500 ppm) and mice (4000 and 2000 ppm). It was carcinogenic to ♂ and ♀ mice producing haemangiosarcomas and hepatocellular carcinomas. There was no

conclusive evidence in rats although there was a positive, but not statistically significant, association between the concentration administered to ♂ rats and the incidence of adrenal pheochromocytomas (4).

Genotoxicity

Not identified as a mutagen in the L5178Y tk+ /tk- mouse lymphoma cell forward mutation assay (5).

Legislation

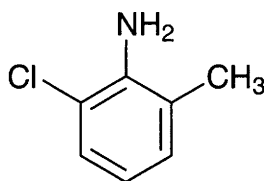
Limited under EC Directive on Drinking Water Quality 80/778/EEC. Organochlorine compounds: guide level 1 µg l⁻¹ (6).

Included in Schedule 6 (Release into Land: Prescribed Substances) of Statutory Instrument No. 472, 1991 (7).

References

1. Schafer, E. W. et al *Arch. Environ. Toxicol.* 1983, **12**, 355-382.
2. *Progress Report for Contract No. NCI-E-C-72-3252* 1973, Litton Bionetics, Inc., Bethesda, MD, USA.
3. Ashby, J. et al *Mutat. Res.* 1988, **204**, 17-155.
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5. McGregor, D. B. et al *Environ. Mol. Mutagen.* 1988, **12**, 85.
6. *EC Directive Relating to the Quality of Water Intended for Human Consumption* 1982, 80/778/EEC, Office for Official Publications of the European Communities, 2 rue Mercier, L-2985 Luxembourg.
7. S. I. 1991 No. 472 *The Environmental Protection (Prescribed Processes and Substances) Regulations* 1991, HMSO, London, UK

c297 6-chloro-o-toluidine



C₇H₈ClN

Mol. Wt. 141.60

CAS Registry No. 87-63-8

Synonyms 2-amino-3-chlorotoluene; 6-chloro-2-methylaniline; 2-chloro-6-methylbenzenamine; 6-chloro-2-toluidine

EINECS No. 201-759-2

RTECS No. XU 5100000

Uses Herbicide intermediate.

Physical properties

M. Pt. 2°C B. Pt. 215°C Flash point 98°C Specific gravity 1.152 at 20°C with respect to water at 4°C

Occupational exposure

UN No. 2239 HAZCHEM Code 2X Conveyance classification toxic substance

Environmental fate

Degradation studies

Degraded by *Rhodococcus rhodochrous* which was isolated from soil (1).

Legislation

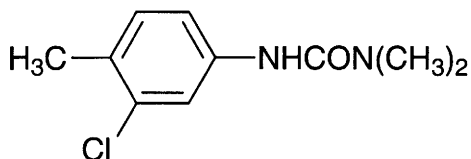
Limited under EC Directive on Drinking Water Quality 80/778/EEC. Organochlorine compounds: guide level $1 \mu\text{g l}^{-1}$ (2).

Included in Schedule 6 (Release into Land: Prescribed Substances) of Statutory Instrument No. 472, 1991 (3).

References

1. Voelskow, H. et al (Hoechst A.-G.) Ger. Offen. DE 3,417,443 (Cl. C12N1/20) 14 Nov. 1985, (*Chem. Abstr.*, **104**, 94856z).
2. EC Directive Relating to the Quality of Water Intended for Human Consumption 1982, 80/778/EEC, Office for Official Publications of the European Communities, 2 rue Mercier, L-2985 Luxembourg.
3. S. I. 1991 No. 472 *The Environmental Protection (Prescribed Processes and Substances) Regulations 1991*, HMSO, London, UK

c298 chlorotoluron



$\text{C}_{10}\text{H}_{13}\text{ClN}_2\text{O}$

Mol. Wt. 212.68

CAS Registry No. 15545-48-9

Synonyms *N'*-(3-chloro-4-methylphenyl)-*N,N*-dimethylurea; 3-(3-chloro-4-methylphenyl)-1,1-dimethylurea; 3-(3-chloro-*p*-tolyl)-1,1-dimethylurea; Dicuran; Afraclor; Agritoluron; Camal; Chlortocide

EINECS No. 239-592-2

RTECS No. YS 7230000

Uses Herbicide.

Physical properties

M. Pt. 147°C **Specific gravity** 1.40 at 20°C with respect to water at 4°C **Partition coefficient** $\log P_{\text{ow}}$ 2.29

Volatility v.p. 7.78×10^{-8} mmHg

Solubility Water: 70 mg l^{-1} at 20°C . Organic solvents: acetone, benzene, dichloromethane, propanol

Ecotoxicity

Fish toxicity

LC_{50} (96 hr) rainbow trout $20\text{--}35 \text{ mg l}^{-1}$ (1).

LC_{50} (96 hr) bluegill sunfish $40\text{--}50 \text{ mg l}^{-1}$ (1).

LC_{50} (96 hr) carp $>100 \text{ mg l}^{-1}$ (1).

Environmental fate

Nitrification inhibition

No effect on nitrification of ammonia was noted when applied to a sandy clay loam soil at 0.0001–0.001%.

Nitrification was 85–90% in the first 16 days and was complete after 16–24 days. At 0.01%, nitrification was 27–38% in the first 32 days and completed over 32–64 days. At 0.1% nitrification of 15–18% in the first 32 days and only 36% after 64 days (2).

Degradation studies

50% degradation in soil 30–40 day (1).

Ninety strains of micromycetes isolated from soil were cultivated in liquid synthetic medium with 100 mg l^{-1} chlorotoluron for five days. The chlorotoluron concentration was $>50\%$ depleted by 4% of the strains (3).

Abiotic removal

50% hydrolysis in 18-45 months (calc.) (1).

Mammalian & avian toxicity

Acute data

LD₅₀ oral rat >10 g kg⁻¹ (1).

LD₅₀ percutaneous rat 2000 mg kg⁻¹ (1).

LC₅₀ inhalation rat 1300 mg m⁻³ (duration unspecified) (4).

Sub-acute and sub-chronic data

No-effect level for rats, 90-day feeding trial, 800 mg kg⁻¹ diet. No-effect level for dogs, 90-day feeding trial, 600 mg kg⁻¹ diet (1).

Teratogenicity and reproductive effects

Oral ♂ rats (10 wk) 0.2 or 2.0 mg kg⁻¹ day⁻¹ 5 day wk⁻¹ caused no changes in testes and spermatozoa (5).

Oral ♂ rats (10 wk) 0.2 or 2.0 mg kg⁻¹ day⁻¹ 5 day wk⁻¹ were mated with intact ♀. The offspring had reduced body weight and length. Doses of 2.0 or 20 mg kg⁻¹ in diet had no effect on the foetuses. It was concluded that the observed adverse effects were due to the method of administration (5).

Metabolism and toxicokinetics

Oral mammal >90% is excreted via urine and faeces within 24 hr. In rats administration (route not specified) of ¹⁴C-tolyl labelled herbicide revealed that the methyl ring substituent was subjected to stepwise oxidation yielding first the corresponding hydroxymethyl and then the carboxy derivative. The combined *N*-dimethylation/side-chain oxidation pathway is: 3-(3-chloro-4-hydroxymethylphenyl)-1,1-dimethylurea; 3-(3-chloro-4-carboxyphenyl)-1,1-dimethylurea; 3-(3-chloro-4-hydroxymethylphenyl)-1-methylurea; 3-(3-chloro-4-carboxyphenyl)-1-methylurea; 3-(3-chloro-4-hydroxymethylphenyl)urea; and 3-(3-chloro-4-carboxyphenyl)urea (6).

Whole cells and microsomal fractions of *Saccharomyces cerevisiae* expressing human cytochrome P450 3A4 metabolised chlorotoluron to four metabolites: hydroxylated-*N*-monomethylated, hydroxylated ring methylated, *N*-dimethylated, and *N*-monodemethylated products. Chlorotoluron metabolism was absolutely dependent on NADPH (7).

Irritancy

Reported to be non-irritating to skin and eyes of rabbit (1).

Genotoxicity

Seedlings of bread wheat (*Triticum aestivum* L. em Thell cv. Pitoma) treated with 0.1 or 10 µM chlorotoluron for 24 hr and allowed to recover in tap water for 24 hr showed mitotic inhibition in root-tip cells, chromosomal aberrations and mitotic abnormalities (8).

Legislation

Limited under EC Directive on Drinking Water Quality 80/778/EEC. Herbicides: maximum admissible concentration 0.1 µg l⁻¹ (9).

Included in Schedule 6 (Release into Land: Prescribed Substances) of Statutory Instrument No. 472, 1991 (10).

Other comments

Advisory value for drinking water, Department of the Environment, 80 µg l⁻¹ (11).

WHO Class Table 5 (1).

US EPA Toxicity Class IV (1).

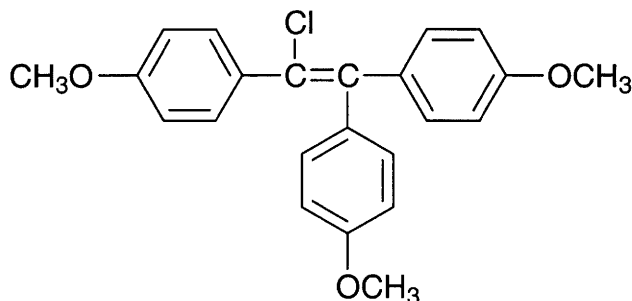
Metabolic pathways reviewed (12).

References

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2. Haleami, M. A. et al *Pak. J. Sci. Ind. Res.* 1988, **31**(11), 798-800, (*Chem. Abstr.* **10**, 168067r).

3. Vroumsia, T. et al *Chemosphere* 1996, **33**(10), 2045-2056.
4. Perkow, W. *Wirksubstanzen der Pflanzenschutz und Schadlings-Bekämpfungsmittel* 1976, Verlag Paul Parey, Berlin, Germany.
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6. Kearney, P. C. et al (Eds.) *Herbicides: Chemistry Degradation and Mode of Action* 2nd ed., 1975, 248, Mercel Dekker, NY, USA.
7. Mehmood, Z. et al *Chemosphere* 1995, **31**(11/12), 4515-4529.
8. Pavlica, M. et al *Period. Biol.* 1996, **98**(3), 387-390.
9. *EC Directive Relating to the Quality of Water Intended for Human Consumption* 1982, 80/778/EEC, Office for Official Publications of the European Communities, 2 rue Mercier, L-2985 Luxembourg.
10. *S. I. 1991 No. 472 The Environmental Protection (Prescribed Processes and Substances) Regulations* 1991, HMSO, London, UK.
11. *Guidance on Safeguarding the Quality of Public Water Supplies* 1989, 99, HMSO, London, UK.
12. Roberts, T.R. et al (Eds.) *Metabolic Pathways of Agrochemicals. Part 1: Herbicides and Plant Growth Regulators* 1998, The Royal Society of Chemistry, Cambridge, UK

c299 chlorotrianisene



$C_{23}H_{21}ClO_3$

Mol. Wt. 380.87

CAS Registry No. 569-57-3

Synonyms tri-*p*-anisylchloroethylene; ethylene, chlorotris(*p*-methoxyphenyl)-; benzene, 1,1',1''-(1-chloro-1-ethenyl-2-ylidene)tris(4-methoxy)-; TACK

EINECS No. 209-318-6

RTECS No. KV 0600000

Uses Oestrogen.

Physical properties

M. Pt. 114-116°C

Solubility Water: 1 in 4200 in water. Organic solvents: acetone, benzene, chloroform, diethyl ether, ethanol

Mammalian & avian toxicity

Carcinogenicity and chronic effects

Available animal data are insufficient to allow an evaluation of the carcinogenicity of the compound (1,2). Oral ♂, ♀ rat (2 yr) 0, 0.5, 0.2, 2 mg kg⁻¹ day⁻¹. The incidences of pituitary tumours were 1, 1 and 0 in treated ♂, compared to 4 in ♂ controls, and 2, 0 and 0 in treated ♀, compared to 4 in ♀ controls. Mammary tumours occurred in 1 ♂ given 2 mg kg⁻¹ day⁻¹, compared with 0 in ♂ controls, and in 2, 0 and 2 ♀ given 0.05, 0.2 and 2 mg kg⁻¹ day⁻¹ respectively, compared with 8 in ♀ controls. At the end of 2 yr the number of survivors were 9/20 ♂ and 12/20 ♀ controls, 15/20 ♂ and 19/20 ♀ given 0.05 mg kg⁻¹, 18/20 ♂ and 17/20 ♀ given 0.2 mg kg⁻¹, and 12/20 ♂ and 11/20 ♀ given 2 mg kg⁻¹ (1).

Metabolism and toxicokinetics

Stored preferentially in adipose tissue (1).

Genotoxicity

Salmonella typhimurium TA98, TA100, TA1535, TA1537 with and without metabolic activation negative (3).

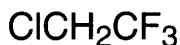
Legislation

Limited under EC Directive on Drinking Water Quality 80/778/EEC. Organochlorine compounds: guide level $1 \mu\text{g l}^{-1}$ (4).

References

1. IARC Monograph 1979, **21**, 139-146.
2. IARC Monograph 1987, **Suppl. 7**, 68.
3. Zeiger, E. et al *Environ. Mutagen.* 1987, **9**(Suppl. 9), 1-109.
4. EC Directive Relating to the Quality of Water Intended for Human Consumption 1982, 80/778/EEC, Office for Official Publications of the European Communities, 2 rue Mercier, L-2985 Luxembourg

c300 2-chloro-1,1,1-trifluoroethane



$\text{C}_2\text{H}_2\text{ClF}_3$

Mol. Wt. 118.49

CAS Registry No. 75-88-7

Synonyms chloro-1,1,1-trifluoroethane; 1-chloro-2,2,2-trifluoroethane; 2,2,2-trifluorochloroethane; 1,1,1-trifluoro-2-chloroethane; 1,1,1-trifluorethyl chloride

EINECS No. 200-912-0

RTECS No. KH 8008500

Uses Blowing agent. Refrigerant. Intermediate in synthesis of halothane.

Physical properties

M. Pt. -105.5°C B. Pt. 6.93°C Specific gravity 1.389 at 0°C with respect to water at 4°C

Occupational exposure

UN No. 1983 HAZCHEM Code 2RE Conveyance classification non-flammable non-toxic gas

Environmental fate

Abiotic removal

On the basis of its calculated rate of reaction with hydroxyl radicals, estimated tropospheric $t_{1/2}$ 5 yr (1).

Mammalian & avian toxicity

Acute data

LC_{50} (1 hr) inhalation mouse 15 pph (2).

Carcinogenicity and chronic effects

No adequate data for evaluation of carcinogenicity in humans, limited evidence for carcinogenicity in animals, IARC classification group 3 (3).

Oral gavage rats (52 wk) 300 mg kg^{-1} , 5 day wk^{-1} in corn oil caused reduced growth and increased aggressive behaviour. The incidence of uterine carcinomas was 15/35 in ♀ and the incidence of benign (often bilateral) interstitial-cell neoplasms of the testes was 29/36 in treated ♂ (4).

Teratogenicity and reproductive effects

Oral gavage rat (52 wk) 300 mg kg⁻¹, 5 day wk⁻¹ caused arrest of spermatogenesis and seminiferous tubular atrophy (4).

Metabolism and toxicokinetics

Inhalation ♂ Fischer 344 rats (2 hr) 1% 2-chloro-1,1,1-trifluoroethane. Metabolites found in the urine collected in the first 24 hr after exposure were 2,2,2-trifluoroethyl glucuronide, trifluoroacetic acid, trifluoroacetaldehyde hydrate, trifluoroacetaldehyde-urea adduct, inorganic fluoride, and a minor unidentified metabolite. With NADPH-fortified rat liver microsomes chloro-1,1,1-trifluoroethane was converted into dichlorofluoroacetic acid (5).

Genotoxicity

Salmonella typhimurium TA98, TA100 and TA1535 with and without metabolic activation negative (4,6).

Legislation

Limited under EC Directive on Drinking Water Quality 80/778/EEC. Organochlorine compounds: guide level 1 µg l⁻¹ (7).

Included in Schedules 4 and 6 (Release into Air and Land: Prescribed Substances) of Statutory Instrument No. 472, 1991 (8).

Other comments

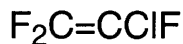
Reviews on experimental toxicology and human health effects listed (9).

Chemical intermediate in the production of the anaesthetic halothane. Human exposure results from the presence as a low level impurity in, and as a metabolite of, halothane.

References

1. Makide, Y. et al *Proc. Natl. Acad. Sci. USA* 1981, **78**, 5933-5937.
2. *Br. J. Anaesth.* 1965, **37**, 716.
3. *IARC Monograph* 1987, **Suppl.** 7, 60.
4. Longstaff, E. et al *Toxicol. Appl. Pharmacol.* 1984, **72**, 15-31.
5. Yin, H. et al *Chem. Res. Toxicol.* 1995, **8**(2), 262-268.
6. Waskell, L. *Anesthesiology* 1979, **50**, 9-12.
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8. *S.I. 1991, No.472 The Environmental Protection (Prescribed Processes and Substances) Regulations* 1991, HMSO, London, UK.
9. *ECETOC Technical Report No. 71* 1996, European Centre for Ecotoxicology and Toxicology of Chemicals, 4 Avenue E. Van Nieuwenhuysse (Bte 6), B-1160 Brussels, Belgium

c301 chlorotrifluoroethylene



C₂ClF₃

Mol. Wt. 116.47

CAS Registry No. 79-38-9

Synonyms chlorotrifluoroethene; 1-chloro-1,2,2-trifluoroethylene; trifluorochloroethylene; trifluorovinyl chloride

EINECS No. 201-201-8

RTECS No. KV 0525000

Uses Chemical intermediate. Monomer for resins which are used as high performance lubricants, plastics and elastomers.

Physical properties

M. Pt. -157.5°C B. Pt. -27.9°C Flash point -27.8°C Specific gravity 1.54 at -60°C with respect to water at 4°C Volatility v.den. 4.13
Solubility Organic solvents: benzene, chloroform

Occupational exposure

UN No. 1082 HAZCHEM Code 2WE Conveyance classification flammable gas

Mammalian & avian toxicity

Acute data

LC₅₀ (7 hr) inhalation mouse 3000 ppm (1).

LC₅₀ (4 hr) inhalation rat 1000 ppm (2).

Sub-acute and sub-chronic data

Inhalation ♂ rats 395 ppm (1882 mg m⁻³) for 4 hr day⁻¹ for 5 consecutive days. Within 1 day of exposure, diuresis, increased water intake, decreased urine osmolarity, increased urinary lactate dehydrogenase activity and increased plasma creatinine and urea nitrogen were found. On continued exposure, values for these parameters declined or returned to control levels. By the 3rd day coagulative necrosis of the kidney involving primarily the pars recta, but extending to the pars convoluta, of the proximal tubule was present. Regeneration was apparent by the 3rd day and additional necrosis was minimal (3).

Metabolism and toxicokinetics

Oxidatively metabolised by cytochrome P₄₅₀ to intermediates which inactivate the cytochrome P₄₅₀ by destroying haem, and to epoxides which may react with cellular macromolecules or decompose to other products (species unspecified) (4).

Irritancy

Application to intact rabbit skin did not produce any signs of irritation. However, continued skin contact was reported to produce an allergic response in some individuals. The fluid produced mild conjunctival redness when instilled into rabbit eye 1 hr following application, but recovery occurred within 24 hr (5).

Legislation

Included in Schedule 4 (Release into Air: Prescribed Substances) of Statutory Instrument No. 472, 1991 (6).

References

1. *Acta Biol. Med. Germ.* 1968, **21**, 377.
2. *Fluorine Chemistry Reviews* 1967, **1**, 197.
3. Buckley, L. A. et al *Fundam. Appl. Toxicol.* 1982, **2**(4), 181.
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6. S. I. 1991 No. 472 *The Environmental Protection (Prescribed Processes and Substances) Regulations* 1991, HMSO, London, UK

c302 chlorotrifluoromethane



CClF_3

Mol. Wt. 104.46

CAS Registry No. 75-72-9

Synonyms trifluorochloromethane; Genetron 13

EINECS No. 200-894-4

RTECS No. PA 6410000

Uses Fire extinguishing agent. Lubricant. Refrigerant. Propellant for aerosol sprays. Etching gas in production of integrated circuits.

Physical properties

M. Pt. -181°C B. Pt. -82°C Volatility v.p. 400 mmHg at -92.7°C

Occupational exposure

DE-MAK 1000 ppm (4300 mg m^{-3})

UN No. 1022 HAZCHEM Code 2RE Conveyance classification non-flammable non-toxic gas

Other effects

Other adverse effects (human)

There are isolated reports of poisoning from exposure to fluorocarbon propellants and some studies have shown a higher incidence of coronary heart disease among exposed clinical pathologists, hospital personnel and refrigerant mechanics (1).

Legislation

Included in Schedule 4 (Release into Air: Prescribed Substances) of Statutory Instrument No. 472, 1991 (2).

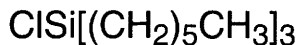
Other comments

Present in landfill gas. Indirect effects from accumulation in stratosphere may lead to substantial effects on human health due to ozone depletion with resulting increase in effects of UVB radiation (3).

References

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2. S. I. 1991 No. 472 *The Environmental Protection (Prescribed Processes and Substances) Regulations* 1991, HMSO, London, UK.
3. *International Programme on Chemical Safety* 1990, 164, WHO, Geneva, Switzerland

c303 chlorotrihexylsilane



$\text{C}_{18}\text{H}_{39}\text{SiCl}$

Mol. Wt. 319.05

CAS Registry No. 3634-67-1

Synonyms trihexylsilane, Si-chloro-

EINECS No. 222-851-9

B. Pt. 153.5°C at 5 mmHg Flash point >110°C Specific gravity 0.871

Ecotoxicity

Bioaccumulation

No or low bioaccumulation (1).

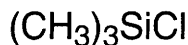
Legislation

Included in Schedule 6 (Release into Land: Prescribed Substances) of Statutory Instrument No. 472, 1991 (2).

References

1. *JETOC Newsletter* 1988, (6), 15-17, Japan Chemical Industry Ecology Toxicology and Information Center.
2. S. I. 1991 No. 472 *The Environmental Protection (Prescribed Processes and Substances) Regulations* 1991, HMSO, London, UK

c304 chlorotrimethylsilane



C₃H₉ClSi

Mol. Wt. 108.64

CAS Registry No. 75-77-4

Synonyms trimethylchlorosilane; silane, chlorotrimethyl-

EINECS No. 200-900-5

RTECS No. VV 2710000

Uses Preparation of volatile derivatives of a wide range of biologically active compounds for GC analysis. Silylating agent. Intermediate for silicone fluids. Chain-terminating agent imparting water repellency.

Physical properties

M. Pt. -40°C B. Pt. 57°C Flash point -27°C Specific gravity 0.858 at 25°C with respect to water at 4°C

Solubility Water: <5 mg ml⁻¹ at 19°C. Organic solvents: acetone, benzene, diethyl ether, ethanol

Occupational exposure

UN No. 1298 HAZCHEM Code 4WE Conveyance classification flammable liquid, corrosive

Environmental fate

Abiotic removal

Rapidly hydrolysed to hexamethyldisiloxane.

Mammalian & avian toxicity

Acute data

LD₅₀ intraperitoneal mouse 750 mg kg⁻¹ (1).

LD₅₀ oral Sprague Dawley rat 5.6 (♂), 6.63 (♀) ml kg⁻¹ (2).

Metabolism and toxicokinetics

Rapidly hydrolysed upon contact with tissue fluids releasing hydrochloric acid (3).

Irritancy

Reported to be strongly irritating to the eyes, skin and mucous membranes of rabbits (2).

Genotoxicity

Salmonella typhimurium TA97, TA98, TA100, TA1535, TA1537 without metabolic activation positive (4).

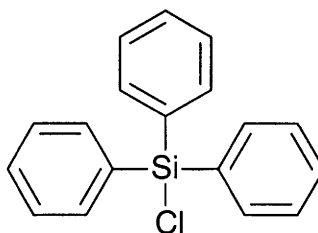
Legislation

Included in Schedule 6 (Release into Land: Prescribed Substances) of Statutory Instrument No. 472, 1991 (5).

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c305 chlorotriphenylsilane



$C_{18}H_{15}ClSi$

Mol. Wt. 294.86

CAS Registry No. 76-86-8

Synonyms triphenylsilyl chloride

EINECS No. 200-989-0

RTECS No. VV 2720000

Uses Catalyst for epoxy resins.

Physical properties

M. Pt. 92-94°C B. Pt. 378°C

Ecotoxicity

Bioaccumulation

No or low bioaccumulation (1).

Mammalian & avian toxicity

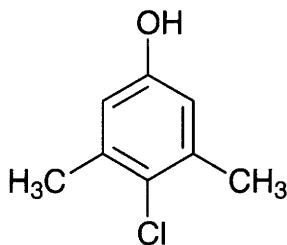
Acute data

LD₅₀ intravenous mouse 56 mg kg⁻¹ (2).

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C306 4-chloro-3,5-xyleneol



C_8H_9ClO

Mol. Wt. 156.61

CAS Registry No. 88-04-0

Synonyms 4-chloro-3,5-dimethylphenol; *p*-chloro-*m*-xyleneol; chloroxylenol; Nipacide MX; Ottasept Extra

EINECS No. 201-793-8

RTECS No. ZE 6850000

Uses Skin and wound disinfectant. Preservative in textiles, cosmetics, dyestuffs, paints, detergents, adhesives and other preparatives. Acaricide.

Physical properties

M. Pt. 115.5°C **B. Pt.** 246°C

Solubility Water: 0.33 g l⁻¹ at 20°C. Organic solvents: diethyl ether, ethanol, fixed oils, terpenes

Occupational exposure

Supply classification harmful

Risk phrases Harmful if swallowed – Irritating to eyes and skin – May cause sensitisation by skin contact (R22, R36/38, R43)

Safety phrases Keep out of reach of children (if sold to general public) – Avoid contact with the skin – Wear suitable gloves (S2, S24, S37)

Ecotoxicity

Invertebrate toxicity

EC₅₀ (5 min) *Photobacterium phosphoreum* 1.99 ppm Microtox test (1).

EC₅₀ (24, 48 hr) *Daphnia magna* 4.7 mg l⁻¹ and 4.5 mg l⁻¹, respectively (2).

Mammalian & avian toxicity

Acute data

LD₅₀ oral rat 3830 mg kg⁻¹ (3).

LD_{Lo} oral mouse 1260 mg kg⁻¹ (4).

LD₅₀ intraperitoneal mouse 115 mg kg⁻¹ (4).

Carcinogenicity and chronic effects

♀ Mice were treated by dermal application 2 × wk⁻¹ for 6, 12 and 18 months. No significant effects on survival were apparent and no skin tumours were observed (5).

Teratogenicity and reproductive effects

Oral administration to rats of 17,100 mg kg⁻¹ total dose on days 1-19 pregnancy produced teratogenic effects (6).

Metabolism and toxicokinetics

In humans, following accidental ingestion, about one-third excreted as glucuronide and sulfate conjugates in the urine (7).

Sensitisation

May cause allergic contact dermatitis in man (8).

Other effects

Any other adverse effects

Liver may be an important target of toxicity: administration of 78 mg l⁻¹ to primary culture of rat hepatocytes caused cytotoxicity, morphological changes and interfered with metabolic function (9).

Legislation

Limited under EC Directive on Drinking Water Quality 80/778/EEC. Organochlorine compounds: guide level 1 µg l⁻¹ (10).

Included in Schedule 6 (Release into Land: Prescribed Substances) of Statutory Instrument No. 472, 1991 (11).

Other comments

Effective as a disinfectant against *Streptococcus* spp. but less active against *Staphylococcus* spp. and Gram-negative organisms and is often inactive against *Pseudomonas* spp. (7).

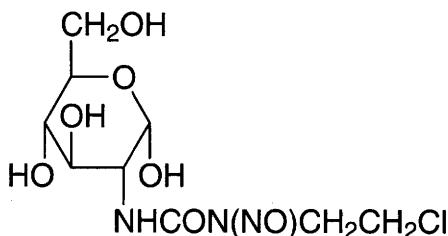
Toxicity reviewed (12).

Pharmacokinetics and metabolism reviewed (13).

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c307 chlorozotocin



C₉H₁₆ClN₃O₇

Mol. Wt. 313.69

CAS Registry No. 54749-90-5

Synonyms 2-([(2-chloroethyl)nitrosoamino]carbonyl)amino-2-deoxy-D-glucose; D-glucopyranose, 2-([(2-chloroethyl)nitrosoamino]carbonyl)amino-2-deoxy-, 1-(2-chloroethyl)-1-nitroso-3-(D-glucos-2-yl)urea; 2-[3-(2-chloroethyl)-3-nitrosoureido]-2-deoxy-D-glucopyranose; 1-(2-chloroethyl)-3-(D-glucopyranos-2-yl)-1-nitrosourea; DCNU

RTECS No. LZ 5758000

Uses Antineoplastic agent.

Physical properties

M. Pt. 147-148°C Partition coefficient $\log P_{ow}$ 0.477 (1)

Solubility Water: miscible

Mammalian & avian toxicity

Acute data

LD₅₀ intravenous, intraperitoneal rat 22-28 mg kg⁻¹ (2,3).

LD₅₀ subcutaneous mouse 66 mg kg⁻¹ (4).

Sub-acute and sub-chronic data

♂ Rats were administered a single subcutaneous dose of 12.5, 25 or 40 mg kg⁻¹. The high dose produced acute cortical necrosis involving the proximal tubules, followed by later necrotic changes in the collecting ducts in the inner medulla. Karyomegaly was noted at 10 days in occasional cells of the papillary collecting ducts and urinary epithelium lining the papilla. The intermediate dose produced similar though less severe injury of later onset while no histopathological effect was observed following the lower dose (5).

Central nervous system vascular necrosis was observed in beagle dogs treated at 1.5 to 2.0 mg kg⁻¹ once a wk for 2 wk, or with a single intraventricular dose of 10 mg kg⁻¹ (6).

Intraperitoneal injections at 20 mg kg⁻¹ to mice reduced peripheral lymphocyte counts by 50% in three days.

Spleen weights were decreased by about 40% and the response to mitogens was markedly reduced (7).

Carcinogenicity and chronic effects

There is sufficient evidence for carcinogenicity to animals. No data were available from studies in humans.

However, noting that chlorozotocin is an alkylating agent which is structurally similar to other chloroethyl nitrosoureas shown to be carcinogenic, the IARC working group made an overall evaluation that it is probably carcinogenic to humans, IARC classification group 2A (8).

National Toxicology Program classification: reasonably anticipated to be a human carcinogen (9).

Rats were given intraperitoneal injections at 0.4 or 2.0 mg kg⁻¹ once a wk for up to 800 days. Sarcomas and mesotheliomas of the peritoneal cavity occurred in 13/20 and 14/20 in the high and low dose ♂ respectively, compared to 0/20 in controls and in 16/20 and 10/20 in the high and low dose ♀, respectively (2).

Groups of 30 rats were given intravenous injections at 9.5, 19 or 38 mg m⁻² (body surface) every 6 wk (10 applications in total). The animals were observed for life. Malignant tumours of the nervous system, lung and forestomach were found in 4 to 5% of treated animals compared to 0 to 1% in control groups (10).

Metabolism and toxicokinetics

After an intravenous dose of 120 mg m⁻² (body surface), to humans, the disappearance curve of the N-nitroso group from the circulation exhibited three successive exponential phases, with $t_{1/2}$ of 3-4.5 min, 6-12 min and 18-30 min, respectively. 24 hr after administration of either ethyl or glucose radiolabelled chlorozotocin, 82-84% of the blood-borne radioactivity was bound to protein; after 7 days 2% of the peak radioactivity value was detected in the blood. By 48 hr, 50% of the radioactivity from [ethyl-¹⁴C]chlorozotocin and 58% of that from [glucose-¹⁴C]chlorozotocin was excreted in the urine. Only 5-8% was excreted as the intact drug (11).

Genotoxicity

Induced base-pair substitutions but not frameshift mutations in *Salmonella typhimurium* TA100, TA1535 with and without metabolic activation (12-14).

Induced sex-linked recessive mutations in *Drosophila melanogaster* (15).

Induced mutation in the *hprt* locus in V79 Chinese hamster cells (16).

Induced sister chromatid exchanges in mouse L 1210 leukaemia cells (17).

A single intraperitoneal dose of 31.4 mg kg⁻¹ induced DNA strand breaks and interstrand cross-links in rat bone marrow cells *in vivo* (18).

Other effects

Other adverse effects (human)

Progressive anaemia was noted in a 46-yr-old woman following intravenous administration 120 mg m⁻² body surface every 6 wk for 18 months, for treatment of bronchoalveolar carcinoma. Over the following 4 to 6 wk fatal

renal failure developed (19).

Thrombocytopenia, leucopenia, elevated aminotransferase activity, nausea and vomiting were seen in patients after intravenous administration, generally at doses of 120 mg m⁻² (body surface) or higher (11).

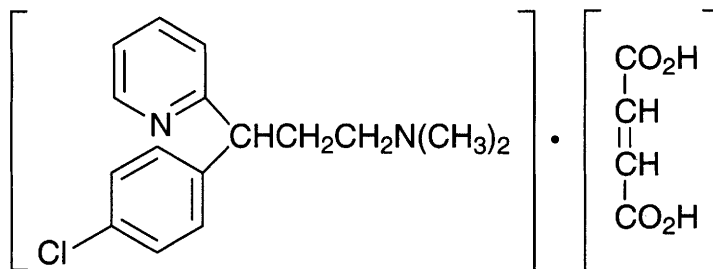
Any other adverse effects

Renal toxicity, acute tubular necrosis, bone marrow hypoplasia and lymphoid atrophy were produced with intravenous administration to mice, dog and monkey. Effects were dose related (20).

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c308 chlorpheniramine maleate



C₂₀H₂₃ClN₂O₄

Mol. Wt. 390.87

CAS Registry No. 113-92-8

Synonyms γ-(4-chlorophenyl)-N,N-dimethyl-2-pyridinepropanamine, (Z)-2-butenedioate (1:1);

(±)-3-(4-chlorophenyl)-N,N-dimethyl-3-(2-pyridyl)propylamine hydrogen maleate; Teldrin; Chlor-Trimeton

EINECS No. 204-037-5

RTECS No. US 6475000

Uses Antihistamine.

Physical properties

M. Pt. 130-135°C

Solubility Water: 160 mg ml⁻¹ at 25°C. Organic solvents: chloroform, ethanol, methanol; slightly soluble in benzene, ether

Mammalian & avian toxicity

Acute data

LD₅₀ oral redwing blackbird, starling 75, 100 mg kg⁻¹, respectively (1).

LD₅₀ oral mouse, rat 160, 300 mg kg⁻¹, respectively (2,3).

LD₅₀ subcutaneous rat 365 mg kg⁻¹ (4).

LD₅₀ subcutaneous mouse 100 mg kg⁻¹ (5).

LD₅₀ intraperitoneal mouse 77 mg kg⁻¹ (5).

Carcinogenicity and chronic effects

The National Toxicology Program tested rats and mice via gavage. Rats (2 yr) 30 and 60 mg kg⁻¹; and mice 50 and 200 mg kg⁻¹ 5 × wk⁻¹. There was no evidence of carcinogenicity (6).

Teratogenicity and reproductive effects

Lowest toxic dose, reproductive effects, oral mouse (1-21 days of gestation) 420 mg kg⁻¹ (7).

Metabolism and toxicokinetics

Following oral administration to humans and experimental animals ³H-chlorpheniramine maleate is absorbed rapidly and quantitatively from the gut. Although plasma levels of total radioactivity are prolonged, plasma t_{1/2} of chlorpheniramine is only 12-15 hr in man and 3 hr in dog. t_{1/2} in man is about 3 times longer than therapeutic effect (8).

Genotoxicity

Salmonella typhimurium TA97, TA98, TA100, TA1535, TA1537 with or without metabolic activation negative (9).

Chromosomal aberrations and sister chromatid exchanges in CHO cells negative. Mutation in mouse lymphoma cells negative (10).

Gives a false-positive in the *in vitro* alkaline elution/rat hepatocyte assay for DNA damage (11).

Other effects

Other adverse effects (human)

The first known case of agranulocytosis was reported as being due to the widely used over-the-counter antihistamine, chlorpheniramine (12).

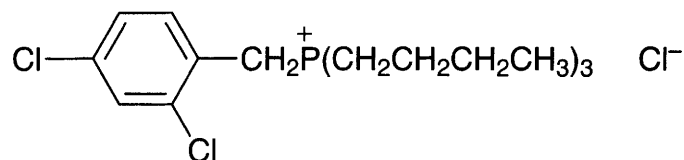
Central nervous depression is usually the dominant reaction in adults, evidenced by drowsiness, lethargy, fatigue, hypnosis and coma. Related nervous symptoms include vertigo, ataxia, tinnitus and blurred vision (13).

Inhibition of human blood platelet aggregation, IC₅₀ 50 mg l⁻¹ (14).

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C309 chlorphonium chloride



$\text{C}_{19}\text{H}_{32}\text{Cl}_3\text{P}$

Mol. Wt. 397.79

CAS Registry No. 115-78-6

Synonyms tributyl[(2,4-dichlorophenyl)methyl]phosphonium chloride;
2,4-dichlorobenzyltributylphosphonium chloride; Phosfleur

EINECS No. 204-105-4

RTECS No. TA 2975000

Uses Plant growth regulator.

Physical properties

M. Pt. 114-20°C Volatility v.p. 6.975×10^{-7} mmHg

Solubility Water: 960 g l⁻¹ at 20°C. Organic solvents: acetone, methanol

Occupational exposure

Supply classification toxic

Risk phrases Harmful in contact with skin – Toxic if swallowed – Irritating to eyes and skin (R21, R25, R36/38)

Safety phrases Keep locked up and out of the reach of children (if sold to general public) – Wear suitable protective clothing, gloves and eye/face protection – In case of accident or if you feel unwell, seek medical advice immediately (show label where possible) (S1/2, S36/37/39, S45)

Ecotoxicity

Fish toxicity

LC₅₀ (96 hr) rainbow trout 115 mg l⁻¹ (1).

Environmental fate

Degradation studies

Degradation t_{1/2} in standard German soil 2.2 & 2.3 > 28 months when stored under BBA conditions (1).

Mammalian & avian toxicity

Acute data

LD₅₀ oral redwing blackbird > 100 mg kg⁻¹ (2).

LD₅₀ oral rat 210 mg kg⁻¹ (1).

LD₅₀ dermal rabbit 750 mg kg⁻¹ (1).

Irritancy

Reported to be irritating to skin and eyes (species unspecified) (1).

Genotoxicity

Negative in dominant lethal mutagenicity assay in mice *in vivo* (3).

Other effects

Any other adverse effects

Intraperitoneal administration to adult ♂ rats stimulated incorporation of radioactive acetate into cholesterol in

organs including the liver and adrenal glands. However, liver preparations from treated rats did not incorporate acetate *in vitro* at an increased rate. This effect was not seen with weanlings, or when cholesterol precursors, glucose and mevalonate, were administered (4).

Legislation

Limited under EC Directive on Drinking Water Quality 80/778/EEC. Pesticides: maximum admissible concentration 0.1 µg l⁻¹ (5).

Included in Schedule 6 (Release into Land: Prescribed Substances) of Statutory Instrument No. 472, 1991 (6).

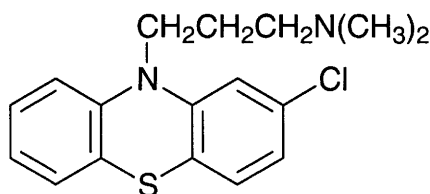
WHO toxicity class II (7).

EPA toxicity class II (1).

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C310 chlorpromazine



C₁₇H₁₉ClN₂S

Mol. Wt. 318.87

CAS Registry No. 50-53-3

Synonyms 2-chloro-*N,N*-dimethyl-10*H*-phenothiazine-10-propanamine;

2-chloro-10-(3-dimethylaminopropyl)phenothiazine; *N*-(3-dimethylaminopropyl)-3-chlorophenothiazine;

Largactil (as hydrochloride)

EINECS No. 200-045-8

RTECS No. SN 8925000

Uses Antiemetic. Antipsychotic. Tranquiliser. Peripheral vasodilator used in treatment of snake venom and toxin poisoning.

Physical properties

B. Pt. 200-205°C at 0.8 mmHg **Partition coefficient** log P_{ow} 5.35 **Volatility** v.p. 2.46 × 10⁻¹⁰ mmHg at 25°C

Solubility Organic solvents: chloroform, diethyl ether, ethanol, methanol

Mammalian & avian toxicity

Acute data

LD₅₀ oral starling >100 mg kg⁻¹ (1).

LD₅₀ oral rat 142 mg kg⁻¹ (2).
LC₅₀ (2 hr) inhalation rat, mouse 209 mg m⁻³ (3).
LD₅₀ intravenous rabbit, dog, rat, mouse 16-30 mg kg⁻¹ (4-7).
LD₅₀ subcutaneous mouse, rat 33, 75 mg kg⁻¹, respectively (7,8).

Carcinogenicity and chronic effects

Long-term drug therapy and ultraviolet radiation (period not specified) in hairless mice were shown to yield an increase in tumour incidence and in the proportion of malignant to benign skin tumours (9).

Teratogenicity and reproductive effects

Chlorpromazine was administered orally to rats of both sexes at 25, 50 and 100 mg kg⁻¹ every day for 2 wk before mating. This treatment was administered over three generations. The incidence of insemination and pregnancy in the F₀ generation decreased, but did not decrease in the F₁ generation. While no influence on the number of myometrial glands, on length of pregnancy or on delivery was noted in either the F₀ or F₁ ♀, the number of surviving foetuses and newborns decreased in a dose-dependent fashion. The body weight of the F₀ and F₁ generation decreased depending on dose, but the body weight of the F₂ generation increased. The weight of the adrenal, pituitary and prostate glands in ♂ and pituitary and uterus in ♀ decreased in the F₀ generation in rats administered 100 mg kg⁻¹ (10).

TD_{Lo} (5 day pregnant) intramuscular rat 20 mg kg⁻¹ caused pre-implantation mortality and still birth (11).

Metabolism and toxicokinetics

Metabolised in man by mixed function oxidase system via Phase I hydroxylation, *N*-demethylation, *S*-oxidation, *N*-oxidation and Phase II conjugation to form glucuronides. Plasma t_{1/2} 4 hr (12).

There may be at least 10-12 metabolites formed in humans. The most important are 2-chlorpromazine, chlorphenothiazine, methoxy and hydroxy products and glucuronide conjugates of the hydroxylated compounds. In the urine, 7-hydroxylated and dealkylated metabolites and their conjugates predominate (13).

Although the plasma t_{1/2} has been reported to be only a few hr, elimination of metabolites may be very prolonged. Chlorpromazine binds extensively to plasma proteins. It is widely distributed in the body and crosses the blood-brain barrier to achieve higher concentrations in the brain than in the plasma. Chlorpromazine and its metabolites also cross the placental barrier and are excreted in the milk (14).

Irritancy

Urticaria or dermatitis is reported to occur in ~5% of patients (13).

Phototoxicity was studied in hairless mice exposed to a light source of 290-700 nm. Chlorpromazine was found to be phototoxic, as determined by the oedematous response of skin, at doses comparable to those used clinically (10).

Genotoxicity

Salmonella typhimurium TA100 with metabolic activation positive (14).

Escherichia coli WP2 *uvrA*, WP2 *trp* with metabolic activation positive (15).

Induced an increase in chromosomal aberrations and sister chromatid exchanges in human lymphocytes *in vitro* (16).

Other effects

Other adverse effects (human)

Deaths from toxic reactions reported (17).

Shows antidopaminergic activity. A patient treated with chlorpromazine suffered from severe fluid retention (18). Since 1988 in the UK at least 52 people are known to have died after taking antipsychotic drugs (including chlorpromazine). Reports of sudden deaths among patients first appeared in 1977 but the issue remains unresolved because no alternative therapies exist. One patient who died was taking 1400 mg chlorpromazine day⁻¹ (4 × the recommended dose) (19).

Of 556 patients who received chlorpromazine, adverse reactions attributed to the drug occurred in 68 (12.2%). Reactions were life threatening in 1.3%. Drowsiness or disorientation and hypotension were the most common adverse effects (20).

Chlorpromazine has been reported to cause aplastic anaemia. Agranulocytosis has also been associated with its use and an incidence of 1 in 1300 has been reported (21).

Any other adverse effects

Pretreatment of σ^7 Wistar (WF/NCr) rats with 40-120 $\mu\text{mol kg}^{-1}$ chlorpromazine reduced the testicular toxicity of cadmium (a single subcutaneous injection of 25 $\mu\text{mol kg}^{-1}$) as indicated by reductions in vascular lesions and Hb contents (22).

Chlorpromazine reduced neurological function deficits relative to controls during central nervous system ischaemia in rabbits, despite a reduction in blood pressure (23).

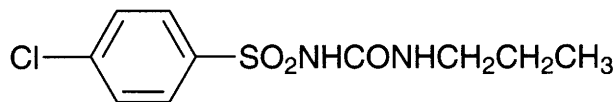
Other comments

Chlorpromazine is strongly adsorbed by soft plastics such as silicone, latex and PVC (14).

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c311 chlorpropamide



$\text{C}_{10}\text{H}_{13}\text{ClN}_2\text{O}_3\text{S}$

Mol. Wt. 276.74

CAS Registry No. 94-20-2

Synonyms 1-[(p-chlorophenyl)sulfonyl]-3-propylurea; 4-chloro-N-[(propylamino)carbonyl]-benzenesulfonamide; N-propyl-N'-p-chlorophenylsulfonylcarbamide; Dabinese; Diabinese; Mellinese

EINECS No. 202-314-5

RTECS No. YS 6650000

Uses Antidiabetic. Oral hypoglycaemic, used in treatment of diabetes mellitus.

Physical properties

M. Pt. 127-129°C

Solubility Water: 2.2 g l⁻¹ pH 6 and 25°C. Organic solvents: soluble in ethanol, moderately soluble in chloroform, sparingly soluble in ether and benzene

Mammalian & avian toxicity

Acute data

LD₅₀ oral mouse, rat 1546, 2150 mg kg⁻¹, respectively (1,2).

LD₅₀ intraperitoneal rat 580 mg kg⁻¹ (3).

LD₅₀ intravenous mouse, rat 500, 590 mg kg⁻¹, respectively (4).

Sub-acute and sub-chronic data

TD_{Lo} (4 wk) oral human 300 mg kg⁻¹ caused blood granulocytopenia, leucopenia and body temperature increase (5).

Carcinogenicity and chronic effects

The National Toxicology Program tested rats and mice via feed. Negative evidence for carcinogenicity (6).

Teratogenicity and reproductive effects

TD_{Lo} (1-26 wk pregnant) woman 1358 mg kg⁻¹ caused stillbirth (7).

Metabolism and toxicokinetics

Metabolised by mixed function oxidase system via Phase I hydroxylation and hydrolysis (8).

In humans chlorpropamide is readily absorbed from the gastro-intestinal tract and is extensively bound to plasma proteins. The plasma t_{1/2} is about 35 hr. It is partly metabolised in the liver to metabolites with some hypoglycaemic activity. The metabolites and unchanged drug are excreted in the urine (9).

Other effects

Other adverse effects (human)

A consistent feature of chlorpropamide toxicity is hyperinsulinaemia and hypoglycaemia (10).

A patient's hypoglycaemia was due to an excessive pharmacological effect of chlorpropamide. The action may be prolonged in the elderly (11).

A few cases of hypoglycaemia seen in a hospital in Nigeria over a 3-yr period, 1985-1988, were caused by some patients indulging in self-medication with chlorpropamide without being diabetic (12).

Adverse effects associated with the administration of chlorpropamide include gastro-intestinal disturbances such as nausea, vomiting, heartburn, anorexia, constipation, diarrhoea and a metallic taste. There may also be headache, dizziness, weakness, paraesthesia and tinnitus. Skin rashes, pruritus and photosensitivity have been reported (9).

Legislation

Limited under EC Directive on Drinking Water Quality 80/778/EEC. Organochlorine compounds: guide level 1 µg l⁻¹ (13).

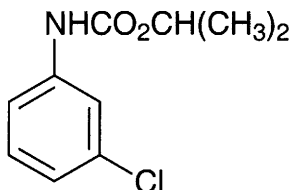
Included in Schedule 6 (Release into Land: Prescribed Substances) of Statutory Instrument No. 472, 1991 (14).

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c312 chlorpropham



C₁₀H₁₂ClNO₂

Mol. Wt. 213.66

CAS Registry No. 101-21-3

Synonyms (3-chlorophenyl)carbamic acid, 1-methylethyl ester; *N*-(3-chlorophenyl)carbamic acid, isopropyl ester; *m*-chlorocarbamilic acid, isopropyl ester; isopropyl 3-chlorocarbamate; AAservo; Anti-Gro; Birgin; Bud Nip; Chlorizyl; Furloe

EINECS No. 202-925-7

RTECS No. FD 8050000

Uses Pesticide. Herbicide. Plant growth regulator.

Physical properties

M. Pt. 40.7-41.1°C **B. Pt.** 247°C (decomp.) **Specific gravity** 1.180 at 30°C **Volatility** v.p. 10⁻⁵-10⁻⁶ mmHg at 25°C

Solubility Water: 88 mg l⁻¹. Organic solvents: readily soluble in most organic solvents

Ecotoxicity

Fish toxicity

LC₅₀ (48 hr) bluegill sunfish 8 mg l⁻¹ (1).

LC₅₀ (48 hr) bass 10 mg l⁻¹ (2).

Invertebrate toxicity

Concentrations of 10 mg l⁻¹, 1 mg l⁻¹, and 0.2 mg l⁻¹ reduced the percentage of *Lymnaea* eggs developing during the first 20 days to 89.7%, 77.5% and 15.2% respectively. EC₅₀ 14.9 mg l⁻¹ (3).

Bioaccumulation

Earthworms concentrated chlorpropham 5 × in 6 hr. Similar uptake in *Lymnaea stagnalis* and *Physa fontinalis* has been demonstrated, but relative to fresh weight, *Lymnaea* concentrated chlorpropham from a 10 mg l⁻¹ solution only 2 × over 6 hr. The level in living tissue should be higher because binding to shell and tissue is unlikely to occur at the same levels (3).

Environmental fate

Nitrification inhibition

Nitrification in soil was completely inhibited at a concentration of 80 ppm (4).

Degradation studies

Biodegradation by bacteria *Pseudomonas striata* $t_{1/2}$ 3 days at pH 7 (5).

Soil microbes degraded chlorpropham to 3-chloroaniline by an enzymic hydrolysis reaction with the liberation of carbon dioxide. $t_{1/2}$ in soil ~65 days at 15°C and 30 days at 29°C (2).

Mammalian & avian toxicity

Acute data

LC₅₀ oral redwing blackbird >500 mg kg⁻¹ (6).

LC₅₀ oral mallard duck >200 mg kg⁻¹ (2).

LD₅₀ oral rat 1200 mg kg⁻¹ (7).

LD₅₀ oral rabbit 5 g kg⁻¹ (8).

LD₅₀ intraperitoneal rat 700 mg kg⁻¹ (9).

LD₅₀ intraperitoneal mouse 2600 mg kg⁻¹ (9).

Sub-acute and sub-chronic data

Oral ♂ and ♀ F344 rats (13 wk) were administered 0-30,000 ppm in the diet. Spleen and liver weights were dose-dependently increased. The highest dose caused depression of body weight gain. There was evidence of toxicity to erythrocytes (10).

Carcinogenicity and chronic effects

No adequate evidence for carcinogenicity to humans, inadequate data for evaluation of carcinogenicity to animals, IARC classification group 3 (11).

In 2-yr feeding trials, rats and dogs receiving 2000 mg kg⁻¹ diet showed no ill-effects (2).

Gavage mice (both sexes) 464 mg kg⁻¹ day⁻¹ in gelatine at 7 days of age, and then the same amount (not adjusted for increased body weight) daily up to 4 wk of age. Subsequently the mice were given 1112 mg kg⁻¹ diet until the mice were 78 wk of age. The incidence of tumours was not significantly greater than for controls (12).

Subcutaneous administration of a single dose of 1000 mg kg⁻¹ to mice on day-28 of life did not cause an increased incidence of tumours when observed up to 78 wk of age (13).

In a two-stage skin carcinogenesis experiment, groups of mice received a single dose of 15 mg in 1% tragacanth by gavage, or the same dose wkly for 10 wk, or orally at 1000 mg kg⁻¹ diet for 6 months. Croton oil was used as a promoter, applied dermally at 5% in olive oil twice wkly for 6 months. Chlorpropham treatment caused increased incidence of skin papillomas (14).

This result, however, was not confirmed in a subsequent experiment (15).

Teratogenicity and reproductive effects

Chlorpropham was administered by gavage to pregnant mice on day-8.3 of gestation at 0, 750, 1500, and 3000 mgkg⁻¹ body weight and the mice were killed on day-18 of gestation. In the highest dosage group brachyury was significantly increased, the total resorption rate was significantly increased, and the average foetal body weight of each sex was significantly reduced. The total incidence of external malformations was significantly increased in the two highest dose groups in a dose-related manner (16).

Metabolism and toxicokinetics

After oral or intraperitoneal administration of ¹⁴C-isopropyl and ¹⁴C-ring labelled chlorpropham to rats, the 4-day urinary excretions were 50% and 85% of the dose, respectively. In the case of the isopropyl-labelled compound an additional 17-20% of the dose was excreted as carbon dioxide via the lungs (17).

When pregnant rats were given ¹⁴C-chlorpropham, the radioactivity was transferred to the foetuses and its level did not decline in foetal tissues as rapidly as it did in the maternal organs. The pups of lactating rats that were given labelled substance also contained radioactivity (18).

Under physiological conditions in isolated rat hepatocyte suspensions, chlorpropham caused a cytolytic effect, modified membrane permeability, and reduced the intracellular ATP level. It was metabolised mainly into 4-OH chlorpropham sulfate (37%) and glucuronide conjugates (18%) (19).

Genotoxicity

Salmonella typhimurium TA98, TA100, TA1535, TA1537, TA1538 with and without metabolic activation negative (20).

Other effects

Any other adverse effects

Concentrations of 2.1-10.6 mg l⁻¹ inhibited mitosis in *Acer* cell suspension cultures and produced giant cells. Metabolic activity was disturbed by 21.3 mg l⁻¹, which resulted in increased cell size, dry matter and protein content. The antimitotic effect depends on the carbamic function associated with a phenyl ring with a free *para* position. The isopropyl moiety reinforces the specific inhibitory effect on mitosis. Antimitotic activity is also increased by chlorination of the *meta* position, as shown by the formation of giant cells at concentrations of 2.1 mg l⁻¹ (21). Chlorpropham had a cytolytic effect on rat hepatocyte suspension, and caused a reduction in intracellular ATP and K⁺ levels (22).

Legislation

Maximum permissible concentration in domestic water in the former USSR 1.0 mg l⁻¹ (23).
Limited under EC Directive on Drinking Water Quality 80/778/EEC. Pesticides: maximum admissible concentration 0.1 µg l⁻¹ (24).
Included in Schedule 6 (Release into Land: Prescribed Substances) of Statutory Instrument No. 472, 1991 (25).
WHO Class Table 5 (26).
EPA Toxicity Class III (2).

Other comments

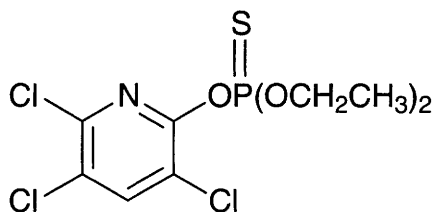
Residues have been detected in water, crops and fish tissues.
Seven herbicides were used to test the suitability of a new pollen tube growth system for toxicology screening of phytoeffectors. The sequence of herbicides with increasing toxicity was: glyphosate, chlorpropham, DCMU, phenmedipham, DDT, DNOC, and DNBP. This order correlates well with the LD₅₀ sequence in rats (27).

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C313 chlorpyrifos



$C_9H_{11}Cl_3NO_3PS$

Mol. Wt. 350.59

CAS Registry No. 2921-88-2

Synonyms *O,O*-diethyl *O*-(3,5,6-trichloro-2-pyridyl) phosphorothioate; 3,5,6-trichloro-2-pyridyl diethyl phosphorothionate; Dursban; Chemicide; Brodan; Cortilan; Elafos; Fantom

EINECS No. 220-864-4

RTECS No. TF 6300000

Uses Insecticide. Acaricide.

Physical properties

M. Pt. 42-43.5°C **B. Pt.** 160°C (decomp.) **Specific gravity** 1.398 at 43°C with respect to water at 1°C

Partition coefficient $\log P_{ow}$ 4.699 **Volatility** v.p. 1.87×10^{-5} mmHg at 25°C

Solubility Water: 1.4 mg l⁻¹ at 25°C. Organic solvents: isooctane, methanol

Occupational exposure

FR-VME 0.2 mg m⁻³

UK-LTEL 0.2 mg m⁻³

UK-STEL 0.6 mg m⁻³

US-TWA 0.2 mg m⁻³

Supply classification toxic, dangerous for the environment

Risk phrases Toxic in contact with skin and if swallowed – Very toxic to aquatic organisms, may cause long-term adverse effects in the aquatic environment (R24/25, R50/53)

Safety phrases Keep locked up and out of the reach of children (if sold to general public) – After contact with skin, wash immediately with plenty of water – Wear suitable protective clothing and gloves – In case of accident or if you feel unwell, seek medical advice immediately (show label where possible) – This material and/or its container must be disposed of as hazardous waste – Avoid release to the environment. Refer to special instructions/safety data sheet (S1/2, S28, S36/37, S45, S60, S61)

Ecotoxicity

Fish toxicity

LC₅₀ (24 hr) goldfish 0.18 mg l⁻¹ (1).

LC₅₀ (96 hr) rainbow trout 0.003-0.011 mg l⁻¹ (1).

LC₅₀ (96 hr) catfish (*Clarias lazera*) 11.1 mg l⁻¹ (2).

LC₅₀ (24, 96 hr) freshwater catfish *Heteropneustes fossilis* in static acute toxicity tests 5.60 and 2.20 mg l⁻¹, respectively (3).

LC₅₀ (96 hr) *Tilapia zillii* 0.0274 mg l⁻¹ (4).

Exposure of the catfish (*Heteropneustes fossilis*) to 2 mg l⁻¹ caused histopathological changes in the kidney. After 72

hr the glomeruli were shrunken, blood cells in the glomeruli became vacuolated and the lumina of the tubules were dilated. After 96 hr these changes were exaggerated and the tubules were fragmented and necrotic (5).

Invertebrate toxicity

LD₅₀ oral bee 250 ng bee⁻¹ (1).

LD₅₀ contact to bee 59 ng bee⁻¹ (1).

LC₅₀ (96 hr) *Gammarus lacustris*, *Gammarus fasciatus* 0.11-0.32 µg l⁻¹ (6,7).

LC₅₀ (96 hr) *Mytilus galloprovincialis* 22.5 mg l⁻¹. No-observable-adverse-effect concentration 4.9 mg l⁻¹ (8).

EC₅₀ (24 hr) *Artemia* sp. (Artoxkit M) 2 mg l⁻¹, *Brachionus plicatilis* (Rotoxkit M) 1.7 mg l⁻¹ (9).

LC₅₀ (48 hr, 96 hr) *Ceriodaphnia dubia* static test 0.058-0.079 and 0.089-0.122 µg l⁻¹, respectively (10).

Daphnia pulex lowest no-observed-effect concentration ca. 0.05 µg l⁻¹ (actual concentration). EC₅₀ population size after 2 days exposure 0.38 (laboratory) and 0.31 (field) µg l⁻¹, and after 7 days exposure 0.25 (laboratory) and 0.34 (field) µg l⁻¹ (11).

The pheromonal communication of *Trichogramma brassicae* was studied after exposure to an LD_{0.1} of chlorpyrifos. Exposed ♂s showed a significantly decreased response to ♀ pheromone. The response of ♂s to the pheromone of exposed ♀s was slightly increased (12).

Bioaccumulation

In rainbow trout the bioconcentration factor was 14 (13).

The average bioconcentration factor in the whole body of the carp is 460. The excretion rate constants from the whole body of the carp and of the willow shiner are 0.02 and 0.04 hr⁻¹, respectively (14).

The bioconcentration factor in the guppy is ~1700 and t_{1/2} of tissue chlorpyrifos 31-38 hr (15).

Lipid-based bioconcentration factor *Mytilus edulis* exposed to 1 or 3.2 mg l⁻¹ for 38 days 482±86. This value was lower than expected for the K_{ow} of chlorpyrifos, suggesting metabolic biotransformation of the parent pesticide (16).

Environmental fate

Degradation studies

t_{1/2} in dry loam soil 4 wk and in silt loam 12 wk. In both these soils sterilisation by autoclaving increased t_{1/2} to 24 wk (17).

Aspergillus niger degraded 72.3% of a sample of chlorpyrifos during a 14-day incubation period; *Trichoderma viride* degraded 95.7%. The toxic metabolite 3,5,6-trichloropyridinol was not detected (18).

Abiotic removal

Very resistant to leaching in soil, t_{1/2} in soil 80-100 day. Slowly degraded to organochlorine compounds and carbon dioxide (1).

Hydrolysis products include 3,5,6-trichloro-2-pyridiol (major product) and various trichloropyridyl phosphorothioates. Hydrolysis t_{1/2} 35-78 days. Photolysis t_{1/2} at the water surface during mid-summer is ~3-4 wk (19,20).

Calculated t_{1/2} in sandy soil 81 days (21).

Adsorption and retention

Soil sorption constants were 2740 and 995 for a clay loam and high clay soil, respectively (22).

If released to water chlorpyrifos partitions significantly from the water column to sediments. Desorption from sediments can then contribute to long-term residual concentration in the water column (23).

Mammalian & avian toxicity

Acute data

LD₅₀ oral rat 135-160 mg kg⁻¹ (24).

LD₅₀ oral guinea pig 504 mg kg⁻¹ (1).

LD₅₀ oral rabbit 1000-2000 mg kg⁻¹ (25).

LD₅₀ oral redwing blackbird, starling 13, 75 mg kg⁻¹, respectively (26).

LD₅₀ oral chicken 32 mg kg⁻¹ (1).

LC₅₀ (4 hr) inhalation rat >0.2 mg l⁻¹ (1).

LD₅₀ dermal rabbit ≈2000 mg kg⁻¹ (27).
LD₅₀ intraperitoneal mouse 192 mg kg⁻¹ (28).

Sub-acute and sub-chronic data

LC₅₀ (8 day) oral ring-necked pheasant 553 mg kg⁻¹ (29).
LC₅₀ (8 day) oral mallard duck ~940 mg kg⁻¹ (29).
LC₅₀ (8 day) oral Japanese quail 299 mg kg⁻¹ (29).
Lowest human no-observed-effect level 0.014 mg kg⁻¹ day⁻¹ (duration unspecified) (30).
Lowest rat no-observed-effect level 30 µg kg⁻¹ day⁻¹ (duration unspecified) (30).
Four doses of 25 mg kg⁻¹ for 12 hr each applied to skin of humans caused depressed plasma cholinesterase activity (31).
Rats were exposed by inhalation to concentrations of 0, 5.2, 10.3 or 20.6 ppb, 6 hr day⁻¹, 5 days wk⁻¹ for 13 wk. No clinical or histopathological effects were observed, including no differences from controls in plasma, red blood cell or brain cholinesterase activities (32).

Teratogenicity and reproductive effects

No evidence of teratogenic or reproductive effects in ♂ and ♀ rats fed 1 mg kg⁻¹ day⁻¹ during a three generation reproduction and fertility study (33).
Oral administration of chlorpyrifos to rats at parentally toxic dose levels (up to 15 mg kg⁻¹ day⁻¹ was not embryo lethal, embryo/foetotoxic, or teratogenic and did not adversely affect fertility or the structure or function of the reproductive organs (34).
Intraperitoneal exposure of chlorpyrifos (0.03-0.3 mg kg⁻¹) to rat embryos *in utero* on days 0-7 or 7-21 of gestation induced physical abnormalities and embryotoxicity (35).
Daily subcutaneous injection of 4.5 or 9.0 mg kg⁻¹ in neonatal rats for 15 days, beginning 7 days after birth, decreased the weights of ♂ and ♀ reproductive organs and suppressed testosterone and oestradiol levels (36).
Quail eggs treated immediately prior to incubation at 2 × the recommended field application level had a significantly greater rate of hatching deformity and a longer incubation period (37).

Metabolism and toxicokinetics

Following oral administration to rats, dogs and other mammals, rapid metabolism occurred, with the principal metabolites being 3,5,6-trichloro-2-pyridinol and monoethyl chlorpyrifos. Excretion principally in the urine (1).
Following intraperitoneal injection of 0.2 mg l⁻¹ (kg⁻¹ to rats, both chlorpyrifos and 3,5,6-trichloro-pyridinol blood levels were maximum after 5 hr. Blood t_{1/2} were 8.1 hr and 24.6 hr, respectively (38).

Genotoxicity

Induced chromosomal aberrations in the meristems of onion (*Allium cepa*) and barley with and without metabolic activation (39).
Induced genetic damage in *Drosophila melanogaster* (40).
Farm-grade chlorpyrifos (Durmet) is genotoxic in the *Drosophila melanogaster* mosaic wing spot and sex-linked recessive lethal tests (41).
Induced chromosomal aberrations in human lymphoid cells *in vitro* (42).

Other effects

Other adverse effects (human)

Extensive and unusual patterns of defects of the brain, eyes, ears, palate, teeth, heart, feet, nipples and genitalia were exhibited by four children exposed to chlorpyrifos *in utero*. The growth of each child was retarded and three had hypotonia and profound mental retardation (43).
Spray workers exposed to 0.5% emulsion in field trials for malaria control showed measurable decreases in plasma and red blood cell cholinesterase activities (44).
Plasma cholinesterase activities were found to be decreased in eight termite control workers. The lowest level was <50% of the mean value for each of the workers, and <10% in 3 workers. No marked subjective or objective abnormalities were seen in the workers. When exposure ceased cholinesterase activity levels returned to normal in all workers (45).

Human volunteers ingesting 0.1 mg kg⁻¹ for 4 wk showed significant inhibition of plasma cholinesterase activity (46).

Highly toxic through inhalation and skin absorption. Systemic effects which include nausea, vomiting, abdominal cramps, muscular fasciculations, cyanosis and coma occur within 2-8 hr (47).

Any other adverse effects

In rodents acutely exposed to organophosphate, hypothermia is a commonly reported thermoregulatory response. Long-Evans rats have been shown also to exhibit a delayed hyperthermic response following the initial hypothermia when exposed to the organophosphate chlorpyrifos (48).

Legislation

Limited under EC Directive on Drinking Water Quality 80/778/EEC. Pesticides: maximum admissible concentration 0.1 µg l⁻¹ (49).

EPA Toxicity Class II (50).

Acceptable daily intake in humans 0.0015 mg kg⁻¹ day⁻¹ (51).

WHO Toxicity Class II (52).

Other comments

In a study of accumulation in the Mediterranean mussel *Mytilus galloprovincialis* bioconcentration factors were determined experimentally. The authors concluded that the bioaccumulation ability in living tissues represents a potential environmental risk to marine organisms and humans (53).

Residues have been isolated from soils, crops and animal fats.

Molecular connectivities play a major role in describing the toxicity of organophosphorus pesticides to honeybees (54).

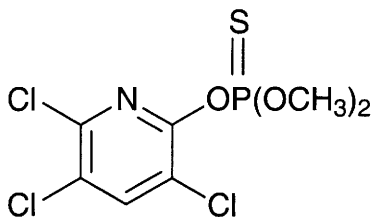
Environmental fate of chlorpyrifos reviewed (55).

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c314 chlorpyrifos-methyl



$C_7H_7Cl_3NO_3PS$

Mol. Wt. 322.54

CAS Registry No. 5598-13-0

Synonyms O,O-dimethyl O-(3,5,6-trichloro-2-pyridyl) phosphorothioate; Reldan; Graincoat; Meticlor; Nuvagrain; Smite; Zertell

EINECS No. 227-011-5

RTECS No. TG 0700000

Uses Insecticide. Acaricide.

Physical properties

M. Pt. 45.5-46.5°C **Partition coefficient** $\log P_{ow}$ 4.24 (1) **Volatility** v.p. 4.22×10^{-5} mmHg at 25°C

Solubility Water: 5 mg l⁻¹ at 25°C. Organic solvents: acetone, benzene, chloroform, diethyl ether, hexane, methanol

Ecotoxicity

Fish toxicity

LC₅₀ (96 hr) brown trout 0.3 mg l⁻¹ (1).

Invertebrate toxicity

LD₅₀ contact bee 0.38 µg bee⁻¹ (1).

LC₅₀ (36 hr) crayfish 4 µg l⁻¹ (2).

Bioaccumulation

The average bioconcentration factor in the whole body of the willow shiner *Gnathopogon caeruleus* is 802 and the excretion rate constant from the whole body of the fish 0.01 hr⁻¹ (3).

Environmental fate

Degradation studies

Undergoes microbial degradation to 3,5,6-trichloropyridin-2-ol which is subsequently degraded to organochlorine compounds and carbon dioxide. t_{1/2} in soil 36 hr to 33 day depending on soil type and microbial activity (1).

Mammalian & avian toxicity

Acute data

LD₅₀ oral redwing blackbird, starling >100 mg kg⁻¹ (4).

LD₅₀ oral rat, mouse, guinea pig, rabbit 1830-2250 mg kg⁻¹ (5,6).

LC₅₀ (4 hr) inhalation rat >670 mg m⁻³ (1).

LD₅₀ dermal rat 3713 mg kg⁻¹ (7).

LD₅₀ subcutaneous mouse 23.8 g kg⁻¹ (8).

LD₅₀ intraperitoneal mouse 2325 mg kg⁻¹ (9).

Oral goat, single dose of 150, 300, 600 or 1200 mg kg⁻¹. The highest dose caused death in the two animals treated within 1 and 16 hr (10).

Sub-acute and sub-chronic data

LD₅₀ (8 day) mallard duck 2500-5000 mg kg⁻¹ (1).

Carcinogenicity and chronic effects

Oral rat, dog (2 yr) no-adverse-effect concentration on plasma cholinesterase levels 0.1 mg kg⁻¹ day⁻¹ (1).

Metabolism and toxicokinetics

Following oral administration to rats it is rapidly metabolised. Principal metabolite detected 3,5,6-trichloropyridin-2-ol which is excreted in the urine (1).

Irritancy

Dermal mouse (24 hr) 500 mg caused mild irritation (11).

Legislation

Limited under EC Directive on Drinking Water Quality 80/778/EEC. Pesticides: maximum admissible concentration 0.1 µg l⁻¹ (12).

Included in Schedule 6 (Release into Land: Prescribed Substances) Statutory Instrument No. 472, 1991 (13).

WHO Class Table 5 (14).

EPA Toxicity Class III (1).

Acceptable daily intake (man) 0.01 mg kg⁻¹ (1).

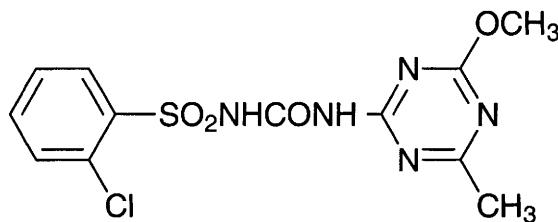
Other comments

Cholinesterase activity inhibitor (1).

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C315 chlorsulfuron



C₁₂H₁₂ClN₅O₄S

Mol. Wt. 357.78

CAS Registry No. 64902-72-3

Synonyms 2-chloro-*N*[[[(4-methoxy-6-methyl-1,3,5-triazin-2-yl)amino]carbonyl]benzenesulfonamide; 1-(2-chlorophenylsulfonyl)-3-(4-methoxy-6-methyl-1,3,5-triazin-2-yl)urea; Glean; Telar

EINECS No. 265-268-5

RTECS No. YS 6640000

Uses Selective pre- and post-emergence systemic herbicide.

Physical properties

M. Pt. 174-178°C **Partition coefficient** log *P*_{ow} = 0.10 **Volatility** v.p. 2.26 × 10⁻⁸ mmHg at 25°C

Solubility Water: 300 mg l⁻¹ at 25°C (pH 5.0), 27.9 g l⁻¹ at 25°C (pH 7.0). Organic solvents: acetone, acetonitrile, dichloromethane, toluene

Occupational exposure

Supply classification dangerous for the environment

Risk phrases Very toxic to aquatic organisms, may cause long-term adverse effects in the aquatic environment (R50/53)

Safety phrases This material and/or its container must be disposed of as hazardous waste – Avoid release to the environment. Refer to special instructions/safety data sheet (S60, S61)

Ecotoxicity

Fish toxicity

LC₅₀ (96 hr) bluegill sunfish, rainbow trout >250 mg l⁻¹ (1).

Invertebrate toxicity

EC₅₀ (96 hr) *Chlorella saccharophila*, *Scenedesmus acutus*, and *Pseudanabaena galeata* 74.5, 0.19, and 21.1 mg l⁻¹, respectively (2).

EC₅₀ *Chlorella fusca* inhibition of reproduction 1.1 µmol l⁻¹ at pH6.5, 44.0 nmol l⁻¹ at pH 5.0 (3).

Toxicity to other species

Green pea (*Pisum sativum*) plants were most susceptible to the influence of chlorsulfuron at the development stage when they possessed 6 expanded leaves and one visible flower bud. At that stage, application of chlorsulfuron at 0.8% of the recommended field rate reduced the seed yield of treated plants to 1% that of control plants without severely altering the height or appearance of mature plants (4).

Bioaccumulation

Bioconcentration factor in *Chlorella fusca* <9 at pH 6.0, 53 at pH 5.0. It is suggested that chlorsulfuron penetrates the algal cell membranes in its undissociated state and accumulates via an ion-trapping mechanism (3).

Environmental fate

Degradation studies

In soil products of hydrolysis are metabolised to low molecular weight compounds by soil microflora (1).
t_{1/2} in dry soil 6-8 days (5).

Abiotic removal

50% hydrolysis 28-56 days in aqueous solutions at pH 5.7-7.0 at 20°C (1).

Phytotoxicity completely removed by incorporation of activated carbon at a rate of 50 kg ha⁻¹ in soil incorporated with 1.25 and 2.50 g ha⁻¹ chlorsulfuron (6).

Adsorption and retention

Leached out of sandy soil more rapidly than in organic soil. Rate of leaching was slowest in clay soil (7).

Mammalian & avian toxicity

Acute data

LD₅₀ oral rat 5550-6290 mg kg (1,8).

LD₅₀ oral bobwhite quail >5000 mg kg⁻¹ (1).

LC₅₀ (4 hr) inhalation rat >5900 mg m⁻³ (9).

LD₅₀ dermal rabbit >3400 mg kg⁻¹ (1).

LD₅₀ intraperitoneal rat 1450 mg kg⁻¹ (1).

Sub-acute and sub-chronic data

LD₅₀ (8 day) mallard duck >5000 mg kg⁻¹ (1).

Carcinogenicity and chronic effects

The no-effect-level for rats, 2-yr feeding trial, 100 mg kg⁻¹ diet. The no-effect level for mice, 2-yr feeding trial, 500 mg kg⁻¹ diet (1).

Irritancy

Reported to be a mild eye irritant. Non-irritating and non-sensitising to skin (species unspecified) (1).

Legislation

Limited under EC Directive on Drinking Water Quality 80/778/EEC. Pesticides: maximum admissible concentration 0.1 µg l⁻¹ (10).

WHO Class Table 5 (11).

EPA Toxicity Class IV (1).

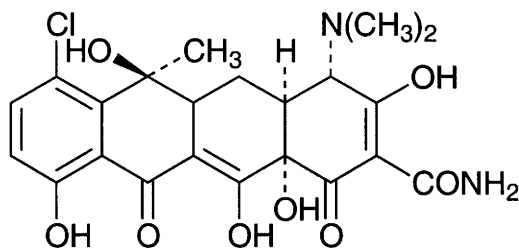
Other comments

Metabolic pathways reviewed (12).

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c316 7-chlortetracycline



$C_{22}H_{23}ClN_2O_8$

Mol. Wt. 478.89

CAS Registry No. 57-62-5

Synonyms 7-chloro-4-(dimethylamino)-1,4,4a,5,5a,6,11,12a-octahydro-3,6,10,12,12a-pentahydroxy-6-methyl-1,11-dioxo-[4S-(4 α ,4a α ,5a α ,6 β ,12a α)]-2-naphthacenecarboxamide; naphthacenecarboxamide; Aureomycin (as hydrochloride)

EINECS No. 200-341-7

RTECS No. QI 7750000

Uses Antibiotic. Treatment of osteoporosis and glaucoma. Veterinary growth promoter.

Physical properties

M. Pt. 168-169°C **Partition coefficient** $\log P_{ow}$ -0.93 to -1.47 (hydrochloride)

Solubility Water: 500-600 mg l⁻¹. Organic solvents: cellosolve, dioxane

Ecotoxicity

Bioaccumulation

Following oral administration 30 mg kg⁻¹ for 7 days to rainbow trout maintained at 9.7°C, concentrations were 17-157 µg kg⁻¹ in muscle tissue and 15-31 µg kg⁻¹ in blood. On day-8 after initiation of treatment, levels were <5 µg kg⁻¹ in muscle tissue (1).

Mammalian & avian toxicity

Acute data

LD₅₀ oral mouse 1500 mg kg⁻¹ (2).

LD₅₀ intravenous mouse, rat 100-120 mg kg⁻¹ (3).

Teratogenicity and reproductive effects

Pregnant rats were administered doses of 250, 1500 and 3000 ppm diet from days 7-18 of gestation. Maternal body weight gain was enhanced dose-dependently. Dose-related incidence of intra-uterine death, and foetal skeletal and visceral anomalies were also observed. Growth of newborn was depressed (4).

Metabolism and toxicokinetics

Following the intravenous administration of 0.9 mg kg⁻¹ to turkeys, 8.5% of the dose appeared in the bile in 4 hr. The peak bile/plasma ratio was 254 at 2 hr. This ratio was >1.0 from 10-240 min after administration (5).

In humans, some 47% of the oral dose was reported to be bound to serum proteins. The serum t_{1/2} was 5.6 hr and 18% was excreted in the urine (6).

Other effects

Other adverse effects (human)

Diffuses across the placenta and appears in foetal circulation (7).

Any other adverse effects

Intraperitoneal administration of 400 mg kg⁻¹ caused potentially lethal metabolic acidosis. Accompanying hyperkalaemia resulted in cardiac arrhythmias (species and duration unspecified) (8).

Legislation

Limited under EC Directive on Drinking Water Quality 80/778/EEC. Organochlorine compounds: guide level 1 µg l⁻¹ (9).

Included in Schedule 6 (Release into Land: Prescribed Substances) of Statutory Instrument No. 472, 1991 (10).

Often administered as the monohydrochloride (CAS RN:64-75-5). Acceptable Daily Intake 0.015 mg kg⁻¹ (temporary), acceptable levels of residues (calculated as base) in mg kg⁻¹: milk 0-0.2; meat 0-0.05; eggs 0-0.05 (11).

Other comments

Isolated from substrate of *Streptomyces aureofaciens*. Residues have been found in various foods, including eggs, dairy products, meat and honey.

May be effective as a sterilising agent in women (12).

Reported to be adsorbed onto the surface of borosilicate glass (13).

Rats with suppressed bone protein synthesis due to induced diabetes were administered 5 mg day⁻¹ for 3 wk.

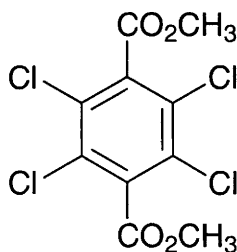
Bone protein synthesis increased to normal values, also associated with the prevention of the development of osteoporosis (14).

Reported to be strongly bound to tooth enamel and dentine of rats following intraperitoneal administration at 50 mg kg⁻¹ wkly for 6 wk (15).

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C317 chlorthal-dimethyl



C₁₀H₆Cl₄O₄

Mol. Wt. 331.97

CAS Registry No. 1861-32-1

Synonyms 2,3,5,6-tetrachloro-1,4-benzenedicarboxylic acid, dimethyl ester; dimethyl 2,3,5,6-tetrachloroterephthalate; Dacthal

EINECS No. 217-464-7

RTECS No. WZ 1500000

Uses Selective non-systemic herbicide.

Physical properties

M. Pt. 154-155°C **Volatility** v.p. $<5.04 \times 10^{-4}$ mmHg at 40°C

Solubility Water: <0.5 mg l⁻¹ at 25°C. Organic solvents: acetone, benzene, carbon tetrachloride, dioxane, toluene, xylene

Environmental fate

Degradation studies

In soil microbial degradation yields monomethyl tetrachloroterephthalate and 2,3,5,6-tetrachloroterephthalic acid (chlorthal). Duration of residual activity in soil ~3 months (1).

Calculated $t_{1/2}$ in sandy soil 45 days (2).

Abiotic removal

Hydrolysis is a primary factor in removal from soil (3).

Adsorption and retention

Adsorbed by organic matter in soil (3).

Mammalian & avian toxicity

Acute data

LD₅₀ oral rat >3000 mg kg⁻¹ (1).

LC₅₀ (4 hr) inhalation rat 5 mg l⁻¹ (4).

LD₅₀ dermal rabbit >10 g kg⁻¹ (1).

LD₅₀ intravenous mouse 320 mg kg⁻¹ (5).

Carcinogenicity and chronic effects

2-yr feeding trial in rats 10 g kg⁻¹ diet caused no ill-effects. 2 yr feeding trial in dog 10 g kg⁻¹ diet caused no ill-effects (1).

Metabolism and toxicokinetics

In mammals, following oral administration, metabolised to monomethyl tetrachloroterephthalate and 2,3,5,6-tetrachloroterephthalic acid (chlorthal) which are eliminated in urine (1).

No residues were detected in the milk of dairy cows fed chlorthal-dimethyl (6).

Irritancy

3 mg instilled into rabbit eye caused mild irritation which subsided within 24 hr (7).

Genotoxicity

Salmonella typhimurium TA98, TA100, TA1535, TA1537, TA1538 with and without metabolic activation negative (8).

Other effects

Any other adverse effects

100 or 250 mg kg⁻¹ was administered orally to 11 yearling buffalo. After 24 hr, blood samples showed that both dose levels caused significant hyperglycaemia and hyperglobulinaemia as well as significant reduction in the albumin/globulin ratio and serum phosphorus, while no significant effects on total serum protein, alkaline phosphatases or calcium levels were observed (9).

Legislation

Limited under EC Directive on Drinking Water Quality 80/778/EEC. Pesticides: maximum admissible concentration 0.1 µg l⁻¹ (10).

WHO Toxicity Class Table 5 (11).

EPA Toxicity Class (formulation) IV (12).

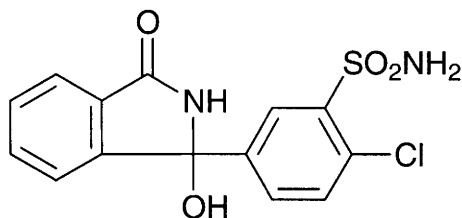
Other comments

Human volunteers have ingested 50 mg without detectable adverse effects (13).

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C318 chlorthalidone



C₁₄H₁₁ClN₂O₄S

Mol. Wt. 338.77

CAS Registry No. 77-36-1

Synonyms 2-chloro-5-(2,3-dihydro-1-hydroxy-3-oxo-1*H*-isoindol-1-yl)benzenesulfonamide; 3-hydroxy-3-(4-chloro-3-sulfonylphenyl)phthalimidine; 2-chloro-5-(1-hydroxy-3-oxo-1-isoindolin-1-yl)benzenesulfonamide; chlorophthalidolone; Hydroton; Thalitone

EINECS No. 201-022-5

RTECS No. DB 1556000

Uses Diuretic. Antihypertensive.

Physical properties

M. Pt. 224-226°C (decomp.), range may extend from 218 to 264°C on slow heating

Solubility Water: 120 mg l⁻¹ at 20°C. Organic solvents: diethyl ether, ethanol, methanol

Mammalian & avian toxicity

Acute data

LD₅₀ oral rat, mouse, guinea pig, rabbit >5 g kg⁻¹ (1).

Metabolism and toxicokinetics

Following oral administration to humans, erratically absorbed from the gastro-intestinal tract. Its prolonged circulating t_{1/2} of 35-54 hr has been reported to be due to its strong binding to red blood cells. During long-term administration 30-60% has been reported to be excreted unchanged in urine. Reported to cross the placental barrier and be excreted in breast milk (2).

With 50-100 mg doses, urinary excretion is ~65%; renal clearance is decreased at an oral dose of 200 mg and there is a concomitant decrease in the percentage excreted unchanged. Sequestered in erythrocytes, t_{1/2} longer in blood than plasma (3).

Irritancy

Exposure can cause dermatitis (species unspecified) (4).

Other effects

Other adverse effects (human)

Severe pancreatitis has occurred during pregnancy (5).

Daily oral administration of 100 mg induced an abnormal secretion of antidiuretic hormone in a 60-yr-old woman with mild hypertension and nephrolithiasis (6).

Mean serum cholesterol concentrations rose by 5.2% and serum triglyceride concentrations by 25.7% in 32 hypersensitive patients administered 50 mg twice wkly to 100 mg daily for ~6 months (7).

Sexual dysfunction, characterised by impotence or decreased libido, was associated with administration in five men (8).

In a survey of patients undergoing antihypertension therapy, sexual dysfunction was the most frequent side-effect, with an incidence of 4.4% (9).

Acute transient myopia has been reported in patients, appearing within 1-3 days of administration. Young pregnant women appear particularly prone to this side-effect (10).

Legislation

Limited under EC Directive on Drinking Water Quality 80/778/EEC. Organochlorine compounds: guide level 1 $\mu\text{g l}^{-1}$ (11).

Included in Schedule 6 (Release into Land: Prescribed Substances) of Statutory Instrument No. 472, 1991 (12).

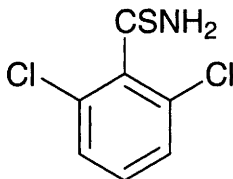
Other comments

Part of a formulation, reported to aid topical hair growth in a bald person by relaxation of the smooth muscles in the small blood vessels in the papilla part of connective tissue of skin supplying the hair follicle and thereby increasing blood flow to the hair matrix (13).

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c319 chlorthiamid



$\text{C}_7\text{H}_5\text{Cl}_2\text{NS}$

Mol. Wt. 206.09

CAS Registry No. 1918-13-4

Synonyms 2,6-dichlorothiobenzamide; 2,6-dichlorobenzenecarbothioamide; chlorthiamide; chlorothiamide; Prefix; Granamide; HTG 10; Proterox

EINECS No. 217-637-7

RTECS No. CV 3850000

Uses Herbicide.

Physical properties

M. Pt. 151-152°C Volatility v.p. 9.8×10^{-7} mmHg at 20°C

Solubility Water: 950 mg l^{-1} at 21°C. Organic solvents: aromatic and chlorinated hydrocarbons

Occupational exposure

Supply classification harmful

Risk phrases Harmful if swallowed (R22)

Safety phrases Keep out of reach of children (if sold to general public) – Wear suitable protective clothing (S2, S36)

Ecotoxicity

Fish toxicity

LC₅₀ (48 hr) harlequin fish 33 ppm. Tested in standard quality dilution water (hardness 20 ppm CaCO₃) (1).

LC₅₀ (48 hr) guppy 41 mg l⁻¹ (2).

Invertebrate toxicity

Not toxic to bees (3).

Environmental fate

Degradation studies

Undergoes microbial degradation to 2,6-dichlorobenzamide and 2,6-dichlorobenzoic acid (4).

Abiotic removal

In soil, converted into dichlobenil. Duration of residual activity in soil is 5-7 months (4).

Mammalian & avian toxicity

Acute data

LD₅₀ oral mouse, rat 500, 750 mg kg⁻¹, respectively (4).

LD₅₀ oral chicken 500 mg kg⁻¹ (4).

LD₅₀ dermal rat >1000 mg kg⁻¹ (4).

Sub-acute and sub-chronic data

In rat feeding experiments (duration unspecified) 100 mg kg⁻¹ caused reversible hepatocellular alterations. Oral administration in rats caused sedation and narcosis (5).

Metabolism and toxicokinetics

Oral rat rapidly metabolised chlorthiamid, 70% was eliminated via urine within 24 hr (6).

Following oral administration to goats and rodents, all metabolites detected were benzonitriles with a variety of hydroxyl and chlorine ring substituents. No hydrolysis of the nitrile group in chlorthiamid to either an amide or an acid was detected. Urine was the major route of excretion, however enterohepatic circulation occurred. Whole-body autoradiography of ¹⁴C-labelled compound in mice showed the presence of bound residues in the mucosa of the nasal cavity, trachea, tongue, oesophagus, kidneys, liver and intestinal contents (7).

Genotoxicity

Salmonella typhimurium TA98, TA100 with and without metabolic activation negative (8).

Escherichia coli PQ37 with and without metabolic activation negative (9).

Salmonella typhimurium microsome test (strains unspecified) showed chlorthiamid had mutagenicity at a concentration level of 1 ng plate⁻¹ (1).

Other effects

Any other adverse effects

Single intraperitoneal injections of 12, 25 and 50 mg kg⁻¹ induced extensive destruction of the olfactory organs in mice. Necrosis of the Bowman's glands was evident first, whereas degeneration and necrosis of the olfactory neuroepithelium developed less rapidly (6,10).

Legislation

Limited under EC Directive on Drinking Water Quality 80/778/EEC. Pesticides: maximum admissible concentration $0.1 \mu\text{g l}^{-1}$ (11).

WHO Toxicity Class III (12).

EPA Toxicity Class (formulation) III (3).

Other comments

Reported to inhibit the synthesis of cellulose in cotton (13).

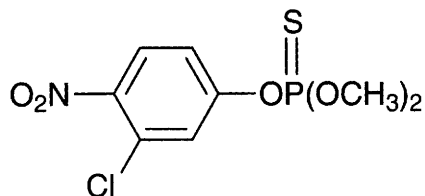
Odour threshold concentration 0.01 ppm (2).

Residues detected in groundwater supplies (14).

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c320 chlorthion



$\text{C}_8\text{H}_9\text{ClNO}_5\text{PS}$

Mol. Wt. 297.66

CAS Registry No. 500-28-7

Synonyms *O*-(3-chloro-4-nitrophenyl) *O,O*-dimethyl phosphorothioate; *p*-nitro-*m*-chlorophenyl dimethyl thionophosphate; phosphorothioic acid, *O*-(3-chloro-4-nitrophenyl) *O,O*-dimethyl ester

EINECS No. 207-902-5

RTECS No. TE 8050000

Uses Insecticide. Aphicide. (Now superseded).

Physical properties

M. Pt. 21°C **B. Pt.** 125°C **Specific gravity** 1.437 at 20°C with respect to water at 4°C

Volatility v.p. $7.0 \times 10^{-6} \text{ mmHg}$ at 30°C

Solubility Water: 6.25 mg l^{-1} at 20°C . Organic solvents: miscible benzene, diethyl ether, ethanol

Occupational exposure

Supply classification harmful

Risk phrases Harmful by inhalation, in contact with skin and if swallowed (R20/21/22)

Safety phrases Keep out of reach of children (if sold to general public) – Keep away from food, drink and animal feeding stuffs (S2, S13)

Ecotoxicity

Fish toxicity

LC₅₀ (96 hr) fathead minnow 2800 µg l⁻¹ (1).

LC₅₀ (96 hr) bluegill sunfish 700 µg l⁻¹ (1).

The lethal body burden in guppies that had died of chlorthion exposure was established at 122 µg fish⁻¹.

However, fish that died within 24 hr of exposure to high chlorthion concentrations had lethal body burdens 6 to 10 × higher (2).

Invertebrate toxicity

EC₅₀ (48 hr) *Daphnia magna* 4.5 µg l⁻¹ (3).

Mammalian & avian toxicity

Acute data

LD₅₀ oral redwing blackbird, starling 280 mg kg⁻¹ (4).

LD₅₀ oral mouse, rat 794, 880 mg kg⁻¹, respectively (5,6).

LD₅₀ intraperitoneal rat 750 mg kg⁻¹ (7).

Sub-acute and sub-chronic data

Oral rat (60 day) 50 and 100 mg kg⁻¹ in diet caused 50% cholinesterase activity inhibition. 200 mg kg⁻¹ day⁻¹ produced 75% cholinesterase activity inhibition and was not tolerated for more than 5-10 days. There was 40% mortality at 100 mg dose. 50 mg dose was tolerated without mortality for 60 days (8).

Carcinogenicity and chronic effects

Oral rat (1 yr) 25, 100 and 250 ppm in diet caused retarded growth only at the highest dose level (9).

Irritancy

Dermal rabbit 1500 mg kg⁻¹ caused no signs of toxicity (10).

Other effects

Other adverse effects (human)

Depression of whole blood cholinesterase activity was reported in workers who had sprayed this insecticide (11).

Legislation

Limited under EC Directive on Drinking Water Quality 80/778/EEC. Pesticides: maximum admissible concentration 0.1 µg l⁻¹ (12).

Other comments

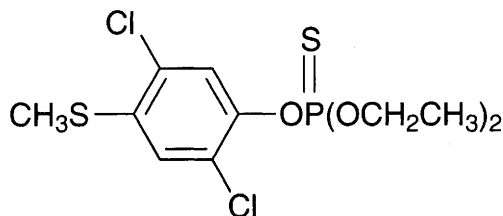
Health hazards reviewed (13).

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c321 chlorthiophos



C₁₁H₁₅Cl₂O₃PS₂

Mol. Wt. 361.25

CAS Registry No. 21923-23-9; 60238-56-4
(for mixed isomer)

Synonyms phosphorothioic acid, O-[2,5-dichloro-4-(methylthio)phenyl] O,O-diethyl ester;
O-[2,5-dichloro-4-(methylthio)phenyl] O,O-diethyl phosphorothioate; Celathion

EINECS No. 244-663-6

RTECS No. TF 1590000

Uses Insecticide. Acaricide. (Now superseded).

Physical properties

B. Pt. 153-158°C at 0.013 mm Hg **Specific gravity** 1.35 at 20°C with respect to water at 4°C

Volatility v.p. 4×10^{-4} mmHg

Solubility Water: 0.3 mg l⁻¹. Organic solvents: miscible with all common organic solvents

Occupational exposure

Supply classification very toxic

Risk phrases Toxic in contact with skin – Very toxic if swallowed (R24, R28)

Safety phrases Keep locked up and out of the reach of children (if sold to general public) – After contact with skin, wash immediately with plenty of water – Wear suitable protective clothing and gloves – In case of accident or if you feel unwell, seek medical advice immediately (show label where possible) (S1/2, S28, S36/37, S45)

Ecotoxicity

Fish toxicity

LC₅₀ (96 hr) bluegill sunfish 1.3 mg l⁻¹ (1).

LC₅₀ (96 hr) rainbow trout 0.019 mg l⁻¹ (1).

Mammalian & avian toxicity

Acute data

LD₅₀ oral chicken, quail 45 mg kg⁻¹ (2).

LD₅₀ oral rat, mouse 91 mg kg⁻¹ (3).

LD₅₀ dermal rabbit, rat 48, 58 mg kg⁻¹, respectively (2).

LD₅₀ subcutaneous rabbit 31 mg kg⁻¹ (3).

Sub-acute and sub-chronic data

LC₅₀ (8 day) oral mallard duck, bobwhite quail 200-213 mg kg⁻¹ diet (1).

Carcinogenicity and chronic effects

In 2-yr feeding trials, no-effect level for rats based on erythrocyte cholinesterase activity inhibition was 1.6 mg kg⁻¹ diet (1).

Metabolism and toxicokinetics

Degradation in animals and plants is rapid. Major metabolites include sulfoxide and sulfone (3).

Other effects

Any other adverse effects

The main feature of toxic mechanism is inhibition of esterase activity, particularly cholinesterase activity (4).

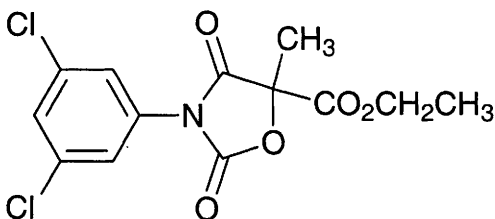
Legislation

Limited under EC Directive on Drinking Water Quality 80/778/EEC. Pesticides: maximum admissible concentration 0.1 µg l⁻¹ (5).

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C322 chlozolate



C₁₃H₁₁Cl₂NO₅

Mol. Wt. 332.14

CAS Registry No. 84332-86-5

Synonyms ±3-(3,5-dichlorophenyl)-2,4-dioxo-5-methyl-5-oxazolidinecarboxylic acid, ethyl ester; dichlozolate

EINECS No. 282-714-4

RTECS No. RP 7190000

Uses Fungicide.

Physical properties

M. Pt. 112.6°C **Flash point** <200°C **Specific gravity** 1.441 at 20°C **Partition coefficient** $\log P_{ow}$ 3.15 at 22°C
(1) **Volatility** v.p. 0.09×10^{-6} mmHg
Solubility Water: ~2 ppm at 25°C. Organic solvents: acetone, 1,2-dichloroethane, ethyl acetate, xylene

Ecotoxicity

Fish toxicity

LC₅₀ (96 hr) trout 28 mg l⁻¹ (1).

Environmental fate

Abiotic removal

In solution undergoes hydrolysis at pH 5-9 (1).

Mammalian & avian toxicity

Acute data

LD₅₀ oral rat, mouse 4.5, 10 g kg⁻¹, respectively (1).

LD₅₀ oral bobwhite quail >9 g kg⁻¹ (1).

LC₅₀ (duration unspecified) inhalation rat >10 g l⁻¹ (2).

LD₅₀ dermal rat >5 g kg⁻¹ (1).

Sub-acute and sub-chronic data

No-effect level 90-day feeding trial in rat 200 mg kg⁻¹ diet. No-effect level 6-month feeding trial in dog 300 mg kg⁻¹ diet (1).

Irritancy

Reported to be non-irritating and non-sensitising to skin (species unspecified) (1).

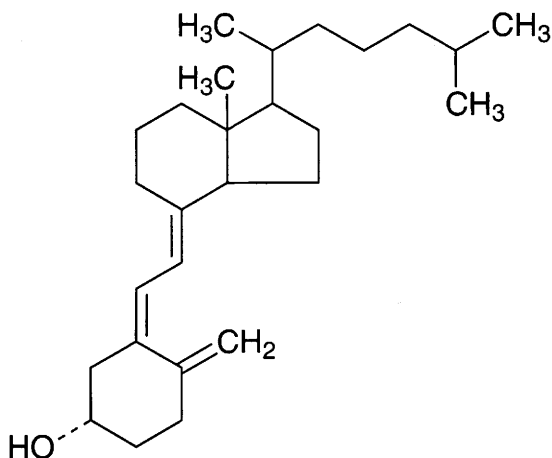
Legislation

Limited under EC Directive on Drinking Water Quality 80/778/EEC. Pesticides: maximum admissible concentration 0.1 µg l⁻¹ (3).

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C323 cholecalciferol



C₂₇H₄₄O

Mol. Wt. 384.65

CAS Registry No. 67-97-0

Synonyms calciol; vitamin D₃; 7-dehydrocholesterol, activated; delsterol; Deparal; Ricketon; (3 β ,5Z,7E)-9,10-secocholesta-5,7,10(19)-trien-3-ol; 9,10-secocholesta-5,7,10(19)-trien-3 β -ol; Muritan; Quintox; Racumin D; Rampage

EINECS No. 200-673-2

RTECS No. VS 2900000

Uses Nutritional factor. For the prevention of rickets.

Occurrence In fish liver oils. Produced from 7-dehydrocholesterol, a sterol present in mammalian skin.

Physical properties

M. Pt. 84-85°C

Solubility Organic solvents: acetone, chloroform, ethanol, hexane

Mammalian & avian toxicity

Acute data

LD₅₀ oral rat, dog 42, 80 mg kg⁻¹ respectively (1,2).

LD₅₀ intraperitoneal mouse 136 mg kg⁻¹, (3).

Teratogenicity and reproductive effects

Subcutaneous rat, lowest toxic dose 90 mg kg⁻¹ day⁻¹ on days 12-20 of gestation – foetotoxicity (4).

Intramuscular rat, 3000 or 7500 IU on day 10 of gestation induced a significant increase in body weight gain of pups, promoting soft tissue growth by enhancing cellular proliferation and hypertrophy (5).

Metabolism and toxicokinetics

Absorbed by the intestinal jejunal cells in the rat (6).

Metabolites identified in blood plasma included 25-hydroxyvitamin D₃, 24,25-dihydroxyvitamin D₃ and 1,25-dihydroxyvitamin D₃ (7).

1,23-dihydroxy-24,25,26,27-tetranorvitamin D₃ is a further metabolite of 1,25-dihydroxyvitamin D₃ in perfused rat kidney (8).

Vitamin D₃ was reduced by 95% in human skin samples exposed to sunlight for 3 hr in the month of June. During December 30% reduction was observed. Radiation of 290-335 nm in the solar spectrum was responsible for the breakdown of vitamin D₃. The degradation products were identified as 5,6-transvitamin D₃ and suprasterols (9). Vitamin D and metabolites are excreted mainly in the bile with only small amounts appearing in the urine.

Enterohepatic recycling is negligible. Certain vitamin D substances may be excreted into breast milk in humans (10).

Genotoxicity

Salmonella typhimurium TA98, TA100, TA1535, TA1537 with and without metabolic activation negative (11).

Other effects

Other adverse effects (human)

Excessive intake leads to hypercalcaemia (10).

Other comments

Vitamin D₃ mediates intestinal calcium absorption, bone calcium metabolism and, probably, muscle activity (10).

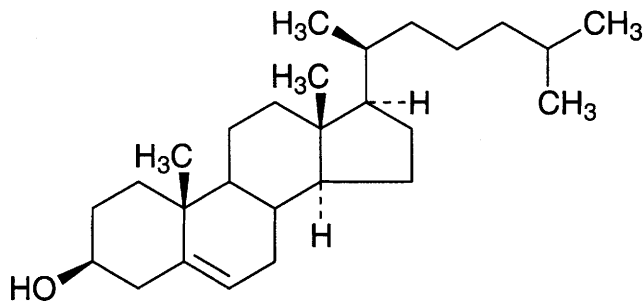
Vitamin D₃ modulated colonic carcinogenicity in rats induced by 1,2-dimethylhydrazine (12).

Metabolism of vitamin D₃ and vitamin D₃-induced proliferation of HL-60 cells reviewed (13).

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C324 cholesterol



C₂₇H₄₆O

Mol. Wt. 386.66

CAS Registry No. 57-88-5

Synonyms cholestrin; cholest-5-en-3-β-ol; cholesterin; cholesteryl alcohol; Fancol CH; Loralan-CH

EINECS No. 200-353-2

RTECS No. FZ 8400000

Uses Emulsifying agent.

Occurrence Found in all body tissues especially in the brain, spinal cord and in animal fats, oils and egg yolk.

Physical properties

M. Pt. 148.5°C **B. Pt.** 360°C (some decomposition), 233°C at 0.5 mmHg **Specific gravity** 1.067 at 20°C with respect to water at 4°C

Solubility Water: 2 mg l⁻¹. Organic solvents: benzene, chloroform, diethyl ether, dioxane, ethanol, petroleum ether, pyridine

Environmental fate

Degradation studies

BOD₂₅₃₅ 0.83 in seawater with an inoculum of enrichment cultures of hydrocarbon oxidising bacteria. Theoretical oxygen demand (ThOD) 3.12 mg l⁻¹ O₂ (1).

Mycobacterium strain DP isolated from marine coastal sediment oxidised cholesterol in Tween 80-cholesterol (2.59 mM) medium. Products included 4-cholesten-3-one, 4-androsten-13,17-dione, 1,4-androstadien-13,17-dione, testosterone and 1-dehydrotestosterone. All cholesterol disappeared in ~4 days (2).

Growing *Bifidobacterium* sp. are able to remove cholesterol from TPY medium containing oxgall both by precipitation and by assimilation (3).

Pseudomonas sp. strain ST-200 isolated from humus soil was shown to oxidise the C-3 and C-6 positions by introduction of a hydroxyl or ketone group (4).

Mammalian & avian toxicity

Carcinogenicity and chronic effects

Inadequate evidence for carcinogenicity to animals and to humans, IARC classification group 3 (5).

Studies for carcinogenicity in mice by subcutaneous and oral administration and by bladder implantation were all inadequate for evaluation. Tests in combination with various carcinogens on laboratory animals were also reported to give results which were inadequate to assess the carcinogenesis-enhancing potential of cholesterol (6). Feeding of cholesterol to rats exposed to a mammary carcinogen did not affect the incidence of mammary tumours (7). Feeding cholesterol to rats after administration of a colon carcinogen *N*-methyl-*N*-nitrosourea resulted in a lower incidence of colon tumours (8).

In a cohort study of 89,538 nurses in USA, there was no increased risk of breast cancer associated with dietary fat or dietary cholesterol (9).

Dietary cholesterol intake was greater in patients in a case-control study of colorectal cancer than in controls, but the risk ratios were lower than for saturated fat intake (10).

A study of 4,035 residents of California, USA, aged 40-89, showed no association between plasma cholesterol and cancer morbidity or mortality over a 7-yr period for either men or women for any cancer site (11).

A case-control study of 37 cases of primary brain tumours found elevated levels of cholesterol (12).

A study of family history of cancers was found to be positively associated with serum cholesterol levels in young adults (13).

Teratogenicity and reproductive effects

Rats were administered daily subcutaneous injections of 5, 10 and 15 mg on days 8-14 of gestation. Cleft palate was reported in 27, 52 and 57% of offspring, respectively. No cleft palate occurred in controls (14).

Following daily subcutaneous administration of 20 mg to pregnant rats, a general reduction in foetal size was seen, and 112/286 pups had gross oral clefts. No histologically detectable cleft anomaly was observed in foetuses from rats injected with 6 mg (15).

Metabolism and toxicokinetics

May be obtained via diet or by biosynthesis in the liver. Secreted into the plasma from intestine, mainly as a component of chylomicrons which are quickly degraded and removed by the liver (16).

It is reported that most people in Western societies ingest between 500-800 mg day⁻¹ and absorb 300-400 mg day⁻¹ (17). While virtually all nucleated mammalian cells can synthesise cholesterol, in humans the liver and intestine account for >95% of total cholesterol produced in the body (18).

Cholesterol is metabolised in the liver, the main metabolic pathway being conversion into the two primary bile salts, cholic acid and chenodeoxycholic acid. These, after conjugation with either glycine or taurine, pass into the intestine via the bile, where they are further metabolised by bacterial enzymes to yield the secondary bile acids, deoxycholic acid and lithocholic acid. Cholesterol is also reduced to cholestanol in the liver (19).

In the intestine the principal bacterial metabolites are coprostanol (a stereoisomer of cholesterol) and cholestanone (20).

In the adrenal cortex, testes and ovaries, cholesterol serves as the precursor for the synthesis of steroid hormones. Cholesterol is converted via pregnenolone into progesterone, which in turn is the precursor of androgens (e.g. testosterone and androsterone), oestrogens (e.g. oestrone and oestradiol), and of the adrenal corticosteroids (e.g. cortisol, corticosterone and aldosterone) (21).

In the skin there is evidence that cholesterol may be oxidised photochemically by irradiation with UV light (240-440 nm) to cholesterol α -epoxide (22).

A hydrolysis product of cholesterol, α -epoxide, cholestane-3 β ,5 α ,6 β -triol, is excreted in increased amounts in the faeces of patients with colon cancer. Various intestinal metabolites, such as the neutral steroids and the hydrolysis products of cholesterol and the epoxide, are also reported to be excreted in increased amounts in the faeces of patients with colon cancer (23).

Five major classes of lipoprotein serve to transport and regulate the supply of cholesterol to different body tissues: chylomicrons, very low density lipoproteins, intermediate density lipoproteins, low density lipoproteins and high density lipoproteins. Cholesterol can exist either in the unesterified form or as an ester of long chain fatty acids. The former, often termed 'free cholesterol' is the metabolically active form (18).

Genotoxicity

Salmonella typhimurium TA100, TA1535 with and without metabolic activation negative (24).

Mutagenicity was reported to be associated with polar cholesterol autooxidation products generated during oxidation of the sterol B-ring and of the side-chain (25).

The metabolite cholesterol α -epoxide damaged chromosomes and initiated DNA repair synthesis in human fibroblasts *in vitro* (26).

Cholesterol α -epoxide transformed embryo cells *in vitro* (27).

Cholestan-3 β ,5 α ,6 β -triol, a metabolite of cholesterol α -epoxide, also induced transformation in hamster embryo cells *in vitro* (28).

Other effects

Other adverse effects (human)

Substantial epidemiological evidence has established a positive correlation between the risk of coronary heart disease and increasing levels of total and low-density lipoprotein (LDL) cholesterol in the blood (29).

The risk of developing peripheral vascular disease was also reported to be increased by raised blood cholesterol levels. By contrast, the risk of cholesterol gallstone formation may be increased by a serum cholesterol-lowering diet (30).

Thirty two volunteers in the Netherlands participated in three controlled dietary trials in 1982. A low cholesterol diet in the 1st half of the study and a high cholesterol diet in the 2nd half of the trial was given. Responsiveness showed a positive correlation with serum high-density lipoprotein (HDL) and with serum total cholesterol level on a high-cholesterol diet (31).

Cholesterol supersaturation of bile and high biliary protein are of key importance in the rapid formation of cholesterol crystals and therefore may be a possible risk factor in the pathogenesis of cholesterol gallstones (32).

Other comments

Cigarette smoking was associated with significant increases in total cholesterol circulation levels and decreases in high-density lipoproteins (HDL) values (33).

Obesity in adolescents and oral contraceptive use have a deleterious effect on adult cholesterol and low-density lipoprotein (LDL) levels (34).

Cholesterol levels and human cancer mortality have been extensively reviewed (35-38).

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c325 cholestyramine

CAS Registry No. 11041-12-6

Synonyms cholestyramine resin; Questran (as the chloride)

EINECS No. 234-270-8

RTECS No. FZ 9310000

Uses Ion-exchange resin used as hypolipidaemic agent in the treatment of hypercholesterolaemia.

Physical properties

Solubility Water: insoluble. Organic solvents: insoluble in alcohol, benzene, chloroform, ether

Ecotoxicity

Invertebrate toxicity

As the concentration of cholestyramine was increased in the diet of *Heliothis zea* to 6%, the number of larval moths increased from 5 or 6, to 7 or 8, the time required for the onset of pupation increased from 11 or 12, to 20 days and the number of adults that emerged decreased from >70% to 0% (1).

Mammalian & avian toxicity

Acute data

LD₅₀ oral rabbit, rat, mouse >3->7.5 g kg⁻¹, respectively (2).

LD₅₀ intraperitoneal rat, mouse >1.6->4 g kg⁻¹, respectively (2).

LD₅₀ subcutaneous rat, mouse >1.2->3 g kg⁻¹, respectively (2).

Sub-acute and sub-chronic data

Rats were administered cholestyramine at 5% diet (duration unspecified). Serum and liver cholesterol were significantly reduced in treated animals compared to controls. Histological examination of the small and large bowel revealed statistically significant increase in both proximal and distal small bowel and distal large bowel mucosal thickness (3).

Carcinogenicity and chronic effects

Groups of rats administered a single intragastric dose of 5 mg of 7,12-dimethylbenzanthracene were fed a diet containing 4% cholestyramine for 100 or 200 days. The incidence of malignant mammary tumours increased 5-fold and tumour weight 12-fold compared to rats administered 7,12-dimethylbenzanthracene alone (4).

Metabolism and toxicokinetics

Unaffected by digestive enzymes, remains unchanged in the gastro-intestinal tract, and is not absorbed (5).

Other effects

Other adverse effects (human)

Hypoprothrombinaemia has been observed (5).

The most common reported side-effects are nausea, constipation, heartburn and abdominal pains.

Cholestyramine has been reported to cause steatorrhoea by interfering with the absorption of fats and therefore decreased absorption of the fat-soluble vitamins, such as vitamins A, D, E and K (6).

Any other adverse effects

An enriched diet (concentration unspecified) to weaned rabbits resulted in lowering of plasma cholesterol and decreased activity of aortic acyl-CoA cholesterol acyl transferase with no changes in aortic acid and neutral cholesteryl esterase activity. At 9 wk after cessation of cholestyramine treatment, enhanced activity of both aortic esterases was noted despite normalisation of plasma cholesterol (7).

Rats were fed a basal diet supplemented with 5% cholestyramine for 8 days. Bile flow and biliary secretion of bile acids and phospholipids were decreased whereas biliary cholesterol secretion remained unchanged. In the biliary bile acid component, a marked increase of chenodeoxycholic acid with a concomitant decrease of β -muricholic acid was observed. Faecal excretion of total sterols and bile acids increased 3- and 4-fold, respectively (8).

Other comments

Should not be administered during pregnancy. Children with heterozygous familial hypercholesterolaemia should not be given this resin therapy until 6-yr of age (9).

Cholestyramine is a strongly basic ion-exchange resin containing quaternary ammonium functional groups which are attached to a styrene-divinylbenzene copolymer (about 2% divinylbenzene). It is used in the chloride form (6).

Cholestyramine administered in the diet at 5% was reported to inhibit the intestinal absorption of orally administered doses of polychlorinated biphenyls (PCBs) (10).

Stable to ~150°C.

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c326 choline



C₅H₁₄NO

Mol. Wt. 104.17

CAS Registry No. 62-49-7

Synonyms choline ion; ethanaminium (1+), 2-hydroxy-*N,N,N*-trimethyl; (2-hydroxyethyl)trimethylammonium

EINECS No. 200-535-1

RTECS No. FZ 9625000

Uses Catalyst for cyanoethylations. Lipotropic.

Occurrence Found in many plants and animal organs, e.g. bile, brain, yolk of eggs, hops, belladonna and *Strophanthus*. Constituent of lecithin.

Physical properties

Solubility Water: very soluble. Organic solvents: ethanol

Ecotoxicity

Invertebrate toxicity

Tetrahymena thermophila grown with 10 mM choline in the medium showed an increase in the level of phosphatidylethanolamine from 41% to 45% of the total phospholipid with a corresponding decrease in 2-aminoethylphosphoglyceride compared to control cells. The increased incorporation of ethanolamine into phospholipids in choline-grown cells may reflect regulation of the phosphatidylethanolamine biosynthetic pathway by choline (1).

Mammalian & avian toxicity

Acute data

LD₅₀ oral rat 6640 mg kg⁻¹ (2).

LD₅₀ intraperitoneal rat 400 mg kg⁻¹ (2).

Carcinogenicity and chronic effects

♀ AKR/J mice fed diets supplemented with methionine and choline (dose unspecified), spontaneously developed thymic lymphoma, with close to 100% mortality by 12-13 months of age (3).

Metabolism and toxicokinetics

Intestinal absorption of choline from the rat jejunum was investigated in an *in situ* ligated loop and an *in vitro* everted sac method. Choline was absorbed rapidly from the ligated jejunum. In the *in vitro* experiments choline was transported from the mucosal fluid to the intracellular fluid against a concentration gradient, and the rate of

tissue uptake was highly affected by incubation temperature, aerobic condition and the presence of a metabolic inhibitor (4).

Other effects

Any other adverse effects

Oral F344 rat (1 wk) methionine and choline deprivation in diet. Rats on methionine- and choline-free diet suffered weight loss and significantly decreased sperm counts 4 wk after the end of treatment (5).

Other comments

Choline homeostasis in the brain and lipids and acetyl choline synthesis reviewed (6,7).

Structure, physiological functions and nutritional requirements of choline reviewed in relation to dietary intake of phosphatidylcholine (8).

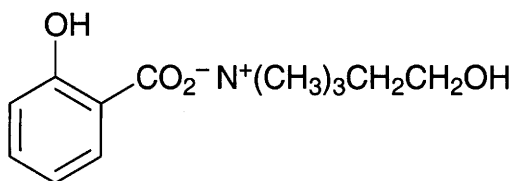
Choline in animal nutrition reviewed (9,10).

Action of methionine as a liver carcinogen and of possible mechanisms by which methionine and choline deficiencies stimulate liver cancer reviewed (11).

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c327 choline salicylate



$C_{12}H_{19}NO_4$

Mol. Wt. 241.29

CAS Registry No. 2016-36-6

Synonyms choline salicylate B; choline salicylic acid salt; 2-hydroxy-*N,N,N*-trimethylethanaminium, 2-hydroxybenzoic acid salt (1:1); (2-hydroxyethyl)trimethylammonium salicylate; 2-hydroxy-*N,N,N*-trimethylethanaminium salt with 2-hydroxybenzoic acid (1:1); salicylic acid, choline salt

EINECS No. 217-948-8

RTECS No. GA 6475000

Physical properties

M. Pt. 49.5°C

Solubility Water: freely soluble. Organic solvents: acetone, ethanol, ether, other hydrophilic solvents

Mammalian & avian toxicity

Acute data

LD₅₀ oral mouse 2690 mg kg⁻¹ (1).

LD₅₀ subcutaneous mouse 1000 mg kg⁻¹ (1).

References

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c328 chromic acid



CrH₂O₄

Mol. Wt. 118.01

CAS Registry No. 7738-94-5

Synonyms

EINECS No. 231-801-5

Uses In chromating baths for galvanising steel. Corrosion inhibitor. Oxidising agent in organic chemistry.

Occupational exposure

SE-LEVL 0.02 mg m⁻³ (as Cr)

SE-STEL 0.06 mg m⁻³ (as Cr)

UK-LTEL MEL 0.05 mg m⁻³ (as Cr)

US-TWA 0.05 mg m⁻³ (as Cr)

UN No. 1755 HAZCHEM Code 2X Conveyance classification corrosive substance

Supply classification oxidising

Supply classification toxic

Risk phrases May cause cancer by inhalation (R49)

Mammalian & avian toxicity

Carcinogenicity and chronic effects

Sufficient evidence in humans for carcinogenicity of Cr(VI) compounds as encountered in chromate production, pigment production and chromium plating, limited evidence for carcinogenicity of chromium trioxide (chromic acid) in animals, IARC classification group 1 (1).

Inhalation (12 month) chromic acid mist (1.81 mg Cr⁶⁺, 120 min, 2 × wk⁻¹) mice. Perforated nasal septa, emphysema, pulmonary adenomatous metaplasia, papillomas in nasal epithelia and pulmonary adenoma found on sacrifice (2).

Irritancy

Ulceration and perforation of the nasal septum was one of the most frequently encountered chronic effects of occupational exposure in humans (3).

Sensitisation

Chromium is an important skin sensitizer. Sensitisation usually occurs after 6-9 months (but may occur as early as 3 months). The effect of oxidation state on sensitisation is controversial (3).

Genotoxicity

Salmonella typhimurium TA1535 without metabolic activation negative, TA100 without metabolic activation positive, TA1537, TA1538, TA98 without metabolic activation weakly positive (4).

Significantly increased frequency of sister chromatid exchanges in lymphocytes of a worker occupationally exposed to chromic acid fumes (5).

Other effects

Other adverse effects (human)

A fatal case of acute chromic acid ingestion is reported. An employee in a metal plating works ingested 20-30 ml; metabolic acidosis, hypotension and renal failure developed within the first day. An oesophogram performed at 10 days showed perforation of the stomach, and endoscopy 2.5 wk after ingestion showed extensive oesophageal, gastric and duodenal ulceration. Death, probably from severe gastro-intestinal haemorrhage occurred a month after ingestion (6).

Legislation

Limited under EC Directive on Drinking Water Quality 80/778/EEC. Chromium: maximum admissible concentration 50 µg l⁻¹ (7).

Included in Schedule 6 (Release into Land: Prescribed Substances) Statutory Instrument No. 472, 1991 (8).

Covered in the UK by the Control of Carcinogenic Substances, Control of Substances Hazardous to Health Regulations 1988 (9).

Other comments

Genotoxicity reviewed (10).

Toxicity (11-14) and hazardous reactions reviewed (15).

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Cr

Mol. Wt. 52.00

CAS Registry No. 7440-47-3

Synonyms chrome; chromium metal

EINECS No. 231-157-5

RTECS No. GB 4200000

Uses Manufacture of alloys. Chrome plating. Pigment manufacture.

Occurrence Obtained from chrome ore, chromite (FeCr_2O_4). Reported abundance in Earth's crust: 100-300 ppm.

Physical properties

M. Pt. 1900°C B. Pt. 2642°C Specific gravity 7.14

Occupational exposure

FR-VME 0.5 mg m⁻³JP-OEL 0.05 mg m⁻³SE-LEVL 0.5 mg m⁻³UK-LTEL 0.5 mg m⁻³US-TWA 0.5 mg m⁻³

Ecotoxicity

Fish toxicity

LC₅₀ (24-240 hr) common guppy 49-19.25 mg l⁻¹ (as $\text{K}_2\text{Cr}_2\text{O}_7$) (1).Carbohydrate, protein and lipid contents in tissues of the carp *Catla catla* are depleted under the sublethal stress of chromium (2).

Chromium is genotoxic to the common loach and induces micronuclei formation in the erythrocytes (3).

Invertebrate toxicity

Daphnia magna brood size insensitive to acute chromium exposure (4).EC₅₀ (48 hr) *Daphnia magna* 1.79 ppm (5).

Bioaccumulation

Minimum effect concentration (4 wk) for *Allorchestes compressa* >250 µg l⁻¹ in flowing seawater; concentration in the amphipod was >46 µg g⁻¹ dry weight. Accumulation of chromium showed some evidence of metabolic regulation (6).

Environmental fate

Nitrification inhibition

Inhibition of nitrification/denitrification using activated sludge 1.0 mg l⁻¹ *Nitrosomonas* sp. toxicity threshold 1.0 mg l⁻¹. Inhibition of nitrification-biological filtration, slight inhibition at 20 mg l⁻¹. Inhibition of denitrification/nitrification using rotating disc, threshold 9.0 mg l⁻¹ and 1.0 mg l⁻¹, respectively (7).

Mammalian & avian toxicity

Acute data

LD_{Lo} oral human 50-70 mg kg⁻¹ (soluble salts) (8).

Sub-acute and sub-chronic data

Daily exposure to 3.1 mg m⁻³ as Cr metal (60-80% particles diameter <7 µm) for 4 wk produced no adverse effects in the lungs of rabbits (9).

Carcinogenicity and chronic effects

Inadequate evidence for carcinogenicity to humans and animals, IARC classification group 3 (10).

Fifty ♂ mice were given six intrapleural injections of 10 µg Cr powder in 0.2 ml of a 2.5% gelatin saline solution every other wk. No tumours were observed after 14 wk (11).

According to IARC these tests were inadequate (12).

Intratracheal instillation of 100 mg chromium metal did not produce lung tumours in ♀ rats (13).

No injection-site tumours observed in ♂ rats 24 months after intramuscular injection of 2 mg chromium powder (14).

Teratogenicity and reproductive effects

Chromium induced embryotoxicity and foetotoxicity in mice treated during the pregestational period. Gross and skeletal abnormalities were seen in the pups of mice treated pregestationally with chromium (15).

Metabolism and toxicokinetics

Guinea pig liver and kidney enzyme activities and blood glucose and haemoglobin levels increased after 15 or 30 days of dermal exposure to chromium. The concentration of chromium in the tissues increased with duration of exposure (16).

Sensitisation

Human allergic reactions (local stomatitis or general or local contact dermatitis) from chromium in dental prosthesis reported (17).

Other effects

Other adverse effects (human)

Workers in a bichromate-producing plant in England had higher concentrations of chromium in whole blood, plasma and urine than controls. There was a modest increase in chromium concentration in lymphocytes compared to controls but DNA strand breaks in lymphocytes and 8-hydroxy-2'-deoxyguanosine in lymphocytes and urine showed no statistically significant differences among the exposed and control groups (18).

Legislation

Limited under EC Directive on Drinking Water Quality 80/778/EEC. Chromium: maximum admissible concentration 50 µg l⁻¹ (19).

UK National Environmental Quality Standards for List II Substances which includes chromium (WRC Report Ref. TR207). Fresh water: direct – 50 µg Cr l⁻¹ total (95% of samples must comply); abstraction to potable supply – 75 µg Cr l⁻¹ total maximum allowable concentration. For the protection of sensitive aquatic life dissolved annual average should not exceed: 5 µg Cr l⁻¹ (0-50 mg l⁻¹ CaCO₃); 10 µg Cr l⁻¹ (50-100 mg l⁻¹ CaCO₃); 20 µg Cr l⁻¹ (100-200 mg l⁻¹ CaCO₃); 50 µg Cr l⁻¹ (200-250+ mg l⁻¹ CaCO₃). For the protection of other aquatic life dissolved annual average should not exceed: 150 µg Cr l⁻¹ (0-50 mg l⁻¹ CaCO₃); 175 µg Cr l⁻¹ (50-100 mg l⁻¹ CaCO₃); 200 µg Cr l⁻¹ (100-200 mg l⁻¹ CaCO₃); 250 µg Cr l⁻¹ (200-250+ mg l⁻¹ CaCO₃). For the protection of salt water life, dissolved annual average should not exceed: 15 µg Cr l⁻¹ (20).

Other comments

The toxicity of chromium is dependent on the ability of the organism to absorb it. Therefore toxicity data refer to bioavailable forms, such as the ion in solution or particulated matter.

A ubiquitous element; all plants contain up to 0.19 mg kg⁻¹ chromium (as chromium salt) on a weight basis. A substantial amount is diverted from the environmental cycle by discharge into streams, run-off and disposal to sea.

Reviews on human health effects, experimental toxicology, environmental effects, ecotoxicology and exposure listed (21).

Toxicity reviewed (22-29).

Genotoxicity reviewed (30,31).

Mechanisms of chromium carcinogenicity and toxicity reviewed (32).

Chromium-induced kidney disease reviewed (33).

Reproductive toxicology and teratogenicity reviewed (34,35).

Bacterial and algal toxicity reviewed (36,37).

Bioavailability and mobility reviewed (38).

Toxicity to soil microorganisms reviewed (39).

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C330 chromium(III)



Cr

Mol. Wt. 52.00

CAS Registry No. 16065-83-1

Synonyms chromium(3+)

RTECS No. GB 6261000

Occupational exposure

JP-OEL 0.5 mg m⁻³ (as Cr)

SE-LEVL 0.5 mg m⁻³

UK-LTEL 0.5 mg m⁻³

US-TWA 0.5 mg m⁻³ (as Cr)

Ecotoxicity

Fish toxicity

LC₅₀ (96 hr) rainbow trout 4.4 mg l⁻¹ (1).

LC₅₀ (96 hr) zebra fish 58.5 mg l⁻¹ (2).

Invertebrate toxicity

LC₅₀ (48 hr) *Daphnia magna* 2 mg l⁻¹ (3).

LC₅₀ (48, 96 hr) *Asellus aquaticus* 937, 442 mg l⁻¹, respectively (4).

Environmental fate

Nitrification inhibition

4000 mg l⁻¹ NH₄⁺ and 12 mg l⁻¹ Cr³⁺ caused a 50% reduction in methanogenic activity of an anaerobic sludge.

Inhibition by Cr³⁺ was reverted by its removal following addition of Fe and increasing the biomass (5).

Mammalian & avian toxicity

Carcinogenicity and chronic effects

Inadequate evidence for carcinogenicity of trivalent chromium compounds to humans and animals, IARC classification group 3 (6).

No evidence of excess human cancers in two industries where only trivalent chromium compounds were used (7).

Teratogenicity and reproductive effects

Exposure to trivalent chromium during mid-pregnancy may be detrimental for development of the rat conceptus (8).

Metabolism and toxicokinetics

0.5-3% of total intake of trivalent chromium is absorbed into the body; excretion is almost solely via urine. After intestinal absorption, chromium is taken up by plasma protein fractions, mainly transferrin. Inhaled chromium is bound to albumin (7).

Irritancy

Trivalent chromium compounds do not cause ulceration but prolonged contact can cause skin lesions in humans (7).

Sensitisation

Chromium is an important skin sensitiser. Sensitisation usually occurs after 6-9 months (but may occur as early as 3 months). The effect of oxidation state on sensitisation is controversial (7).

Genotoxicity

Trivalent chromium compounds did not induce micronuclei in bone-marrow cells of mice treated *in vivo*.

Neither sister chromatid exchange nor unscheduled DNA synthesis was induced in human cells *in vitro*; results

for chromosome aberration induction were conflicting as were results for chromosome aberrations, mutation and sister chromatid exchanges in cultured rodent cells. Trivalent chromium compounds did not induce mutation in bacteria but induced DNA damage (7).

Other effects

Any other adverse effects

Toxic effects from trivalent chromium reported only after parenteral administration (mouse, rat, rabbit, dog) (7).

Legislation

Limited under EC Directive on Drinking Water Quality 80/778/EEC. Chromium: maximum admissible concentration 50 µg l⁻¹ (9).

Other comments

Trivalent chromium compounds may be contaminated with hexavalent chromium compounds (7).
Acute and chronic toxicity, genotoxicity and carcinogenicity reviewed (10-13).

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c331 chromium(vi)

Cr⁶⁺

Cr

Mol. Wt. 52.00

CAS Registry No. 18540-29-9

Synonyms chromium(6+)

RTECS No. GB 6262000

Occupational exposure

FR-VME 0.05 mg m⁻³ (as Cr)

JP-OEL 0.05 mg m⁻³ (as Cr)

SE-LEVL 0.5 mg m⁻³

UK-LTEL MEL 0.05 mg m⁻³ (as Cr)

US-TWA 0.05 mg m⁻³ (as Cr)

Ecotoxicity

Fish toxicity

- LC₅₀ (96 hr) striped catfish 200 mg l⁻¹ (1).
LC₅₀ (96 hr) fathead minnow 36.2 mg l⁻¹ (2).
LC₅₀ (96 hr) giant gourami 45.2 mg l⁻¹ (3).
LC₅₀ (28 day) rainbow trout 0.19 mg l⁻¹ (4).

Invertebrate toxicity

- LC₅₀ (48 hr) *Monodonata turbinata* 51.9 ppm (non-acclimated), 72.8 ppm (acclimated) (5).
LC₅₀ *Macrobrachium lamerrei* 1.84 mg l⁻¹ (6).
Mortality of nematode *Steinernema carpocapsae* after 96 hr exposure to 35 mg l⁻¹ Cr(vi) 2.3% (7).

Mammalian & avian toxicity

Carcinogenicity and chronic effects

Sufficient evidence in humans for carcinogenicity of Cr(vi) compounds as encountered in chromate production, pigment production and chromium plating. Sufficient evidence in animals for carcinogenicity of calcium chromate, zinc chromates, strontium chromate and lead chromates; limited evidence in animals for carcinogenicity of sodium dichromate; inadequate evidence in animals for barium chromate, IARC classification group 1 (8).

Teratogenicity and reproductive effects

Oral administration to ♀ mice (days 14-19 of pregnancy) of 500 or 750 ppm chromium(vi) in drinking water caused a decrease in gestational weight gain and postimplantation loss, and decreased foetal weight and crown-rump length. In the 750 ppm group, fetuses showed significant increases in drooping wrists, subdermal haemorrhagic patches, kinky and short tails and reduced ossification (9).
Oral administration to ♀ rats 250, 500 or 750 ppm chromium(vi) in drinking water pregestationally caused a lower degree of toxicity than in mice (10).

Metabolism and toxicokinetics

Gastro-intestinal absorption of 3-6% g total intake of hexavalent chromium reported. Gastric juice plays a role detoxifying ingested hexavalent chromium by reducing it to trivalent chromium, which is poorly absorbed (11). Hexavalent chromium usually forms strong oxidising chromate and dichromate and is easily reduced to trivalent chromium under physiological conditions (8).

Intravenously injected chromium(vi) is converted by mice into chromium(v), detectable in the liver and the blood. The results of *in vitro* experiments suggest that this is a chromium(v)-NAD(P)H complex and that NAD(P)H/flavoenzymes are the major one-electron reductants responsible for chromium(vi) reduction *in vivo* (12).

Human volunteers ingested 1 l of deionised water containing 0.1-10.0 mg l⁻¹ chromium(vi) in three doses of 333 ml at 6 hr intervals. The erythrocyte chromium profiles suggest that chromium(vi) is reduced to chromium(III) before entering the bloodstream (13).

Irritancy

Hexavalent chromium compounds cause marked respiratory tract irritation (11).

Genotoxicity

Hexavalent chromium induced dominant lethal mutations, chromosome aberrations and micronuclei in rodents (*in vivo*). Induced chromosomal aberrations, sister chromatid exchanges and DNA damage in cultured human cells. Induced chromosomal aberrations, sister chromatid exchanges, DNA damage, transformation and mutation in cultured rodent cells. Induced aneuploidy in *Drosophila melanogaster*, mitotic recombination in yeast, mutation and DNA damage in bacteria (8).

Studies on chromium platers and smokers suggest sister chromatid exchange analysis in human lymphocytes is not a good indicator of possible mutagenic effects of chromium(vi) exposure (14).

Other effects

Other adverse effects (human)

Hexavalent chromium induced reductions in both blastogenesis and immunoglobulin production in cultured human lymphocytes in relation to its ability to enter the cells (15).

Bone marrow stromal cells were cultured with metal ions found in commonly used orthopaedic implants, such as Co-Cr-Mo alloy, in concentrations of 50 ppb to 50 ppm individual ions or combinations representing the alloy composition. After 48 hr, total cell number, cell protein and mitochondrial activity were measured; chromium(vi) was grossly cytotoxic, and the ion solution representing Co-Cr-Mo alloy was moderately toxic at concentrations close to those measured in the fibrous membrane surrounding orthopaedic implants (16).

Any other adverse effects

EC₅₀ inhibition of DNA synthesis by 3T3 cells 16.6 mM Cr(vi). Results of exposure of 3T3 cells for 16 hr to 3.13-100 mM Cr(vi) indicated that cytoskeletal injury may be an important part of the mechanism of Cr(vi) injury (17).

Legislation

Limited under EC Directive on Drinking Water Quality 80/778/EEC. Chromium: maximum admissible concentration 50 µg l⁻¹ (18).

Included in Schedule 4 (Release into Air: Prescribed Substances) Statutory Instrument No. 472, 1991 (19).

Other comments

Short-term exposure to hexavalent chromium was hazardous to ♂ rat reproduction (20).

Reviews on human health effects, experimental toxicology, physico-chemical properties, environmental effects, ecotoxicology, exposure levels, epidemiology and workplace experience listed (21).

Genotoxicity (22) and toxicity reviewed (23-25).

Carcinogenicity of chromium(vi) compounds reviewed (26,27).

Toxicity of trivalent and hexavalent chromium compounds reviewed (28).

Bioaccumulation and toxicology of chromium and implications for wildlife reviewed (29).

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c332 chromium(III) acetate



$\text{C}_6\text{H}_9\text{CrO}_6$

Mol. Wt. 229.13

CAS Registry No. 1066-30-4

Synonyms chromium triacetate; chromic acetate; acetic acid, chromium(3+) salt

EINECS No. 213-909-4

RTECS No. AG 2975000

Uses Used in the dyeing and tanning industries. In the hardening of photographic emulsions. Polymerisation and oxidation catalyst.

Occupational exposure

JP-OEL 0.5 mg m⁻³ (as Cr)

UK-LTEL 0.5 mg m⁻³ (as Cr)

US-TWA 0.5 mg m⁻³ (as Cr)

Ecotoxicity

Toxicity to other species

LD_{Lo} intravenous frog 6185 mg kg⁻¹ (1).

Environmental fate

Degradation studies

The influence of trivalent chromium compounds on the biological and physico-chemical properties of soil was tested in pot experiments with soil from mixed oak-pine woods and the needles of Scots pine. No marked influence was found on the total number of soil bacteria but changes did occur to their physiological state. The structure of humic acid from treated soil differed from control soil. Chromium triacetate was immobilised to a greater extent than other chromium salts (2).

Mammalian & avian toxicity

Acute data

LD_{Lo} intravenous rabbit, mouse 1600, 2290 mg kg⁻¹, respectively (3).

Carcinogenicity and chronic effects

Cr(III) compounds are not classifiable as to their carcinogenicity in humans or animals, IARC classification group 3 (4).

Of 34 rats given intramuscular injections of chromium triacetate, one animal developed an injection-site tumour. In 34 rats given intrapleural implantations in mutton tallow, one implantation-site tumour was observed (5).

54 ♂/54 ♀ Weanling Swiss mice and 46 ♂/50 ♀ weanling rats received 5 mg l⁻¹ chromic triacetate in drinking water for life. The incidence of tumours at various sites was not significantly different from that in controls (6,7).

42 Rats, ~3 months old, received 8 intrapleural implantations over 13 months of 25 mg chromium triacetate in gelatin capsules. No implantation-type tumour was observed after 2 yr (8).

Genotoxicity

Salmonella typhimurium TA92, TA97, TA98, TA100, TA102, TA1535, TA1537, TA1538, TA1978 with and without metabolic activation negative (9).

No SOS response was induced in *Escherichia coli* GC2375, UA4202 or PQ30 (10).

Escherichia coli PQ37 low increase in SOS-inducing activity was observed (11).

Legislation

Limited under EC Directive on Drinking Water Quality 80/778/EEC. Chromium: maximum admissible concentration 50 µg l⁻¹ (12).

Other comments

Hazards and safety aspects have been reviewed (13).

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C333 chromium(II) chloride



Cl₂Cr

Mol. Wt. 122.90

CAS Registry No. 10049-05-5

Synonyms chromous chloride

EINECS No. 233-163-3

RTECS No. GB 5250000

Uses In chromium plating. Reducing agent. As oxygen absorbent.

Physical properties

M. Pt. 824°C Specific gravity 2.751 at 14°C with respect to water at 4°C

Solubility Water: soluble (very hygroscopic). Organic solvents: ethanol

Occupational exposure

SE-LEVL 0.5 mg m⁻³ (as Cr)

UK-LTEL 0.5 mg m⁻³ (as Cr)

Mammalian & avian toxicity

Acute data

LD₅₀ oral rat 1870 mg kg⁻¹ (1).

Intraperitoneal ♀ rats 3.5 mg Cr(II) kg⁻¹ in saline, significant hyperglycaemia was observed at 30 min and 1 hr but blood glucose levels were not significantly raised at 2 hr or later (2).

Genotoxicity

Syrian hamster embryo cells chromosomal aberrations negative (3).

Induced infidelity in DNA synthesis with poly(d(A-7)) as template in the presence of avian myeloblastosis virus DNA polymerase (4).

Other comments

Toxicity reviewed (5).

Chromous salts hydrolyse in water to yield ionic chromium. The divalent chromous form is readily oxidised to trivalent chromium, and to higher valencies.

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C334 chromium(III) chloride



Cl₃Cr

Mol. Wt. 158.35

CAS Registry No. 10025-73-7

Synonyms chromic chloride; Chrometrace (hexahydrate)

EINECS No. 233-038-3

RTECS No. GB 5425000

Uses Used in chromium plating. Manufacture of chromium metal and compounds. Polymerisation catalyst. Textile mordant. Waterproofing agent. Corrosion inhibitors.

Physical properties

M. Pt. 1152°C B. Pt. 1300°C (sublimes) Specific gravity 2.87 at 25 °C

Solubility Water: 585 g l⁻¹ at 25°C (hexahydrate), insoluble (anhydrous). Organic solvents: ethanol (hexahydrate)

Occupational exposure

SE-LEVL 0.5 mg m⁻³ (as Cr)

UK-LTEL 0.5 mg m⁻³ (as Cr)

US-TWA 0.5 mg m⁻³ (as Cr)

Ecotoxicity

Fish toxicity

No carp deaths occurred when exposure concentrations were 5 or 10 ppm but the mortality at 20 ppm chromium increased with exposure time (1).

Invertebrate toxicity

EC₅₀ (48, 96 hr) *Asellus aquaticus* 937, 442 mg l⁻¹ (2).

EC₅₀ (48 hr, 96 hr) *Crangonyx pseudogracilis* 388, 291 mg l⁻¹ (2).

EC₅₀ (24 hr) *Daphnia magna* 111 mg l⁻¹. *Daphnia magna* (21 day) reproduction test; no-observed-adverse-effect concentration 3.4 mg l⁻¹ (3).

Bioaccumulation

Humic acid (50 mg l⁻¹) significantly decreased bioaccumulation of chromium chloride in *Daphnia magna* (4).

Mammalian & avian toxicity

Acute data

LD₅₀ oral rat 1870 mg kg⁻¹ (5).

LC₅₀ (2 hr) inhalation mouse 31.5 mg m⁻³ (6).

LD_{Lo} dermal guinea pig 202 mg kg⁻¹ (7).

LD_{Lo} intravenous intraperitoneal mouse 400-435 mg kg⁻¹ (8,9).

LD_{Lo} intraperitoneal guinea pig 200 mg kg⁻¹ (9).

Sub-acute and sub-chronic data

4 mg Cr(III) as CrCl₃ in 0.2 ml aqueous solution was administered subcutaneously to ♂ mice. After 30 days, testis weight was decreased 75% in treated animals (10).

No toxic effects were observed in rats fed 25 ppm Cr(III) in drinking water for 1 yr (11).

0.6 mg m⁻³ Cr(III) as chromic chloride 3 hr day⁻¹, daily for 9 months caused chronic bronchial and alveolar inflammation in rats (12).

Carcinogenicity and chronic effects

Inadequate evidence for carcinogenicity of trivalent chromium compounds to humans and animals, IARC classification group 3 (13).

No evidence of excess human cancers in two industries where only trivalent chromium compounds were used (14).

Intrabronchial implantation of 0.4 mg Cr(III) as the chloride did not significantly increase incidence of squamous metaplasia in Wistar rats, and there were no squamous carcinomas (15).

Teratogenicity and reproductive effects

Intraperitoneal injection of 9.8-24.4 mg kg⁻¹ on day-8 of gestation caused a dose-dependent increase in frequency of exencephaly and rib fusion in ICR mice (16).

Metabolism and toxicokinetics

Four hours after intratracheal instillation in rabbits, 85% of the Cr remained in the lungs and 8% was found in the urine; after uptake, Cr was confined mainly to plasma (17).

A single intraperitoneal injection to mice resulted in 45% retention of Cr 3 wk after the injection (18).

Of total intake of trivalent chromium 0.5-3% is absorbed into the body; excretion is almost solely via urine (species unspecified) (14).

After intratracheal injection of chromic chloride to experimental animals, 70% remained in the lung after 10 min, 13% after 60 days (species unspecified) (14).

Trivalent chromium is the most stable oxidation state. May form ligands with nucleic acids, proteins and organic acids. Biological membranes appear impermeable to trivalent chromium but phagocytosis of particles can occur (13).

After intestinal absorption, chromium is taken up by plasma-protein fractions, mainly transferrin. Inhaled chromium is bound to albumin (14).

Over 99% administered chromium recovered in faeces of humans after oral administration of chromic chloride (13).

Irritancy

Trivalent chromium compounds do not cause ulceration but prolonged contact reportedly causes skin lesions in man (14).

Sensitisation

Chromium is an important skin sensitiser. Sensitisation in man usually occurs after 6-9 months (but may occur as early as 3 months). The effect of oxidation state on sensitisation is controversial (14).

Dermal application of chromium chloride to guinea pigs 2 wk after intramuscular injection of 2 mg potassium dichromate did not induce contact sensitivity (19).

Genotoxicity

Salmonella typhimurium TA98, TA100, TA1535, TA1537 with and without metabolic activation negative (20).

Salmonella typhimurium TA100 with and without metabolic activation negative (21).

No SOS response was induced in *Escherichia coli* GC2375, UA4202 or PQ30 (22).

SOS chromotest on *Escherichia coli* negative (23).

Bacillus subtilis 17A *rec* assay negative (24).

Chinese hamster ovary cells sister chromatid exchanges weakly positive (25); negative results also reported (26,27).

Syrian hamster embryo cells chromosomal aberrations negative (28).

Cultured PHA-stimulated human lymphocytes sister chromatid exchanges negative (29).

Induced chromosomal aberrations in human peripheral blood lymphocytes (30).

Liver and kidney DNA isolated 1-40 hr after an intraperitoneal injection in rats showed no evidence of strand breaks or cross-links (31,32).

Other effects

Any other adverse effects

Toxic effects from trivalent chromium reported only after parenteral administration (mouse, rat, rabbit, dog) (14).

Legislation

Limited under EC Directive on Drinking Water Quality 80/778/EEC. Chromium: maximum admissible concentration 50 µg l⁻¹ (33).

Other comments

Trivalent chromium compounds may be contaminated with hexavalent chromium compounds (13).

Genotoxicity reviewed (14,34).

Toxicity reviewed (12,35,36).

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c335 chromium(III) fluoride



CrF_3

Mol. Wt. 108.99

CAS Registry No. 7788-97-8

Synonyms chromic fluoride

EINECS No. 232-137-9

RTECS No. GB 6125000

Uses Used in printing and dyeing woollens. Mothproofing agent. Colouring and hardening marble. Treating silk and polishing metals. Halogenation catalyst.

Physical properties

M. Pt. 1100°C B. Pt. sublimes at 1100-1200°C Specific gravity 3.8

Occupational exposure

DE-MAK 2.5 mg m⁻³ (as F) (inhalable dust fraction)

FR-VME 2.5 mg m⁻³ (as F)

SE-LEVL 0.5 mg m⁻³ (as Cr)

UK-LTEL 0.5 mg m⁻³ (as Cr)

US-TWA 0.5 mg m⁻³ (as Cr)

UN No. 1756 (solid)

UN No. 1757 (solution) HAZCHEM Code 2X Conveyance classification corrosive substance

Mammalian & avian toxicity

Acute data

LD_{Lo} oral rat 150 mg kg⁻¹ (1).

Carcinogenicity and chronic effects

Inadequate evidence for carcinogenicity of trivalent chromium compounds to humans and animals, IARC classification group 3 (2).

No evidence of excess human cancers in two industries where only trivalent chromium compounds were used (3).

Metabolism and toxicokinetics

0.5-3% of total intake of trivalent chromium is absorbed into the body; excretion is almost solely via urine. After intestinal absorption, chromium is taken up by plasma protein fractions, mainly transferrin. Inhaled chromium is bound to albumin (3).

Irritancy

Trivalent chromium compounds do not cause ulceration but prolonged contact can cause skin lesions (3).

Sensitisation

Chromium is an important skin sensitiser. Sensitisation usually occurs after 6-9 months (but may occur as early as 3 months). The effect of oxidation state on sensitisation is controversial (3).

Other effects

Any other adverse effects

Toxic effects from trivalent chromium reported only after parenteral administration (rat, mouse, rabbit, dog) (3).

Legislation

Limited under EC Directive on Drinking Water Quality 80/778/EEC. Chromium: maximum admissible concentration 50 µg l⁻¹ (4).

Other comments

Trivalent chromium compounds may be contaminated with hexavalent chromium compounds (3).

Genotoxicity (5) and toxicity reviewed (6,7).

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C336 chromium(III) nitrate



CrN_3O_9

Mol. Wt. 238.01

CAS Registry No. 13548-38-4

Synonyms chromic nitrate; nitric acid, chromium(3+) salt

EINECS No. 236-921-1

RTECS No. GB 6280000

Uses Preparation of chromium catalysts. Corrosion inhibition. Used in textiles. Manufacture of chromium oxide.

Physical properties

M. Pt. 66°C B. Pt. 100°C (decomp.) Specific gravity 1.8

Solubility Water: 74% at 25°C. Organic solvents: acetone, dimethyl sulfoxide, ethyl acetate

Occupational exposure

SE-LEVL 0.5 mg m⁻³ (as Cr)

UK-LTEL 0.5 mg m⁻³ (as Cr)

US-TWA 0.5 mg m⁻³ (as Cr)

UN No. 2720 HAZCHEM Code 1Y Conveyance classification oxidising substance

Mammalian & avian toxicity

Acute data

LD₅₀ oral mouse, rat 2976, 3250 mg kg⁻¹, respectively (1,2).

LD₅₀ dermal mouse 3232 mg kg⁻¹ (2).

LD₅₀ intraperitoneal mouse 110 mg kg⁻¹ (2,3).

Sub-acute and sub-chronic data

2 mg Cr(III) kg⁻¹ in 1 ml saline was administered to rats intraperitoneally daily for 3-6 wk. Histopathological changes to liver, kidney, testes and brain were observed after 3 wk. The myocardium was normal after 3 wk but was congested after 6 wk. No haematological changes were produced (4,5).

The effects on lungs were studied when 0.6 or 2.3 mg Cr(III) m⁻³ 6 hr day⁻¹, 5 day wk⁻¹ (duration unspecified), was inhaled by ♂ rabbits. At 2.3 mg m⁻³ nodular granulomatous accumulation of alveolar macrophages was prominent (6).

Carcinogenicity and chronic effects

Inadequate evidence for carcinogenicity of trivalent chromium compounds to humans and animals, IARC classification group 3 (7).

No evidence of excess human cancers in two industries where only trivalent chromium compounds were used (8).

Metabolism and toxicokinetics

0.5-3% of total intake of trivalent chromium is absorbed into the body, excretion is almost solely via urine (8).

Irritancy

Trivalent chromium compounds do not cause ulceration but prolonged contact reportedly causes skin lesions (species unspecified) (8).

Genotoxicity

Salmonella typhimurium TA92, TA97, TA98, TA100, TA102, TA1535, TA1537, TA1538, TA1978 with and without metabolic activation negative (9-12).

SOS Chromotest in *Escherichia coli* GC2375, UA4202 and PQ30 negative (13).

SOS Chromotest in *Escherichia coli* PQ37 negative (14).

Rec assay with *Bacillus subtilis* 17A, 45T (rec⁻) negative. *Escherichia coli* uvrA⁻ negative (15).

Other effects

Any other adverse effects

Toxic effects from trivalent chromium reported only after parenteral administration (mouse, rat, rabbit, dog) (8).

Legislation

Limited under EC Directive on Drinking Water Quality 80/778/EEC. Chromium: maximum admissible concentration 50 µg l⁻¹ (16).

Included in Schedule 6 (Release Into the Land: Prescribed Substances of Statutory Instrument No. 472, 1991 (17).

Other comments

Trivalent chromium compounds may be contaminated with hexavalent chromium compounds (7).

Powerful oxidiser which may ignite organic compounds on contact.

Toxicity of inorganic chromium compounds, including chromic nitrate, has been reviewed (18).

Genotoxicity (19) and toxicology (20) reviewed.

Chromous salts hydrolyse in water to yield ionic chromium. The divalent chromous form is readily oxidised to trivalent chromium and to higher valencies.

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C337 chromium(vi) oxide



CrO_3

Mol. Wt. 99.99

CAS Registry No. 1333-82-0

Synonyms chromium trioxide; chromic anhydride; chromic trioxide; monochromium trioxide

EINECS No. 215-607-8

RTECS No. GB 6650000

Uses Chromium plating. Copper stripping. Aluminium anodising. Corrosion inhibitor. Photography. Purifying oil and acetylene. Hardening microscopical preparations. Oxidising agent in organic chemistry. In solution used as a topical antiseptic and astringent for veterinary purposes.

Physical properties

M. Pt. 197°C **B. Pt.** decomp. **Specific gravity** 2.70

Solubility Water: 61.7 g l⁻¹ at 0°C, 67.45 g l⁻¹ at 100°C

Occupational exposure

FR-VME 0.05 mg m⁻³ (as Cr)

FR-VLE 0.1 mg m⁻³ (as Cr)

JP-OEL 0.05 mg m⁻³ (as Cr)

SE-LEVL 0.5 mg m⁻³ (as Cr)

UK-LTEL MEL 0.05 mg m⁻³ (as Cr)

US-TWA 0.05 mg m⁻³ (as Cr)

UN No. 1463 (anhydrous) **HAZCHEM Code** 2W **Conveyance classification** oxidising substance, corrosive

Supply classification oxidising, corrosive

Supply classification toxic

Supply classification dangerous for the environment

Risk phrases May cause cancer by inhalation – Contact with combustible material may cause fire – Toxic if swallowed – Causes severe burns – May cause sensitisation by skin contact – Very toxic to aquatic organisms, may cause long-term adverse effects in the aquatic environment (R49, R8, R25, R35, R43, R50/53)

Safety phrases Avoid exposure – obtain special instruction before use – In case of accident or if you feel unwell, seek medical advice immediately (show label where possible) – This material and/or its container must be disposed of as hazardous waste – Avoid release to the environment. Refer to special instructions/safety data sheet – Restricted to professional users (S53, S45, S60, S61)

Ecotoxicity

Fish toxicity

LC₅₀ (96 hr) *Channa punctatus* 40 mg l⁻¹ (1).

Mammalian & avian toxicity

Acute data

LD₅₀ oral rat 80 mg kg⁻¹ (2).

LD₂₀ subcutaneous dog 330 mg kg⁻¹ (3).

LD₅₀ intraperitoneal mouse 29 mg kg⁻¹ (4).

Signs of acute oral toxicity include diarrhoea, cyanosis, gastric bleeding and ulceration, and apnoea (5).

Carcinogenicity and chronic effects

Sufficient evidence in humans for carcinogenicity of Cr(vi) compounds as encountered in chromate production, pigment production and chromium plating, limited evidence for carcinogenicity of chromium trioxide in animals, IARC classification group 1 (6).

Injection-site tumours in rats after intramuscular injection of 25 mg sintered chromium trioxide but no significant difference in pattern of distant tumours (7).

Increased incidence of bronchial squamous metaplasia and one squamous carcinoma (none in controls) in Wistar rats after intrabronchial implantation of 1 mg Cr(VI) as the trioxide (8).

No injection-site tumours in mice after subcutaneous injection of 10 mg sintered chromium trioxide (7).

Teratogenicity and reproductive effects

Single intravenous injection of 5, 7.5, 10 or 15 mg kg⁻¹ on day-8 of gestation. Dose-dependent increase in malformations (delayed skeletal ossification, exencephaly, cleft palate). 75% maternal mortality at 15 mg kg⁻¹ (9). Intravenous injection of 8 mg kg⁻¹ on day-8 of gestation caused increased incidence of cleft palate in LVG, LSH and MHA hamsters (10).

Intravenous injection of 2.6, 3.9 or 5.2 mg Cr(VI) kg⁻¹ as the trioxide to hamsters on day-8 of gestation caused dose-dependent embryo/foeto-lethality and resorption (11).

Metabolism and toxicokinetics

Chromate is reduced by the involvement of glutathione as well as by a Cr(V)glutathione intermediate (12).

Gastro-intestinal absorption of 3-6% of total intake of hexavalent chromium reported. Gastric juice plays a role detoxifying ingested hexavalent chromium by reducing it to trivalent chromium, which is poorly absorbed (13).

Hexavalent chromium usually forms strongly oxidising chromate and dichromate ions, which readily cross biological membranes and are easily reduced to trivalent chromium under physiological conditions (6).

Irritancy

Repeated contact causes eczematous dermatitis, especially in hypersensitive people, and deep perforating ulcers (chrome holes). Causes eye inflammation (14).

Readily absorbed in bronchopulmonary tract causing corrosive reactions (15).

Airborne chromium trioxide fume irritates mucous membranes (15).

Nasal irritation reported in workers exposed to chromium trioxide (>1 µg m⁻³ Cr) and nasal perforation in 66% of those exposed to peak levels >20 µg m⁻³ Cr (6).

Inhalation of chromium trioxide fumes may cause bronchial asthma (6).

Sensitisation

Allergic contact dermatitis reported from Scandinavia in three workers who were exposed to cement containing high chromate concentrations (15).

Genotoxicity

Salmonella typhimurium TA1535 without metabolic activation negative, TA100 without metabolic activation positive, TA98, TA1537, TA1538, without metabolic activation weakly positive (16-18).

Salmonella typhimurium TA92, TA97, TA100, TA102, TA1978 without metabolic activation positive (19).

Bacillus subtilis rec assay positive (20).

Escherichia coli WP2 UvrA positive (17).

Chinese hamster ovary cells sister chromatid exchanges positive (21).

Syrian hamster embryo cells chromosomal aberrations positive (22).

C3H mouse mammary carcinoma FM34 cells chromosomal aberrations positive (23).

Cultured Chinese hamster ovary cells chromosomal aberrations and sister chromatid exchanges positive (24).

Chromium trioxide-treated Chinese hamster ovary K1 cells showed highly sequence-specific mutations in the hprt locus (25).

Drosophila melanogaster sex chromosome loss and non-disjunction negative (26).

Drosophila melanogaster wing spot test positive (27).

Increased frequency of sister chromatid exchanges in ♂ human chromosome plates exposed to chromium trioxide fumes (6).

Other effects

Other adverse effects (human)

Electroplating workers exposed to levels as low as 0.06 mg m⁻³ suffered from nasal irritation (28).

An increase in lung and other cancers in chrome plate workers in England has been reported (29). Inhalation causes perforated nasal septum, severe lung and liver damage. Ingestion causes thirst, dizziness, abdominal pain, anuria or oliguria and peripheral vascular collapse. Kidney damage may lead to fatal uremia (14).

Hexavalent chromium causes marked respiratory tract irritation (13).

Any other adverse effects

Chromium salts tested in mice and rats caused mild excitation and interfered with pentobarbitone sodium-induced hypnosis (30).

Legislation

Limited under EC Directive on Drinking Water Quality 80/778/EEC. Chromium: maximum admissible concentration 50 µg l⁻¹ (31).

Included in Schedule 4 and 6 (Release into Air / Land: Prescribed Substances) Statutory Instrument No. 472, 1991 (32).

Covered in the UK by the Control of Carcinogenic Substances, Control of Substances Hazardous to Health Regulations 1988 (33).

Other comments

LC₅₀ (96 hr) frog *Rana cyanophlyctis* 135 mg l⁻¹ (34).

The influence of temperature (15-35°C), pH (4.7 and 10), and hardness (10-300 ml CaCO₃) on the toxicity of chromium trioxide to ♀ *Rana cyanophlyctis* was investigated using a static renewal bioassay test. High temperature, low pH, and hardness resulted in a higher mortality rate, whilst low temperature, high pH, and hardness ameliorated the chromium toxicity (35).

Carcinogenicity of chromium(VI) compounds reviewed (36).

Reviews on human health effects, experimental toxicology, physico-chemical properties, environmental effects, ecotoxicology, exposure levels, epidemiology and workplace experience listed (37).

Genotoxicity (38) and toxicity reviewed (39-41).

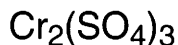
Reproductive toxicology reviewed (42).

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c338 chromium(III) sulfate



$\text{Cr}_2\text{O}_12\text{S}_3$

Mol. Wt. 392.18

CAS Registry No. 10101-53-8

Synonyms chromic sulfate; chromatin B; dichromium sulfate; dichromium trisulfate; sulfuric acid, chromium(3+) salt (3:2); Chromosal

EINECS No. 233-253-2

RTECS No. GB 7200000

Uses Insolubilisation of gelatin. Used in the tanning industry. In catalyst preparation. Mordant in the textile industry. Chrome plating. Paints, inks and glazes for porcelain.

Physical properties

Specific gravity 3.012

Solubility Water: 120-1200 g l⁻¹ at 0-20°C (hydrates). Organic solvents: ethanol

Occupational exposure

SE-LEVL 0.5 mg m⁻³ (as Cr)

UK-LTEL 0.5 mg m⁻³ (as Cr)

US-TWA 0.5 mg m⁻³ (as Cr)

Ecotoxicity

Fish toxicity

At concentrations of >100 mg l⁻¹ in water, chromic sulfate caused damage to the gills, liver and intestine of carp and bighead (*Aristichthys nobilis*) (1).

Mammalian & avian toxicity

Acute data

LD₅₀ intraperitoneal mouse 28.1 mg Cr kg⁻¹ (2).

LD_{Lo} intravenous rabbit 215 mg kg⁻¹ (3).

Sub-acute and sub-chronic data

Oral rats (90 days) 100 mg kg⁻¹ day⁻¹. Total red blood cell counts and haemoglobin levels fell indicating anaemia; the red blood cells were microcytic (4).

Carcinogenicity and chronic effects

Inadequate evidence for carcinogenicity of trivalent chromium compounds to humans and animals, IARC classification group 3 (5).

No evidence of excess human cancers in two industries where only trivalent chromium compounds were used (6). Three groups of 10 ♂/10 ♀ mice, 6-10 wk old, given intraperitoneal injection in tricaprylin 3 × wk⁻¹ for 8 wk (total dose 2400, 1200 or 480 mg kg⁻¹) were killed 30 wk after the first injection. No significantly increased incidence of pulmonary adenomas was observed (7,8).

Metabolism and toxicokinetics

0.5-3% of total intake of trivalent chromium is absorbed into the body; excretion is almost solely via urine (6).

Irritancy

Trivalent chromium compounds do not cause ulceration but prolonged contact reportedly causes skin lesions (6).

Sensitisation

Moderate skin sensitisation has been induced in humans by topical application in petrolatum (9).

May cause sensitisation to workers in tanneries and users of chrometannery leather products (10).

Genotoxicity

Salmonella typhimurium TA98, TA100 with and without metabolic activation negative (11).

Bacillus subtilis rec assay negative (12,13).

Syrian hamster embryo cells chromosome aberrations negative (14).

Other effects

Other adverse effects (human)

The association between chromate leather tanning and different occupational diseases including dermatitis has been reported (15).

75% of chromium-sensitive subjects were allergic to basic chromic sulfate (16).

No evidence of dermal absorption in a human volunteer who immersed a hand in tanning liquor for 1 hr. Fatal chromium intoxication occurred after accidental submersion in hot (70°C) chromic sulfate tanning liquor (5).

Any other adverse effects

Toxic effects from trivalent chromium reported only after parenteral administration (mouse, rat, rabbit, dog) (6).

Legislation

Limited under EC Directive on Drinking Water Quality 80/778/EEC. Chromium: maximum admissible concentration 50 µg l⁻¹ (17).

Reportable quantity controlled in USA by Federal Comprehensive Environmental Response, Compensation and Liability Act (18).

Other comments

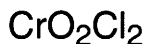
Trivalent chromium compounds may be contaminated with hexavalent chromium compounds (6).

Toxicity (19,20) and genotoxicity reviewed (21).

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c339 chromyl chloride



Cl_2CrO_2

Mol. Wt. 154.90

CAS Registry No. 14977-61-8

Synonyms chromic oxychloride; chromium oxychloride; chromium(vi) dioxychloride; chlorochromic anhydride; dichlorodioxochromium

EINECS No. 239-056-8

RTECS No. GB 5775000

Uses Catalyst for polymerisation of olefins. Oxidation of hydrocarbons. Production of aldehydes and ketones. Preparation of various coordination complexes of chromium.

Physical properties

M. Pt. -96.5°C **B. Pt.** 117°C **Specific gravity** 1.91 at 25°C with respect to water at 4°C

Volatility v.p. 20 mmHg at 20°C

Solubility Water: hydrolyses. Organic solvents: acetic acid, benzene, carbon disulfide, carbon tetrachloride, chloroform, ether, nitrobenzene

Occupational exposure

FR-VME 0.05 mg m⁻³ (as Cr)

JP-OEL 0.05 mg m⁻³ (as Cr)

SE-LEVL 0.5 mg m⁻³ (as Cr)

UK-LTEL MEL 0.05 mg m⁻³ (as Cr)

US-TWA 0.025 ppm (0.16 mg m⁻³)

UN No. 1758 HAZCHEM Code 4W Conveyance classification corrosive substance

Supply classification oxidising

Supply classification toxic

Supply classification corrosive, dangerous for the environment

Risk phrases Contact with combustible material may cause fire – Causes severe burns – May cause cancer by inhalation – May cause heritable genetic damage – May cause sensitisation by skin contact – Very toxic to aquatic organisms, may cause long-term adverse effects in the aquatic environment (R8, R35, R49, R46, R43, R50/53)

Safety phrases Avoid exposure – obtain special instruction before use – In case of accident or if you feel unwell, seek medical advice immediately (show label where possible) – This material and/or its container must be disposed of as hazardous waste – Avoid release to the environment. Refer to special instructions/safety data sheet (S53, S45, S60, S61)

Mammalian & avian toxicity

Acute data

LD₅₀ subcutaneous mouse 5.45 mg kg⁻¹ (1).

Carcinogenicity and chronic effects

Sufficient evidence in humans for carcinogenicity of Cr(vi) compounds as encountered in chromate production, pigment production and chromium plating, IARC classification group 1 (2).

Metabolism and toxicokinetics

Gastro-intestinal absorption of 3-6% of total intake of hexavalent chromium reported. Gastric juice plays a role detoxifying ingested hexavalent chromium by reducing it to trivalent chromium, which is poorly absorbed (3). Hexavalent chromium usually forms strong oxidising chromate and dichromate ions, which readily cross biological membranes and are easily reduced to trivalent chromium under physiological conditions (3).

Irritancy

Hexavalent chromium compounds cause marked respiratory tract irritation (3).

Genotoxicity

Salmonella typhimurium TA1535 without metabolic activation negative, TA100 without metabolic activation positive, TA98, TA1537, TA1538 with metabolic activation weakly positive (4).

Salmonella typhimurium TA100 without metabolic activation, liquid and vapour phase, positive (5).

Other effects

Other adverse effects (human)

Hexavalent chromium compounds, administered orally or parenterally, cause gastro-intestinal, renal and haematopoietic effects (3).

Legislation

Limited under EC Directive on Drinking Water Quality 80/778/EEC. Chromium: maximum admissible concentration 50 µg l⁻¹ (6).

Included in Schedule 4 and 6 (Release into Air/Land: Prescribed Substances) Statutory Instrument No. 472, 1991 (7).

Covered in the UK by the Control of Carcinogenic Substances, Control of Substances Hazardous to Health Regulations 1988 (8).

Other comments

Reviews on human health effects, experimental toxicology, physico-chemical properties, environmental effects, ecotoxicology, exposure levels, epidemiology and workplace experience listed (9).

Genotoxicity reviewed (10).

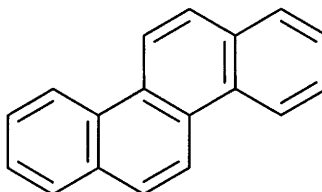
Carcinogenicity of chromium(vi) compounds reviewed (11).

Toxicity reviewed (12-14).

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C340 chrysene



C₁₈H₁₂

Mol. Wt. 228.29

CAS Registry No. 218-01-9

Synonyms 1,2-benzophenanthrene; benzo[a]phenanthrene; 1,2,5,6-dibenzonaphthalene

EINECS No. 205-923-4

RTECS No. GC 0700000

Occurrence Coal tar. Crude petroleum.

Physical properties

M. Pt. 254°C **B. Pt.** 448°C **Specific gravity** 1.274 at 20°C with respect to water at 4°C

Partition coefficient log P_{ow} 5.86

Solubility Water: 0.6 µg l⁻¹ at 25°C. Organic solvents: carbon disulfide, diethyl ether, ethanol, toluene

Ecotoxicity

Invertebrate toxicity

LC₅₀ (96 hr) *Neanthes arenaceodentata* >1 ppm (1).

Lethal threshold concentration (24 hr) *Daphnia magna* 0.7 µg l⁻¹ (2).

Bioaccumulation

24 hr *Daphnia magna* log bioconcentration factor 3.7845 (2).

Environmental fate

Degradation studies

Biodegraded by white rot fungus (3).

May be utilised by axenic cultures of microorganisms e.g. *Pseudomonas paucimobilis* EPA505, which may have novel degradative systems (4,5).

Pseudomonas paucimobilis EPA 505 grown on fluoranthene degraded 82.8% of chrysene after incubation with 10 ppm for 17 hr. The major degradation product was a highly polar compound (6).

Degradation of chrysene by fungi and bacteria of hazardous waste-contaminated soil was almost nil (7).

Mammalian & avian toxicity

Carcinogenicity and chronic effects

No adequate data on carcinogenicity to humans, limited evidence for carcinogenicity to animals, IARC classification group 3 (8).

TD_{Lo} subcutaneous mouse 200 mg kg⁻¹ tumorigenic (9).

Teratogenicity and reproductive effects

2.0 mg kg⁻¹ chrysene (5.5%) caused 15% embryo mortality in chickens (10).

Metabolism and toxicokinetics

Metabolites include 1,2,3- and 4-hydroxychrysene and *trans*-1,2- as well as *trans*-3,4-dihydroxydihydrochrysene in human and Syrian hamster epithelial lung cells, whereas K-region oxidation is at most a very minor pathway (11,12).

1,2-dihydrochrysene-1,2,9-triol is a metabolite in rat liver microsomal preparations (13).

Chrysene metabolism by isolated rat liver microsomal P450 system did not result in formation of the carcinogen chrysene dihydrodiolepoxide. Pretreatment of rats with benzo[a]pyrene, benzo[b]fluoranthene, benzo[i]fluoranthene, 5,6-benzoflavone, PCBs or phenobarbital induced P450 isoenzymes to convert the primary metabolite of chrysene, 1,2-dihydroxy-1,2-dihydrochrysene, into chrysene, and 1,2-dihydroxy-1,2-dihydrochrysene into chrysene dihydrodiolepoxide (14).

Genotoxicity

Salmonella typhimurium TA97, TA98, TA100 with metabolic activation positive (15).

Escherichia coli PQ37 SOS chromotest with metabolic activation positive (16).

Induced TG resistance in human epithelial teratocarcinoma cell clone (P3) co-cultured in a cell-mediated assay with human breast carcinoma cells (17).

In vitro human B-lymphoblastoid cells forward mutation assay positive (18).

Other effects

Any other adverse effects

Chrysene is a potent inducer of rat hepatic CYP1A1 activity (19).

Legislation

Limited under EC Directive on Drinking Water Quality 80/778/EEC. Polycyclic aromatic hydrocarbons: maximum admissible concentration 0.2 µg l⁻¹ (20).

Other comments

From cigarette smoke at 1.5-13.3 ng m⁻³ in community air (21).

Also found during distillation or pyrolysis of fats or oils.

Detected in river sediments (22,23).

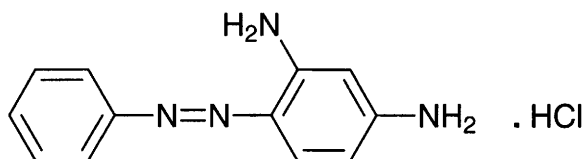
Reviews on human health effects, environmental effects, experimental toxicology, epidemiology and workplace experience listed (24).

Metabolism reviewed (25).

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C341 chrysoidin



$C_{12}H_{13}ClN_4$

Mol. Wt. 248.71

CAS Registry No. 532-82-1

Synonyms Basic Orange 2; 1,3-benzenediamine, 4-(phenylazo)-, monohydrochloride; Chrysoidine; C.I. 11270; 2,4-diaminoazobenzene hydrochloride

EINECS No. 208-545-8

RTECS No. ST 3380000

Uses Dyestuff. Biological stain. Antiseptic.

Physical properties

M. Pt. 118-118.5°C

Solubility Water: 5.5% at 15°C. Organic solvents: acetone, ethanol, ethylene glycol

Mammalian & avian toxicity

Carcinogenicity and chronic effects

Inadequate evidence for carcinogenicity to humans, limited evidence for carcinogenicity in animals, IARC classification group 3 (1).

Oral mice (duration and concentration unspecified) caused liver cell tumours, leukaemia and reticulum cell sarcomas (2).

Irritancy

May cause irritation (species unspecified) (3).

Genotoxicity

Salmonella typhimurium TA1538 without metabolic activation negative; with metabolic activation positive (4).

Saccharomyces cerevisiae caused cell death and growth inhibition and increased frequency of point and cytoplasmic mutations (5).

Other effects

Other adverse effects (human)

Bladder cancer was reported in three amateur anglers exposed to chrysoidine-dyed maggots (6).

Any other adverse effects

When fed to mice only very small amounts were found bound to liver proteins (7).

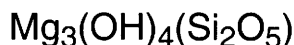
Other comments

Inhibited the *in vitro* growth of six species of fungi at concentrations of 100 mg l⁻¹ (8).

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c342 chrysotile



$\text{Mg}_3\text{Si}_2\text{O}_9\text{H}_4$

Mol. Wt. 277.11

CAS Registry No. 12001-29-5

Synonyms chrysotile asbestos; asbestos, white; serpentine; serpentine chrysotile

RTECS No. CI 6478500

Uses Formerly used in heat-resistant insulators, cements, furnace and hot pipe coverings, inert filler medium, fireproof gloves, friction materials and textile products.

Occurrence In the rock-forming mineral serpentine.

Physical properties

M. Pt. 800-850°C (decomp.) Specific gravity 2.55

Occupational exposure

SE-LEVL 0.2 fibre ml⁻¹

UK-LTEL control limit 0.5 fibres ml⁻¹ (4 hr)

UK-STEL control limit 1.5 fibres ml⁻¹ (10 min)

US-TWA 2 fibres cc⁻¹

Mammalian & avian toxicity

Acute data

LD_{Lo} intraperitoneal rat 300 mg kg⁻¹ (1).

Carcinogenicity and chronic effects

Sufficient evidence for carcinogenicity to humans, sufficient evidence for carcinogenicity to animals, IARC classification group 1 (2).

National Toxicology Program tested rats and hamsters via feed. Some evidence of carcinogenic activity in ♂ rats, designated non-carcinogen in hamsters (3).

Some evidence of carcinogenicity in ♂ rats, no evidence in ♀ rats (4).

Pulmonary fibrosis reported in rats, monkeys, hamsters, rabbits and guinea pigs following inhalation of chrysotile. Exposure was in the order of 10 mg m⁻³ for 6-12 months. Its ability to cross the gut wall is still debated; it seems likely that if it does occur it is very limited (5).

One inhalation study on rats found chrysotile to be more fibrogenic than crocidolite or amosite, probably due to longer fibres being more fibrogenic (6).

Asbestosis occurred in rats exposed to 9.7-14.7 mg m⁻³ for periods of 1 day to 24 months (7).

Some microscopic evidence of cellular damage in the intestinal mucosa of rats fed 0.5 or 50 mg day⁻¹ for 1 wk or 14 months (8).

No pathological changes found on histological examination of gastro-intestinal tissue of rats fed 250 mg wk⁻¹ for up to 25 months (9).

Bronchial carcinomas and pleural mesotheliomas developed in rats following inhalation exposure to chrysotile. Shorter fibres are less fibrogenic and carcinogenic; Potts hypothesis states that maximum carcinogenicity results from fibres 20 µm long and 0.125 µm in diameter (5).

The latency period for mesothelioma to develop is long (2).

Some studies found no (4,10-12) or only slightly increased (13-17) risk of lung cancer with chrysotile exposure.

Higher risk ratios of 2-3.5 were found in chrysotile miners (18) and textile workers (19,20).

One study found no mesothelioma in chrysotile-exposed workers (21).

Combined exposure to chrysotile and amphiboles has a multiplicative effect on risk ratios of mesotheliomas (22).

With regard to lung cancer, the effect of asbestos exposure and smoking are synergistic (23).

Data from intrapleural or intraperitoneal injection or implantation suggest a dose-response relationship for malignant tumour incidence following chrysotile exposure, and that lifetime risk of mesothelioma is greater in animals exposed at a younger age (5).

Epidemiological studies indicate increased colon cancer risk in asbestos-exposed workers; evaluation of colon tissue of 44 such patients identified chrysotile in nine, amosite in three, no other forms of asbestos were found (24).

Metabolism and toxicokinetics

Inhaled fibres deposit by sedimentation, diffusion, impaction and interception in airways of the respiratory system. Asbestos particles move through the epithelium to the lung interstitium where the fibres react with macrophages and fibroblasts. Two human studies gave evidence for the penetration and migration of asbestos. After intrapleural or subcutaneous inoculation (species unspecified), occasional asbestos fibres or bodies reported in other tissues, including pancreas, spleen and thyroid. There is no information on how fibres reach these sites (25).

Peritoneal mesothelioma in humans, excess cancer of the stomach, colon, rectum and cancers at other non-respiratory sites could result from the migration of fibres to and across the gastro-intestinal mucosa, by transdiaphragmatic migration or lymphatic-haematogenous transport (26).

In vitro incubation with rat lung microsomes adsorbed haem proteins, cytochrome P₄₅₀ and P₄₄₈ with decreased dependent monooxygenase activities (27).

Following a single intratracheal injection to ♂ hamsters of 1 mg, pulmonary interstitial and pleural fibrosis were observed after six months. Other observations suggested that fibres were continuously being coated in the lung, that short and thin fibres were cleared from the lung and that slight leaching of magnesium from the surface of chrysotile fibres took place over time (28).

Genotoxicity

Salmonella typhimurium TA1535, TA1538 with or without metabolic activation negative (29).

Did not cause DNA breakage in tracheal epithelial cells (5).

Escherichia coli B/r, WP2, WP2 *UvrA*, WP2 *UvrA polA* with or without metabolic activation negative (29).

Cultured human fibroblasts sister chromatid exchanges negative but induced mitotic delay in CHO-K1 cells and human fibroblasts (30).

Syrian hamster cell transformation positive (31).

BALB/c3T3 mouse cell transformation positive (32).

In vitro rodent cells (rat, Syrian or Chinese hamster) chromosome aberrations, sister chromatid exchanges, aneuploidy and micronuclei positive (33).

In vitro rat hepatocyte unscheduled DNA synthesis negative (34).

In vivo mouse bone marrow cells micronucleus test negative (35).

In vivo monkey bone marrow cells chromosomal aberrations negative (35).

In the AL cell system, which detects intragenic and multilocus mutations, chrysotile is a strong mutagen, causing large scale deletions of base pairs in the induced mutants (36).

Other effects

Other adverse effects (human)

A number of cases of chrysotile-induced mesothelioma have been reported in humans (37).

In the case of railroad machinists employed in the steam locomotive era, who were exposed to chrysotile, one mesothelioma occurred for every 13 machinists during the years 1920-1929 and constituted 34% of all cancer deaths (38).

A birth cohort of 11,379 workers exposed to chrysotile, born between 1891-1920, and who had worked for at least a month in the mines and mills of Quebec were followed-up. In all, there were 10,939 men and women. By the end of 1975, 4463 men and 84 women had died (39). These workers represent the only cohort of asbestos workers in the world in which health effects have been correlated with definitive exposure data defined as fibres ml⁻¹ (40).

A follow-up, 1982-86, to a retrospective cohort study, 1972-81, of 5893 workers in asbestos (chrysotile) factories in China found 36.9% of deaths were due to malignant tumours. Among 496 deaths, there were 183 cancers and 67 lung cancers; the relative risk of lung cancer was 5.32 (p<0.01) and the standardised relative risk was 4.2 (p<0.01). Among 148 deaths from asbestosis, 33 were complicated with lung cancer. There was a positive correlation between exposure to asbestos and incidence of lung cancer and asbestosis (41).

A study of 316 middle-aged ♂ workers found that exposure to chrysotile at levels below the threshold limit value of 2 fibres ml⁻¹ had no effect on their forced expiratory volume (42).

A cohort of 7887 men and 576 women asbestos cement workers in Denmark, exposed mainly to chrysotile asbestos had a borderline statistically significant excess of colorectal cancer. The overall excess risk of colorectal cancer was confined to the period 15 year or more since first employment and there was a 50% excess risk of colorectal cancer morbidity among men employed in the Danish asbestos cement industry over the period 1928-1950. A recent re-analysis of colorectal cancer morbidity in a cohort of Swedish asbestos cement workers also showed an increased standardised incidence ratio with a 15 year latency and the possible role of chrysotile asbestos in the aetiology of colorectal cancer remains open (43,44).

Legislation

Federally regulated carcinogen (NIOSH) in USA. Use in UK controlled by legislation (45).
Included in Schedule 4 (Release into Air: Prescribed Substances) of Statutory Instrument No. 472, 1991 (46).

Other comments

Chrysotile asbestos, in contrast to amphibole forms of asbestos, is frequently claimed to be only a minor cause of malignant pleural mesothelioma, a fatal cancer of the thoracic cavity lining. Reported data from animal and human studies, however, do not support widely quoted evidence in respect of the inertness of chrysotile fibres in mesotheliomas. Contrary evidence indicates that chrysotile asbestos, which contributed 95% of asbestos use world wide, is as potent as amphibole asbestos and it can be concluded that it is the main cause of pleural mesotheliomas in humans (47).

Human bronchial epithelial cells were exposed to 0-4 µg cm⁻² chrysotile for 24-96 hr. A concentration-dependent inhibition of cell proliferation and colony-forming efficiency was seen, although most of the cells were still viable. At the highest dose level, a 2.7-fold increase in binuclei and a 1.6-fold increase in micronuclei were seen after 72 hr. Exposure to chrysotile did not induce significant chromosomal aberrations, although structural effects were observed after 24 hr. These findings are in contrast to the high level of chromosomal aberrations observed in some rodent cell cultures (48).

The cytotoxic and mutagenic effects of chrysotile may occur as a result of enhanced oxygen radical generation by phagocytes (49,50).

Reviews on human health effects, experimental toxicology and environmental effects listed (51).

Reproductive toxicology reviewed (52).

Carcinogenicity of chrysotile reviewed (53).

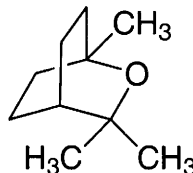
Review of macrophage-associated responses to chrysotile (54).

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c343 cineole



C₁₀H₁₈O

Mol. Wt. 154.25

CAS Registry No. 470-82-6

Synonyms 1,8-cineole; 1,8-epoxy-*p*-menthane; 1,3,3-trimethyl-2-oxabicyclo[2.2.2]octane; limonene oxide; Cajeputol; Eucalyptol; Terpan; Zadoary oil

EINECS No. 207-431-5

RTECS No. OS 9275000

Uses Pharmaceutical in cough syrups and expectorants. Flavouring agent. Perfumery. Disinfectant.

Occurrence Major constituent of oil of eucalyptus and oil of cajeput. Constituent of rosemary oil, tea tree oil and lavender oil.

Physical properties

M. Pt. 1-2°C **B. Pt.** 176-177°C **Flash point** 48°C **Specific gravity** 0.921-0.923

Solubility Water: <0.1 mg ml⁻¹ at 20°C. Organic solvents: chloroform, diethyl ether, dimethyl sulfoxide, ethanol

Environmental fate

Degradation studies

Facultatively denitrifying bacteria are able to utilise cineole as sole carbon and energy source (1).

Mammalian & avian toxicity

Acute data

Repellency toxicity index (R_{50}) oral redwing blackbird 1.57 mg kg⁻¹ (2).

LD₅₀ oral rat 2480 mg kg⁻¹ (3).

LD₅₀ subcutaneous mouse 1070 mg kg⁻¹ (4).

LD₅₀ intramuscular mouse 100 mg kg⁻¹ (5).

Metabolism and toxicokinetics

Intragastric rat (duration unspecified) 800 mg kg⁻¹. The following metabolites were identified in the urine: 1,8-dihydroxy-10-carboxy-*p*-menthane, 2-hydroxycineole and 3-hydroxycineole. Administered as an aerosol, cineol induced the cytochrome P-450 system of the liver but not the lung (6).

An inhalation study in human subjects found that cineole is well absorbed with a peak plasma concentration after ~18 minutes. Elimination from the blood occurs in two stages, with a mean distribution half-life of 6.7 minutes and an elimination half-life of 104.6 minutes (7).

Irritancy

ID₅₀ (irritant dose in 50% individuals) 1.867 µg 5 µl⁻¹ after 3.5 hr in the open mouse ear assay; the adverse effects did not last more than 12 hr (8).

Dermal rabbit (duration unspecified) 2% in ethanol produced no irritation (9).

Patch tests in 25 human subjects of 0.0, 3.8, 8.0, 12.0, 16.0, 19.9, 24.0 and 28.1% cineole in soft white paraffin for 21 days did not show skin irritation (10).

Genotoxicity

In vitro Chinese hamster ovary cells cineol did not enhance sister chromatid exchanges induced by mitomycin C (11).

In vitro Chinese hamster ovary cells without metabolic activation sister chromatid exchanges positive only at doses that induced cell cycle delay (12).

Other effects

Other adverse effects (human)

Human systemic effects include epigastric burning with nausea and vomiting, vertigo, ataxia, muscle weakness, stupor, pallor and oedema. Rarely symptoms may be delayed for 2 hr (13).

Any other adverse effects

Subcutaneous rat (dose unspecified) to pregnant rats enhanced the liver microsomal enzyme activity of both mothers and foetuses. Does not cross the blood-milk barrier in amounts sufficient to affect the hepatic microsomal enzymes of the offspring, but it penetrates the placental tissue and stimulates the foetal liver (14).

Other comments

Dietary administration to rats (dose and duration unspecified) caused no significant chemopreventative activity using a 7,12-dimethylbenz[*a*]anthracene (DMBA) induced rat mammary carcinogenesis rate (15).

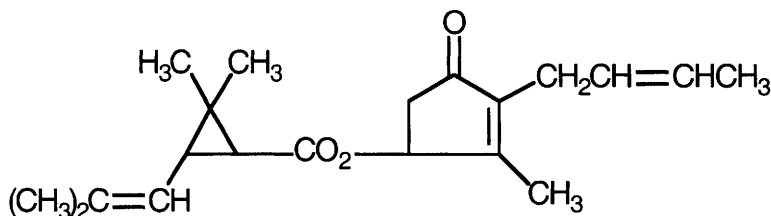
Recent skin irritancy and bioactivity investigations reviewed (16).

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c344 cinerin I



$C_{20}H_{28}O_3$

Mol. Wt. 316.44

CAS Registry No. 25402-06-6

Synonyms 2,2-dimethyl-3-(2-methyl-1-propenyl)cyclopropanecarboxylic acid, 3-(2-butenyl)-2-methyl-4-oxo-2-cyclopenten-1-yl ester; Pyrethrin

EINECS No. 246-948-0

RTECS No. GZ 1540000

Uses Insecticide.

Occurrence Present in extracts of the chrysanthemum plant *Pyrethrum cinerariaefolium* together with other pyrethrins.

Physical properties

B. Pt. 136-138°C at 0.008 mmHg

Solubility. Organic solvents: carbon tetrachloride, ethanol, ethylene dichloride, kerosene, nitromethane, petroleum ether

Occupational exposure

UK-LTEL 5 mg m⁻³

UK-STEL 10 mg m⁻³

Supply classification harmful

Risk phrases Harmful if swallowed (R22)

Safety phrases Keep out of reach of children (if sold to general public) (S2)

Ecotoxicity

Fish toxicity

LC₅₀ (96 hr) (pyrethrins) coho salmon, channel catfish 39, 114 mg l⁻¹, respectively(1).

LC₅₀ (96 hr) (pyrethrins) rainbow trout, bluegill sunfish, 5.2, 10 µg l⁻¹, respectively (1).

Highly toxic to fish (1).

Invertebrate toxicity

LD₅₀ (pyrethrins) oral, contact bee 22, 130-290 ng bee⁻¹, respectively (1).

Toxic to bees, but shows repellent effect (1).

Mammalian & avian toxicity

Acute data

LD₅₀ (pyrethrins) oral rat 1030-2370 mg kg⁻¹ (1).

LD₅₀ (pyrethrins) oral mouse 273-796 mg kg⁻¹ (1).

LD₅₀ (pyrethrins) dermal rat >1500 mg kg⁻¹ (1).

LD₅₀ (pyrethrins) dermal rabbit 5000 mg kg⁻¹ (1).

Metabolism and toxicokinetics

In mammals, pyrethrins are rapidly degraded in the stomach by hydrolysis of the ester bond to harmless metabolites (1).

Mouse liver microsomal mixed function oxidase oxidises the methyl, methylene and alkylene substituents to form alcohols, aldehydes, carboxylic acids, epoxides and dihydrodiols (2).

Sensitisation

Crude pyrethrin extracts have been reported to cause dermatitis in sensitised individuals (species unspecified) (1).

Other effects

Other adverse effects (human)

Human systemic effects include diarrhoea, convulsions, prostration, injury to liver and kidneys. Death occurs from respiratory paralysis (3).

Legislation

EEC maximum residue levels (pyrethrins): cereals 3 ppm; fruit and vegetables 1 ppm (1).

Limited under EC Directive on Drinking Water Quality 80/778/EEC. Pesticides: maximum admissible concentration 0.1 µg l⁻¹ (4).

Included in Schedule 6 (Release into Land: Prescribed Substances) of Statutory Instrument No. 472, 1991 (5).

WHO Toxicity Class II (6).

EPA Toxicity Class (formulation) III (1).

ADI (man) 0.04 mg kg⁻¹ (1).

Other comments

Toxicology of pyrethroids reviewed (7).

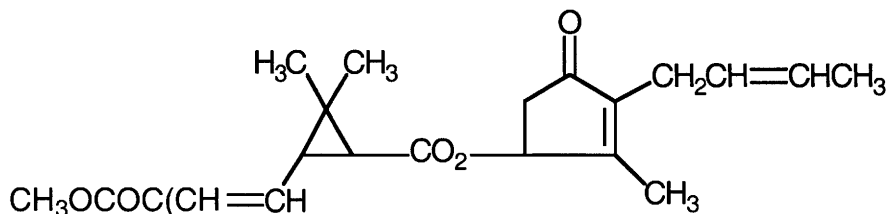
Air and surface samples taken following indoor applications of natural pyrethroids were analysed by high resolution gas chromatography and mass spectroscopy. Pyrethroids persist on surfaces ≥60 hr after application (8).

The term pyrethrins is used collectively for the six insecticidal constituents pyrethrin I and II, jasmolin I and II and cinerin I and II, which are present in extracts of the chrysanthemum plant *Pyrethrum cinerariaefolium* and its flowers.

References

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C345 cinerin II



$C_{21}H_{28}O_5$

Mol. Wt. 360.45

CAS Registry No. 121-20-0

Synonyms 3-[2-methyl-3-(methoxy carbonyl)-1-propenyl]-2,2-dimethylcyclopropanecarboxylic acid, 3-(2-butenyl)-2-methyl-4-oxo-2-cyclopenten-1-yl ester; Pyrethrin

EINECS No. 204-454-2

Uses Insecticide.

Occurrence Present in extracts of the chrysanthemum plant *Pyrethrum cinerariaefolium* together with other pyrethrins.

Physical properties

B. Pt. 182-184°C at 0.001 mmHg

Solubility. Organic solvents: carbon tetrachloride, ethanol, ethylene dichloride, kerosene, nitromethane, petroleum ether

Occupational exposure

UK-LTEL 5 mg m⁻³

UK-STEL 10 mg m⁻³

Supply classification harmful

Risk phrases Harmful if swallowed (R22)

Safety phrases Keep out of reach of children (if sold to general public) (S2)

Ecotoxicity

Fish toxicity

LC₅₀ (96 hr) (pyrethrins) coho salmon, channel catfish 39, 114 mg l⁻¹, respectively (1).

LC₅₀ (96 hr) (pyrethrins) rainbow trout, bluegill sunfish 5.2, 10 µg l⁻¹, respectively (1).

Highly toxic to fish (1).

Invertebrate toxicity

LD₅₀ (pyrethrins) oral, contact bee 22, 130-290 ng bee⁻¹, respectively (1).

Pyrethrins are toxic to bees, but have a repellent effect (1).

Mammalian & avian toxicity

Acute data

LD₅₀ (pyrethrins) oral rat 1030-2370 mg kg⁻¹ (1).

LD₅₀ (pyrethrins) oral mouse 273-796 mg kg⁻¹ (1).

LD₅₀ (pyrethrins) dermal rat 1500 mg kg⁻¹ (1).

LD₅₀ (pyrethrins) dermal rabbit 5000 mg kg⁻¹ (1).

Metabolism and toxicokinetics

In mammals, pyrethrins are rapidly degraded in the stomach, by hydrolysis of the ester bond to harmless metabolites (1).

Sensitisation

In humans crude extracts of pyrethrins may cause dermatitis in sensitised individuals (1).

Other effects

Other adverse effects (human)

Human systemic effects include diarrhoea, convulsions, prostration, injury to liver and kidneys. Death occurs from respiratory paralysis (2).

Legislation

EEC maximum residue levels (pyrethrins): cereals 3 ppm; fruit and vegetable 1 ppm (1).

Limited under EC Directive on Drinking Water Quality 80/778/EEC. Pesticides: maximum admissible concentration $0.1 \mu\text{g l}^{-1}$ (3).

Included in Schedule 6 (Release into Land: Prescribed Substances) of Statutory Instrument No. 472, 1991 (4).

WHO Toxicity Class II (5).

EPA Toxicity Class (formulation) (1).

ADI (man) 0.04 mg kg^{-1} (1).

Other comments

Toxicology of pyrethroids reviewed (6).

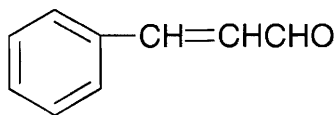
Air and surface samples taken following indoor applications of natural pyrethroids were analysed by high resolution gas chromatography and mass spectroscopy. Pyrethroids persist on surfaces ≥ 60 hr after application (7).

The term pyrethrins is used collectively for the six insecticidal constituents pyrethrin I and II, jasmolin I and II and cinerin I and II which are present in extracts of the chrysanthemum plant *Pyrethrum cinerariaefolium* and its flowers.

References

1. *The Pesticide Manual* 11th ed., 1997, The British Crop Protection Council, Farnham, UK.
2. *Chem. Pestic.* 1971, 131.
3. *EC Directive Relating to the Quality of Water Intended for Human Consumption* 1982, 80/778/EEC, Office for Official Publications of the European Communities, 2 rue Mercier, L-2985 Luxembourg.
4. S. I. 1991 No. 472 *The Environmental Protection (Prescribed Processes and Substances) Regulations* 1991, HMSO, London, UK.
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6. Timofiyevskaya, L. A. et al *Pyrethroids in Reviews of Scientific Literature in Russian on Selected Hazardous Chemicals* 1993, Richardson, M. L. (Ed.), (Eng. Trans.), UNEP/IRPTC No. 119, Geneva, Switzerland.
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C346 cinnamaldehyde



C₉H₈O

Mol. Wt. 132.16

CAS Registry No. 104-55-2

Synonyms 2-phenyl-2-propenal; cinnamic aldehyde; phenylacrolein; cinnamal; 3-phenylpropenal; β-phenylacrolein

EINECS No. 203-213-9

RTECS No. GD 6475000

Uses Flavour and perfume industries.

Occurrence Found in Ceylon and Chinese cinnamon oils.

Physical properties

M. Pt. -7.5°C **B. Pt.** 246°C (some decomp.) **Flash point** 111°C **Specific gravity** 1.048-1.052 at 25°C

Partition coefficient log P_{ow} 1.88 **Volatility** v.p. 1 mmHg at 76.1°C; v.den. 4.6

Solubility Water: slightly soluble in water. Organic solvents: miscible with ethanol, ether, chloroform, oils

Mammalian & avian toxicity

Acute data

LD₅₀ oral rat 2220 mg kg⁻¹ (1).

LD₅₀ oral mouse 2225 mg kg⁻¹ (2).

LD₅₀ oral redwinged blackbird 96 mg kg⁻¹ (3).

LD₅₀ oral guinea pig 1160 mg kg⁻¹ (1).

LD₅₀ intraperitoneal mouse 610 mg kg⁻¹ (2).

LD₅₀ intraperitoneal mouse 200 mg kg⁻¹ (4).

LD_{Lo} parenteral mouse 200 mg kg⁻¹ (5).

LD₅₀ intravenous mouse 75 mg kg⁻¹ (6).

Teratogenicity and reproductive effects

Teratogenic effects observed in young chick embryos administered 0.5 μmol per embryo (7).

Irritancy

Dermal human (48 hr) 48 mg caused severe irritation effects (8).

Sensitisation

Sensitivity to cinnamaldehyde has been reported. Temporary estimated acceptable intake of cinnamaldehyde: up to 0.7 mg kg⁻¹ body weight. Further studies are required (9).

Genotoxicity

Salmonella typhimurium, 1500 μg plate⁻¹, microsomal mutagenicity assay positive (10).

Ames *Salmonella* reversion assay negative (11).

Salmonella typhimurium TA1335, TA1537, TA97, TA98, TA100, 100 μg plate⁻¹, with and without metabolic activation negative (12).

Escherichia coli WP2 uvrA reversion test negative (11).

Bacillus subtilis DNA-repair test (Rec assay) without activation positive (11).

Parenteral *Drosophila melanogaster* 2 pph caused sex chromosome loss and nondisjunction (13).

Mouse leukocytes, 31.5 mg l⁻¹, DNA inhibition assay positive (14).

Chromosomal aberrations were detected in cultured hamster fibroblasts exposed to 15 mg l⁻¹ (10).

Other comments

Literature on cinnamaldehyde reviewed (15).

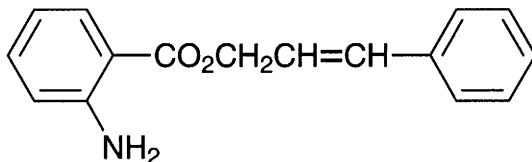
Diverse (even contradictory) genetic activity reviewed (16).

Combustible liquid. May ignite after a delay period in contact with NaOH. When heated to decomposition it emits acrid smoke and fumes.

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C347 cinnamyl anthranilate



C₁₆H₁₅NO₂

Mol. Wt. 253.30

CAS Registry No. 87-29-6

Synonyms 2-aminobenzoic acid, 3-phenyl-2-propenyl ester; 3-phenyl-2-propen-1-yl anthranilate; 3-phenyl-2-propenyl anthranilate; anthranilic acid, cinnamyl ester; cinnamyl o-aminobenzoate; cinnamyl 2-aminobenzoate; cinnamyl alcohol anthranilate

EINECS No. 201-738-8

RTECS No. CB 2725000

Uses Food flavouring agent (synthetic grape or cherry). Fragrance in soaps and perfumes.

Physical properties

M. Pt. 61-61.5°C **B. Pt.** 332°C **Specific gravity** 1.18 at 15.5°C

Solubility Water: <1 mg ml⁻¹ at 17°C. Organic solvents: acetone, chloroform, diethyl ether, dimethyl sulfoxide, ethanol

Mammalian & avian toxicity

Acute data

LD₅₀ oral rat >5 g kg⁻¹ (1).

LD₅₀ dermal rabbit >5 g kg⁻¹ (1).

Sub-acute and sub-chronic data

♀ B6C3F1 mice and ♀ F344 rats were fed diets containing 0-3.0% cinnamyl anthranilate for periods of 1, 4, and 13 wk. All treatments produced marked dose-dependent increases in relative liver weight and hepatic peroxisome proliferation in the mouse but only small increases in the rat (2).

Carcinogenicity and chronic effects

No adequate data for carcinogenicity to humans, limited evidence for carcinogenicity to animals, IARC classification group 3 (3).

Tumours found in kidney and pancreas of ♂ rats and liver carcinomas and adenomas in ♂ and ♀ mice when administered via food (4).

Mice were fed 15 or 30 g kg⁻¹ (total dose) in the diet for 103 wk. Dose-related reductions in mean body weight were noted in both sexes, and there was a significant dose-related incidence of hepatocellular carcinomas in both sexes, compared to controls. Some metastases were observed in the lungs of high-dose ♀ (5).

Following thrice wkly intraperitoneal injections in mice, 24 doses of 500 mg kg⁻¹ or 100 mg kg⁻¹, an increased incidence of lung tumours was observed (6).

Teratogenicity and reproductive effects

In the chicken embryo test, no effect on structural or functional development was observed in embryos or hatched chicks given doses up to 10 mg egg⁻¹ (7).

Genotoxicity

Salmonella typhimurium TA98, TA100, TA1535, TA1537, TA1538, with and without metabolic activation negative (4,8).

In vitro Chinese hamster ovary cells chromosomal aberrations, sister chromatid exchanges with and without metabolic activation negative (9).

In vitro mouse lymphoma cells mutation assay without metabolic activation negative, with metabolic activation positive (9).

Drosophila melanogaster sex-linked recessive lethal mutation assay negative (10).

In vivo mouse bone marrow micronucleus assay negative (11).

Other comments

Due to absence of epidemiological data, no evaluation of the carcinogenicity of cinnamyl anthranilate to humans can be made (12).

World Health Organisation recommendation not to be used in food (13).

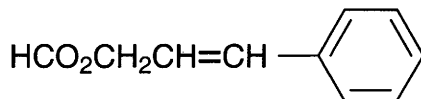
Reviews on physico-chemical properties, human health effects, exposure levels, experimental toxicology, workplace experience and epidemiology listed (14).

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C348 cinnamyl formate



$\text{C}_{10}\text{H}_{10}\text{O}_2$

Mol. Wt. 162.19

CAS Registry No. 104-65-4

Synonyms cinnamyl alcohol, formate; cinnamyl methanoate; 2-propen-1-ol, 3-phenyl-, formate; γ -phenylallyl formate

EINECS No. 203-223-3

RTECS No. UD 5530000

Uses Fragrance.

Physical properties

M. Pt. 0°C **B. Pt.** 250-254°C **Flash point** 100°C **Specific gravity** 1.077-1.082 at 20°C

Solubility Organic solvents: chloroform, diethyl ether, fixed oils

Mammalian & avian toxicity

Acute data

LD₅₀ oral rat 2900 mg kg⁻¹ (1).

Legislation

Limited under EC Directive on Drinking Water Quality 80/778/EEC. Substances extractable in chloroform. Guide level: 0.1 mg l⁻¹ dry residue (2).

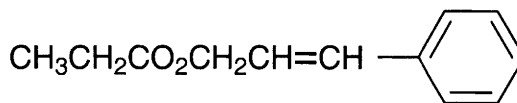
Other comments

Experimental toxicology and human health effects reviewed (3).

References

1. Denine, E. P. *Food Cosmet. Toxicol.* 1973, **14**, 719.
2. *EC Directive Relating to the Quality of Water Intended for Human Consumption* 1982, 80/778/EEC, Office for Official Publications of the European Communities, 2 rue Mercier, L-2985 Luxembourg.
3. *BIBRA Toxicity Profiles* 1991, British Industrial Biological Research Association, Carshalton, UK

C349 cinnamyl propionate



$\text{C}_{12}\text{H}_{14}\text{O}_2$

Mol. Wt. 190.24

CAS Registry No. 103-56-0

Synonyms 3-phenyl-2-propenyl propionate; cinnamyl alcohol, propionate; propionic acid, cinnamyl ester

EINECS No. 203-124-5

RTECS No. GE 2360000

Uses Fragrance.

Physical properties

B. Pt. 289°C **Flash point** 100°C **Specific gravity** 1.029-1.033 at 20°C

Solubility Organic solvents: miscible with chloroform, diethyl ether, ethanol

Mammalian & avian toxicity

Acute data

LD₅₀ oral rat 3400 mg kg⁻¹ (1).

LD₅₀ dermal rabbit >5 g kg⁻¹ (1).

Irritancy

Dermal rabbit (24 hr) 500 mg caused mild irritation (1).

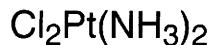
Other comments

Experimental toxicology and human health effects reviewed (2).

References

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2. *BIBRA Toxicity Profiles* 1991, British Industrial Biological Research Association, Carshalton, UK

C350 cisplatin



$\text{Cl}_2\text{H}_6\text{N}_2\text{Pt}$

Mol. Wt. 300.05

CAS Registry No. 15663-27-1

Synonyms *cis*-dichlorodiamineplatinum(II); *cis*-platinum II; *cis*-DDP; Neoplatin; Platistin; Istin; Platinol

EINECS No. 239-733-8

RTECS No. TP 2450000

Uses Antineoplastic agent.

Physical properties

M. Pt. 270°C **Partition coefficient** log P_{ow} -21.9 (1)

Solubility Water: 2.53 g l⁻¹ at 25°C (slowly changes to *trans* form). Organic solvents: dimethylformamide

Occupational exposure

UK-LTEL MEL 0.002 mg m⁻³ (as Pt)

Ecotoxicity

Toxicity to other species

Adult frogs were injected with a single dose of 10-40 mg kg⁻¹. Tonoclonic seizures were observed 3-5 wk later. The seizures could be induced repeatedly, and the animals appeared entirely normal between seizures. Vacuolation, which consisted of swollen astrocytic processes in the neuropil and around the neurons, was observed. No generalised oedema on swelling of perivascular astrocyte food processes was seen (2).

Mammalian & avian toxicity

Acute data

LD₅₀ oral rat 26 mg kg⁻¹ (3).

LD₅₀ intravenous mouse 11 mg kg⁻¹ (4).

LD₅₀ intraperitoneal guinea pig 10 mg kg⁻¹ (5).

LD₅₀ subcutaneous rat 8 mg kg⁻¹ (3).

LD₅₀ intraperitoneal, intravenous rat 7-9 mg kg⁻¹ (6,7).

Rats were administered a single intravenous injection of up to 9 mg kg⁻¹. The DNA content, thymidine kinase activity and cellularity were decreased in the bone marrow in a dose-dependent manner within 48 hr. The protein content of bone marrow was not affected in the period (7).

Intraperitoneal administration of a single dose of 6 mg kg⁻¹ induced renal damage in rats, characterised by a decrease in glomerular filtration and tubular secretion as a result of direct damage to the renal tubular cells (8).

Rats were administered a single intraperitoneal dose of 7.7 mg kg⁻¹. Damage to the organ of Corti of the middle ear was evident in rats sacrificed on day-3 (9).

Carcinogenicity and chronic effects

Inadequate evidence for carcinogenicity to humans, sufficient evidence for carcinogenicity to animals, IARC classification group 2A (10).

Powerful carcinogen in animal tests, induced lung tumours in mice, initiated skin tumours when applied to mice and induced sarcomas upon subcutaneous injection (11).

Mice were given intraperitoneal injections of 3.25 mg kg⁻¹ wkly for 10 wk, or 1.62 mg kg⁻¹ wkly for 19 wk. An increase in lung adenomas observed in all treated groups compared to controls. In a parallel experiment, one group of mice were administered cisplatin in croton oil to shaved areas of skin. Papillomas and carcinomas of the skin along with small numbers of internal neoplasms were induced (12).

The incidences of epidermoid carcinomas and of both malignant and benign tumours of internal organs were increased in mice but no significant difference from controls was observed. In two studies intraperitoneal injection induced leukaemia (10).

Teratogenicity and reproductive effects

♂ Rats administered five daily injections of 2 mg kg⁻¹ were observed to suffer a progressive but reversible loss of germ cells from the seminiferous epithelium of the testes. Testosterone levels were reduced, but were sufficient to support complete spermatogenesis. Observed effects on testicular androgen-binding protein indicated that the germinal regression was due to the effect on Sertoli cell function (13).

♀ Rats were treated with a single dose of cisplatin on one day during the period of organogenesis.

Embryolethality was greatest after cisplatin treatment on days 6-9 and decreased with advancing gestational age. The critical period for induction of teratogenesis was between days 5-8. Malformations were mainly of the limb buds (14).

Metabolism and toxicokinetics

After rapid intravenous injection, high concentrations were found in kidneys, liver, intestine and testes of patients. Only a small portion was excreted by the kidney during the first 6 hr. After five days up to 45% was recovered in the urine. When infused, the plasma t_{1/2} was shorter and the amount of drug excreted was greater (15).

Plasma $t_{1/2}$ 25-49 min to 58-73 hr in man (16).

Rats were administered a single injection of 8 mg kg⁻¹. Platinum levels peaked at 2213 ng ml⁻¹ in the plasma, 907 ng g⁻¹ in the epididymis, and 614 ng g⁻¹ in the testes within 1 hr. Plasma concentration fell to 111 ng ml⁻¹ after 16 hr. In the testes the platinum level fell to 346 ng g⁻¹ and a secondary peak of 518 mg g⁻¹ was recorded after three days. The epididymal concentration showed a second peak after two days, but no platinum was detected after five days (17).

Sensitisation

Allergic phenomena, rash and asthma have been reported in some patients (18).

Genotoxicity

Salmonella typhimurium TA98, TA100 with and without metabolic activation positive (19).

In vitro chinese hamster V79 cells induced chromosomal aberrations and sister chromatid exchanges (20).

Induced sex-linked mutations and gave positive eye mosaic assay in *Drosophila melanogaster* (21,22).

Induced micronuclei and binuclei in Chinese hamster ovary cells *in vitro* (23).

Mutagenic to human lymphocytes *in vitro* (24,25).

Induced sister chromatid exchanges and chromosomal aberrations in mouse bone marrow cells *in vivo* (26).

Other effects

Other adverse effects (human)

The effect of three cycles of heavy-dose cisplatin (40 mg m⁻² body-surface) for five days on renal tubular function was evaluated in 30 patients. A significant impairment of proximal tubule salt and water reabsorptions was observed, but also, distal tubular function seemed to be affected (27).

Excessive renal salt excretion was reported in 7/70 patients treated with cisplatin. They had severe persistent orthostatic hypotension requiring prolonged treatment with fluorocortisone and sodium chloride supplements. Six of these patients had hyponatraemia (33-39 mg l⁻¹) (28).

Toxic effects following therapeutic administration in humans include toxicity to the kidneys, bone marrow, peripheral nerves and gut. Progressive anaemia and direct antiglobulin-positive haemolysis and loss of hearing and tinnitus have also been reported (29).

Any other adverse effects

The major toxic effect caused by cisplatin is dose-related and cumulative damage to renal tubular function. With higher doses or repeat courses, irreversible kidney damage may occur. Ototoxicity is manifested by tinnitus and hearing loss in the high frequency range (30,31).

Inhibited glucose metabolism and protein synthesis in rat intestinal cells *in vitro* (32).

Other comments

Concurrent administration of *p*-aminobenzoic acid reduced the toxicity of cisplatin in rats without compromising its antitumour activity against P388 leukaemia (33).

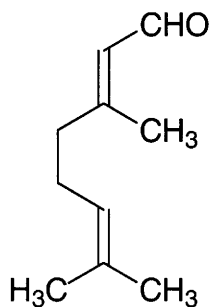
N-*p*-carboxybenzyl-D-glucamine dithiocarbamate (CBDG) (40 µmol kg⁻¹ intravenously) reduced the renal damage in rats from an intravenous dose of cisplatin (20 µmol kg⁻¹). The antitumour efficacy of cisplatin in Walker 256 carcinoma-bearing rats was not affected by CBDG (34).

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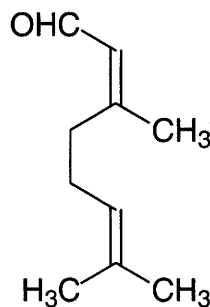
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C351 citral



citral a



citral b

C₁₀H₁₆O

Mol. Wt. 152.24

CAS Registry No. 5392-40-5

Synonyms 3,7-dimethyl-2,6-octadienal; NCI-C56348; geranial; neral; geranialdehyde

EINECS No. 226-394-6

RTECS No. RG 5075000

Uses In the synthesis of vitamin A, ionone and methylionone. In perfumes. Used as a flavour adjuvant.

Occurrence Constituent of oil of lemon grass. Also found in oils of verbena, lemon, and orange.

Physical properties

B. Pt. 92-93°C at 2.6 mmHg; 229°C (decomp.) **Flash point** 101°C **Specific gravity** 0.891-0.897 g ml⁻¹ at 15°C
Volatility v.p. 1 mmHg at 61.7°C, 760 mmHg at 228°C
Solubility Water: 0.1-1 mg ml⁻¹ at 18°C. Organic solvents: ≥100 mg ml⁻¹ at 21°C acetone, 95% ethanol and DMSO

Ecotoxicity

Invertebrate toxicity

Citral at a concentration of 400 ppm completely suppressed the growth of *Aspergillus nidulans*, *A. niger*, *Alternaria tenuis*, *Colletotrichum capsici*, *C. gloeosporioides*, *Curvularia lunata*, *Penicillium italicum*, and *Rhizopus arrhizus* mycelia attacking *Phaseolus radiatus* in storage. The minimum inhibitory concentration against *Aspergillus flavus* was 300 ppm (1).

Mammalian & avian toxicity

Acute data

LD₅₀ oral rat 4960 mg kg⁻¹ (2).
LD₅₀ oral mouse 6000 mg kg⁻¹ (3).
LD₅₀ intraperitoneal rat 460 mg kg⁻¹ (4).

Sub-acute and sub-chronic data

Gastric intubation to rats of 1.5 g kg⁻¹ day⁻¹ for five days induced peroxisome proliferation and raised levels of microsomal cytochrome P450 IVA1 (5).

Oral F344 rats and B6C3F1 mice 0-10% citral (microcapsules) in diet (equivalent to 0-2280 mg kg⁻¹ for rats and 0-8550 mg kg⁻¹ for mice). No mortalities occurred in mice or rats. Decreased body weights occurred in mice receiving the 10% concentration and in rats receiving the 5 and 10% concentrations. Absolute weights of the liver, kidney and spleen decreased in rats receiving the 10% concentration. Minimal to mild hyperplasia and/or squamous metaplasia of the respiratory epithelium in the anterior portion of the nasal passage of rats fed concentrations of 5 or 10% occurred (1).

Gavage B6C3F1 mice (14 days) 0-2137 mg kg⁻¹ daily. Mortalities were 5/5 ♀s and 5/5 ♂s for mice administered the highest dose and 2/5 ♂s for mice administered 1068 mg kg⁻¹. Cytoplasmic vacuolisation was observed in all ♀ mice 1068 and 2137 mg kg⁻¹ and in ♂ mice dosed with 2137 mg kg⁻¹. Dose-related increases in absolute liver weights occurred in ♂ and ♀ mice. Necrosis, ulceration, and/or acute inflammation of the forestomach occurred in the high-dose mice of both sexes. Inflammation and/or hyperplasia of the forestomach occurred in ≈50% of ♂ and ♀ mice administered 1068 mg kg⁻¹. Gavage F344 rats (14 days) 0-2280 mg kg⁻¹ daily suffered no toxic effects except for minimal hyperplasia of the squamous epithelium of the stomach in high-dose ♂s (1).

Teratogenicity and reproductive effects

Pregnant Sprague-Dawley rats exposed to citral 0-68 ppm by inhalation 6 hr day⁻¹ on gestation days 6-15 were killed on gestation day-20 and fetuses were evaluated for gross, visceral, and skeletal malformations. Maternal toxicity was observed in rats receiving 68 ppm, with reduced body weight gains, ocular opacity, breathing difficulty, nasal discharge, and salivation. Lower doses were not maternally toxic and did not produce developmental toxicity in the fetuses (6).

Oral pregnant Wistar rats 0-1000 mg kg⁻¹ administered on gestation days 6-15 and Caesarean sections carried out on gestation day-21. No-observed-adverse-effect level for embryofoeto-toxicity <60 mg kg⁻¹ body weight (7).

Metabolism and toxicokinetics

Following intravenous or oral administration of ♂ Fischer rats of ¹⁴C-labelled citral, urine was the major route of elimination of citral-derived radioactivity, followed by faeces, ¹⁴CO₂, and expired volatiles. No effect on disposition was observed for an oral dose of 5-500 mg kg⁻¹. Within 5 minutes of an intravenous dose no unmetabolised citral could be detected in the blood, and within 4 hr 25% of the administered dose had been eliminated via the bile. Citral is rapidly metabolised and excreted and therefore significant bioaccumulation probably does not occur (8).

Rats and mice administered ^{14}C -labelled citral orally had excreted most of the radioactivity within 72 and 120 hr, respectively. The authors suggest that any hazard associated with tissue accumulation after prolonged exposure should be minimal (9).

Investigations of citral metabolism by rat hepatic mitochondrial and cytosolic fractions indicate that direct aldehyde dehydrogenase-mediated oxidation of citral is unlikely to occur *in vivo*, but rather that it may undergo an aldehyde dehydrogenase-mediated reduction to the corresponding alcohol or may be metabolised via other pathways prior to oxidation by aldehyde dehydrogenase (10).

Regio-selective oxidation of citral in rabbits occurred with carboxylation of a *trans*-positioned methyl group (11).

Irritancy

Non-irritant to skin of σ rats (12).

Severely irritating in the human patch test at 32% concentration (13).

Sensitisation

Did not sensitise σ rats when applied dermally (12).

Other effects

Any other adverse effects

Dermal σ and φ rats (90 days) 0.2 ml 15.4% solution of citral (equivalent to $185 \text{ mg kg}^{-1} \text{ day}^{-1}$) did not cause irritation or sensitisation but in σ rats caused an increase in the number of sebaceous gland lobules and hyperplasia of sebaceous cells in each gland (12).

Adolescent (6-wk-old) rats administered citral for 3 months developed typical lesions of benign prostatic hyperplasia (14).

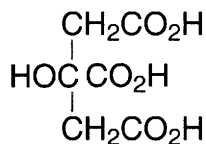
Other comments

When applied as a fumigant citral was 2.9 (2.5-3.3) times more toxic to tracheal mites than to their honey bee hosts. Probit regressions for bee and mite mortality were parallel (15).

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C352 citric acid



C₆H₈O₇

Mol. Wt. 192.13

CAS Registry No. 77-92-9

Synonyms 2-hydroxy-1,2,3-propanetricarboxylic acid; Citro; Hydrocerol A

EINECS No. 201-069-1

RTECS No. GE 7350000

Uses Acidulant in beverages, confectionery. Manufacture of pharmaceutical syrups and effervescent powders and tablets. Used to adjust pH of foods and as synergistic antioxidant, in jellies, jams and processed cheese. Manufacture of alkyl resins, citric acid salts. Sequestering agent to remove trace metals. Mordant to brighten colours. Used in electroplating, special inks. Reagent for albumin, mucin, glucose, bile pigment. Anticoagulant in blood products.

Occurrence Widely distributed in plants and in animals tissues and fluids.

Physical properties

M. Pt. 152-154°C (anhydrous) **B. Pt.** decomp. **Specific gravity** 1.665 (anhydrous) at 20°C

Partition coefficient log P_{ow} -1.72 (1)

Solubility Water: 590 g l⁻¹ at 20°C. Organic solvents: diethyl ether, ethanol

Ecotoxicity

Fish toxicity

LC₁₀₀ goldfish 894 mg l⁻¹ lifetime exposure in hard water (2).

LC₀ goldfish 625 mg l⁻¹ lifetime exposure in hard water (2).

Invertebrate toxicity

LC₁₀₀ *Daphnia magna* 120 mg l⁻¹ lifetime exposure in soft water (2).

LC₀ *Daphnia magna* 80 mg l⁻¹ lifetime exposure in soft water (2).

Toxicity threshold: *Pseudomonas putida* >10 g l⁻¹; *Scenedesmus quadricauda* 640 mg l⁻¹; *Entosiphon sulcatum* 485 mg l⁻¹ (3).

Environmental fate

Nitrification inhibition

Nitrosomonas sp. 100 mg l⁻¹ no inhibition of ammonia oxidation (4).

Degradation studies

70-100% removal by activated sludge (rotating cylinder) at 20°C for 120 hr (5).

BOD₅ 0.420; BOD₂₀ 0.610; ThOD 0.686 mg l⁻¹ O₂, respectively (6).

Biodegradable (7).

Mammalian & avian toxicity

Acute data

LD₅₀ oral mouse, rat 5, 6.7 g kg⁻¹, respectively (8).

LD₅₀ subcutaneous mouse, rat 2700, 5500 mg kg⁻¹, respectively (8).

LD₅₀ intraperitoneal rat 883 mg kg⁻¹ (9).

LD₅₀ intravenous mouse 42 mg kg⁻¹ (9).

Metabolism and toxicokinetics

Metabolised via the tricarboxylic acid cycle, citrate is enzymatically oxidised to succinate by animal tissues (10).

Irritancy

Dermal rabbit (24 hr) 500 mg produced moderate irritation and 750 µg instilled into rabbit eye for 24 hr produced severe irritation (11).

A severe eye and moderate skin irritant. Citrus juice phytophotodermatoses with long hyperpigmented macular lesions (species unspecified) (12).

A 3% solution applied to human skin caused sensory irritation (13).

Genotoxicity

Citric acid did not induce sister chromatid exchanges in *in vitro* Chinese hamster ovary cells (14).

Other effects

Other adverse effects (human)

Two cases of hypersensitivity to citric acid in the form of chronic buccal aphthous ulcers were reported in humans (15).

Citrate toxicity has been held responsible for the deaths of persons given rapid massive transfusions with blood containing citrate anticoagulant solutions (16).

Other comments

Citric acid, when used as an anticoagulant during the storage of blood was shown to have greater myocardial effects on the neonatal heart than in the adult, with impairment of systolic and diastolic function (17).

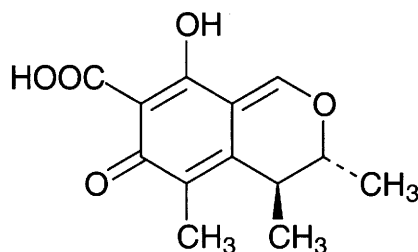
Produced from crude sugar solutions (molasses), by fermentation with strains of *Aspergillus niger*.

Experimental toxicology and human health effects reviewed (18).

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C353 citrinin



$C_{13}H_{14}O_5$

Mol. Wt. 250.25

CAS Registry No. 518-75-2

Synonyms (3*R*-trans)-4,6-dihydro-8-hydroxy-3,4,5-trimethyl-6-oxo-3*H*-2-benzopyran-7-carboxylic acid;
(3*R*,4*S*-4,6-dihydro-8-hydroxy-3,4,5-trimethyl-6-oxo-3*H*-2-benzopyran-7-carboxylic acid

EINECS No. 208-257-2

RTECS No. DJ 2275000

Occurrence Antibiotic substance produced by a white spore fungus, *Aspergillus niveus*, and in small quantities by *Penicillium citrinum*.

Physical properties

M. Pt. 175°C (dec.)

Solubility Water: insoluble. Organic solvents: acetone, benzene, chloroform, dioxane, ethanol

Occupational exposure

UN No. 2811

Ecotoxicity

Invertebrate toxicity

Growth inhibition assay *Bacillus thuringiensis* 0.1 g l⁻¹ (1).

Swarming inhibition assay *Azospirillum brasilense* >1.0 g l⁻¹, *Proteus mirabilis* 0.6 g l⁻¹ (1).

EC₅₀ (15 min) *Photobacterium phosphoreum* 16.9 ppm Microtox test (2).

Minimum effective concentration of citrinin required to elicit a toxic response in adult *Hydra attenuata* 30 mg l⁻¹, and in the regenerating hydra 20 mg l⁻¹. The Hydra developmental hazard index was 1.5, classifying citrinin as a coeffective developmental toxin (3).

Intracoelomically injected into cockroaches, citrinin induced behavioural changes, tremor and death, by acting on the central nervous system (4).

Mammalian & avian toxicity

Acute data

LD₅₀ oral ♂ mice 112 mg kg⁻¹ (in equal parts DMSO and 50% ethanol) (5).

LD₅₀ intraperitoneal ♂, ♀ mice 58, 62 mg kg⁻¹, respectively (in DMSO-50% ethanol) (4).

The death rate and pathological changes produced were similar whether a single dose or multiple doses were given; lesions were confined to the kidneys (5).

Oral rabbit 67 or 120 mg kg⁻¹ resulted in ultrastructural lesions in the kidneys by 4 hr (6).

Sub-acute and sub-chronic data

Oral ♂ broiler chicks were fed a diet containing 0, 100, 220, 330 and 440 ppm citrinin from day-old to 3-wk of age. Chicks in the 330 and 440 ppm groups showed decreased body weight, and those in the 440 ppm group showed decreased feed utilisation. Detectable amounts of citrinin were found in the liver and blood of high-dose chicks (7).

Carcinogenicity and chronic effects

No adequate data for carcinogenicity to humans, limited evidence for carcinogenicity to animals, IARC classification group 3 (8).

Oral administration to ♂ Fischer 344 rats (6-wk-old) of 0 and 0.1% citrinin in diet resulted in benign renal tumours in all treated rats sacrificed at 40, 60 and 80 wk. No renal tumours occurred in the control group (9).

Broiler chicks fed 260 ppm citrinin in diet for 6 wk developed anaplastic areas in the kidney and pancreas, and increased mitosis of tubular epithelial cells in the kidney (10).

Teratogenicity and reproductive effects

Subcutaneous injection pregnant Sprague-Dawley CD-1 rats (on one of days 3-15 of gestation) 35 mg kg⁻¹ citrinin in 5% sodium bicarbonate. One-third to one-half of the dams in each group of at least ten rats died, and most of the remainder had reduced body-weight gain. Rats treated on days 8 or 10 produced 70-75% live offspring, while those in other groups showed fewer resorptions. Foetal weight was reduced in all groups, and minor foetal anomalies occurred in all groups. Major internal soft tissue malformations were seen, such as enlarged kidneys, internal hydrocephalus and cleft palate (11).

In vitro rat whole embryo culture 0 to 300 mg l⁻¹ for 45 hr resulted in concentration-dependent reduction in yolk sac diameter, crown-rump length, somite number, protein and DNA contents. No dysmorphogenesis was observed; at 250 mg l⁻¹, severe diffuse mesodermal and ectodermal necrosis was observed. No gross or histological changes were seen at lower concentrations of citrinin (3).

Metabolism and toxicokinetics

Radioactively-labelled citrinin was given to ♂ rats by intravenous injection, as a single dose of 3 mg kg⁻¹; 0.5 hr after administration, 14.7 and 5.6% of total radioactivity was detected in the liver and kidneys, respectively. At 6 hr, this fell to 7.5 and 4.7%, respectively. The concentration of ¹⁴C in plasma was 9.2% of the total at 0.5 hr, and 4.7% at 6 hr; plasma elimination rates with half-lives of 2.6 and 14.9 hr were observed. By 24 hr, ~80% of the administered dose was excreted in urine and faeces (12).

Genotoxicity

Salmonella typhimurium TA98, TA100, TA1535, TA1537, TA1538 with and without metabolic activation negative (13).

Saccharomyces cerevisiae D3 mitotic gene conversion test with and without metabolic activation negative (14).

In vitro rat hepatocytes and human embryonic hepatocytes induction of unscheduled DNA synthesis negative (15).

Chinese hamster V79 cells with metabolic activation, induction of chromosomal aberrations positive, sister chromatid exchange negative (16).

Other effects

Any other adverse effects

In mice given 15, 25 or 35 mg citrinin kg⁻¹ for 6 wk by intraperitoneal injection, the levels of ATP-ase, hexokinase and lactate dehydrogenase activity and of lactic acid and pyruvic acid decreased in the blood, liver, kidneys and brain. Glucose levels in the blood, kidneys and brain increased, and glycogen content of the liver decreased. Serum cortisol, triiodothyronine and thyroxine levels increased, and serum insulin levels decreased (17).

Citrinin intoxication induces acute nephrotoxicosis in dogs. Induced renal lesions are mainly in the proximal convoluted tubule, and accompanied by proteinuria, glucosuria and numerous granular casts in the urine sediment. These lesions are detectable before increased blood urea and creatinine levels (18).

Other comments

Mildly stimulates the immune system in mice (19).

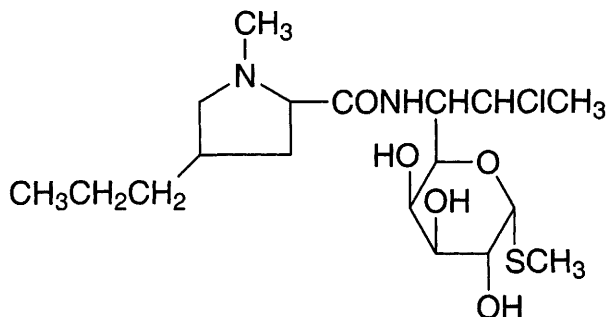
Not commercially developed as an antibiotic due to its toxic effects in animal studies (12).

Determination and toxicity of citrinin reviewed (20).

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c354 clindamycin



$C_{18}H_{33}ClN_2O_5S$

Mol. Wt. 424.99

CAS Registry No. 18323-44-9

Synonyms 7(S)-chloro-7-deoxylincomycin; (2S-trans)-methyl-7-chloro-6,7,8-trideoxy-6-[[[(1-methyl-4-propyl-2-pyrrolidinyl)carbonyl]amino]-1-thio-L-threo-D-galacto-octopyranoside; Cleocin

EINECS No. 242-209-1

RTECS No. RH 6300000

Uses Antibiotic.

Occurrence Isolated from *Streptomyces lincolnensis*.

Physical properties

M. Pt. 141-143°C (hydrochloride)

Solubility Water: miscible (base). Organic solvents: dimethylformamide, ethanol, methanol, pyridine

Mammalian & avian toxicity

Acute data

LD_{Lo} oral hamster, rabbit 1 mg kg⁻¹ (1,2).

LD₅₀ intravenous mouse 245 mg kg⁻¹ (3).

LD₅₀ intraperitoneal mouse 361 mg kg⁻¹ (3).

LD₅₀ subcutaneous rat 2620 mg kg⁻¹ (4).

Sub-acute and sub-chronic data

Four healthy cats were orally administered 25 or 50 mg kg⁻¹ daily for 6 wk. No significant change in Factor-VII activity was observed. Thus, orally administered clindamycin did not reduce the synthesis of vitamin K-dependent clotting factors (5).

Rats were administered 40 mg kg⁻¹ daily for 4 wk by intravenous injection. No deaths occurred and no adverse effects were observed in the clinical signs: body weight, food and water consumption, ophthalmic observations, urine analysis, clinical biochemistry, organ weights, necropsy and histopathologic findings (6).

Metabolism and toxicokinetics

Following oral dosing to cats for 10 days at 5.5 or 11 mg kg⁻¹ twice daily, or 22 mg kg⁻¹ once daily, concentrations of the unmetabolised clindamycin were found to be highest in the lungs, with tissue/serum ratios >3 in all groups. The tissue/serum ratio was >1 in all tissues except bone, cerebrospinal fluid, brain and skeletal muscle. The active metabolite was *N*-desmethylclindamycin (7).

Healthy men were given three intravenous injections of 1200 mg at 12 hr intervals. The mean maximum, 1 hr post-dose and minimum serum concentrations at steady-state were 17.2, 9.8 and 0.6 µg ml⁻¹. The serum concentration remained >2 µg mg⁻¹ for 7 hr (8).

Following oral administration (concentration and species unspecified) nearly completely absorbed. 10% excreted unchanged in the urine and small quantities in the faeces. Most of drug metabolised and excreted in urine and bile (9).

Sensitisation

Contact allergy was reported in a 31-yr-old woman without any history of allergy (10).

Other effects

Other adverse effects (human)

Pseudomembranous colitis is the most important toxic effect associated with the use of clindamycin (11).

May cause significant diarrhoea or colitis in patients (12).

Any other adverse effects

Reported to block neuromuscular transmission. The mechanism of blockage was demonstrated to involve the antagonism of Ca²⁺ entry through voltage-regulated channels in the nerve terminal membrane (13).

Other comments

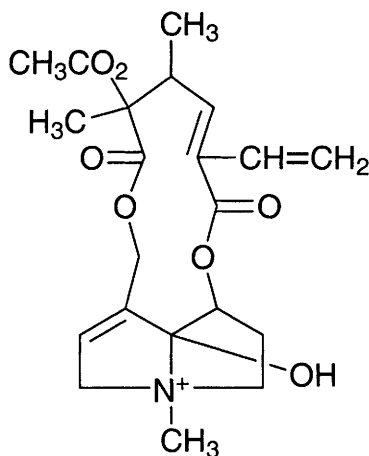
An acidic environment unfavourably affects the activity of clindamycin against clinical isolates of *Helicobacter pylori* (14).

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c355 clivorine



$C_{21}H_{28}NO_7$

Mol. Wt. 406.46

CAS Registry No. 33979-15-6

Synonyms 12-(acetyloxy)-14,15,20,21-tetradehydro-15,20-dihydro-8-hydroxy-4-methyl-11,16-dioxoseneconium, (8e,12β,14Z)-

RTECS No. VT 5800000

Occurrence Alkaloid isolated from *Ligularia clivorum*.

Physical properties

M. Pt. 148-150°C

Mammalian & avian toxicity

Carcinogenicity and chronic effects

Oral rat (340 day) 0.005% solution in drinking water. 8/12 animals developed tumours in the liver, 2/12 developed haemangioendothelial sarcomas and 6/12 developed neoplastic nodules (1).

Genotoxicity

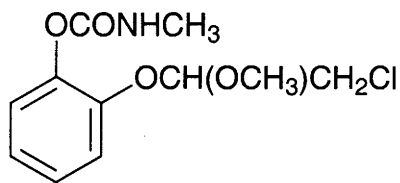
Salmonella typhimurium TA100 with metabolic activation positive (2).

In vitro hamster hepatocytes, unscheduled DNA synthesis positive, *in vitro* mouse hepatocytes unscheduled DNA synthesis negative (3).

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C356 cloethocarb



$C_{11}H_{14}ClNO_4$

Mol. Wt. 259.69

CAS Registry No. 51487-69-5

Synonyms 2-(2-chloro-1-methoxyethoxy)phenyl methylcarbamate; Lance

EINECS No. 257-236-4

RTECS No. SK 4925000

Uses Superseded insecticide and nematocide.

Physical properties

M. Pt. 80°C Volatility v.p. 7.52×10^{-8} mmHg at 20°C

Solubility Water: 1.3 g kg⁻¹ at 20°C. Organic solvents: acetone, chloroform, ethanol

Mammalian & avian toxicity

Acute data

LD₅₀ oral rat, mouse 35, 70 mg kg⁻¹, respectively (1).

LD₅₀ dermal rat 4000 mg kg⁻¹ (1).

Sub-acute and sub-chronic data

In 1-yr feeding trials, no-effect level for rats was 25 mg kg⁻¹ diet, and for mice was 10 mg kg⁻¹ diet (1).

Other effects

Any other adverse effects

Obstruction of the gastro-intestinal or urogenital tract (species unspecified) (2).

Asthma, diabetes, cardiovascular disease have been reported (species unspecified) (3).

Legislation

Limited under EC Directive on Drinking Water Quality 80/778/EEC. Pesticides: maximum admissible concentration 0.1 µg l⁻¹ (4).

WHO Toxicity Class Ib (5).

EPA Toxicity Class II (1).

Other comments

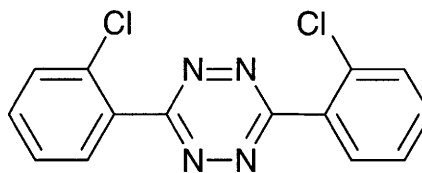
Highly toxic cholinesterase inhibitor (3).

Environmental degradation: residual activity in the range 3-7 wk (1).

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C357 clofentezine



C₁₄H₈Cl₂N₄

Mol. Wt. 303.15

CAS Registry No. 74115-24-5

Synonyms 3,6-bis(2-chlorophenyl)-1,2,4,5-tetrazine; Apollo; Acaristop; Panatac

EINECS No. 277-728-2

RTECS No. XF 6860000

Uses Acaricide.

Physical properties

M. Pt. 179-182°C **Partition coefficient** log *P*_{ow} 4.1 (1) **Volatility** v.p. 9.8×10^{-7} mmHg at 25°C

Solubility Water: 0.029 mg l⁻¹. Organic solvents: benzene, chloroform, dichloromethane, hexane

Ecotoxicity

Fish toxicity

LC₅₀ (96 hr) rainbow trout >0.015 mg l⁻¹ (1).

LC₅₀ (96 hr) bluegill sunfish >0.25 mg l⁻¹ (1).

Invertebrate toxicity

EC₅₀ (48 hr) *Daphnia* sp. >1.45 µg l⁻¹ (1).

LD₅₀ oral bee >20 µg bee⁻¹ (1).

LC₅₀ (duration unspecified) contact bee >1500 ppm (1).

Subjecting the rove beetle *Aleochara bilineata* to a concentration of clofentezine equal to the highest recommended dosage for practical use resulted in no adult mortality, insignificant reduction in egg production and a 28% reduction in egg hatching (2).

Environmental fate

Degradation studies

In soil, major degradation products are 2-chlorobenzoic acid, and finally, carbon dioxide. *t*_{1/2} 65-85 days at 15°C and 28-56 days at 25°C, depending on soil type (1).

¹⁴C-radiolabelled clofentezine was applied at ~ field rate to three soil types: clay, loamy sand and clay loam. The treated soils were incubated under aerobic and anaerobic conditions for 1 yr at 25°C and a moisture content of 50%. Rapid degradation of clofentezine in the three soils resulted in 50% loss of pesticide within 4-8 wk. The principal degradative route, under aerobic conditions, was hydrolytic cleavage of the tetrazine ring leading to the formation of 2-chlorobenzoic (2-chlorobenzylidene) hydrazide. Further breakdown occurred with up to 50% of the applied radioactivity being mineralised to ¹⁴CO₂ when radiolabelled clofentezine was applied to surface water of sediment/water systems. In two sediment types *t*_{1/2} of 2-7 days were observed with substantial degradation to ¹⁴CO₂. In a range of mobility studies, using both active ingredient and formulated products, clofentezine was found to be of extremely low mobility in all soil types (3).

Abiotic removal

In water, 2-chlorobenzonitrile was the major product formed by hydrolysis and photodegradation (1).

Mammalian & avian toxicity

Acute data

LD₅₀ oral rat, mouse >3200 mg kg⁻¹ (4).

LD₅₀ oral mallard duck >3000 mg kg⁻¹ (1).

LD₅₀ oral bobwhite quail >7500 mg kg⁻¹ (1).

LC₅₀ (4 hr) inhalation rat >9 mg l⁻¹ (1).

LD₅₀ dermal rat >2100 mg kg⁻¹ (1).

Sub-acute and sub-chronic data

Five-day dietary LC₅₀ mallard duck >20 g kg⁻¹ in diet (1).

Carcinogenicity and chronic effects

Oral rat (2 yr) 40 mg kg⁻¹ diet, no adverse effects reported (1).

Metabolism and toxicokinetics

Following oral administration to rats, mice and rabbits clofentezine was metabolised by hydroxylation and exchange of the chlorine atoms on the rings for methylthio groups. Metabolism in calf and baboon was via hydroxylation and conjugation. Excretion occurred within 24-48 hr mainly in the faeces, with urinary levels ranging from 1-2% in the dog and 25-37% in the rabbit (5).

Other effects

Any other adverse effects

Rat hepatocytes were incubated with 10⁻³M chlorfentezine *in vitro*. As a percentage of controls, cell viability was 90.7 (45 min) and 93.8 (90 min); non-protein sulfhydryl contents 82.8 (45 min) and 77.5 (90 min). 10⁻³M chlorfentezine uncoupled state-4 respiration in isolated mitochondria. 10⁻⁵M chlorfentezine was antioxidative with respect to isolated microsomal lipid peroxidation (6).

Legislation

Limited under EC Directive on Drinking Water Quality 80/778/EEC. Pesticides: maximum admissible concentration 0.1 µg l⁻¹ (7).

WHO Toxicity Class Table 5 (8).

EPA Toxicity Class (formulation) III (1).

TDI (man) 0.02 mg kg⁻¹ (1).

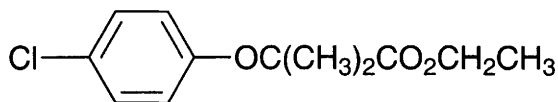
Other comments

Mode of action – inhibits embryo development (1).

Metabolism and pharmacokinetics reviewed (9).

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C₁₂H₁₅ClO₃

Mol. Wt. 242.70

CAS Registry No. 637-07-0

Synonyms ethyl 2-(4-chlorophenoxy)-2-methylpropionate; ethyl clofibrate; 2-(4-chlorophenoxy)-2-methylpropionic acid ethyl ester; 2-(*p*-chlorophenoxy)-2-methylpropionic acid, ethyl ester; ethyl chlorophenoxyisobutyrate; ethyl α-(*p*-chlorophenoxy)isobutyrate; Amotril; Cinnanizin; Lipamid

EINECS No. 211-277-4

RTECS No. UE 9480000

Uses A drug used to lower plasma lipid levels. Causes inhibition of cholesterol synthesis and increased excretion of neutral sterols.

Physical properties

B. Pt. 148-150°C at 20 mmHg **Flash point** 110°C **Specific gravity** 1.138-1.144 at 20°C

Solubility Organic solvents: acetone, chloroform, diethyl ether, miscible with ethanol

Mammalian & avian toxicity

Acute data

LD₅₀ oral rat, mouse 1280, 1650 mg kg⁻¹, respectively (1).

LD₅₀ intraperitoneal rat 910 mg kg⁻¹ (2).

LD₅₀ intraperitoneal mouse 540 mg kg⁻¹ (3).

LD₅₀ intravenous mouse >500 mg kg⁻¹ (4).

Sub-acute and sub-chronic data

TD_{Lo} (6 day intermittent) oral man 171 mg kg⁻¹ produced muscle weakness (5).

Oral administration of 500 mg 4 × over 24 hr to 12 healthy women induced an increase in intragastric acidity from 100-130 g l⁻¹. No significant change in plasma gastrin concentration was observed. Thus anti-secretory effect and gastrin-induced cell proliferation is unlikely to occur with the use of this drug (6).

Acute reversible renal failure, due to interstitial nephritis, has been reported with the use of the drug (7).

Liver biopsies on 40 patients, before and after 3 months clofibrate therapy, demonstrated no significant histological changes of fatty infiltration in 13 patients receiving 500 mg day⁻¹. Of 17 patients with distinct fatty degeneration before treatment with 1.5 g day⁻¹, six improved, three deteriorated and eight remained unchanged. No adverse effects were observed (8).

Of about 5000 patients, 72 reported sexual dysfunction, 14 ceased treatment because of impotence (9).

An increased incidence of angina pectoris, intermittent claudication, pulmonary embolism and cardiac arrhythmias (other than fibrillation) were reported among patients receiving clofibrate (10).

Carcinogenicity and chronic effects

Inadequate evidence for carcinogenicity to humans, limited evidence for carcinogenicity to animals, IARC classification group 3 (11).

Rats were fed clofibrate at a dietary concentration of 0.5% v/w for up to 28 months. One or more hepatocellular carcinomas developed in 10/11 treated rats compared with 0/14 controls. Five of the animals with hepatocellular carcinomas showed metastases. In addition, pancreatic acinar carcinomas were found in 2/11 rats, a dermatofibrosarcoma in one rat and a leiomyoma of the intestine in one rat. No such tumours were seen in controls (12).

Evidence for increased mortality from a variety of cancers, mainly gastro-intestinal, was shown on a randomised clinical trial of clofibrate in men with elevated serum cholesterol levels (13).

One man developed adenocarcinoma of the jejunum, which is rare, after taking 1-1.5 g day⁻¹ clofibrate for 15 yr. He had also taken phenindione, propranolol and cholestyramine intermittently for 8 yr (14).

Teratogenicity and reproductive effects

Oral Wistar rats 150 mg kg⁻¹ day⁻¹ from day 16-22 gestation caused decreased birthweight and increased liver weight of the young rats and perinatal mortality. In offspring of dams treated during last week of pregnancy and during lactation increased liver weight was observed in newborn but this disappeared after 1 wk without treatment (15).

Metabolism and toxicokinetics

Phase II metabolism conjugation to form glucuronide (species unspecified) (16).

After oral administration in rats, rapidly hydrolysed to clofibric acid. In urine, clofibric acid is present free and conjugated with glucuronic acid. In man it is completely absorbed by the intestine but appears in the plasma as the de-esterified *p*-chlorophenoxyisobutyric acid. Peak concentrations of the acid appear in the plasma within 4 hr of oral administration of the drug. Almost all the acid is excreted in the urine, about 60% as the glucuronide (17). In humans, the plasma elimination $t_{1/2}$ ranges between 12-25 hr (18).

Genotoxicity

Salmonella typhimurium TA98, TA100, TA1535, TA1537, TA1538 with and without metabolic activation negative (19).

In vitro mouse splenic lymphocytes with and without metabolic activation no DNA damage induced (19).

In vitro human lymphocytes induced chromosomal aberrations and sister chromatid exchanges; *in vivo* rat bone marrow cells chromosomal aberrations negative (20).

Other effects

Other adverse effects (human)

A strong association between clofibrate and gallstone formation has been documented (21).

A WHO sponsored study of about 15,000 men, for a period of 13.2 yr, showed a noticeably lower incidence of heart attack in hypertensive heavy smokers. Clofibrate apparently reduced fibrinogen levels (22).

Common side-effects of clofibrate therapy include gastro-intestinal upsets, weight gain, headache, dizziness, fatigue, rashes, pruritis, alopecia, anaemia or leucopenia (23) and a flu-like syndrome associated with severe muscle cramps and tenderness, stiffness and weakness (24).

Any other adverse effects

Clofibrate induced hepatic peroxisome proliferation in rodents, associated with enhanced synthesis of peroxisomal marker enzymes (fatty acid β -oxidation enzymes and catalase) (25).

Clofibrate enhances the DNA damaging action and cytotoxicity of nitrosoureas in L1210 cells (26).

Clofibrate was found to potentiate the activities of hepatic lipid metabolising enzymes in the peroxisomal fraction from rat livers but not from guinea pigs (27,28).

Transferred across the placenta and into milk. Post-natal increase in liver α -glycerophosphate dehydrogenase has been reported in newborn rats whose mothers were fed clofibrate (29).

Legislation

Limited under EC Directive on Drinking Water Quality 80/778/EEC. Organochlorine compounds: guide level 1 $\mu\text{g l}^{-1}$ (30).

Included in Schedule 6 (Release into Land: Prescribed Substances) of Statutory Instrument No.472, 1991 (31).

Other comments

Earlier reports that clofibrate is uterotrophic to the rat have not been confirmed in studies involving a range of test protocols and dose levels. The compound was also inactive in a human oestrogen receptor (hER α) yeast oestrogenicity test (32).

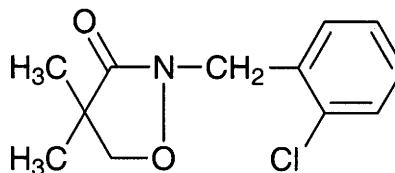
The drug is contra-indicated in patients with impaired renal or hepatic functions and in pregnant and nursing women. Patients with coronary artery diseases may be at risk (33).

Clofibric acid, the active form of clofibrate is a hydrolysis product and has been detected in effluents from sewage treatment plants as a result of human consumption (16).

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c359 clomazone



$C_{12}H_{14}ClNO_2$

Mol. Wt. 239.70

CAS Registry No. 81777-89-1

Synonyms dimethazone; 2-[(2-chlorophenyl)methyl]-4,4-dimethyl-3-isoxazolidinone

RTECS No. NY 2977000

Uses Herbicide.

Physical properties

M. Pt. 25°C **B. Pt.** 275°C **Flash point** 70-75°C (closed cup) **Specific gravity** 1.192 (20°C)
Partition coefficient $\log P_{ow}$ 2.5 (1) **Volatility** v.p. 1.44×10^{-4} mmHg
Solubility Water: 1.1 g l⁻¹. Organic solvents: miscible with acetone, acetonitrile, chloroform, cyclohexanone, dichloromethane, heptane, methanol, toluene

Ecotoxicity

Fish toxicity
LC₅₀ (96 hr) rainbow trout and bluegill sunfish 19-34 mg l⁻¹ (1).

Environmental fate

Degradation studies
 $t_{1/2}$ in soil 10-130 days (1).

Adsorption and retention
Adsorbed by kaolinite and montmorillonite, adsorption increasing with the cation charge (2).

Mammalian & avian toxicity

Acute data
LC₅₀ oral bobwhite quail, mallard duck > 2510 mg kg⁻¹ (1).
LD₅₀ oral rat 1370-2080 mg kg⁻¹ (1).
LC₅₀ (4 hr) inhalation rat 4800 mg m⁻³ (3).
LD₅₀ dermal rabbit > 2000 mg kg⁻¹ (1).

Sub-acute and sub-chronic data
Oral dog (1 yr) no-adverse-effect level 500 mg kg⁻¹ diet (1).

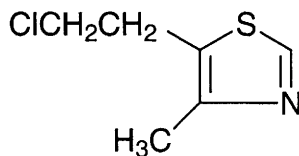
Legislation

Limited under EC Directive on Drinking Water Quality 80/778/EEC. Pesticides: maximum admissible concentration 0.1 µg l⁻¹ (4).
Included in Schedule 6 (Release into Land: Prescribed Substances) Statutory Instrument No. 472, 1991 (5).
EPA Toxicity Class (formulation) III (3).
WHO Toxicity Class II (6).
ADI (proposed) 0.043 mg kg⁻¹ body weight (3).

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6. *The WHO Recommended Classification of Pesticides by Hazard and Guidelines to Classification* 1998-1999 WHO/PCS/98.21.

C360 clomethiazole



C₆H₈ClNS

Mol. Wt. 161.65

CAS Registry No. 533-45-9

Synonyms chlorethiazol; 5-(2-chloroethyl)-4-methylthiazole; 4-methyl-5-(β-chloroethyl)thiazole; Distranevrin; Hemineurin

EINECS No. 208-565-7

RTECS No. XJ 3850000

Uses Hypnotic and sedative. Symptomatic treatment of alcohol withdrawal. Intermediate in some processes of vitamin B₁ manufacture.

Physical properties

B. Pt. 92°C at 7 mmHg **Specific gravity** 1.233 at 25°C with respect to water at 4°C

Solubility Organic solvents: miscible with chloroform, diethyl ether, ethanol

Mammalian & avian toxicity

Acute data

LD₅₀ oral mouse 2110 mg kg⁻¹ (1).

LD₅₀ intraperitoneal mouse 190 mg kg⁻¹ (2).

LD₅₀ intravenous mouse 94 mg kg⁻¹ (3).

Metabolism and toxicokinetics

Rapidly absorbed from gastro-intestinal tract. Effective within 15-30 min with duration of action of 4-6 hr (4).

Plasma t_{1/2} 4 hr (5).

Excreted unchanged in human urine and dog bile. Formation of 4-chlorohippuric acid, the major urinary metabolite in human, involves non-enzymatic hydrolysis followed by oxidation and conjugation of 4-chlorobenzaldehyde product of hydrolysis (6).

Metabolites identified in urine of rats and mice were *p*-chlorobenzoic acid, *p*-chlorohippuric acid, *N*-methyl-*p*-chlorobenzamide, 2-(*N*-methyl-*N*-(*p*-chlorobenzoyl) carbamoyl)ethylsulfonic acid, 3-sulfopropionic acid and the glucuronide of *p*-chlorobenzene (4).

Other effects

Other adverse effects (human)

In humans, clomethiazole may produce nasal irritation and sneezing, conjunctival irritation, headache and gastro-intestinal disturbances including nausea and vomiting. Phlebitis or thrombophlebitis can occur after intravenous administration. Other reported adverse effects include fever, cough, increased bronchial secretion, tachycardia and cardiac arrhythmias. Excessive doses may produce coma, respiratory depression, hypotension and hypothermia. Pneumonia may follow increased respiratory secretion (7).

A risk of dependence exists when using clomethiazole to treat alcoholism. However experience over 15 yr at an alcoholic unit shows clomethiazole is extremely valuable in the treatment and prophylaxis of severe alcohol withdrawal syndromes. It is stressed that the medication should be used for limited periods only, e.g. 6-7 days (8).

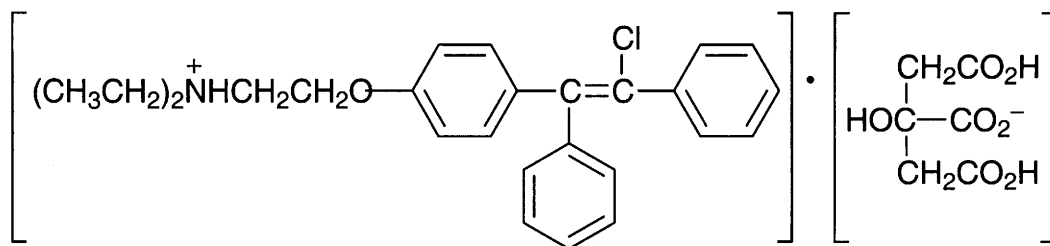
Other comments

Acts by depressing polysynaptic reflexes preferentially over monosynaptic reflexes (9).

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c361 clomiphene citrate



C₃₂H₃₆ClNO₈

Mol. Wt. 598.09

CAS Registry No. 50-41-9

Synonyms 2-[4-(2-chloro-1,2-diphenylethenyl)phenoxy]-N,N-diethylethanamine; 2-[p-(2-chloro-1,2-diphenylvinyl)phenoxy]triethylamine; clomiphene dihydrogen citrate; Clomid

EINECS No. 200-035-3

Uses Drug for treatment of infertility in women. Induces ovulation in anovulatory and oligo-ovulatory women. Also used in men to treat oligospermia.

Physical properties

M. Pt. 116.5-118°C

Solubility Water: slightly soluble in water. Organic solvents: methanol

Mammalian & avian toxicity

Carcinogenicity and chronic effects

Inadequate evidence of carcinogenicity in animals and humans, IARC classification group 3 (1).

A single subcutaneous injection of 10-500 µg to 1-day-old ♀ rats induced multiple abnormalities of the reproductive tract, including cystic ovaries, ovarian hyperplasia, hilus-cell tumours, oviductal hyperplasia, pyometra, epithelial metaplasia and cystic hyperplasia. Uterine tumours were also induced. High-dose animals (500 µg), 80-100% abnormalities detected, while in intermediate and low-dose animals 10-50% abnormalities were detected (2).

A case of granulosa-cell tumour of the ovary was reported in a 28 yr old woman who had received clomiphene citrate treatment for two cycles (two 5-day courses of 100 mg day⁻¹) (3).

Two cases of bilateral breast cancer were reported in women aged 28 and 29 who had received such therapy (4).

A 28-yr-old man who had received 1 mg of the *trans* isomer (enclomiphene) daily for 10 wk developed a germ-cell tumour with elements of seminoma and mature adult teratoma (5).

It is reported that the reversal of an endometrial carcinoma to a normal secretory endometrium followed repetitive induction of ovulation with clomiphene citrate (6). Testicular tumours were reported in three young men who had received clomiphene as part of a sex hormone treatment for oligospermia (7). A hepatoblastoma was reported in a ♀ infant whose mother had received clomiphene citrate for infertility (8). A liver-cell adenoma was reported in a woman who had received treatment for oligomenorrhoea (9). Unilateral testicular neoplasms occurred in 2/650 oligospermic men who had received daily treatment for 3 wk, then a wk of rest, followed by monthly treatment for 6-12 months (10).

Teratogenicity and reproductive effects

Subcutaneous ♀ rats (7-10 day gestation) 20 mg kg⁻¹ was lethal to the mothers (11).

Oral mice (1-4 day gestation) 1-3 mg kg⁻¹ terminated pregnancy (12).

In humans effects on the foetus, after treatment of the mother, have included anencephaly, neural tube defects and some multiple abnormalities (13).

Oral administration of 5-16 mg kg⁻¹ when given to mice in early gestation caused inhibition of implantation. It caused a dose-dependent increase in the number of dead foetuses but had no effect on litter size when given during the middle stages of gestation. A slight increase in morphological abnormalities (clubfoot) was observed, and ossification was accelerated in all groups (14).

Metabolism and toxicokinetics

Clomiphene citrate is absorbed from the gastro-intestinal tract and slowly excreted through the liver into the bile. The biological t_{1/2} (humans) is reported to be 5 days. Enterohepatic recirculation is reported to occur (13).

Genotoxicity

In vivo mouse bone marrow cells failed to induce chromosomal aberrations (15).

In vivo mouse micronucleus test negative (15).

Other effects

Other adverse effects (human)

Hydatidiform mole was observed in two pregnant patients following induction of ovulation by clomiphene citrate (16).

Rapid enlargement of uterine fibroids has also been reported (17).

Systemic effects include hot flushes, abdominal discomfort, nausea, vomiting, nervous tension and insomnia, headache and dizziness (18).

Treatment leads to an increased risk of multiple births. Reported side-effects include reversible ovarian enlargement, vasomotor flushes resembling menopausal symptoms, and abdominal or pelvic pain, sometimes with nausea or vomiting (13).

Legislation

Limited under EC Directive on Drinking Water Quality 80/778/EEC. Organochlorine compounds: guide level 1 µg l⁻¹ (19).

Included in Schedule 6 (Release into Land: Prescribed Substances) of Statutory Instrument No. 472, 1991 (20).

Other comments

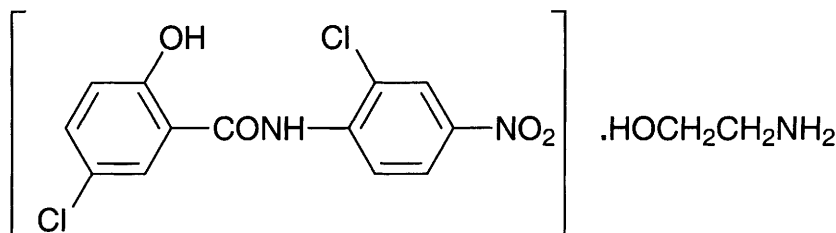
The *cis* form is reported to possess anti-oestrogenic activity while the *trans* form is oestrogenic. It thus has slight oestrogenic and anti-oestrogenic effects, depending on species and on other factors, such as treatment schedule (21).

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c362 clonitralid



$C_{15}H_{15}Cl_2N_3O_5$

Mol. Wt. 388.21

CAS Registry No. 1420-04-8

Synonyms 2',5-dichloro-4'-nitrosalicylanilide, ethanolamine salt; 5,2-dichloro-4-nitrosalicylic anilide, 2-aminoethanol salt; niclosamide, 2-hydroxyethylamine salt

EINECS No. 215-811-7

RTECS No. VN 8575000

Uses Molluscicide. Used in human and veterinary medicine as a cestocide and trematocide.

Physical properties

M. Pt. 208°C (decomp.)

Solubility Water: 100 mg l⁻¹ at 20°C. Organic solvents: isopropanol 250 mg l⁻¹, *n*-hexane, toluene <100 mg l⁻¹

Ecotoxicity

Fish toxicity

Exposure of *Clarias lazera* for 6 months induced 14% mortality at 0.1 mg l⁻¹ and 95% mortality at 0.3 mg l⁻¹ (1). Larval lampreys and rainbow trout fry were exposed to their 9 hr LC₁₀₀ for 9 hr. In lampreys, ion-uptake cells of the respiratory lamellae of the gills showed cell rounding, enlargement of mitochondrial profiles, vacuolisation of the cytoplasm and widening of the intercellular spaces. Trout gills were unaffected by this exposure (2).

Invertebrate toxicity

Clonitralid is more effective at killing the miracidia of *Schistosoma mansoni* in waters of higher temperatures, lower pH values, lower degrees of hardness and lower levels of salt (3).

LC₅₀ (2, 4, 6 hr) *Schistosoma mansoni* cercariae 0.07, 0.04, 0.03 ppm, respectively (4).

Toxicity to other species

Bufo regularis were force fed with 0.3 mg (6 mg kg⁻¹) throughout the non-breeding season (Nov-Feb).

Lymphosarcomas were detected in 2/100 animals. This low incidence, compared to earlier findings in toads during the breeding season (data not reported), was suggested to be linked to the level of sex hormones (5).

Environmental fate

Abiotic removal

Decomposes under UV irradiation (6).

Mammalian & avian toxicity

Acute data

LD₅₀ oral redwing blackbird >96 mg kg⁻¹ (7).

LD₅₀ oral rabbit, rat 4->10 g kg⁻¹ (8).

LD₅₀ dermal rat >1400 mg (as 70% wettable powder) kg⁻¹ (9).

LC₅₀ rat (4 × 1 hr) 2.54-5.75 mg (as 70% wettable powder) l⁻¹ air (9).

LD₅₀ intraperitoneal rat 250 mg kg⁻¹ (10).

Carcinogenicity and chronic effects

Oral rat (319 day) 1250 mg kg⁻¹ caused a reduction of body weight in ♂ rats (11).

Metabolism and toxicokinetics

In rats, ~33% of the dose was absorbed from the gastro-intestinal tract and was eliminated in the urine within 24 hr, the remainder was eliminated in faeces. Major excretory product was 2,5'-dichloro-4'-aminosalicylanilide (12).

Irritancy

In rabbits, an emulsifiable concentrate (250 g l⁻¹) and a wettable powder (700 g kg⁻¹) had a strong irritating effect on the mucosal membranes of the eye and were locally corrosive to the cornea. The two formulations also elicited skin reactions in rabbits (11).

Genotoxicity

Salmonella typhimurium TA98, TA1538 with metabolic activation positive (13).

Other effects

Any other adverse effects

Symptoms of acute poisoning include disturbances in behaviour, hyponoea, convulsions and sedation (species unspecified) (4).

When ethanol and clonitralid (2000 mg kg⁻¹) were administered concurrently to ♂ mice, toxicity was enhanced (14).

Legislation

Limited under EC Directive on Drinking Water Quality 80/778/EEC. Pesticides: maximum admissible concentration 0.1 µg l⁻¹ (15).

Other comments

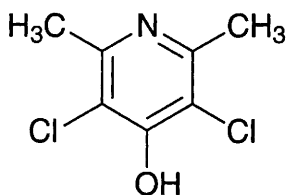
Clonitralid is highly toxic to freshwater snails *Lymnaea auricularia* and their eggs, as well as to non-target species, such as freshwater fish *Esomus danricus*, freshwater bug *Plea pelopea* a predator of mosquito larvae *Sphaerodema rusticum* and a biological control agent of snails and dragon fly nymph, *Pantala* sp. (16).

Laboratory trials of a controlled release clonitralid formulation found it to be 100% lethal to the snail *Indoplanorbis exustus* in the presence of zebra fish, which showed no obvious intoxication (17).

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C363 clopidol



C₇H₇Cl₂NO

Mol. Wt. 192.04

CAS Registry No. 2971-90-6

Synonyms 3,5-dichloro-2,6-dimethyl-4-pyridinol; meticlorpindol; methylchloropindol; Clopidol; Coyden 25; Coyden; Lerbek

EINECS No. 221-008-2

RTECS No. UU 7711500

Uses Therapeutic drug for veterinary purposes, used as a coccidiostat.

Physical properties

M. Pt. >320°C

Solubility Water: practically insoluble

Occupational exposure

FR-VME 10 mg m⁻³

US-TWA 10 mg m⁻³

Ecotoxicity

Invertebrate toxicity

Toxoplasma gondii grown in human fibroblast cultures showed 50% inhibition when exposed to 1 µg clopidol ml⁻¹ (1).

Mammalian & avian toxicity

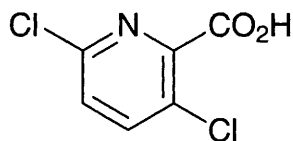
Acute data

LD₅₀ oral rat 1800 mg kg⁻¹ (2).

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c364 clopyralid



C₆H₃Cl₂NO₂

Mol. Wt. 192.00

CAS Registry No. 1702-17-6

Synonyms 3,6-dichloro-2-pyridinecarboxylic acid; 3,6-dichloropicolinic acid; Dow Shield; Lermol; Lontrol; Lontryx; Shield; Stinger

EINECS No. 216-935-4

RTECS No. TJ 7550700

Uses Systemic post-emergence herbicide.

Physical properties

M. Pt. 151-152°C **Specific gravity** 1.57 at 20°C **Partition coefficient** log P_{ow} -1.81 at pH 5

Volatility v.p. 9.975 × 10⁻⁶ mmHg

Solubility Water: 7.85 g l⁻¹ (distilled water, 20°C). Organic solvents: acetonitrile, *n*-hexane, methanol

Occupational exposure

Supply classification irritant

Supply classification dangerous for the environment

Risk phrases Risk of serious damage to eyes – Toxic to aquatic organisms, may cause long-term adverse effects in the aquatic environment (R41, R51/53)

Safety phrases Keep out of reach of children (if sold to general public) – In case of contact with eyes, rinse immediately with plenty of water and seek medical advice – Wear eye/face protection – Avoid release to the environment. Refer to special instructions/safety data sheet (S2, S26, S39, S61)

Ecotoxicity

Fish toxicity

LC₅₀ (96 hr) rainbow trout, bluegill sunfish 103-125 mg l⁻¹ (1,2).

Invertebrate toxicity

LD₅₀ (48 hr) oral bee and contact bee >100 µg bee⁻¹ (2).

Environmental fate

Degradation studies

Microbial degradation occurs in soil. Following an application rate of 0.25-1 mg kg⁻¹, the t_{1/2} under favourable microbiological conditions is ~49 days (3).

At 20°C and 30°C the rate of degradation was 3 × faster in clay loam soil than in clay and sandy loam soils (4). Soil with high microbial biomass degraded clopyralid faster than those with lower biomass. Higher temperatures and higher soil moistures also led to more rapid degradation. Carbon dioxide was the sole detected metabolite (4).

Field dissipation studies found that 50% of the initial concentration of clopyralid disappeared in 8-14 days, and had low mobility through the soil, in contrast to the findings of laboratory soil column leaching studies (5).

Abiotic removal

Photochemical degradation is accelerated by the presence of sodium humates (6).

Mammalian & avian toxicity

Acute data

LD₅₀ oral mallard duck >600 mg kg⁻¹ (7).

LD₅₀ oral rat 4,300-5,000 mg kg⁻¹ (2).

LD₅₀ oral bobwhite quail >4600 mg kg⁻¹ (3).

LD₅₀ dermal rabbit >2000 mg kg⁻¹ (8).

LD₅₀ intraperitoneal rat 900 mg kg⁻¹ (8).

Sub-acute and sub-chronic data

Oral ♀ rabbit (13 day) 1000 mg kg⁻¹ day⁻¹ caused decreased body weight gain (9).

Carcinogenicity and chronic effects

Oral rat (2 yr) 50 mg kg⁻¹ diet no adverse effects reported (2).

Teratogenicity and reproductive effects

TD_{Lo} (6-15 days of gestation) oral rat 150 mg kg⁻¹ specific developmental abnormalities (musculo-skeletal system) (9).

Mouse spermatozoa showed a significant increase in the incidence of anomalies in the heads after treatment with clopyralid (10).

Metabolism and toxicokinetics

In rats, following oral administration, there is rapid and almost quantitative elimination in the urine (11).

Irritancy

In man, eye contact may cause severe irritation, corneal damage, permanent impairment of vision and possibly blindness (11).

Other effects

Any other adverse effects

Inhalation may cause respiratory tract irritation. Ingestion of excessive amounts has been reported to cause lethargy (species unspecified) (11).

Legislation

Limited under EC Directive on drinking Water Quality 80/778/EEC. Pesticides: maximum admissible concentration 0.1 µg l⁻¹ (12).

Other comments

Two submersed aquatic macrophytes, *Potamogeton pectinatus* L. and *Myriophyllum sibiricum* Komarov were grown in the presence of 0.01 or 0.1 mg clopyralid l⁻¹. Weight gain (growth) was not inhibited in either species, but 0.01 mg l⁻¹ stimulated growth and flowering by *M. sibiricum* and both concentrations stimulated tuber production by *P. Pectinatus* (13).

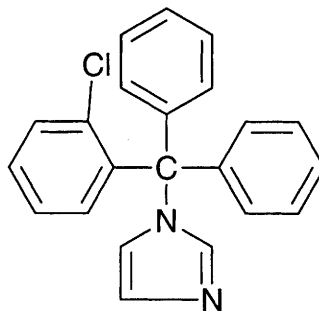
Residues have been detected in water, sediments and soil.

Metabolic pathways reviewed (14).

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c365 clotrimazole



$C_{22}H_{17}ClN_2$

Mol. Wt. 344.84

CAS Registry No. 23593-75-1

Synonyms 1-(*o*-chloro- α,α -diphenylbenzyl)imidazole; 1-[(2-chlorophenyl)diphenylmethyl]-1*H*-imidazole; (chlorotrityl)imidazole; Lotrimin; Mycelex

EINECS No. 245-764-8

RTECS No. NI 4377000

Uses Antifungal treatment.

Physical properties

M. Pt. 147-149°C

Solubility Water: miscible. Organic solvents: acetone, benzene, chloroform, ethyl acetate, methanol, toluene

Ecotoxicity

Fish toxicity

Clotrimazole non-competitively inhibits *in vivo* and *in vitro* gizzard shad hepatic microsomal ethoxyresorufin *O*-deethylase activity (1).

Rainbow trout ovarian microsomal aromatase showed 50% inhibition when exposed to 5×10^{-7} M clotrimazole (2).

Mammalian & avian toxicity

Acute data

LD₅₀ oral rat, mouse 708, 923 mg kg⁻¹, respectively (3).

LD₅₀ intraperitoneal rat, mouse 347, 445 mg kg⁻¹, respectively (4).

Teratogenicity and reproductive effects

TD_{Lo} (7-12 day pregnant) subcutaneous mouse 600 mg kg⁻¹ specific developmental abnormalities (4).

Metabolism and toxicokinetics

In rats, 90% clotrimazole absorbed following oral administration. It appeared in most tissues, including skin, within 4 hr. After 25 hr, highest levels were in adipose tissue, and adrenals, liver and skin. Urinary excretion was minor. Within 48 hr, 90% of the dose was recovered in faeces, primarily from biliary excretion. Only metabolites of clotrimazole were found in urine and bile (5).

Absorbed from the gastro-intestinal tract. Metabolised in the liver to inactive compound and then excreted in the faeces and urine. When applied topically it penetrates the epidermis but with little systemic absorption. In women slight absorption has been reported following administration of vaginal tablets (6).

Irritancy

A formulation containing 1% clotrimazole and 0.05% betamethesone applied to intact rabbit skin for 21-25 days. Non-irritant, erythema produced was equivalent to that produced by the vehicle cream (7).

TD_{Lo} (7 day skin) intravaginal woman 28 mg kg⁻¹ primary irritation (8).

Results from patch test in human volunteers indicated that tinctures containing 1% clotrimazole caused no drug-related irritant response (9).

Sensitisation

Contact allergic dermatitis has been reported in patients (6).

Other effects

Other adverse effects (human)

Adverse effects reported following oral administration include gastro-intestinal disturbances, urinary symptoms, elevation of liver enzymes and mental depression (6).

Any other adverse effects

Reported to induce hepatic microsomal cytochrome P450 following administration by injection of 69 mg kg⁻¹ to rats (10).

Other comments

Reported to inhibit human adrenal steroidogenic enzymes *in vitro* (11).

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Synonyms coal tar pitch; coal tar extract; coking tar; Fototar; Special Pitch 4

EINECS No. 232-361-7

RTECS No. GF 8600000

Uses Aluminium smelting. Surface coatings. Roofing. Road surfacing. Refractory bricks. Binding agent in smokeless fuels. Antipruritic, keratoplastic and weak antiseptic.

Physical properties

M. Pt. 73-103°C **B. Pt.** 205-450°C **Specific gravity** 1.18-1.23 at 20°C

Solubility Organic solvents: acetone, benzene, carbon disulfide, chloroform, diethyl ether, ethanol, nitrobenzene

Occupational exposure

UN No. 1136 (distillates) **HAZCHEM Code** 3WE **Conveyance classification** flammable liquid

Mammalian & avian toxicity

Acute data

TD_{Lo} oral mouse 12 g kg⁻¹ (1).

TD_{Lo} dermal mouse 36 g kg⁻¹ (2).

Carcinogenicity and chronic effects

Sufficient evidence for carcinogenicity to humans and animals, IARC classification group 1 (3).

Kidney, skin, bladder and lung cancer developed among coke oven and aluminium potroom workers (4,5-8).

Dermal application to mice produced skin tumours in several studies (4).

Mice were injected twice wkly for 3 wk by intramuscular injection of a solution of coal tar fume condensate in olive oil. After 2 yr, 50/100 mice developed sarcomas at the site of injection (6).

Irritancy

1.7 mg of coal tarpitch applied to skin produced epidermal hyperplasia, accompanied by inflammation and ulceration in mice (9).

15 µg applied to human skin intermittently for 3 days produced mild irritation (10).

10 µl instilled into rabbit eye produced phototoxic keratoconjunctivitis (11).

Cutaneous photosensitivity has been reported in humans (4).

Genotoxicity

Salmonella typhimurium TA98, TA100, TA1537 without metabolic activation negative; with metabolic activation positive (12).

In cultured rodent cells with and without metabolic activation induced sister chromatid exchanges and mutation (13).

Enhanced viral transformation in Syrian hamster embryo cells *in vitro*, but did not cause DNA strand breaks (14).

Other effects

Other adverse effects (human)

Studies based on death certificates corroborated case report evidence of carcinogenicity in humans (4).

Long-term exposure of roofing workers was associated with increased death rate due to non-malignant respiratory diseases (15).

Chronic dermatosis occurred in long-term employees of a coal tar distillery (16).

Any other adverse effects

Between 1936 and 1939, four separate outbreaks of an uncommon disease of young pigs characterised by gross liver lesions were reported in the USA. Subsequent investigation found pigs may be susceptible to the toxic compounds in coal-tar pitch and that ingestion of these materials from hog pastures may have caused the degenerative changes (17).

Legislation

Limited under EC Drinking Water Directive 80/778/EEC. Polycyclic aromatic hydrocarbons: maximum admissible concentration $0.2 \mu\text{g l}^{-1}$ (18).

Covered in the UK by the Control of Carcinogenic Substances, Control of Substances Hazardous to Health Regulations 1988 (19).

Other comments

By-product of coke production. Typically constitutes 15-20% of coking coal. Occurs in atmosphere near coking plants and working areas where the substance is used. Found in water supplies after contact with coated fittings (4).

Contains a large quantity of lower molecular weight, polycyclic aromatic hydrocarbons, including naphthalene, fluorene, anthracene, acridine, carbazole, chrysene, pyrene, phenanthrene which sublime into the air, and benzo-3,4-pyrene which is less volatile (20).

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C367 coal tar volatiles (benzene-soluble)

CAS Registry No. 65996-93-2

Synonyms coal tar pitch volatiles; pitch, coal tar

EINECS No. 266-028-2

RTECS No. GF 8655000

Uses Base for coatings and paints and as a binder for carbon electrodes. Main source of aromatic compounds used as intermediates in the synthesis of dyestuffs, drugs, antiseptics and solvents.

Physical properties

Solubility Organic solvents: benzene, nitrobenzene

Occupational exposure

FR-VME 0.2 mg m⁻³

US-TWA 0.2 mg m⁻³

Mammalian & avian toxicity

Carcinogenicity and chronic effects

Intratracheal rat (10 wk) cumulative doses of 6.5, 136.5 and 200 mg, respectively, to three groups of ten animals. Lesions induced included hyperplastic, metaplastic and dysplastic changes. Lung cancers occurred in 4/32 (medium dose) and 10/40 (high dose) animals. Histological cancer types identified were squamous cell carcinoma, adenocarcinoma and combined squamous/adenocarcinomas. No tumours were found in control animals (1).

Other effects

Other adverse effects (human)

Produced localised increase in pigmentation of skin secondary to phototoxic responses (2).

A minimal time of exposure of 1-5 yr is required to develop occupational cancer. Similarly occupational cancers often develop many years after exposure has ceased (2).

High respiratory related mortality among coke oven workers in Great Britain has been reported (3).

Kidney as well as lung cancer were relatively more prevalent among American coke oven workers exposed 5 yr or more (4).

Deaths from cancer of the lungs and pleura of retired gas workers is \approx twice the expected rate (5).

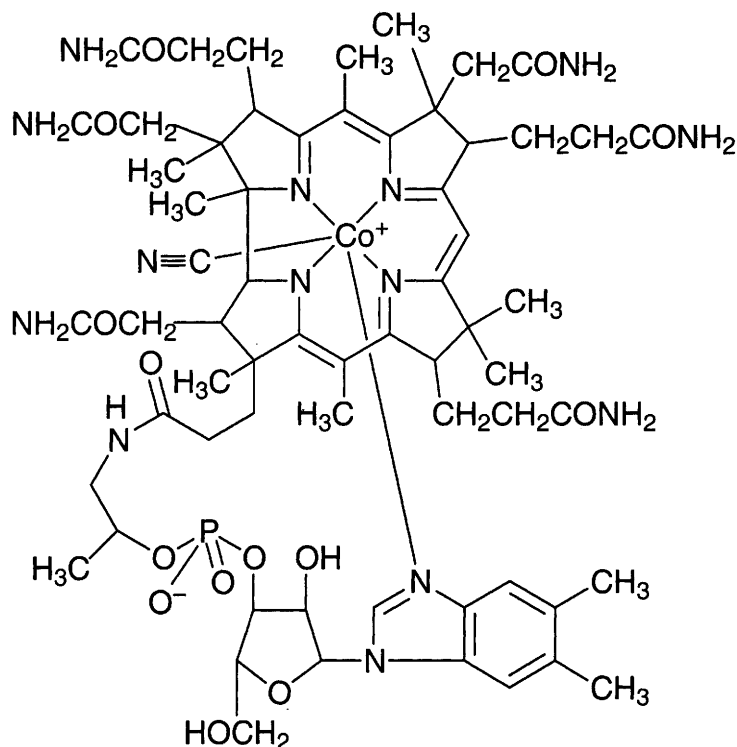
Other comments

Coal tar pitch volatiles are the fused polycyclic hydrocarbons that volatilise from the distillation residues of coal, petroleum, wood. Cancer epidemiology in coal tar pitch volatile-associated industries reviewed (6).

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C368 cobalamin


$$\text{C}_{63}\text{H}_{88}\text{CoN}_{14}\text{O}_{14}\text{P}$$

Mol. Wt. 1355.38

CAS Registry No. 68-19-9

Synonyms vitamin B₁₂; cyanocobalamin; cymolamin; dimethylbenzimidazolylcobamide; 5,6-dimethylbenzimidazolylcobamide cyanide; docabim; erythrotin; Factor II (vitamin); *Lactobacillus lactis* dorner factor; Berubigen; Betalin 12 Crystalline; Biopar Forte; Co bastab; Cyomin; Redisol; Vibalt

EINECS No. 200-680-0

RTECS No. GG 3750000

Uses Haemopoietic vitamin. Nutritional factor.

Occurrence In animal tissues. Found in soil, water, activated sewage sludge, manure and sediments (1).

Physical properties

M. Pt. > 300°C

Solubility Water: 1.2%. Organic solvents: ethanol

Environmental fate

Abiotic removal

Large lipophilic molecules, including vitamin B₁₂ were selectively adsorbed by microencapsulated activated carbon prepared by coating charcoal granules with poly(vinylidene fluoride) or vinylidene chloride/vinyl chloride copolymer (2).

Mammalian & avian toxicity

Acute data

LD_{Lo} oral mouse >5000 mg kg⁻¹ (3).

LD_{Lo} subcutaneous mouse 3 mg kg⁻¹ (4).

LD_{Lo} intraperitoneal mouse 1.4 g kg⁻¹ (5).

Teratogenicity and reproductive effects

Oral ♀ rats 50 µg B₁₂ kg⁻¹ or higher levels in feed before mating, during pregnancy and after delivery. Higher levels increased birth weight, body protein, liver protein, and resistance to infection and diminished total lipids in the offspring. Marginal maternal nutrient supply has a long-term adverse effect on offspring (6).

Metabolism and toxicokinetics

In humans gastro-intestinal absorption occurs principally in the ileum (7).

In guinea pig ileum vitamin B₁₂ and conjugated bile salts are absorbed in the villus and in the rat in the crypt cells (8).

In humans, binds to intrinsic factor and then absorbed from the gastro-intestinal tract. Vitamin B₁₂ is extensively bound to specific plasma proteins, called transcobalamins. It is stored in the liver and excreted in the bile, and undergoes extensive enterohepatic recycling. Urinary excretion accounts for only a small proportion of reduction of vitamin B₁₂. It diffuses into the human placenta and is present in breast milk (9).

Sensitisation

Allergic hypersensitivity has been reported following administration to patients (9).

Genotoxicity

Salmonella typhimurium TA98, TA100, TA1535, TA1537, TA1538 with and without metabolic activation negative (10).

Other comments

Adult requirement ≈2 µg day⁻¹ (9).

Deficiency may occur in strict vegetarians, leading to megaloblastic anaemias and neurological damage.

Pernicious anaemia occurs in patients in the absence of intrinsic factor (9).

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Co

Co

Mol. Wt. 58.93

CAS Registry No. 7440-48-4

Synonyms

EINECS No. 231-158-0

RTECS No. GF 8750000

Uses For manufacturing cobalt salts. Alloying element in superalloys, magnetic and hard-metal alloys. In nuclear technology. Also used in cobalt bomb. Therapeutically used as a trace mineral. In magnetic steel, stainless steel and alloys used in jet turbines and gas turbine generators. In electroplating. Cobalt salts and oxides are used as pigments, source of blue colour in ceramics and glass. Catalysts and drying agents. As a radiation source ^{60}Co is an antineoplastic.

Occurrence Widely distributed in nature, abundance in earth's crust 0.001-0.002%, oxide, sulfide, arsenide and sulfarsenide ores, usually in association with copper and nickel ores, and to a lesser extent of silver, zinc, iron, lead and gold ores. Trace amounts occur in dust, soil, sediments, water, plants and in animal tissues and fluids. A component of vitamin B₁₂.

Physical properties

M. Pt. 1495°C B. Pt. 2870°C Specific gravity 8.92 at 20°C

Solubility Water: insoluble

Occupational exposure

JP-OEL 0.05 mg m⁻³SE-LEVL 0.05 mg m⁻³UK-LTEL MEL 0.1 mg m⁻³US-TWA 0.02 mg m⁻³

Supply classification harmful

Risk phrases May cause sensitisation by skin contact (R43)

Safety phrases Keep out of reach of children (if sold to general public) – Do not breathe dust – Avoid contact with the skin – Wear suitable gloves (S2, S22, S24, S37)

Ecotoxicity

Fish toxicity

LC₅₀ (96 hr) fathead minnow 92 mg (cobaltous bromide) l⁻¹ (1).Rainbow trout tolerated 7-day exposure to 30 mg (Co) l⁻¹. Lethal limit 35 mg (Co) l⁻¹ (2).

Cichlids exposed to sub-lethal concentrations of cobalt for 5, 10 and 15 days showed an adaptive increase in oxygen uptake during the shortest period of exposure (5 days). Erythrocyte production appeared to be increased, while haemoglobin synthesis was inhibited (3).

Invertebrate toxicity

Cobalt has little effect on the apparent water permeability of the shore crab, after 1-hr exposure to 1 mg l⁻¹ dissolved cobalt (4).

EC₅₀ (48 hr) *Daphnia magna* 1.49 mg l⁻¹ (5).

Cobalt is toxic to decomposer basidiomycetes cultures (6).

Chlorella pyrenoidosa grown in the presence of 5×10^{-6} - 10^{-5} M cobalt (as cobalt sulfate hydrate) showed 150-160% increase in fresh weight, 50-60% increase in dry weight, 45-65% increase in chlorophylls a and b content, 55-65% increase in total carotenoids, 19-20% increase in water-soluble proteins and 55-60% increase in monosaccharides, compared to the control culture (7).

Bioaccumulation

The caridean decapod *Palaemon elegans*, amphipod *Echinogammarus pirloti* and the barnacle *Elminius modestus* showed linear accumulation of cobalt from solution over a wide range of dissolved radioactively-labelled cobalt concentration. No significant excretion of accumulated cobalt observed (8).

Tridacna sp. and *Spondylius squamosus* had cobalt tissue levels of 237-1700 $\mu\text{g kg}^{-1}$ and 596-1438 $\mu\text{g kg}^{-1}$, respectively, indicating concentration of the metal (9).

The levels of cobalt metal in the spinal muscular tissue of chubs was investigated. Fresh water concentrations were 0 to 0.084 mg (Co) l^{-1} while tissue concentrations were 0 to 1.810 mg kg^{-1} cobalt, indicating fish muscle bioconcentrates cobalt from water (10).

Environmental fate

Adsorption and retention

Cobalt content of soils ranges from 1-40 mg kg^{-1} (average 8 mg kg^{-1}). Cobalt tends to be deficient in areas where there is granite, sand or limestone and in volcanic and peaty soils. Good drainage may reduce cobalt content. Solubilities of cobalt compounds are pH-dependent. Cobalt is more mobile in acid soils than in alkaline soils (11-13).

Mammalian & avian toxicity

Acute data

LD₅₀ oral rat 6170 mg kg^{-1} (14).

LD_{Lo} intratracheal rat 25 mg kg^{-1} (15).

LD_{Lo} intravenous rat 100 mg kg^{-1} (16).

Sub-acute and sub-chronic data

Intratracheal rats single dose 0.06, 0.3 or 0.6 mg cobalt metal dust per 100 g body weight or monthly doses of 0.06 mg per 100 g body weight for 4 months, had very little observable delayed effect on the lungs (17).

Carcinogenicity and chronic effects

Inadequate evidence for carcinogenicity of cobalt and cobalt compounds in humans, sufficient evidence in animals, IARC classification group 2B (18).

A cohort of 1358 persons who received total hip replacement in New Zealand were studied for cancer incidence between 1966 and 1973. Total cancer incident was similar to that expected for general population but risk increased substantially after 10 yr. A significant overall increase in incidence of tumours of the lymphatic and haematopoietic system reported (19).

Single injection intramuscular rat (2 yr) 28 mg cobalt metal powder (average survival times ♂ 71 wk ♀ 61 wk). Treated animals developed injection site rhabdomyosarcomas (20).

In a supplementary study, intramuscular rat (20 wk) single injection 28 mg cobalt metal powder induced leukocyte infiltration, muscle fibre necrosis and regeneration and a tumour nodule in one animal (21).

Teratogenicity and reproductive effects

In a teratological study, rats were administered 0, 25, 50 and 100 mg kg^{-1} cobalt (as the chloride) by gavage on days 6-15 of gestation. Maternal effects included significant reductions in weight gain and food consumption particularly in the high-dose group. Haematocrit, haemoglobin concentrations, mean corpuscular haemoglobin and reticulocytes were significantly increased in the high-dose group (22).

Chick eggs were injected with 0.1 ml (Co²⁺ salt) egg⁻¹. After 14 days gross malformations detected included reduced body size, micromelia, twisted neck, haemorrhage, everted viscera and microphthalmia (23).

Metabolism and toxicokinetics

About 80% of ingested cobalt is excreted in the urine. Of the remaining, about 15% is excreted in the faeces by an enterohepatic route, while the milk and sweat are other secondary routes of excretion (species unspecified). Rats and cattle, 80% eliminated in faeces (24).

In human autopsy studies, the liver has been shown to contain the highest concentration of cobalt, individual values range from 6-151 $\mu\text{g kg}^{-1}$ (25).

A study using radiolabelled cobalt found that the ratio of inorganic/organic cobalt in the urine of hard metal workers was increased compared to controls (2.3 and 1.01, respectively), showing an increase in the inorganic fraction in the urine of workers (26).

Irritancy

In humans, irritation of mucous membranes may occur at 5-10 $\mu\text{g m}^{-3}$ (27).

Sensitisation

Allergy to cobalt was demonstrated in 75/289 exposed rubber industry workers. Dermatoses were observed in 105/289 cases and dermatitis of hands and forearms were diagnosed in 35 patients (28).

Occupational asthma from cobalt sensitivity was reported in workers exposed to hard metal dust (29).

A study of 2166 consecutive patients patch tested with the standard series of the International Contact Dermatitis Research Group over 6 months, cobalt was 1/8 allergens most often found positive (30).

Genotoxicity

Salmonella typhimurium TA98, TA102, TA1535, TA1537 with metabolic activation negative; TA98, TA1537 without metabolic activation positive (31).

Induced DNA strand breaks in human diploid fibroblasts and Chinese hamster ovary cells *in vitro* (32).

In vivo rats 0.005 mg kg^{-1} cobalt metal in drinking water caused no mutagenic effects (33).

Other effects

Other adverse effects (human)

There were no adverse effects to the erythropoietic system, heart, lung or pancreas among workers exposed to airborne cobalt at 49-1046 $\mu\text{g m}^{-3}$. Blood and urinary levels correlated with air cobalt levels (34).

In 1963 and 1964 some breweries in Canada, US and Belgium added cobalt to beer, which caused an epidemic of acute forms of cardiomyopathy, 'Quebec beer drinkers disease' in Canada. Similar disorders were observed in other countries, although the total number of cases has not been established. Myocardial disorders in cobalt production workers had been observed by industrial physicians (35).

Clinical, radiological and histological findings revealed lung diseases identical to cobalt allergy among diamond polishers in the Antwerp area of Belgium (36).

Epidemiological studies suggest that the incidence of goitre is higher in regions containing increased levels of cobalt in soil and water (37).

A study of industrial exposure to cobalt in 61 female plate painters exposed to cobalt blue dyes found that those exposed to semi-soluble cobalt (in the form of Co-Zn silicate) had a significantly increased urinary cobalt content, and exhibited changes in thyroid hormone levels. Workers exposed to insoluble cobalt (as aluminate) did not have altered thyroid hormone levels, nor increased urinary cobalt content, compared with 48 controls (38).

The cobalt content in tissues surrounding hip arthroplasties and in distant muscle samples has been investigated in ten patients with loosening of prostheses from the implanted shaft and from the *musculus vastus lateralis*. Implants were replaced on average after 12.5 yr. Concentrations of cobalt in the surrounding tissues ranged from 367-6510 $\mu\text{g kg}^{-1}$ and in tissue surrounding the cup 98-16,293 $\mu\text{g kg}^{-1}$. Muscle tissue contained 24-151 $\mu\text{g kg}^{-1}$ cobalt (39).

The major occupational problems relating to cobalt exposure are pulmonary effects. Two types of lung lesions may develop, interstitial fibrosis and occupational asthma (40).

Bronchoalveolar lavage and lymphocyte subpopulation analyses were performed on six asymptomatic workers exposed to cobalt-containing dust. There was marked evidence of tracheobronchitis in all cases, mild increase in total cells recovered at bronchoalveolar lavage and significant increase in T-lymphocytes (41).

There is an increased risk of pneumoconiosis when exposure to cobalt-containing dust exceeds 100 $\mu\text{g m}^{-3}$ (27). Of 236 σ workers exposed to a cobalt inhalation risk, three showed interstitial lung disease, and 20 men had a reduced carbon monoxide transfer coefficient. There were no cases of a significantly altered ventilatory function (42).

A follow-up study of nine subjects with occupational asthma due to cobalt hypersensitivity found that early removal from exposure after onset of asthma is important for recovery or improvement in symptoms and lung function, and that specific and non-specific bronchial hyper-responsiveness may persist, even in asymptomatic individuals no longer exposed to cobalt (43).

In comet assays and cytokinesis-blocked micronucleus tests conducted *in vitro* on isolated human leucocytes it has been observed that the clastogenicity of cobalt-containing dust is significantly enhanced when the cobalt metal is mixed with tungsten carbide dust, although the latter on its own is unable to induce dose-dependent DNA breakage. The authors suggest that when the tungsten carbide is mixed with cobalt their physicochemical characteristics may act as one of the important parameters responsible for the increased incidence of lung cancers observed in the population of hard-metal workers (44).

A study of 82 workers in a cobalt refinery exposed to cobalt dust found that high airborne concentrations of cobalt alone are not sufficient to cause pulmonary fibrosis, although cobalt interaction with other airborne pollutants may result in pathogenesis (45).

A study of 874 women occupationally exposed to cobalt-aluminium spinel found a slightly increased risk of lung cancer compared to controls (46).

Any other adverse effects

Inhalation of the dust may cause pulmonary symptoms. Ingestion of soluble salts produces nausea and vomiting by local irritation (species unspecified) (47).

At a concentration of 5.9 mg l⁻¹ an adverse effect was exerted on the viability of isolated rat Leydig cells of the testes (48).

Cobalt was demonstrated to inhibit the activities of acid phosphatase, glucose-6-phosphatase and lipase in rat liver. Alkaline phosphatase and acid phosphatase were not affected (49).

Legislation

Maximum permissible concentration in domestic water in the former USSR 1 mg l⁻¹ (50).

Included in Schedule 4 (Release into Air: Prescribed Substances) Statutory Instrument No. 472, 1991 (51).

Other comments

Significantly increased levels of cobalt and other metals have been found in malignant and benign brain tumours in patients in Kuwait (52).

Occupational and environmental exposure, metabolism and toxicity of cobalt reviewed (53).

Exposure to cobalt and cancer risk reviewed (54).

Cobalt myocardiopathy reviewed (55).

Toxicology, occupational health hazards and genotoxicity hazards reviewed (56-59).

Mechanistic aspects of the genetic toxicology of cobalt reviewed (60).

An insufficient dietary supply to rats (from 2.5 mg) induced disturbances of iodine, carbohydrate and protein metabolism (61).

Biochemical and nutritional aspects of cobalt and its toxicity in humans and animals reviewed (62).

Cobalt and its compounds have been extensively reviewed (16,63).

≥75 mg kg⁻¹ cobalt have been found in the soil around factories using cobalt powders, higher concentrations may occur in waste metal dumps (12).

Untamined samples of fresh water generally contain low concentrations of cobalt, ranging from 0.1-10 µg l⁻¹ (11).

Concentrations of 0.1-5 µg l⁻¹ have been found in drinking water (64).

Aquatic data reviewed (65).

The main route of absorption during occupational exposure to cobalt is via the respiratory tract, due to inhalation of dusts, fumes or mists containing cobalt or inhalation of gaseous cobalt carbonyl. Exposure occurs during the production of cobalt powder; in hard-metal production, processing and use; in the use of cobalt-containing pigments and driers; and in the regeneration of spent catalysts (18).

Uptake of cobalt by plants is species dependent (66).

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c370 cobalt(II) bromide



Br_2Co

Mol. Wt. 218.74

CAS Registry No. 7789-43-7

Synonyms cobalt(II) bromide; cobalt dibromide; cobaltous bromide

EINECS No. 232-166-7

RTECS No. GF 9595000

Uses Hygrometers. Catalyst for organic reactions.

Physical properties

M. Pt. 678°C (under HBr and N₂) Specific gravity 4.909 at 25°C with respect to water at 4°C

Solubility Water: 112% by weight at 20°C. Organic solvents: acetone, ethanol, methanol, methyl acetate

Occupational exposure

JP-OEL 0.05 mg m⁻³ (as Co)

SE-LEVL 0.05 mg m⁻³ (as Co)

UK-LTEL MEL 0.1 mg m⁻³ (as Co)

US-TWA 0.02 mg m⁻³ (as Co)

Ecotoxicity

Fish toxicity

LC₅₀ (96 hr) fathead minnow 92 mg cobalt (II) bromide l⁻¹ (1).

Bioaccumulation

Food chain contamination potential positive. Microorganisms tend to concentrate cobalt from the surrounding media (2).

Mammalian & avian toxicity

Acute data

LD₅₀ oral rat 406 mg kg⁻¹ (3).

Other effects

Other adverse effects (human)

Severe cardiac failure and some deaths in humans from consumption of large amounts of beer containing the compound used at 1.2-1.5 mg kg⁻¹ to promote foam stabilisation in the beer (4).

A study of people who suffered cobaltous bromide poisoning, showed the hearts of these patients had about ten times higher cobalt concentrations than controls; 0.5 and 0.04 mg kg⁻¹ wet weight, respectively (5). Ingestion caused depression, emaciation, gastroenteric distress, constipation and skin rash. Severe cases may result in psychoses and mental deterioration (2).

Legislation

Included in Schedule 4 (Release into Air: Prescribed Substances) Statutory Instrument No. 472, 1991 (6).

Other comments

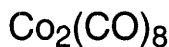
Cobalt and its compounds have been extensively reviewed (7,8).

Hygroscopic; forms hexahydrate in moist air. The toxicity of heavy metals to aquatic biota is dependent on the chemical form of the metal, however it is thought improbable that the anionic moiety of simple cobalt salts (those with common mineral acids) have much influence upon the aquatic toxicology.

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c371 cobalt carbonyl



C₈Co₂O₈

Mol. Wt. 341.95

CAS Registry No. 10210-68-1

Synonyms di-μ-carbonylhexacarbonyldicobalt; dicobalt octacarbonyl; cobalt tetracarbonyl dimer; dicobalt carbonyl; octacarbonyl dicobalt

EINECS No. 233-514-0

RTECS No. GG 0300000

Uses Catalyst. Anti-knock agent in petrol.

Physical properties

M. Pt. 51°C (decomp.) **B. Pt.** decomp. **Specific gravity** 1.87 at 20°C **Volatility** v.p. 0.07 mmHg at 15°C
Solubility Organic solvents: carbon disulfide, diethyl ether, ethanol, naphtha

Occupational exposure

FR-VME 0.1 mg m⁻³ (as Co)

JP-OEL 0.05 mg m⁻³ (as Co)

UK-LTEL MEL 0.1 mg m⁻³ (as Co)

US-TWA 0.1 mg m⁻³ (as Co)

Mammalian & avian toxicity

Acute data

LD₅₀ oral rat 754 mg kg⁻¹ (1).

LD₅₀ oral mouse 378 mg kg⁻¹ (1).

LC₅₀ (2 hr) inhalation rat 27 mg m⁻³ (2).

Sub-acute and sub-chronic data

Inhalation (duration unspecified) 14 mg m⁻³ (as cobalt) by rats, decreased succinate dehydrogenase, lactate dehydrogenase, alkaline phosphatase and cytochrome oxidase activities in the liver, and most of these activities in the kidneys and lungs. Liver enzyme levels returned to almost normal within two days (3).

Other effects

Other adverse effects (human)

Acute poisoning of factory workers caused bronchospasm, respiratory disturbances, focal infiltrations in the lung, dysproteinemia, neutrophil leukocytosis and haemoglobinaemia (4).

Legislation

Included in Schedule 4/6 (Release into Air/Land: Prescribed Substances) Statutory Instrument No. 472, 1991 (5).

Other comments

The toxicity of heavy metals to aquatic biota is dependent on the chemical form of the metal. The preparation, properties and chemistry of cobalt carbonyls reviewed (6,7).

Cobalt and its compounds have been extensively reviewed (8,9).

Toxicity is related to the ready release of carbon monoxide on decomposition.

References

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c372 cobalt(II) chloride



CoCl₂

Mol. Wt. 129.84

CAS Registry No. 7646-79-9

Synonyms cobalt dichloride; cobalt chloride; cobaltous chloride

EINECS No. 231-589-4

RTECS No. GF 980000

Uses Used in invisible ink. Humidity and water indicator. Temperature indicator in grinding. In glass and porcelain painting. Electroplating. Fertiliser and feed additive. Foam stabiliser in beer. Preparation of catalysts. Absorbent for military poison gas and ammonia. Used in the production of vitamin B₁₂.

Physical properties

M. Pt. 724°C (in HCl gas); 400°C (decomp. on long heating in air) **B. Pt.** 1049°C **Specific gravity** 3.367 at 25°C with respect to water at 4°C

Solubility Water: 450 g l⁻¹ at 7°C. Organic solvents: acetone, ethanol, glycerol, methanol, pyridine

Occupational exposure

JP-OEL 0.05 mg m⁻³ (as Co)

SE-LEVL 0.05 mg m⁻³ (as Co)

UK-LTEL MEL 0.1 mg m⁻³ (as Co)

US-TWA 0.02 mg m⁻³ (as Co)

Ecotoxicity

Fish toxicity

LC₅₀ (96 hr) carp embryo 96 mg l⁻¹. Static bioassay in freshwater, pH 7.5, temperature 16°C, water hardness 360 mg l⁻¹ CaCO₃ (1).

The hatching success of common carp was impaired by the addition of cobalt dichloride, impairment was concentration-related. An increased proportion of deformed larvae which had little survival potential was observed. The chief deformity in the hatchlings as a result of exposure was a curvature of the caudal region and poor development of the body beyond the yolk sac (1).

Adult giant gourami exposed to 232.8 mg l⁻¹ for 24, 72 and 96 hr in a freshwater static bioassay. pH was 7.5, temperature 23.6°C, water oxygen content 7.6 mg l⁻¹ and water hardness 164 mg l⁻¹ CaCO₃. Fish had increased blood pyruvate content of 22, 75 and 47%, respectively (2).

LC₅₀ (96 hr) fathead minnow 48 mg l⁻¹ lake water static bioassay, pH 6.5-8.5, temperature 20°C, water hardness 130 mg l⁻¹ CaCO₃ (3).

LC₅₀ (48 hr) *Olyzias latipes* 620 ppm. Near death, balance was lost and lateral turning observed. Visceral organs showed no changes while the skin, oral cavity, pharynx and gill were abnormal after exposure (4).

Invertebrate toxicity

LC₅₀ (96 hr) juvenile *Daphnia magna* 3.2 mg l⁻¹ lakewater static bioassay, pH 6.5-8.5, temperature 20°C, water hardness 130 mg l⁻¹ CaCO₃ (3).

LC₅₀ (96 hr) juvenile *Helisoma trivolvis* >100 mg l⁻¹ lakewater static bioassay, pH 6.5-8.5, temperature 20°C, water hardness 130 mg l⁻¹ CaCO₃ (3).

LC₅₀ (96 hr) juvenile *Gammarus fasciatus*, *Lumbriculus variegatus* >100 mg l⁻¹ lakewater static bioassay, pH 6.5-8.5, temperature 20°C, water hardness 130 mg l⁻¹ CaCO₃ (3).

EC₅₀ (4-7 day) *Spirulina platensis* 23.8-8.1 mg l⁻¹ (5).

EC₅₀ (24, 48 hr) *Daphnia magna* 2.1-1.5 mg l⁻¹ (6).

EC₅₀ (48, 96 hr) *Crangonyx pseudogracilis* 167-39 mg l⁻¹ (7).

EC₁₀₀ (7 day) *Euglena gracilis* 389.5 mg l⁻¹ static bioassay, population growth study. No growth after 15 days (8).

EC₅₀ (1-32 hr) *Zoogloea ramigera* 1-50 mg l⁻¹ static bioassay at 24°C. No growth at 50 mg l⁻¹, prolonged lag-phase dependent on initial toxicant concentration (9).

EC₅₀ (24, 48 hr) *Chironomus tentans* larva 67.9 and 56.9 mg l⁻¹, freshwater static bioassay at pH 6.3, temperature 14°C, water oxygen content 6.5 mg l⁻¹ and water hardness 25 mg l⁻¹ CaCO₃ (10).

Orientation and photokinesis of *Carcinus maenas* and *Palaemon serratus* were investigated. Within 4 days orientation was disturbed by exposure to 0.01-0.1 mg l⁻¹ and in *Palaemon serratus* by 100-500 mg l⁻¹. Photokinesis in *Carcinus maenas* was disturbed by exposure to 1 µg l⁻¹ within 2-3 days (11).

LC₅₀ (route unspecified) *Xenopus laevis* 3245 µg l⁻¹ (12).

Growth of the alga *Scenedesmus quadricauda* on sewage was inhibited by 9.7, 60.7, 93.7 and 98.1% in the presence of 1, 5, 10 and 15 mg Co l⁻¹, respectively. The metal ions affect BOD removal and nutrient absorption, and the activity of catalase, neutral phosphatase, protease and amylase was inhibited (13).

Toxicity to other species

In frog embryo teratogenesis assay using *Xenopus laevis*, embryos were incubated for 96 hr in a range of

concentrations 23.4-2330 mg l⁻¹. At 101 hr post-fertilisation embryos were examined, survival ≥95% and malformations were ≥5%. Malformations were found in >99% of embryos exposed to levels ≥7-27 mg l⁻¹ Co²⁺ (12).

Bioaccumulation

Bullia rhodostoma were exposed to an initial concentration of 0.02 mg l⁻¹ in seawater (intermittent flow), temperature 21-23°C for 3 wk. Bioconcentration 0.71 mg kg⁻¹ wet weight. Bioaccumulation factor 35 (14). The accumulation and excretion of cobalt by marine fish were examined using ⁶⁰cobalt dichloride. The biological t_{1/2} was 166 days at 15°C. The bioconcentration factor was 32 (15).

Environmental fate

Nitrification inhibition

The effect on growth and heterocyst differentiation in nitrogen-fixing cyanobacteria *Anabaena caribialis* and a unicellular green alga *Chlorella vulgaris* was examined. 0.1 ppm stimulated green alga growth, but higher concentrations 5-20 ppm did not produce any growth enhancement, although they supported reduced growth. LD₅₀ for both species was 50 ppm (16).

Adsorption and retention

The effects of pH, calcium carbonate, fly ash, autoclaving, exchangeable cations, alkaline, neutral, and saline salts on the mobility of cobalt was investigated in silt loam and clay loam soils. The mobilities of the chloride were directly proportional to its solubility products. When 5% calcium carbonate or 5% fly ash was added to the soils, mobility of heavy metals decreased. This could be due to increased adsorption of cobalt. When soils treated with calcium, hydrogen or sodium ions were used as adsorbents the mobility of the heavy metals increased in acid-treated soils but decreased in sodium-treated soils. Heavy metal mobility was higher in acid than in alkaline soils. When soils were treated with saline and neutral salts, the movement of heavy metals was greatest with the saline salts and lowest with the alkaline salts (17).

Mammalian & avian toxicity

Acute data

LD₅₀ oral rat 150-500 mg kg⁻¹ (18).

Sub-acute and sub-chronic data

Inhalation rabbit (14-16 wk) 0.4 mg m⁻³ and 2 mg m⁻³ 5 day wk⁻¹ 6 hr day⁻¹. Abnormal macrophage reaction and interstitial inflammation was present in all high-dose animals and 50% of low-dose animals (each study had 8 rabbits) (19).

Carcinogenicity and chronic effects

Possible human carcinogen, IARC classification group 2B (20).

Subcutaneous ♂ rats were administered 40 mg kg⁻¹; 5 daily injections in saline separated by a 9-day interval, and monitored for 1 yr. 8/11 surviving animals had developed subcutaneous fibrosarcomas, 4 of which were distant from injection site (21).

Teratogenicity and reproductive effects

Oral rats (98 day) 265 mg kg⁻¹ diet induced degenerative and necrotic changes in the seminiferous tubules.

Cyanosis and vascular engorgement of the testes were seen on day-35 of treatment. Necrosis, degenerative and necrotic changes changes were observed in the germinal epithelium and Sertoli cells by day-70. Loss of sperm-tail filaments and degeneration of sperm mitochondria were also observed (22).

Intraperitoneal ♂ mice 47.6 mg kg⁻¹ daily for three days caused significant decrease in fertility 2-3 wk later in an acute study. Chronic administration (7-13 wk) 100, 200 and 400 mg l⁻¹ in drinking water caused decreased fertility, sperm concentration, sperm mobility and testicular weight in a time- and dose-dependent manner (23).

Gavage ♀ rats 12, 24 and 48 mg kg⁻¹ day⁻¹ from day-14 gestation through day-21 of lactation caused a reduction in the numbers of litters and the growth and survival of offspring (24).

Gavage pregnant Sprague-Dawley rats (6-15 day gestation) 0, 25, 50 and 100 mg kg⁻¹ Co²⁺ (chloride). Maternal effects included significant reductions in weight gain and food consumption, haematocrit, haemoglobin

concentration, mean corpuscular volume, mean corpuscular haemoglobin and reticulocytes were increased significantly in high-dose animals. No treatment-related changes were recorded in the number of corpora lutea, total implants, resorptions, the number of live and dead fetuses, foetal size parameters or foetal sex distribution. Examination for gross external abnormalities, skeletal malformations or ossification variations revealed no teratogenicity or significant fetotoxicity (25).

Metabolism and toxicokinetics

Gastro-intestinal absorption of radiolabelled cobalt dichloride in rats varied between 11 and 34%, depending on the dose administered (0.01-1000 µg rat⁻¹). Relative absorption decreased with increasing dose. Rapid clearance, 63% via urine within 24 hr (26).

Examination of pregnant mice injected intravenously with radiolabelled cobalt dichloride revealed high activity in maternal liver, kidney, pancreas and cartilage and in the foetal skeleton and other tissues (27).

Sensitisation

Dermal guinea pigs exposed on day 0, 2, 7 and 9 to cobalt dichloride showed contact allergy to patch testing on day-21. Sensitised guinea pigs exposed by inhalation from day 42 for 6 hr a day for 2 wk showed a higher percentage of neutrophils and eosinophils than a non-sensitised group (28).

Genotoxicity

Inactive in the *Escherichia coli* λ prophage induction assay; and conflicting results were obtained in the *Bacillus subtilis* rec⁺/rec⁻ growth inhibition assay (20).

Saccharomyces cerevisiae induced gene conversion (20).

In vitro human lymphocytes induced aneuploidy; *in vitro* Chinese hamster V79 cells positive mutagen (20).

In vitro human lymphocytes micronucleus assay and chromosome aberrations test positive (29).

In vivo intraperitoneal Syrian hamsters induced aneuploidy in bone marrow and testes (20).

In vivo mice induced clastogenic effects in bone marrow cells (30).

Other effects

Other adverse effects (human)

A patient treated with 50 mg day⁻¹ for three months died, autopsy revealed that the myocardial concentration of cobalt was 1.65 mg kg⁻¹ wet weight (25-80 × higher than in controls) (31).

Patients were administered cobalt dichloride 3 × day⁻¹ for several wk (total dose 100 mg) for the treatment of anaemia. Adverse effects to the alimentary tract were observed and included vomiting and anorexia in some patients (32).

The major hazard in cobalt dichloride processing is exposure to the dusts of the finished products (disintegration aerosol) in concentrations from 0.05-53 mg m⁻³ depending on the stage of the technical process. Occupational exposure caused morbidity with temporary disability, a high frequency of the upper respiratory tract diseases; rhinitis, pharyngitis, laryngitis, and irritation of the eyes. ECG examinations revealed marked changes of varying severity in the myocardium among 40-58% of the exposed workers (33).

Any other adverse effects

Duration-dependent changes in the thyroid gland of ♀ mice were seen in response to exposure to cobalt dichloride for 15, 30 or 45 days. The 45-day exposure group exhibited necrotic epithelial cells, lymphocytic infiltration and inflammatory changes in the blood vessels (34).

In albino rats exposed to cobalt dichloride for various durations, histopathological changes and heavy lipofuscin deposition (histochemically identical to that observed in aged animals) were observed (35).

In vitro mouse neuroblastoma cells EC₅₀ (concentration required to cause 50% inhibition of cell proliferation) (24 hr) 200 µM cobalt dichloride. Cobalt exposure induced a marked stimulatory effect on cell enzyme activity (36).

Legislation

Included in Schedule 4 (Release into Air: Prescribed Substances) of Statutory Instrument No. 472, 1991 (37).

Limited under EC Directive on Drinking Water Quality 80/778/EEC. Chlorides: maximum admissible concentration 25 mg l⁻¹ (38).

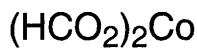
Other comments

Main commercial preparations are the hexahydrate, dihydrate and monohydrated forms.
The toxicity of heavy metals to aquatic biota is dependent on the chemical form of the metal.
Toxicology and human health effects comprehensively reviewed (20,39).
Hygroscopic. Anhydrous form turns pink on exposure to moist air.

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C373 cobalt(II) formate



$\text{C}_2\text{H}_2\text{CoO}_4$

Mol. Wt. 148.97

CAS Registry No. 544-18-3

Synonyms cobaltous formate; formic acid, cobalt(II) salt

EINECS No. 208-864-2

Uses In preparation of cobalt catalysts.

Physical properties

M. Pt. 175°C (decomp.) Specific gravity 2.13 at 22°C with respect to water at 4°C

Solubility Water: miscible

Occupational exposure

JP-OEL 0.05 mg m⁻³ (as Co)

UK-LTEL MEL 0.1 mg m⁻³ (as Co)

Ecotoxicity

Fish toxicity

LC₅₀ (96 hr) fathead minnow 32 mg cobaltous formate l⁻¹ (1).

Legislation

Included in Schedule 4 (Release into Air: Prescribed Substances) Statutory Instrument No. 472, 1991 (2).

Other comments

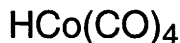
Cobalt and its compounds have been extensively reviewed (3,4).

The toxicity of heavy metals to aquatic biota is dependent on the chemical form of the metal.

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C374 cobalt hydrocarbonyl



C_4HCoO_4

Mol. Wt. 171.98

CAS Registry No. 16842-03-8

Synonyms tetracarbonylhydrocobalt;

RTECS No. GG 0900000

Uses Catalyst in organic reactions.

Physical properties

M. Pt. -33°C B. Pt. 25°C (decomp.)

Solubility Water: 0.5 g l⁻¹

Occupational exposure

FR-VME 0.1 mg m⁻³ (as Co)

JP-OEL 0.05 mg m⁻³ (as Co)

UK-LTEL MEL 0.1 mg m⁻³ (as Co)

US-TWA 0.1 mg m⁻³ (as Co)

Mammalian & avian toxicity

Acute data

LC₅₀ (30 min) inhalation rat 165 mg m⁻³ (1,2).

Legislation

Included in Schedule 4/6 (Release into Air/Land: Prescribed Substances) Statutory Instrument No. 472, 1991 (3).

Other comments

The preparation, properties and chemistry of cobalt carbonyls reviewed (4,5).

Cobalt and its compounds have been extensively reviewed (6,7).

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c375 cobalt naphthoate

CAS Registry No. 57208-09-0

Synonyms naphthalenecarboxylic acid, cobalt salt

Uses Fungicide.

Physical properties

M. Pt. 49°C Specific gravity 0.9 at 20°C

Occupational exposure

JP-OEL 0.05 mg m⁻³ (as Co)

UK-LTEL MEL 0.1 mg m⁻³ (as Co)

Ecotoxicity

Invertebrate toxicity

Toxic to *Dunaliella bioculata* at 0.01-0.7 ppm (1).

Legislation

Included in Schedule 4/6 (Release into Air/Land: Prescribed Substances) Statutory Instrument No. 472, 1991 (2).
Limited under EC Directive on Drinking Water Quality 80/778/EEC. Pesticides: maximum admissible concentration 0.1 µg l⁻¹ (3).

Other comments

The toxicity of heavy metals to aquatic biota is dependent on the chemical form of the metal.
Cobalt and its compounds have been extensively reviewed (4-6).
Experimental toxicology and human health effects reviewed (7).

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C376 cobalt(II) oxide

CoO

CoO

Mol. Wt. 74.93

CAS Registry No. 1307-96-6

Synonyms cobalt(II) oxide; monocobalt oxide; cobalt oxide; cobalt black; cobalt monooxide; cobaltous oxide; C.I. 77322; C.I. Pigment Black 13; Inco

EINECS No. 215-154-6

RTECS No. GG 2800000

Uses Pigment for ceramics. Glass colourising and decolorisation agent. Oxidation catalyst for drying oils, fast-drying paints and varnishes. Preparation of catalysts. Used in the production of semiconductors.

Physical properties

M. Pt. ~1935°C **Specific gravity** 5.7-6.7

Solubility Water: practically insoluble

Occupational exposure

JP-OEL 0.05 mg m⁻³ (as Co)

SE-LEVL 0.05 mg m⁻³ (as Co)

UK-LTEL MEL 0.1 mg m⁻³ (as Co)

US-TWA 0.02 mg m⁻³ (as Co)

Supply classification harmful

Risk phrases Harmful if swallowed – May cause sensitisation by skin contact (R22, R43)

Safety phrases Keep out of reach of children (if sold to general public) – Avoid contact with the skin – Wear suitable gloves (S2, S24, S37)

Mammalian & avian toxicity

Acute data

LD₅₀ oral rat 1700 mg kg⁻¹ (1).

LC₁₀₀ (6 hr) inhalation hamster 100 mg m⁻³ (2).

Carcinogenicity and chronic effects

Possible human carcinogen, sufficient evidence for carcinogenicity to animals, IARC classification group 2B (3).

Inhalation Syrian golden hamsters 0-10 mg m⁻³ cobalt oxide dust 7 hr day⁻¹, 5 day wk⁻¹. No difference in the incidence of any tumour between treated and control groups (4).

Inhalation hamster (lifetime exposure) 10 mg m⁻³ 7 hr day⁻¹, 5 day wk⁻¹ resulted in emphysema and in hyperplastic and hypertrophic changes in alveolar epithelium (4).

Intratracheal instillation Sprague-Dawley rats (2 yr) 78 or 390 mg kg⁻¹ total dose cobalt²⁺ oxide powder in saline. Bronchoalveolar proliferation was observed in 51/100 low-dose animals and 70/100 high-dose animals. In animals given low doses two benign lung tumours observed; while in high-dose animals, one bronchoalveolar carcinoma, three adenocarcinoma and two bronchoalveolar adenomas were observed (5).

Subcutaneous ♂ SpragueDawley rats (2 yr) 2 mg kg⁻¹ Co²⁺ oxide in saline, 5 × wk (two groups); or 10 mg kg⁻¹ in saline once a wk (two groups) (total dose 1000 mg kg⁻¹). Malignant tumours, (histiocytoomas or sarcomas) developed at the injection site in 0/10, 0/10, 5/10 and 4/10 rats in the four groups, respectively (5).

Intraperitoneal Sprague-Dawley rats total dose 600 mg kg⁻¹ (three separate injections, two monthly intervals, 200 mg kg⁻¹) in saline. 14/20 animals developed tumours; ten histiocytoomas, three sarcomas, one mesothelioma (5).

Single intramuscular injection Swiss mice 10 mg site⁻¹ washed powder Co²⁺ oxide (particle size < 5 µm) in 10% aqueous penicillin G procaine, and observed for 110 wk. No tumours developed at injection site, and tumours at other sites were similar in the treated and control groups (6).

Single intramuscular injection Wistar rats (13 wk) 20 mg site⁻¹ washed powder Co²⁺ oxide (particle size < 5 µm) in aqueous penicillin G procaine. 24/30 surviving animals developed rhabdomyosarcomas, metastases were noted in 3/12 tumour-bearing animals (6).

Metabolism and toxicokinetics

Inhalation hamster 0.8 mg cobalt oxide (particle size 1-2.5 µm) pulmonary absorption rapid and high. Elimination was complete six days after exposure. 25% was recovered in the carcass, lung, liver and kidney after 24 hr (2).

Inhalation or instillation dogs and rats, (concentration and duration of exposure unspecified) highest concentrations were found in the lungs. Initial elimination was rapid t_{1/2} 17 hr, however t_{1/2} of cobalt oxide deposited in the lungs of dogs was 36-86 days (7).

Legislation

Included in Schedule 4 (Release into Air: Prescribed Substances) Statutory Instrument No. 472, 1991 (8).

Other comments

Cobalt oxide exists in two valency states (II) and (III).

Commercial oxides are usually not definite chemical compounds but mixtures of the cobalt oxides.

Toxicology and human health effects comprehensively reviewed (3,9).

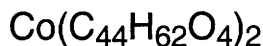
Soluble in hydrochloric, sulfuric and nitric acids. Readily absorbs oxygen. Easily reduced to cobalt by carbon or carbon monoxide.

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c377 cobalt resinate



$\text{C}_{88}\text{H}_{124}\text{CoO}_8$

Mol. Wt. 1368.88

CAS Registry No. 68956-82-1

Synonyms cobalt resinate, precipitated; resin acids and rosin acids, cobalt salts

EINECS No. 273-321-9

RTECS No. GG 2979800

Uses Drying agent for paints, varnishes, inks, concrete. Dyestuffs for fuels, rubber adhesives. Catalyst.

Occupational exposure

JP-OEL 0.05 mg m⁻³ (as Co)

UK-LTEL MEL 0.1 mg m⁻³ (as Co)

UN No. 1318 HAZCHEM Code 1 $\frac{+}{-}$ Conveyance classification flammable solid

Ecotoxicity

Fish toxicity

Rainbow trout exposed to 2 mg l⁻¹ for 24 hr caused decrease in arterial P_{O2} red cell volume, pH and increase in ATP/ Hb ratio, liver dysfunction and increase in plasma bilirubin (1).

Bioaccumulation

Bioconcentrates (2).

Environmental fate

Degradation studies

Biodegrades (2).

Legislation

Included in Schedule 4/6 (Release into Air/Land: Prescribed Substances) Statutory Instrument No. 472, 1991 (3).

Other comments

The toxicity of heavy metals to aquatic biota is dependent on the chemical form of the metal.

Whilst there are no specific human toxicity data on this group of substances, attention is drawn to their general use in painting (4).

Cobalt and its compounds have been extensively reviewed (5,6).

In powder form, it ignites spontaneously in air.

References

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c378 cobalt(II) sulfamate



$\text{CoH}_4\text{N}_2\text{O}_6\text{S}_2$

Mol. Wt. 251.11

CAS Registry No. 14017-41-5

Synonyms cobaltous sulfamate; sulfamic acid, cobalt(II) salt (2:1)

EINECS No. 237-834-1

Uses Flameproofing of fabrics and wood. Phosphates of steel. In plating baths.

Physical properties

Solubility Water: miscible

Occupational exposure

JP-OEL 0.05 mg m⁻³ (as Co)

SE-LEVL 0.05 mg m⁻³ (as Co)

UK-LTEL MEL 0.1 mg m⁻³ (as Co)

US-TWA 0.02 mg m⁻³ (as Co)

Legislation

Included in Schedule 4 (Release into Air: Prescribed Substances) Statutory Instrument No. 472, 1991 (1).

Other comments

Cobalt and its compounds have been extensively reviewed (2,3).

The toxicity of cobalt to aquatic biota is dependent on the chemical form of the metal.

References

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c379 cobalt(II) sulfate



CoO_4S

Mol. Wt. 155.00

CAS Registry No. 10124-43-3

Synonyms sulfuric acid, cobalt(II) salt (1:1); cobalt monosulfate; cobaltous sulfate; cobalt sulfate (1:1); cobalt sulfate

EINECS No. 233-334-2

RTECS No. GG 3100000

Uses Preferred source of water-soluble cobalt, shows less tendency to deliquesce or dehydrate than the chloride or nitrate. Used in pigments and in ceramics, enamels and glazes to prevent discolourisation. Storage batteries and electroplating baths. Drier for varnishes and lithographic inks. Manufacture of vitamin B₁₂. Oxidation catalyst used to remove atmospheric pollutants such as nitrogen and sulfur oxides in waste gases.

Occurrence The hexahydrate occurs in nature as the mineral bieberite.

Physical properties

M. Pt. 735°C (decomp.) **Specific gravity** 3.71 at 25°C with respect to water at 25°C

Solubility Water: 362 g l⁻¹ at 20°C. Organic solvents: methanol

Occupational exposure

JP-OEL 0.05 mg m⁻³ (as Co)

SE-LEVL 0.05 mg m⁻³ (as Co)

UK-LTEL MEL 0.1 mg m⁻³ (as Co)

US-TWA 0.02 mg m⁻³ (as Co)

Mammalian & avian toxicity

Acute data

LD₅₀ oral rat 150-500 mg kg⁻¹ (1).

Carcinogenicity and chronic effects

Possible human carcinogen, IARC classification group 2B (2).

Other effects

Other adverse effects (human)

The major hazard in cobalt sulfate processing is the dust of the finished products (disintegration aerosol) in concentrations from 0.05-53 mg m⁻³ depending on the stage of the technical process. Occupational exposure caused morbidity with temporary disability, a high frequency of the upper respiratory diseases (rhinitis, pharyngitis, laryngitis) and irritation of the eyes. ECG examination revealed marked changes of varying severity in the myocardium among 40-58% of the exposed workers (3).

Legislation

Included in Schedule 4 (Release into Air: Prescribed Substances) Statutory Instrument No. 472, 1991 (4).

Other comments

The toxicity of heavy metals to aquatic biota is dependent on the chemical form of the metal.

Flower bud malformation in the mango plant was decreased, compared to controls, by 93, 94, 87 and 84% in each of the four years, respectively, after a single foliar spray of 1000 ppm cobalt sulfate prior to flower bud differentiation each year. Fruit yield and quality were also improved (5).

Toxicology and human health effects of cobalt and its compounds comprehensively reviewed (2). Addition of 0.8 g l⁻¹ cobalt sulfate to sprinkling irrigation water decreased the uptake of ⁶⁰Co by crops (added at 55 kBq l⁻¹) to 25-83% of controls. ⁶⁰Co is relatively immobile in water because the exchangeable form comprises only 9-12% of the total amount available. Such interactions affect the effectiveness of amending irrigation water with stable isotopes aimed at decreasing the uptake of contaminating radionuclides (6).

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c380 cobalt(II) sulfide

CoS

CoS

Mol. Wt. 91.00

CAS Registry No. 1317-42-6

Synonyms cobalt sulfide; cobalt monosulfide; cobaltous sulfide

EINECS No. 215-273-3

RTECS No. GG 3325000

Uses Catalyst for hydrogenation or hydrodesulfurisation in petroleum refining.

Occurrence Exists in two forms: β-CoS-reddish, silver-white crystals or grey powder and α-CoS-black amorphous powder.

Physical properties

M. Pt. >1100°C Specific gravity 5.45

Occupational exposure

JP-OEL 0.05 mg m⁻³ (as Co)

SE-LEVL 0.05 mg m⁻³ (as Co)

UK-LTEL MEL 0.1 mg m⁻³ (as Co)

US-TWA 0.02 mg m⁻³ (as Co)

Supply classification irritant

Risk phrases May cause sensitisation by skin contact (R43)

Safety phrases Keep out of reach of children (if sold to general public) – Avoid contact with the skin – Wear suitable gloves (S2, S24, S37)

Mammalian & avian toxicity

Acute data

LD₅₀ oral rat >5000 mg kg⁻¹ (1).

Carcinogenicity and chronic effects

Possible human carcinogen, limited evidence for carcinogenicity to animals, IARC classification group 2B (2). Single intramuscular injection 30 ♂, ♀ Wistar rats 20 mg site⁻¹ powdered Co²⁺ sulfide (particle size <5 µm) in penicillin G procaine. 29/30 rats had developed sarcomas 13 wk after treatment. Metastases were noted in 16/29 rats with tumours; no other neoplasm was seen (3).

Single intrarenal injection Sprague-Dawley rats (1 yr) 5 mg kg⁻¹ Co²⁺ sulfide in 0.05 ml glycerine. No tumours observed in kidneys of treated or control animals (4).

Genotoxicity

In vitro Chinese hamster ovary cells without metabolic activation positive for DNA strand breaks (5).

In vitro Syrian hamster embryo cells without metabolic activation cell transformation positive (6).

Legislation

Included in Schedule 4 (Release into Air: Prescribed Substances) Statutory Instrument No. 472, 1991 (7).

Other comments

Toxicology and human health effects comprehensively reviewed (2,8).

The toxicity of heavy metals to aquatic biota is dependent on the chemical form of the metal. Under some aquatic conditions cobalt sulfide can release hydrogen sulfide which is lethal to fish. Hydrogen sulfide toxicity increases with increasing pH.

Occupational exposure risk to workers who regenerate spent catalysts.

References

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C381 cocamide DEA

CAS Registry No. 68603-42-9

Synonyms amides, coco, *N,N*-bis(hydroxyethyl); *N,N*-bis(hydroxyethyl)-coco-amides; Active 2; Amidex 1285; Gafamide CDD-518; Incromide CA

EINECS No. 271-657-0

RTECS No. GG 6200000

Uses Mild surfactant used in hand gels, hand washing liquids, shampoos and some dishwashing liquids.

Environmental fate

Degradation studies

500 mg l⁻¹ compound exposed to 2500 mg l⁻¹ activated sludge solids, slow 6% degradation occurred in 24 hr (1).

Mammalian & avian toxicity

Acute data

LD₅₀ oral rat ≈2000-3000 mg kg⁻¹ (2).

Carcinogenicity and chronic effects

National Toxicology Program skin painting study on rats and mice in progress (3).

Sensitisation

A 27-yr-old mine worker reported acute eczema. Patch-testing with 0.5% petrolatum coconut diethanolamide gave positive result (4).

Reported dermatitis, positive sensitisation results in tests on a woman (5).

Genotoxicity

Salmonella typhimurium TA98, TA100 with and without metabolic activation negative. No morphological transformation of cryopreserved primary hamster embryo cells in culture (2).

Other comments

The Toxicology Design Committee has approved pre-chronic testing of coconut diethanolamide by skin painting in rats and mice (6).

Toxicity has been evaluated (7).

Reviews on human health effects and experimental toxicology listed (8).

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8. *ECETOC Technical Report No. 71* 1996, European Centre for Ecotoxicology and Toxicology of Chemicals, 4 Avenue E. Van Nieuwenhuyse (Bte 6), B-1160 Brussels, Belgium

C382 cochineal

CAS Registry No. 1343-78-8

Synonyms cochineal solution; cochineal tincture

EINECS No. 215-680-6

RTECS No. GG 5350000

Uses Colouring agent for food. Toilet preparations. Source of carmine (the alumina lake) and carminic acid for ink.

Occurrence Extract from dried ♀ insect *Coccus cati*, enclosing the young larvae (1).

Physical properties

M. Pt. 136°C

Solubility Water: miscible. Organic solvents: diethyl ether, ethanol

Mammalian & avian toxicity

Carcinogenicity and chronic effects

Oral mice (2 yr) 0, 3 or 6% cochineal in the diet. Mice in all groups developed tumours including hepatocellular adenomas or carcinomas, pulmonary adenomas or adenocarcinomas and lymphomas or lymphatic leukaemias; the incidences were not significantly different in treated and control groups (1).

Genotoxicity

Salmonella typhimurium TA1538 10% v/v, negative. Test for DNA damage in *Escherichia coli* negative (2).
In vitro hepatocyte primary culture/DNA repair assay negative (3).

Legislation

Permanently listed food colorant exempt from certification, US Federal Food and Drug Administration (4).
Acceptable for use in food (5).
Acceptable daily intake 0 to 2.5 mg kg⁻¹ (5).

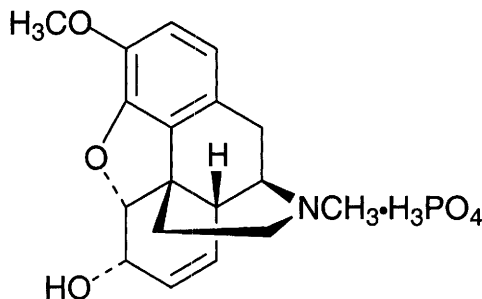
Other comments

Carminic constituents ~10% of extract from insect (5).
Experimental toxicology and human health effects reviewed (6).
Older literature may refer to superseded CAS RN's-93062-68-1;85085-30-9;8047-02-7;8031-23-0.

References

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c383 codeine phosphate



C₁₈H₂₄NO₇P

Mol. Wt. 397.36

CAS Registry No. 52-28-8

Synonyms 7,8-didehydro-4,5-epoxy-3-methoxy-17-methylmorphinan-6-ol phosphate (1:1); Galcodine;
Tricodeine; Colrex Compound

EINECS No. 200-137-8

RTECS No. QD 1310000

Uses Narcotic analgesic. Antitussive.

Occurrence Base present in opium from 0.7 to 2.5% depending on the source.

Physical properties

M. Pt. 220-235°C (decomp.)

Solubility Water: hemihydrate freely soluble in water, sesquihydrate 435 g l⁻¹. Organic solvents: hemihydrate

slightly soluble in ethanol, sesquihydrate soluble in chloroform, ethanol, ether

Mammalian & avian toxicity

Acute data

LD₅₀ oral rat 600 mg kg⁻¹ (1).

LD₅₀ oral mouse 237 mg kg⁻¹ (2).

LD₅₀ intraperitoneal rat, mouse 104, 110 mg kg⁻¹, respectively (3,4).

LD₅₀ intravenous rat, mouse 54, 62 mg kg⁻¹, respectively (5,6).

LD₅₀ intramuscular rat, mouse 191, 208 mg kg⁻¹, respectively (7).

LD₅₀ subcutaneous rat 420 mg kg⁻¹ (1).

Teratogenicity and reproductive effects

TD_{Lo} subcutaneous mouse (9 days pregnant) 110 mg kg⁻¹ was teratogenic causing malformations of the embryonic central nervous system if applied at the time of neural tube closure. Types of malformation included exencephaly, craniorrhachischisis, cervical and thoracolumbar myeloschisis, kinking of the spinal cord and lumbar hydromyelia (8).

Metabolism and toxicokinetics

Following oral administration of 30 mg radioactive codeine phosphate to healthy ♂ subjects, maximum plasma radioactivity concentration occurred after ~1 hr and fell with a t_{1/2} of 3.1 hr. Within 4 hr a mean of 55.2% of the administered dose had been excreted in the urine with 95.1% eliminated after 2 days (9).

Following oral administration of 10 or 20 mg to human volunteers, normorphine was detected in the urine together with other known metabolites. The quantities of each were: total codeine 70%, total morphine 10%, total norcodeine 9% and normorphine <4% (10).

In humans, t_{1/2} in plasma is 2.5 to 3 hr. Elimination t_{1/2} 4.04 hr, mean residence time 3.9 hr (11).

Phase I metabolism occurs via O-demethylation, N-demethylation. Phase II metabolism occurs to form glucuronide and sulfate conjugates (12).

Genotoxicity

Salmonella typhimurium TA97, TA98, TA100, TA1535 with and without metabolic activation negative (13).

Other effects

Other adverse effects (human)

Adverse reactions ranging from tachycardia and cutaneous vasodilation to severe hypertension and apnoea occurred in three children who were given codeine phosphate intravenously (14).

Pulmonary oedema fitting the description of 'heroin lung' has been reported (15).

The serum concentration of codeine in a 3-month-old infant treated with a cough mixture containing 10 mg per 5 ml codeine phosphate was 12 µg ml⁻¹ 3 days following treatment. The infant subsequently died (16).

A 3-month-old infant who had been born prematurely developed near fatal apnoea after two 5 ml doses of linctus (each 5 ml contained 10 mg codeine phosphate) (17).

Codeine phosphate, 50 mg alone and in combination with alcohol 0.5 g kg⁻¹ body weight had a deleterious effect on driving skills in both normal and emergency situations in a simulated driving test (18).

Poison by ingestion, subcutaneous, intravenous, intramuscular and intraperitoneal routes. An overdose produces central nervous system depression, pinpoint pupils and coma (18,19).

May be habit forming (19).

Legislation

Controlled substance (opiate) listed in US Code of Federal Regulations, Title 21 Part 1308.12, 1987 (20).

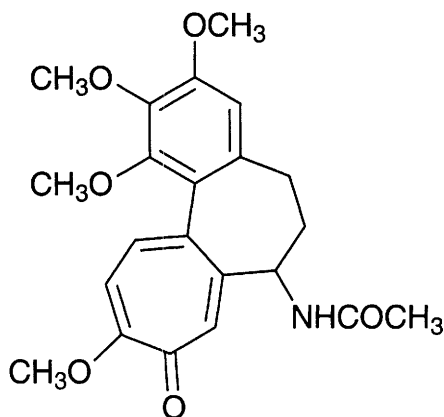
Other comments

Shelf life 1.1 yr, compared to predicted shelf life of ~4.4 yr for codeine sulfate (21).

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C384 colchicine



C₂₂H₂₅NO₆

Mol. Wt. 399.44

CAS Registry No. 64-86-8

Synonyms (S)-N-(5,6,7,9-tetrahydro-1,2,3,10-tetramethoxy-9-oxobenzo[a]heptalen-7-yl)acetamide; 7-acetamido-6,7-dihydro-1,2,3,10-tetramethoxybenzo[a]heptalen-9(5,5H)one; N-acetyltrimethylcolchicine acid, methyl ester; 7-H-colchicine; Colchisol; Colcin; Condylon

EINECS No. 200-598-5

RTECS No. GH 0700000

Uses Used to suppress gout and in the treatment of familial Mediterranean fever. In veterinary medicine as an antineoplastic. Used in phytopathology.

Occurrence A major alkaloid obtained from the corn and seeds of the meadow saffron *Colchicum autumnale* (Liliaceae) and other *Colchicum* sp.

Physical properties

M. Pt. 148-156°C

Solubility Water: 4.5% at 20°C. Organic solvents: benzene, chloroform, diethyl ether, ethanol

Occupational exposure

Supply classification very toxic

Risk phrases Very toxic by inhalation and if swallowed (R26/28)

Safety phrases Keep locked up and out of the reach of children (if sold to general public) – Keep away from food, drink and animal feeding stuffs – In case of accident or if you feel unwell, seek medical advice immediately (show label where possible) (S1/2, S13, S45)

Ecotoxicity

Fish toxicity

LC₅₀ (48 hr) *Dicentrarchus labrax* 1020 mg l⁻¹ (1).

LC₅₀ (24 hr) *Brachydanio rerio* 838-1382 mg l⁻¹. Increased duration of exposure resulted in severely enhanced toxicity (2).

Invertebrate toxicity

Exposure of *Limnaea luteola* to 0.005 ppm colchicine caused teratogenic effects, viz. pear-shaped eggs, loss of cohesion and adhesion among blastomeres, and vesicular exogastrula (3).

Mammalian & avian toxicity

Acute data

LD₅₀ oral redwing blackbird, quail 32, 42 mg kg⁻¹, respectively (4).

LD₅₀ oral mouse 6 mg kg⁻¹ (5).

LD₅₀ intravenous rat, mouse 1.6, 4.1 mg kg⁻¹, respectively (6,7).

LD₅₀ subcutaneous mouse 1.2 mg kg⁻¹ (8).

Fatal oral dose human 7 mg (although doses several times this can be survived) (9).

Sub-acute and sub-chronic data

Rats were given bilateral injections into the nucleus basalis area of the brain at 1 or 2 µg and into the hippocampus at 1.25 or 2.5 µg. Administration into the hippocampus caused a dose-related increase in locomotor activity 7 days after treatment. Administration into the nucleus basalis produced no significant locomotor activity effects compared to controls, but caused a dose-dependent decrease in a step-through passive avoidance task. Administration into the hippocampus had no effect on the behavioural response (10).

Induced some morphological changes in the inner ear sensory cells, including dissociation of Golgi complexes, without impairment of inner ear function, following injection into mice (dose unspecified). Subsequent injection of glycerol, however, impaired hearing and balance. The authors indicated that colchicine affects the inner ear fluid-regulating mechanisms (11).

Teratogenicity and reproductive effects

Gavage pregnant ICR/SIM mice (8-12 day of gestation) single toxic dose evaluation under Chernoff/Karlock development toxicity screen positive teratogen (12).

Metabolism and toxicokinetics

Nine healthy ♂ humans given oral doses of 0.5, 1 and 1.5 mg had plasma and urine samples collected over 48 hr. The lag time and duration were independent of dose. The t_{1/2} in 7/9 subjects was 19.4 hr, in the other two subjects it was estimated as >48 hr. Interpretation of results suggests that plasma concentration plateaus at 2 to 5 hr after ingestion, indicating enterohepatic cycling of colchicine (13).

Intracerebroventricular or intraspinal cord (at lumbar level) injection of small doses (amount unspecified) of tritiated colchicine led to irreversible urine retention in rats. Study of tritium distribution revealed that following intracerebroventricular injection ³H-colchicine diffused into those brain areas that normally exert a facilitatory or inhibitory action on urine excretion, but reached the lumbar region in only modest amounts (0.02%). However,

following intraspinal injection ^3H -colchicine remained at the site of injection, where the sacral micturition centre is located. The results suggest that intracerebroventricular or intraspinal cord injected colchicine induces urine retention by exerting its action at two different levels of the neuronal pathway (14).

Radioimmunoassay was used to study the toxicokinetics of colchicine in seven cases of acute human poisoning. Post-mortem tissue concentrations of colchicine were measured in three further cases. The time of patient admission was important for disposition processes observed. A bi-exponential plasma colchicine decrease with distribution $t_{1/2}$ of 30, 45 and 90 min was observed for early admissions while late admissions showed a mono-exponential decrease. Plasma $t_{1/2}$ ranged from 10.6-31.7 hr. The fraction of unchanged colchicine excreted in the urine was 30%, renal clearance was ~ 13 litres hr^{-1} . Post-mortem tissue analysis showed high accumulation of colchicine in the bone marrow (600 ng g^{-1}), testicle (400 ng g^{-1}), spleen (250 ng g^{-1}), kidney (200 ng g^{-1}), lung (200 ng g^{-1}), heart (95 ng g^{-1}) and brain (125 ng g^{-1}) (15).

Unchanged colchicine was detected in milk within 6 hr of the administration of a single 10 mg oral dose of the alkaloid to lactating sheep, with the maximum concentration occurring in milk 9 hr after dosing. No colchicine was detectable in milk 40 hr after dosing. Post-mortem determinations showed major concentrations of colchicine in the bone marrow, but only trace amounts in heart and muscular tissue (16).

Irritancy

1% solution instilled into rabbit eye for three days caused severe irritation (5).

Genotoxicity

Salmonella typhimurium TA98, TA100, TA1535, TA1537, with metabolic activation negative (17).

Mitotic malsegregation of chromosome VII was not induced in *Saccharomyces cerevisiae* D61.M (18).

Drosophila melanogaster induced mitotic nondisjunction and aneuploidy in the germ-cell lines (19).

In vitro Chinese hamster ovary without metabolic activation positive; with metabolic activation negative for chromosomal aberrations (20).

In vitro human fibroblasts (Downs Syndrome patients) no specific abnormalities detected after exposure to mitotic inhibitors. However, in both normal and Downs Syndrome cell strains, exposure of mitotic inhibitors decreased cellular DNA strand size suggesting the presence of drug-induced DNA strand breaks (21).

In vitro human HeLa cells colchicine inhibited mitosis (22).

In vitro Syrian hamster embryo fibroblast negative (23).

In vitro human lymphocyte cells induced supercontracted chromosomes (24).

Induced cell-cycle lengthening, hyperploidy, polyploidy and micronuclei in mouse bone marrow cells *in vitro* (25,26).

In vivo mice increased incidence of micronuclei in bone marrow polychromatic erythrocytes and peripheral blood normochromic erythrocytes observed compared with controls (27).

Induced micronuclei in *Vicia faba* (28).

Other effects

Other adverse effects (human)

The most frequent adverse effects of colchicine therapy include diarrhoea, nausea, vomiting and abdominal pain. Thrombophlebitis occurred rarely at the site of an intravenous injection and extravasation has caused local irritation. Bone marrow depression with agranulocytosis, thrombocytopenia and aplastic anaemia have occurred on prolonged treatment, as have peripheral neuritis, myopathy, rashes and alopecia (9).

Two cases of fatal colchicine poisoning have been reported (29).

Ingestion of 24 mg colchicine by a 15-yr-old girl caused severe cardiovascular, pulmonary, haematologic, gastro-intestinal and neuromuscular complications, however she ultimately recovered (30).

Following accidental nasal insufflation of 200 mg by a drug abuser, within 24 hr the patient began experiencing gastro-intestinal distress and myalgia. Hypocalcaemia (69 mg l^{-1} on day 5), hypophosphataemia (10 mg l^{-1} on day 5) and thrombocytopenia ($19 \times 10^3 \text{ mm}^{-3}$ on day 8) were observed (31).

Any other adverse effects

Reported to inhibit microtubules by specifically binding to tubulin (32).

When administered to rabbits (dose and duration unspecified) inhibited ovulation (33). Colchicine (1 mg kg⁻¹) functions as an effective antimetabolic agent in 1,2-dichlorobenzene-induced hepatotoxicity in ♂ F344 rats, and does not cause any side-effects apart from suppressing cellular proliferation (34).

Other comments

Colchicine induces autotetraploidy in sugar beet through its mutagenic effect on spindle fibres (35). The chemical properties, pharmacokinetics, toxicity, neurotoxicity, symptoms of poisoning/treatment and therapeutic applications reviewed (36-41).

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Synonyms C.I. 50420; Nigrosine

Uses Dyestuff.

Physical properties

M. Pt. 175°C (decomp., ignites)

Solubility Water: soluble. Organic solvents: ethanol

Environmental fate

Degradation studies

Possibly biodegradable in 42 days (1).

Abiotic removal

Had no substantial effect on oxygen conditions, pH, saprophyte development or total microorganism count at concentrations of 0.001 mg l⁻¹ (2).

Adsorption and retention

DOC (dissolved organic carbon) elimination (96%) colour elimination (75%), only 1% being adsorbed, in short-term biodegradation tests (1).

Mammalian & avian toxicity

Irritancy

Dermatitis reported by a ♂ typist handling carbon papers containing nigrosine (3).

Genotoxicity

Salmonella typhimurium TA98, TA100, TA1538 with or without metabolic activation negative (4).

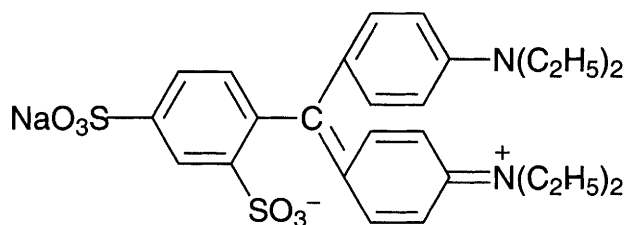
Chinese hamster ovary cells chromosome aberration without metabolic activation negative (5).

Gene conversion diploid yeast BZ 34 negative (6).

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C386 C.I. Acid Blue 1



$C_{27}H_{31}N_2NaO_6S_2$

Mol. Wt. 566.67

CAS Registry No. 129-17-9

Synonyms N-[4[[4-(diethylamino)phenyl](2,4-disulphophenyl)methylene]-2,5-cyclohexadien-1-ylidene]N-ethylethanaminium hydroxide, inner salt, sodium salt; [4-[α -[p-(diethylamino)phenyl]-2,4-disulphobenzylidene]-2,5-cyclohexadien-1-ylidene]diethylammonium hydroxide, inner salt, sodium salt; anhydro-4,4'-bis(diethylamino)triphenylmethanol-2'',4''-disulfonic acid, monosodium salt; Blue VRS; C.I. Food Blue; C.I. 42045; Disulphine Blue; Patent Blue VF; Asian Acid Patent Blue VS 200%; Daiwa Patent Blue VX; Duramine Blue V

EINECS No. 204-934-1

RTECS No. BP 6830000

Uses Colouring medicinal products and (as the 2,5-disulphophenyl isomer) as a diagnostic aid in lymphangiography. Dyeing and printing wool and silk.

Physical properties

Solubility Water: 50 g l⁻¹ at 20°C. Organic solvents: partly soluble in ethanol

Mammalian & avian toxicity

Acute data

LD₅₀ oral mouse, rat >5, 10 g kg⁻¹, respectively (1).

LD₅₀ intraperitoneal mouse 3 g kg⁻¹ (1).

LD₅₀ intravenous mouse 1.2 g kg⁻¹ (2).

Minimum lethal human dose 33 µg kg⁻¹ intravenously (3).

Sub-acute and sub-chronic data

Oral rat (90 day) 1.5% and 3% in feed caused retardation of growth in males and occasional fatty change in the livers of females (4).

Carcinogenicity and chronic effects

No adequate data for human carcinogenicity, limited evidence for animal carcinogenicity, IARC classification group 3 (4).

LD₅₀ subcutaneous rat 3000 mg kg⁻¹ intermittently over 33 wk. Neoplastic effects (5).

TD subcutaneous rat 4050 mg kg⁻¹ intermittently over 45 wk. Equivocal tumorigenic agent (6).

TD₅₀ intramuscular rat 2070 mg kg⁻¹ intermittently over 50 wk. Carcinogenic effects (7).

A high incidence of sarcomas resulted from repeated subcutaneous injection of rats with C.I. Acid Blue (6).

Other effects

Other adverse effects (human)

Salmonella typhimurium microsomal mutagenicity assay positive at 1 mg plate⁻¹ (8).

Other comments

C.I. Acid Blue is not known to occur in nature.

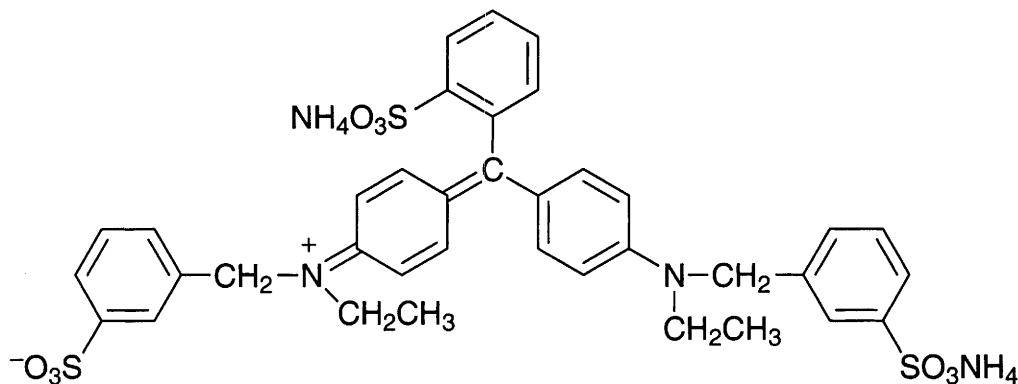
C.I. Acid Blue exhibits high plasma protein binding (9).

Toxicology and biochemistry of C.I. Acid Blue reviewed (10,11).

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C387 C.I. Acid Blue 9



$C_{37}H_{36}N_2O_9S_3Na_2$

Mol. Wt. 794.88

CAS Registry No. 2650-18-2

Synonyms N-ethyl-N-[4-[[4-[ethyl[(3-sulfonphenyl)methyl]amino]phenyl](2-sulfophenyl)methylene]-2,5-cyclohexadien-1-ylidene]-3-sulfobenzenemethanaminium inner salt, diammonium salt; C.I. 42090;

Best Acid Brilliant Blue EA New; Daiwa Brilliant Blue FCF; Duramine Sky Blue A

EINECS No. 220-168-0

RTECS No. BQ 4550000

Uses Dyestuff for wool, silk, nylon, paper, leather, soap and woodstains. Indicator and biological stain.

Physical properties

Solubility Organic solvents: ethanol

Mammalian & avian toxicity

Acute data

LD_{Lo} intravenous human 0.033 mg kg⁻¹ (1).

Carcinogenicity and chronic effects

No adequate data for carcinogenicity to humans, limited evidence for carcinogenicity to animals, IARC classification group 3 (2).

TD_{Lo} (77 wk) 10 g kg⁻¹ intermittently to rats tumorigenic (3).

Sensitisation

Moderate sensitiser in guinea pigs (4).

Genotoxicity

Salmonella typhimurium TA98, TA1538 with metabolic activation positive (5).

L5178Y mouse lymphoma cell forward mutation assay with and without metabolic activation positive (5,6).

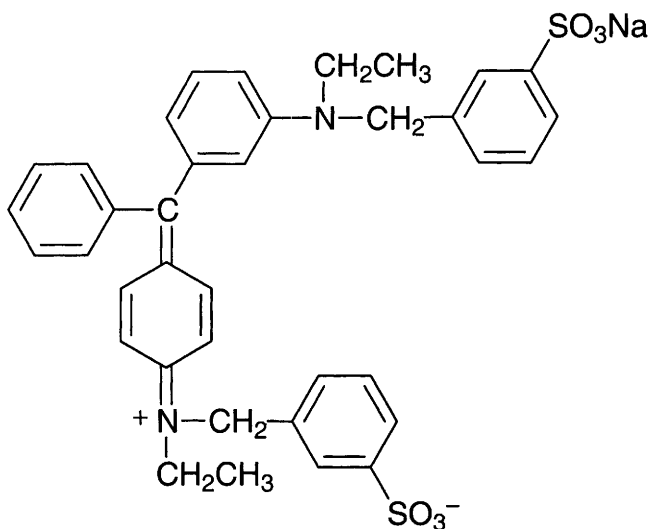
Other effects

Any other adverse effects

C.I. Acid Blue 9 was fed to ♂ and ♀ mice at a dose of 250 mg kg⁻¹ in diet for 7 months. The DNA and RNA content of all organs except the brain decreased and chromosomal aberrations ranged from 29.3-34%. GOT, GPT, and alkaline phosphatase activities of liver and heart tissue were inhibited relative to controls, and ♂ were more affected than ♀. Triiodothyronine and thyronine levels were reduced relative to controls. Blood haemoglobin levels and red and white blood cell count were increased relative to controls. Enlargement of the stomach was evident and histopathological changes in the liver and stomach were seen (7).

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C₃₇H₃₆N₂NaO₆S₂

Mol. Wt. 691.82

CAS Registry No. 4680-78-8

Synonyms N-ethyl-N-(4-[(4-ethyl(3-sulfophenyl)methyl)amino]phenyl)phenylmethylene]-2,5-cyclohexadiene-1-ylidene)-3-sulfobenzenemethanaminium hydroxide, inner salt, sodium salt; Food Green 1; C.I. 42085

EINECS No. 225-132-8

RTECS No. BQ 4375000

Uses Barium and aluminium salts used as pigments. Paper, woodstain, biological stain and indicator. Leather dyestuff.

Physical properties

M. Pt. 255°C (decomp.)

Solubility Organic solvents: ethanol

Ecotoxicity

Fish toxicity

Treatment of 1.4 g l⁻¹ with 10 mg sodium hypochlorite (water chlorination agent) led to formation of 158 mg l⁻¹ chloroform tube⁻¹. Chloroform is highly toxic to fish, LD₅₀ <10 mg l⁻¹ (1).

Mammalian & avian toxicity

Acute data

LD₅₀ oral rat >2000 mg kg⁻¹ (2).

Carcinogenicity and chronic effects

No adequate data for carcinogenicity to humans, limited evidence for carcinogenicity to animals, IARC classification group 3 (3).

Metabolism and toxicokinetics

After oral administration to rats <5% absorbed and excreted unchanged in bile. After intravenous injection in rats 75% excreted in bile within 4 hr (2).

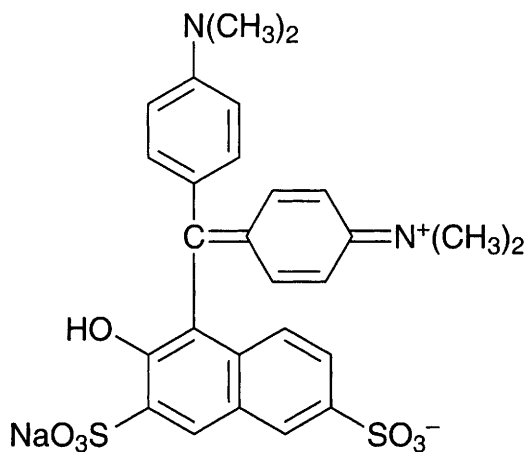
Genotoxicity

Salmonella typhimurium TA98, TA100 with or without metabolic activation negative (4).

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c389 C.I. Acid Green 50



$C_{27}H_{26}N_2O_7S_2Na$

Mol. Wt. 577.63

CAS Registry No. 3087-16-9

Synonyms *N*-[4-[4-(dimethylamino)phenyl](2-hydroxy-3,6-disulfo-1-naphthalenyl)methylene]-2,5-cyclohexadien-1-ylidene-*N*-methylmethanaminium hydroxide, inner salt, monosodium salt; Edicol Supra Green BS; Wool Green S; Lissamine Green B; E142; C.I. 44090; Green S; Acid Brilliant Green BS; Calcocid Green S

EINECS No. 221-409-2

RTECS No. BQ 1150000

Uses Food colouring agent.

Mammalian & avian toxicity

Acute data

LD₅₀ oral rat 2000 mg kg⁻¹ (1).

Sub-acute and sub-chronic data

Oral rat (13 wk) 0, 250, 500, or 1500 mg kg⁻¹ day⁻¹. There was a marked excretion of green colour in the faeces and some in the urine. ♂ rats had increased water and food intake, particularly at the highest dose, with increased body weight gain. Haematological examination revealed mild anaemia for the high-dose group. Higher urinary protein, protein casts, increased caecal weight, thyroid degeneration in ♀ animals, and enlargement of lymph nodes of the small intestine were also reported for the high-dose group (2).

Carcinogenicity and chronic effects

Oral rat 0, 250, 500 or 1000 mg kg⁻¹ day⁻¹ for three generations. Increased spleen weight in both sexes, and increased kidney weight in ♂ rats without histopathological changes were reported for the high-dose group. Reproductive performance was not affected (3).

Teratogenicity and reproductive effects

Oral rats, 0, 250, 500 or 1000 mg kg⁻¹ day⁻¹ on days 0-19 of gestation did not induce any maternal or embryo toxicity or teratogenic effects (4).

Metabolism and toxicokinetics

Poorly absorbed from the gastro-intestinal tract except in high doses. Not metabolised in rats and guinea pigs (5).

Genotoxicity

Salmonella typhimurium TA98, TA1538 with metabolic activation positive (6).

Legislation

Use in food is prohibited in US, Norway, Sweden, Finland, Japan and Canada (5).

UK MAFF Food Advisory Committee recommended that the use of Green S in food is acceptable (7).

Temporary TDI of 0.5 mg kg⁻¹ withdrawn (8).

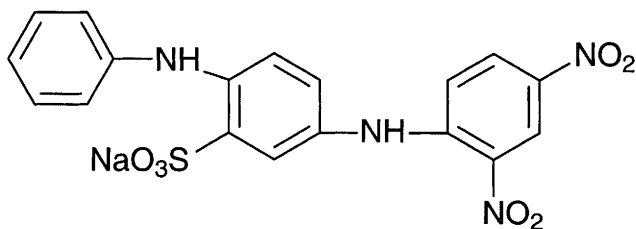
Other comments

Reviews on human health effects, experimental toxicology, physico-chemical properties listed (9).

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c390 C.I. Acid Orange 3



$C_{18}H_{13}N_4NaO_7S$

Mol. Wt. 452.38

CAS Registry No. 6373-74-6

Synonyms 5-[(2,4-dinitrophenyl)amino]-2-(phenylamino)benzenesulfonic acid, sodium salt; C.I. 10385; Anadurm Orange AE 110%; Asian Acid Orange EA; Duramine Yellow AE; Durapel A Yellow AE; Dyacid Yellow A 110%

EINECS No. 228-921-5

RTECS No. DB 5042500

Uses Dyestuff.

Mammalian & avian toxicity

Carcinogenicity and chronic effects

Gavage studies on F344/N rats and B6C3F1 mice dosed 5 days wk^{-1} for 103 wk. In σ rats there was no evidence of carcinogenicity at 375 $mg\ kg^{-1}$ and inadequate data for assessment at 750 $mg\ kg^{-1}$ due to high mortality. Clear evidence of carcinogenesis in \varnothing rats at 750 $mg\ kg^{-1}$ (transitional cell carcinoma in the kidneys). No evidence of carcinogenicity in mice at 125 or 250 $mg\ kg^{-1}$ (σ); 250 or 500 $mg\ kg^{-1}$ (\varnothing) (1).

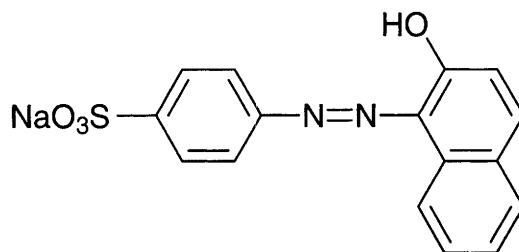
Genotoxicity

Salmonella typhimurium TA97, TA98, TA100, TA1535 with or without metabolic activation positive (2).

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C391 C.I. Acid Orange 7



$C_{16}H_{11}N_2NaO_4S$

Mol. Wt. 350.33

CAS Registry No. 633-96-5

Synonyms 4-[(2-hydroxy-1-naphthalenyl)azo]benzenesulfonic acid, monosodium salt; *p*-[(2-hydroxy-1-naphthyl)azo]benzenesulfonic acid, sodium salt; C.I. 15510; COLO Acid Orange; Devarcid Orange II; Duramine Orange II; Durapel A Orange II; Dyacid Orange II 120%

EINECS No. 211-199-0

RTECS No. DB 7084000

Uses Dyestuff. Biological stain. Indicator.

Physical properties

Solubility Organic solvents: ethanol

Ecotoxicity

Fish toxicity

LC₅₀ (96 hr) fathead minnow 10-180 mg l⁻¹ (1).

Invertebrate toxicity

Selenastrum capricornutum (7,14 days) incubated at 24°C, dyes tested at 1 mg l⁻¹ and 10 mg l⁻¹. C. I. Acid Orange 7 did not inhibit algal growth (1).

Environmental fate

Anaerobic effects

Gradual feeding of C.I. Acid Orange 7 to an active sludge digester, resulting in a final concentration of 140 mg dye l⁻¹ in the digester after 45 days, had no significant effect upon the anaerobic digestion of added sludge over this period. During the course of the experiment some decolorisation was observed. It is suggested that some physical adsorption accompanied by biodegradation and chemical reduction could account for this (1).

Degradation studies

97% of a test concentration of 100 mg l⁻¹ (incubated at 35°C in the presence of an anaerobic sludge inoculum) was degraded in 7 days. 4-Aminobenzenesulfonic acid was identified as a metabolite (2).

Biodegraded by white rot fungus *Phanerochaete chrysosporium*, most extensively in ligninolytic cultures (3).

A dye solution was added to provide a concentration of 25 mg l⁻¹ of organic carbon to an activated sludge 1500 mg l⁻¹ in settled domestic sewage. Oxygen uptake of the system was followed for 7 hr. Oxygen uptake <10% lower than control (1).

To study the effect on stream oxidative process, dye-sewage-sludge systems (dye concentration to yield 25 mg l⁻¹ organic carbon) diluted to 1:10 and 1:100 in river water. No inhibition was observed (1).

DI₅₀ (Degradation Index 50) using caecal microflora from rats was determined to be 288 min (4).

Reduced to some extent under anaerobic conditions by *Clostridium perfringens*, *Clostridium paraputrificum*, *Clostridium leptum*, and *Eubacterium* sp. No mutagenic metabolites, as measured by the umu test, were detected following reduction (5).

Decolorised by *Phanerochaete chrysosporium* (6).

Can be degraded aerobically in an efficient and effective manner in a rotating drum biofilm reactor (7).

Genotoxicity

Salmonella typhimurium TA98 with and without metabolic activation negative (8).

Intraperitoneal injection of the LD₅₀ dose caused dominant lethal mutations in mice (9).

Other effects

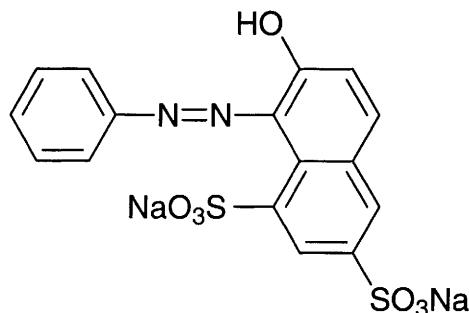
Any other adverse effects

Parenteral administration to rats at a dose of 80 mg kg⁻¹ for three days of C.I. Acid Orange 7 or Metanil Yellow caused a significant induction of ethoxyresorufin-O-deethylase, aniline hydroxylase, aryl hydrocarbon hydroxylase, and aminopyrine N-demethylase. A blend (1:1) of these two dyes showed a synergistic or additive effect on these hepatic parameters. The addition of these two prohibited dyes in food may cause more toxic effects than are produced by each dye individually (10).

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c392 C.I. Acid Orange 10



C₁₆H₁₀N₂Na₂O₇S₂

Mol. Wt. 452.38

CAS Registry No. 1936-15-8

Synonyms 1,3-naphthalenedisulfonic acid, 7-hydroxy-8-(phenylazo)-, disodium salt; C.I. 16230; COLO Acid Orange G; Daiwa Orange G; Devarcid Fast Orange 2GS; Duramine Orange G; Durapel A Orange G; Dyacid Orange G 175%

EINECS No. 217-705-6

RTECS No. QJ 6500000

Uses Biological stain. Dyestuff for wool, leather, in inks and coloured pencils.

Physical properties

Solubility Organic solvents: cellosolve, ethanol

Environmental fate

Degradation studies

Non-degradable in a laboratory-scale aerobic rotating drum biofilm reactor (1).

Mammalian & avian toxicity

Carcinogenicity and chronic effects

No adequate data for carcinogenicity to humans, inadequate evidence for carcinogenicity to animals, IARC classification group 3 (2).

National Toxicology Program investigated in rat, mouse. Rats fed 3000 or 6000 ppm, mice 1000 or 3000 ppm for 103 wk. Designated non-carcinogen in rat and mouse (3).

♂ F-344 rats (2 yr) 3000 ppm in diet. Non-carcinogen but resulted in a decrease in the incidence of mononuclear cell leukaemia. Spleen toxicity studies after 13 wk showed the occurrence of haematopoiesis, haemosiderin, and fibrosis (4)

Metabolism and toxicokinetics

Urine of humans given 20 mg kg⁻¹ contained 95% as *p*-aminophenol, 0.5% as aniline and 1.3% unchanged dye (5).

Genotoxicity

Salmonella typhimurium TA97, TA98, TA100, TA1535, TA1537 with and without metabolic activation negative (6).

In vitro Chinese hamster ovary cells chromosomal aberrations and sister chromatid exchanges with and without metabolic activation negative (7).

Mouse lymphoma L5178Y cell mutagenesis assay without metabolic activation negative (8,9).

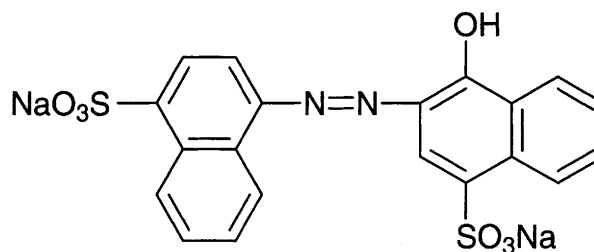
In vivo bone marrow micronucleus and chromosomal aberration tests negative (10).

Significantly increased polyploid cells in *Allium cepa* (11).

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C393 C.I. Acid Red 14



$C_{20}H_{12}N_2Na_2O_7S_2$

Mol. Wt. 502.44

CAS Registry No. 3567-69-9

Synonyms 4-hydroxy-3-[(4-sulfonyl-1-naphthalenyl)azo]-1-naphthalenesulfonic acid, disodium salt; Carmoisine; C.I. 14720; C.I. Food Red 3; Cogilor Rouge 319.11; Daiwa Carmoisine; Duramine Red W; Dyacid Red W

EINECS No. 222-657-4

RTECS No. QK 1925000

Uses Leather, wool and wood dyestuff.

Physical properties

Solubility Water: soluble. Organic solvents: slightly soluble in ethanol

Environmental fate

Degradation studies

Enzymatic action of immobilised and native *Bacillus cereus* No. 45 cells for decolorisation increased during incubation in a solution of 50 ppm C.I. Acid Red 14 at 37°C. 87% dyestuff removal from immobilised cell column continuously treating an Acid Red 14 solution for 14 days, influent concentration 42.1 ppm (1).

Biodegraded and decolorised by *Pseudomonas* 5-59 (2).

Carmoisine was found to be non-biodegradable in a laboratory-scale aerobic rotating drum biofilm reactor (3).

Mammalian & avian toxicity

Acute data

LD₅₀ intraperitoneal rat, mouse 900 mg kg⁻¹ (4).

LD₅₀ intravenous rat, mouse 800 mg kg⁻¹ (5).

Carcinogenicity and chronic effects

No adequate evidence for carcinogenicity in humans, inadequate evidence for carcinogenicity in animals, IARC classification group 3 (6).

National Toxicology Program investigated in rat, mouse. Designated non-carcinogen in rat and mouse (7).

♂ and ♀ rats fed 0, 100, 400 or 1200 mg kg⁻¹ day⁻¹ for 9 wk. Randomly selected offspring fed similarly for 110-115 wk. No evidence of carcinogenicity (8).

Genotoxicity

Salmonella typhimurium TA98, TA100, TA1535, TA1537, TA1538 with and without metabolic activation negative (9).

L5178Y tk⁺/tk⁻ mouse lymphoma assay with or without metabolic activation negative (10).

In vivo mouse bone marrow micronucleus and chromosomal aberration tests negative (11).

Legislation

ADI 0-4 mg kg⁻¹ body weight (12).

Other comments

Reductive cleavage of azo-dyes discussed (13).

Carmoisine on its own was not toxic to *Tetrahymena pyriformis*, but when it was autoclaved with media components such as bactopectone or yeast extract it gave products that completely inhibited cell growth.

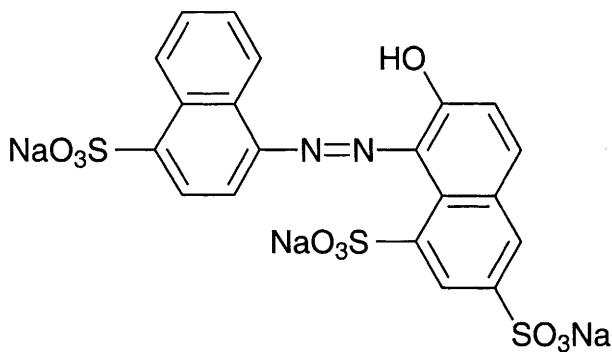
Addition of reducing sugars or compounds containing sulfhydryl groups to the components prior to autoclaving significantly increased the toxicity of the products (14).

Carcinogenic risk to man reviewed (15).

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c394 C.I. Acid Red 18



$C_{20}H_{14}N_2Na_3O_{10}S_3$

Mol. Wt. 607.51

CAS Registry No. 2611-82-7

Synonyms Ponceau 4R; Acid Brilliant Scarlet 3R; Brilliant Ponceau 3R; C.I. 16255; C.I. Food Red 7; Coccine; Cochineal Red A; Food Red 102; 7-hydroxy-8-[(4-sulfo-1-naphthyl)azo]-1,3-naphthalenedisulfonic acid, trisodium salt; Naphthalene Ink Scarlet 4R; Victoria Scarlet 3R; New Coccine

EINECS No. 220-036-2

RTECS No. QJ 6530000

Uses Dyestuff. Colorant in food, medicines and cosmetics.

Physical properties

Solubility Water: miscible

Environmental fate

Degradation studies

BOD₅ 1.23 mg O₂ l⁻¹ using fresh water seed, at an initial concentration of 500 ppm (1).

Abiotic removal

Irradiation with simulated sunlight at 65°C led to the formation of 1-aminonaphthalene (2).

Photolysis t_{1/2} 133 days in water (3).

Adsorption and retention

1% adsorption in activated sludge system at 1 or 5 ppm over 27 days (4).

Mammalian & avian toxicity

Acute data

LD_{Lo} oral mouse 8000 mg kg⁻¹ (5).

LD₅₀ intravenous rat 1000 mg kg⁻¹ (5).

LD₅₀ intraperitoneal rat, mouse 600, 1600 mg kg⁻¹, respectively (6).

Carcinogenicity and chronic effects

Oral rat 0, 50, 500 or 1250 mg kg⁻¹ day⁻¹ for 60 days. The animals were then allowed to mate. At weaning, the offspring were administered the same treatment as their parents until 20% of animals survived (114 wk for ♂, 118 wk for ♀). The high-dose animals had a lower body weight gain without a reduction in food intake. Water intake was higher in the medium- and high-dose groups and this was related to caecal enlargement and softening of the faeces. No adverse changes were seen in blood and urine, except for a higher incidence of ♀ rats with higher levels of protein in the urine at the high dose. No other findings of significance were observed. Survival and tumour incidences were similar in all groups (7).

Teratogenicity and reproductive effects

Oral rat (three-generation) 0, 50, 500 or 1250 mg kg⁻¹ day. No foetotoxic or teratogenic effects were observed, but the skeletons of treated foetuses had a slightly more advanced development than controls (8).

Gavage mouse 7.5, 30 or 100 mg kg⁻¹ day⁻¹ on days 0-7 or 6-18 of gestation. No foetotoxic or teratogenic effects were observed (9).

Genotoxicity

Salmonella typhimurium TA92, TA94, TA98, TA100, TA1535, TA1537 with and without metabolic activation negative (10).

In vitro Chinese hamster fibroblasts without metabolic activation, chromosomal aberrations positive (10).

In vitro primary rat hepatocytes, DNA repair assay negative (11).

Legislation

Approved for use as a food colour (12).

ADI (human) 4 mg kg⁻¹ (13).

Other comments

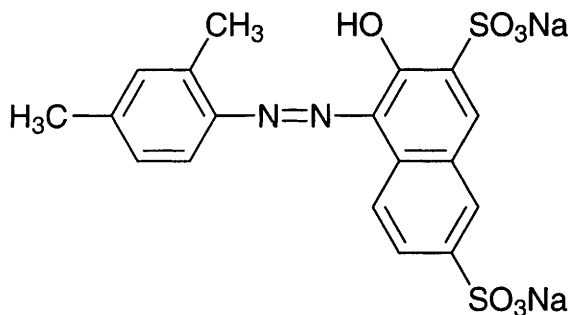
Reviews on human health effects, experimental toxicology, physico-chemical properties listed (14).

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C395 C.I. Acid Red 26



$C_{18}H_{14}N_2Na_2O_7S_2$

Mol. Wt. 480.43

CAS Registry No. 3761-53-3

Synonyms C.I. Food Red 5; C.I. 16150; 4-[(2,4-dimethylphenyl)azo]-3-hydroxy-2,7-naphthalenedisulfonic acid, disodium salt; 3-hydroxy-4-(2,4-xylylazo)-3,7-naphthalenedisulfonic acid, disodium salt; Calcocid Scarlet 2R; Ponceau 2R; Ponceau Red; Ponceau MX; Xylidene Ponceau 2R; Daiwa Ponceau R; Devar Ponceau R

EINECS No. 223-178-3

RTECS No. QJ 6825000

Uses Textile and leather dyestuff. Colour agent for inks, paper pigment, wood stains. Fruit, confectionery and meat products.

Physical properties

Solubility Organic solvents: acetone, ethanol

Ecotoxicity

Fish toxicity

LC₅₀ (96 hr) guppy >400 mg l⁻¹ (1).

Mammalian & avian toxicity

Acute data

LD₅₀ oral rat ≥5.58 g kg⁻¹ (2).

LD₅₀ intraperitoneal rat, mouse 1000, 2000 mg kg⁻¹, respectively (3).

Sub-acute and sub-chronic data

Oral rats (90 day) 5000, 10,000 or 20,000 mg kg⁻¹ in diet caused initial growth retardation (3).

Carcinogenicity and chronic effects

No adequate evidence for carcinogenicity to humans, sufficient evidence for carcinogenicity to animals, IARC classification group 2B (4).

TD_{Lo} (81 wk) oral mouse 136 g kg⁻¹ induced liver tumours (5).

Metabolism and toxicokinetics

After oral administration to rats metabolites detected included: 2,4-dimethylaniline (35%); 3-methyl-4-aminobenzoic acid (6%); and 2,4-dimethylphenylsulfonate (6).

Genotoxicity

Salmonella typhimurium TA98, TA100, TA1535, TA1538 with metabolic activation weakly positive (7).

Salmonella typhimurium TA100 flavin mononucleotide modified assay weakly positive (8).

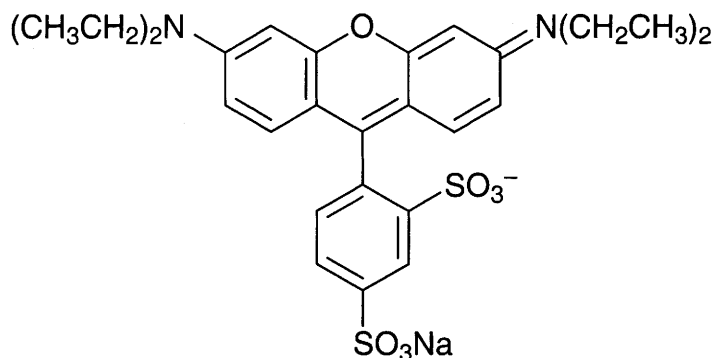
Salmonella typhimurium TA1538 or *Escherichia coli* WP2 *uvrA* modified fluctuation assay negative (8).

Mouse lymphoma assay with or without metabolic activation negative (8).

References

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C396 C.I. Acid Red 52



C₂₇H₂₉N₂NaO₇S₂

Mol. Wt. 580.66

CAS Registry No. 3520-42-1

Synonyms 3,6-bis-(diethylamino)-9-(2,4-disulfophenyl)-xanthylum, inner salt, sodium salt; C.I. 45100; phloxinrhodamine; Food Red 106; Asian Acid Rhodamine B 400%; Best Acid Rhodamine FB 400%; Diawa Acid Rhodamine B; Duramine Rhodamine B; Dyacid Red 4B 400%

EINECS No. 222-529-8

RTECS No. BP 6750000

Uses Dyestuff used in water tracing studies.

Physical properties

M. Pt. decomp.

Ecotoxicity

Invertebrate toxicity

EC₅₀ (72 hr) *Daphnia magna* >150 mg l⁻¹ (1).

Environmental fate

Degradation studies

C.I. Acid Red 52 was not biodegradable (2).

Mammalian & avian toxicity

Acute data

LD₅₀ oral mouse 10,300 mg kg⁻¹ (3).

Genotoxicity

Salmonella typhimurium TA92, TA94, TA98, TA1535, TA1537 with or without metabolic activation negative.

Chromosome test 13.1 mg ml⁻¹: 0% polyploidy; 59% structural aberrations in 48 hr (3).

Single or multiple intraperitoneal injections in mice did not induce micronuclei (4).

Cytotoxicity to cultured foetal rat hepatocytes at 1 mg l⁻¹ (day 4) 33% inhibition; (day 7) 16% inhibition (5).

Sister chromatid exchanges human (HE 2144) cells <10 mg l⁻¹ no exchanges or induction of chromosome breakages (6).

Other comments

Diethylnitrosamine (DENA), a potent animal carcinogen, can be formed in the presence of nitrite (7).

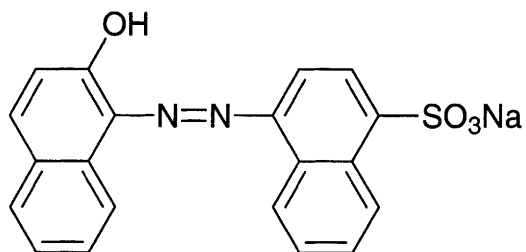
Nitrosation reaction can be inhibited with L-ascorbic acid (7).

When used as a ground water tracer, C.I. Acid Red 52 must not exceed a concentration of 1-2 mg l⁻¹ nor persist for a period greater than 24 hr in the groundwater at the point of groundwater withdrawal or discharge. At this concentration the compound does not present an acutely toxic threat to humans (8).

References

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C397 C.I. Acid Red 88



C₂₀H₁₃N₂NaO₄S

Mol. Wt. 400.39

CAS Registry No. 1658-56-6

Synonyms 4-[(2-hydroxy-1-naphthalenyl)azo]-1-naphthalenesulfonic acid, monosodium salt; C.I. 15620; Asian Acid Red A; COLO Acid Red AV; Durapel A Red A; Dyacid Red J 125%

EINECS No. 216-760-3

RTECS No. QK 2420000

Uses Dyestuff.

Physical properties

M. Pt. 280°C (decomp.)

Environmental fate

Degradation studies

Moderately adsorbed and significantly biodegraded during activated sludge treatment (1,2).

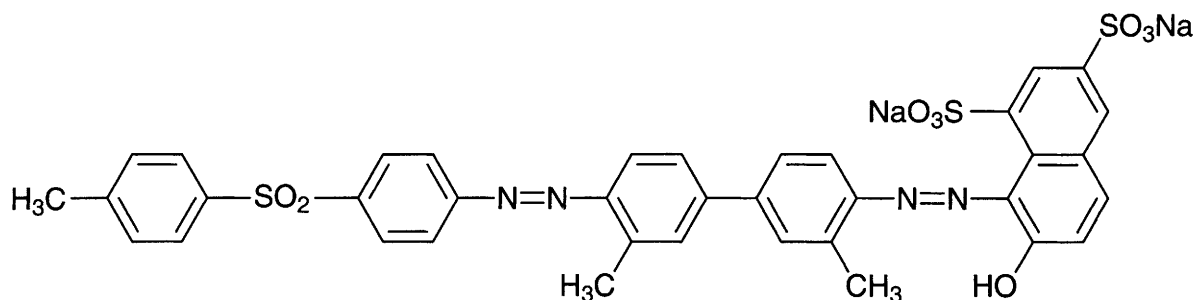
Abiotic removal

Light exposure for >2 wk did not result in photodegradation (1).

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C398 C.I. Acid Red 114



C₃₇H₂₈N₄Na₂O₁₀S₃

Mol. Wt. 830.83

CAS Registry No. 6459-94-5

Synonyms 8-[(3,3'-dimethyl-4'-[(4-[(4-methylphenyl)sulfonyl]oxy]phenyl]azo)][1,1'-biphenyl]-4-yl]azo]-7-hydroxy-1,3-naphthalenedisulfonic acid, disodium salt; C.I. 23635; Evron Red BG

EINECS No. 229-272-0

RTECS No. QJ 6475500

Uses Dyestuff for textiles and leather.

Physical properties

Solubility Organic solvents: ethanol

Environmental fate

Degradation studies

100% of a test concentration of 100 mg l⁻¹ (incubated at 35°C in the presence of an anaerobic sludge inoculum) was degraded in 7 days. 4,4'-Diamino-3,3'-dimethylbiphenyl and 4-methylbenzenesulfonic acid-(4'-aminophenyl) ester identified as metabolites (1).

Mammalian & avian toxicity

Carcinogenicity and chronic effects

National Toxicology Program tested rats via drinking water. Clear evidence of carcinogenicity in ♂ and ♀ rats as demonstrated by a dose-related increase of malignant neoplasms, increase of a combination of malignant and benign neoplasms, or marked increase of benign neoplasms if there was an indication that these could progress to malignancy (2).

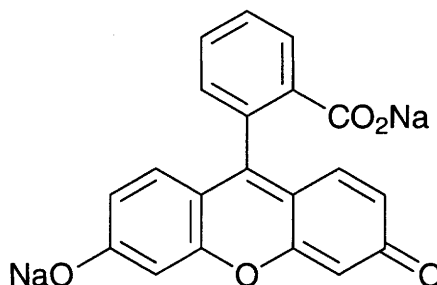
Genotoxicity

Salmonella typhimurium TA98, TA100, TA1535, TA1537 with and without metabolic activation positive (3-5).

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C399 C.I. Acid Yellow 73



C₂₀H₁₀Na₂O₅

Mol. Wt. 376.28

CAS Registry No. 518-47-8

Synonyms Acid Yellow 73; fluorescein; sodium fluoresceinate; hydroxy-*o*-carboxyphenylfluorone, sodium salt; resorcinol phthalein sodium; disodium 6-hydroxy-3-oxo-9-xanthene-*o*-benzoate; C.I. 45350; Fluorescite; Ful-Glo; Daiwa Uranine; Devarcid Uranine SSO

EINECS No. 208-253-0

RTECS No. LM 5425000

Uses Dyestuff for silk and wool. Water marker for air-sea rescue. Groundwater tracer dye. Diagnostic aid in corneal trauma and aid in contact lens fitting. Used in externally applied drugs and cosmetics.

Physical properties

Solubility Water: freely soluble. Organic solvents: slightly soluble in ethanol

Mammalian & avian toxicity

Acute data

LD₅₀ oral mouse, rat 4740, 6720 mg kg⁻¹, respectively (1).

LD₅₀ intraperitoneal mouse 1800 mg kg⁻¹ (2).

LD₅₀ intravenous dog, rat 1 g kg⁻¹ (3).

Carcinogenicity and chronic effects

Subcutaneous administration to rats over 79 wk (total dose 19 g kg⁻¹) equivocal tumorigenic response (4).

Teratogenicity and reproductive effects

Aqueous solution on days 6-19 gestation, administered by gavage to rats (100, 500, 1500 mg kg⁻¹) and rabbits (30, 100, 250 mg kg⁻¹) on days 6-27 of gestation. No evidence of maternal toxicity or teratogenicity (5).

Metabolism and toxicokinetics

t_{1/2} for fluorescein elimination in human breast milk was found to be approximately 62 hr (6).

Irritancy

Non-irritant in the EC eye irritation classification (7).

Sensitisation

Allergic reactions including severe urticaria reported in humans (7).

Genotoxicity

L5178Y mouse lymphoma cell tk+/tk- without metabolic activation positive (8).

DNA-cell binding assay with lysozyme equivocal results (9).

In vivo mouse bone marrow micronucleus and chromosomal aberration tests negative (10).

Other effects

Other adverse effects (human)

Intravenous injection of 14 mg kg⁻¹ over 10 months caused cardiovascular effects in humans (11).

Intravenous injection of 7.1 mg kg⁻¹ caused ocular and gastro-intestinal effects in humans (12).

Nausea, vomiting, shock, respiratory obstruction, hypotension, pancreatitis, cardiac arrest and myocardial infarction reported after intravenous injection. Toxic effects may be due to impurities or defects in the manufacturing process (13).

Any other adverse effects

IC₅₀ yeast test sodium fluorescein 3378 mg l⁻¹ (14).

Other comments

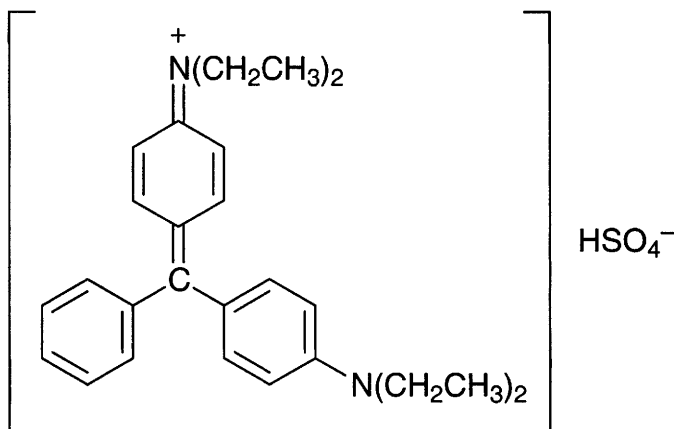
When used as a groundwater tracer, fluorescein concentration must not exceed a concentration of 1-2 mg l⁻¹ nor persist for a period greater than 24 hr in the groundwater at the point of groundwater withdrawal or discharge.

At this concentration fluorescein does not present an acutely toxic threat to humans (15).

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c400 C.I. Basic Green 1



$C_{27}H_{34}N_2O_4S$

Mol. Wt. 482.64

CAS Registry No. 633-03-4

Synonyms [[4-(*p*-(diethylamino)- α -phenylbenzylidene]-2,5-cyclohexadien-1-ylidene]diethylammonium, sulfate(1:1); Aniline Green; Basic Green 1; Benzaldehyde Green; Brilliant Green B; Malachite Green G; C.I. 42040

EINECS No. 211-190-1

RTECS No. BP 6825000

Uses Dyeing silk, wool, leather, jute and cotton. Manufacture of green ink, biological stain and indicators. Disinfectant against Gram-positive bacteria. In treatment of ulcers.

Physical properties

M. Pt. 210°C (decomp.)

Solubility Water: soluble in water. Organic solvents: ethanol

Ecotoxicity

Fish toxicity

Treatment of 965 mg l⁻¹ with 10 mg sodium hypochlorite (water chlorination agent) led to formation of 149 mg l⁻¹ chloroform tube⁻¹. Chloroform is highly toxic to fish, LC₅₀ <10 mg l⁻¹ (1).

LC₅₀ (24, 48 hr) rainbow trout 0.39 and 0.19 ppm, respectively (2).

LC₅₀ (24, 48, 96 hr) rainbow trout 0.121, 0.103, and 0.097 ppm, respectively (3).

Used to prevent attack of *Saprolegnia* on fish eggs and fish, and to control ectoparasites (*Ichthyophthirius multifiliis*).

Chromosome damage was observed in trout eggs and regenerating tissues of fish treated with (unspecified) low concentrations (4).

Environmental fate

Degradation studies

Degraded by the lignin-degrading system of white rot fungus *Phanerochaete chrysosporium* (5).

Mammalian & avian toxicity

Acute data

LD_{Lo} oral rat 1 mg kg⁻¹ (6).

LD_{Lo} intraperitoneal guinea pig, rat 3, 8 mg kg⁻¹, respectively (7).

LD_{Lo} intravenous mouse 3 mg kg⁻¹ (7).

Irritancy

Dermal application to humans of 2 mg over 2 days caused mild irritation (8).

Sensitisation

Sensitivity has occasionally been reported (species unspecified) (9).

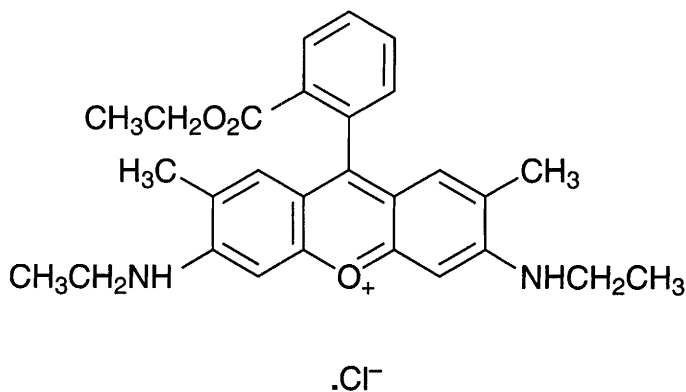
Other comments

Fish toxicity, biodegradability and bioaccumulation reviewed (10).

Malachite green is marketed in at least two formulations, the oxalate and the zinc chloride; a ferric chloride version may be available. The acute lethal toxicity differs depending on the formulation and water chemistry. The dye is precipitated in hard waters, but not in soft. Has been extensively used in fish-farming as a prophylactic fungicide since the 1930s. No clinical history in this context.

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C401 C.I. Basic Red 1

C₂₈H₃₁ClN₂O₃

Mol. Wt. 479.02

CAS Registry No. 989-38-8

Synonyms *o*-[6-(ethylamino)-3-(ethylimino)-2,7-dimethyl-3*H*-xanthen-9-yl]benzoic acid, ethyl ester, monohydrochloride; Basic Red 1; Basic Rhodamine Yellow; rhodamine 6G; C.I. 45160

EINECS No. 213-584-9

RTECS No. DH 0175000

Uses Dyestuff for paper, silk, cotton, wool and leather. Biological stain. Dyestuff used in tunable lasers. Tracing agent in water pollution studies. Absorption indicator.

Physical properties

B. Pt. volatilizes at <200°C

Solubility Water: <1 mg kg⁻¹ at 20°C. Organic solvents: dimethyl sulfoxide, ethanol

Ecotoxicity

Invertebrate toxicity

IC₅₀ (parasite lactate dehydrogenase enzyme assay) *Plasmodium falciparum* D6 clone 144 nM, W2 clone 67 nM (1).

Mammalian & avian toxicity

Acute data

LD_{Lo} oral mouse 50 mg kg⁻¹ (2).

Carcinogenicity and chronic effects

No adequate data for carcinogenicity to humans, limited evidence for carcinogenicity to animals, IARC classification group 3 (3).

Subcutaneous rats (52 wk) total dose 100 mg kg⁻¹ equivocal tumorigenic effects (4).

National Toxicology Program tested rats and mice via feed. Equivocal evidence for carcinogenicity in ♂ and ♀ rats. No evidence in ♂ or ♀ mice (4).

Teratogenicity and reproductive effects

Intraperitoneal mouse (7-10 days gestation) 4 mg kg⁻¹ caused teratogenic effects (5).

Genotoxicity

Salmonella typhimurium TA98, TA100, TA1537, TA1538 with metabolic activation positive (6).

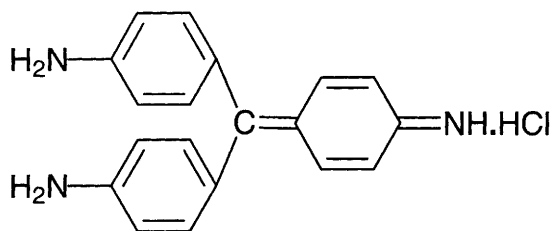
Other comments

Carcinogenic risk to man evaluated (7).

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C402 C.I. Basic Red 9



C₁₉H₁₈ClN₃

Mol. Wt. 323.82

CAS Registry No. 569-61-9

Synonyms C.I. Basic Red 9 monohydrochloride; benzenamine, 4-[(4-aminophenyl)(4-imino-2,5-cyclohexadien-1-ylidene)methyl]-monohydrochloride; Basic Parafuchsin; Calcozine Magenta N; *p*-fuchsin; pararosaniline chloride; *p*-rosaniline HCl; Basic Red 9; C.I. 42500

EINECS No. 209-321-2

RTECS No. CS 9850100

Uses Dyestuff for silk, acrylics, leather and paper. Biological stain.

Physical properties

M. Pt. 268-270°C (decomp.)

Environmental fate

Degradation studies

Degraded by *Bacillus subtilis* (1).

Mammalian & avian toxicity

Acute data

LD₅₀ oral mouse 5000 mg kg⁻¹ (2).

Carcinogenicity and chronic effects

Inadequate evidence for carcinogenicity to humans, limited evidence for carcinogenicity to animals, IARC classification group 3 (3).

National Toxicology Program tested rats and mice via feed. Clear evidence of carcinogenicity in ♂ and ♀ rats and mice. Tumours occurred in liver, subcutaneous tissue, skin, thyroid gland and zymbals gland (4).

Genotoxicity

Salmonella typhimurium TA100 with metabolic activation positive; *Salmonella typhimurium* TA98, TA1537, and *Escherichia coli* WP2, *uvrA* with metabolic activation equivocal (5).

Salmonella typhimurium TA98, TA100 with metabolic activation positive (6).

Chinese hamster ovary cell sister chromatid exchanges, chromosome aberration with and without metabolic activation negative (7).

Other effects

Any other adverse effects

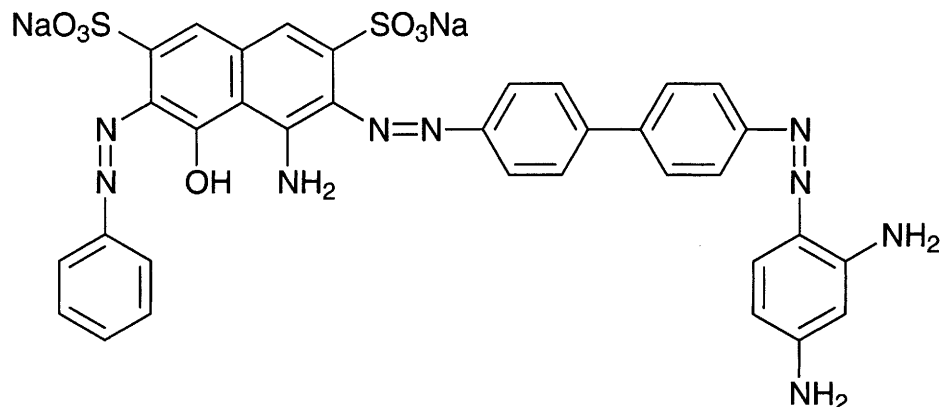
DI₅₀ (concentration that inhibits DNA synthesis by 50%) HeLa S3 cells 300 µM C.I. Basic Red 9 monohydrochloride (8).

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C403 C.I. Direct Black 38



$C_{34}H_{27}N_9Na_2O_7S_2$

Mol. Wt. 783.76

CAS Registry No. 1937-37-7

Synonyms 4-amino-3-((4'-((2,4-diaminophenyl)azo)(1,1'-biphenyl)-4-yl)azo)-5-hydroxy-6-(phenylazo)-2,7-naphthalenedisulfonic acid, disodium salt; Atlantic Black BD; Benzo Leather Black E; Chloramine Carbon Black S; Chrome Leather Black EM; C.I. 30235

EINECS No. 217-710-3

RTECS No. QJ 6160000

Uses Dyestuff for cellulose, wool, silk, leather, plastics, wood, nylon and acetate.

Physical properties

M. Pt. >400°C

Solubility Organic solvents: cellosolve, ethanol

Occupational exposure

Supply classification toxic

Risk phrases May cause cancer – Possible risk of harm to the unborn child (R45, R63)

Safety phrases Avoid exposure – obtain special instruction before use – In case of accident or if you feel unwell, seek medical advice immediately (show label where possible) (S53, S45)

Ecotoxicity

Fish toxicity

LC₅₀ (96 hr) fathead minnow >180 mg l⁻¹ (1).

Invertebrate toxicity

Selenastrum capricornutum (7, 14 day) incubated at 24°C, dyes tested at 1 mg l⁻¹ and 10 mg l⁻¹. Concentrations of 10 mg l⁻¹ inhibited algal growth by >80% after 7 days (1).

Environmental fate

Anaerobic effects

Gradual feeding of C.I. Direct Black 38 to an active sludge digester, resulting in a final concentration of 140 mg dye l⁻¹ in the digester after 45 days, had a significant inhibitory effect upon the anaerobic digestion of added sludge over this period (1).

Degradation studies

To study the effect on stream oxidative processes, dye-sewage sludge systems (dye concentration to yield 25 mg l⁻¹ organic carbon) were diluted to 1:10 and 1:100 in river water. No inhibition was observed (1).

A dye solution was added to provide a concentration of 25 mg l⁻¹ of organic carbon to an activated sludge 1500 mg l⁻¹ in settled domestic sewage. Oxygen uptake of the system was followed for 7 hr. Oxygen uptake <10% lower than control (1).

Mammalian & avian toxicity

Acute data

LD₅₀ oral rat 7600 mg kg⁻¹ (2).

LC_{Lo} (1 hr) inhalation rat 180 g m⁻³ (3).

Carcinogenicity and chronic effects

Inadequate evidence for carcinogenicity to humans, sufficient evidence for (technical grade) carcinogenicity to animals, IARC classification group 2A (2).

National Toxicology Program investigated in rat, mouse. Designated carcinogen in ♂ and ♀ rats. Demonstrated by dose-related increase in malignant neoplasms, increase of a combination of malignant or benign neoplasms, or marked increase of benign neoplasms which progress to malignancy (4).

Teratogenicity and reproductive effects

Subcutaneous injection of 40 mg kg⁻¹ day⁻¹ to 16 rats on days 7, 8 and 9 of gestation did not cause foetal malformations. three dams died and four foetuses resorbed completely (5).

The ♂ offspring of pregnant mice that had been dosed orally on days 8-10 of gestation with C.I. Direct Black 38 had testes reduced in weight up to 30% compared with controls. Some testicular tubules were completely devoid of germ cells. Administration of C.I. Direct Black 38 after day 13 of gestation did not affect testicular function of ♂ offspring (6).

Metabolism and toxicokinetics

Benzidine and monoacetylbenzidine found in urine of rats and mice in 13-wk sub-chronic toxicity studies (7).

Following oral administration of a single dose of 10 mg kg⁻¹ to Syrian golden hamster, 10.7 µg benzidine, 535 µg monoacetylbenzidine, 27.6 µg diacetylbenzidine, 11.5 µg 4-aminobiphenyl and, as alkaline hydrolysable conjugates, 328.5 µg benzidine and 6.3 µg 4-aminobiphenyl, were identified in the urine; thus a total of 10% of the dye is metabolised to benzidine and its metabolic degradation products (8).

Irritancy

100 mg instilled into rabbit eye caused moderate irritation (3).

Genotoxicity

Salmonella typhimurium TA98, TA100, TA1537 with and without metabolic activation positive (9).

In vivo rat (12, 24, 36 hr) 100, 500 mg kg⁻¹ induced unscheduled DNA synthesis in liver and had a weak effect on micronuclei induction in bone marrow. A dose-response relationship was observed (10).

Other comments

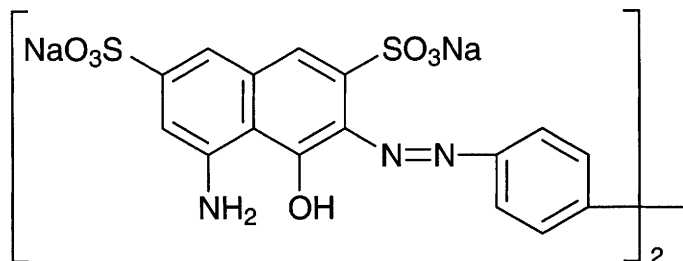
Reviews on human health effects and experimental toxicology listed (11).

Had no substantial effect on oxygen conditions, pH, saprophyte development or total microorganism count at concentrations of 0.001 mg l⁻¹ (12).

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c404 C.I. Direct Blue 6



C₃₂H₂₀N₆Na₄O₁₄S₄

Mol. Wt. 932.77

CAS Registry No. 2602-46-2

Synonyms 2,7-naphthalenedisulfonic acid, 3,3'-[[1,1'-biphenyl]-4,4'-diylbis(azo)]bis(5-amino-4-hydroxy)-, tetrasodium salt; 1-naphthol-3,6-disulfonic acid, 2,2'-(4,4'-biphenylenebisazo)bis(8-amino)-, tetrasodium salt; C.I. 22610; Diphenyl Blue 2B; Indigo Blue 2B; Chrome Leather Blue 2B

EINECS No. 220-012-1

RTECS No. QJ 6400000

Uses Dyestuff for cellulose, silk, wool, nylon, leather and paper.

Occupational exposure

Supply classification toxic

Risk phrases May cause cancer – Possible risk of harm to the unborn child (R45, R63)

Safety phrases Avoid exposure – obtain special instruction before use – In case of accident or if you feel unwell, seek medical advice immediately (show label where possible) (S53, S45)

Ecotoxicity

Fish toxicity

LC₅₀ (96 hr) fathead minnow >180 mg l⁻¹ (1).

Invertebrate toxicity

Selenastrum capricornutum (7, 14 day) incubated at 24°C, dyes tested at 1 mg l⁻¹ and 10 mg l⁻¹. Direct Blue 6 did not inhibit algal growth (1).

A dye solution was added to provide a concentration of 25 mg l⁻¹ in settled domestic sewage. Oxygen uptake of the system was followed for 7 hr. Oxygen uptake <10% lower than control (1).

Environmental fate

Anaerobic effects

Gradual feeding of C.I. Direct Blue 6 to an active sludge digester, resulting in a final concentration of 140 mg dye l⁻¹ in the digester after 45 days, had no significant effect upon the anaerobic digestion of added sludge over this period. During the course of the experiment some decolorisation was observed. It is suggested that some physical adsorption accompanied by biodegradation and chemical reduction could account for this (1).

Degradation studies

To study the effect on stream oxidative processes, dye-sewage sludge systems (dye concentration to yield 25 mg l⁻¹ organic carbon) diluted to 1:10 and 1:100 in river water. No inhibition was observed (1).

Mammalian & avian toxicity

Sub-acute and sub-chronic data

Effects on the liver, spleen, thymus, lymph nodes and bone marrow reported in rats fed diets containing 190-3000 mg kg⁻¹ and mice 750-12500 mg kg⁻¹ for 13 wk (2).

Carcinogenicity and chronic effects

Inadequate evidence for carcinogenicity to humans, sufficient evidence for carcinogenicity to animals, IARC classification group 2A (3).

National Toxicology Program investigated in rat, mouse. Designated carcinogen in ♀ and ♂ rats. Demonstrated by dose-related increases of malignant neoplasms, increase of a combination of benign and malignant neoplasms, or a marked increase of benign neoplasms where these progress to malignancy (4).

Teratogenicity and reproductive effects

7, 14 or 20 mg 100 g⁻¹ administered to Wistar albino rats on day 8 of gestation by intraperitoneal injection. Foetal resorption and foetal malformations (anophthalmia, hydrocephalus and other malformations) reported at 14 and 20 mg 100 g⁻¹. The highest dose also caused maternal toxicity (5).

Metabolism and toxicokinetics

Benzidine and monoacetylbenzidine found in urine of rats and mice in 13-wk sub-chronic toxicity studies (2).

Genotoxicity

Salmonella typhimurium TA98, TA100, TA1535, TA1537, TA1538 with and without metabolic activation negative (6).

Salmonella typhimurium TA98, TA100 with metabolic activation in flavin mononucleotide modified assay positive (7). L5178Y tk⁺/tk⁻ mouse lymphoma assay with or without metabolic activation negative (7).

Chinese hamster ovary cells sister chromatid exchange and chromosomal aberrations with or without metabolic activation negative (8).

Other comments

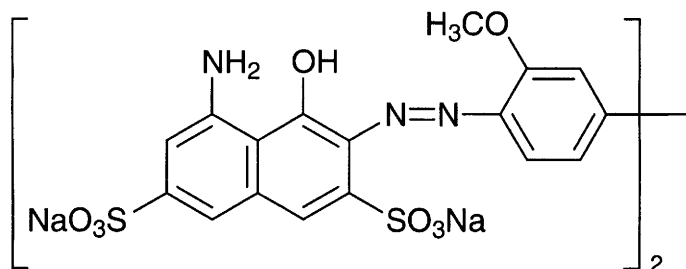
Reviews on human health effects and experimental toxicology listed (9).

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c405 C.I. Direct Blue 15



$C_{34}H_{28}N_6Na_4O_{16}S_4$

Mol. Wt. 996.85

CAS Registry No. 2429-74-5

Synonyms 2,7-naphthalenedisulfonic acid, 3,3'-[(3,3'-dimethoxy-4,4'-biphenylene)bis(azo)]bis(5-amino-4-hydroxy-), tetrasodium salt; C.I. 24400; C.I. Direct Blue 15, tetrasodium salt; Direct Blue 10 G; Phenamine Sky Blue; Asian Direct Sky Blue FF

EINECS No. 219-385-3

RTECS No. QJ 6420000

Uses Colorant.

Ecotoxicity

Fish toxicity

Flow tests on rainbow trout were discontinued because of relatively low toxicity; LC_{50} would be in the order of some hundreds of ppm (a concentration unlikely to occur in practice) (1).

Environmental fate

Degradation studies

100% of a test concentration of 100 mg l⁻¹ (incubated at 35°C in the presence of an anaerobic sludge inoculum) was degraded in 7 days. 4,4'-Diamino-3,3'-dimethoxybiphenyl was identified as a metabolite (2).

Mammalian & avian toxicity

Sub-acute and sub-chronic data

Oral rat (13 wk) 0.063-1.0% for ♀ and 0.125-3.0% for ♂ (in drinking water) caused increased liver and kidney weight and mild chronic nephropathy (3).

Carcinogenicity and chronic effects

National Toxicology Program tested rats via drinking water. Clear evidence of carcinogenicity in ♂ and ♀ rats. Demonstrated by dose-related increase of malignant neoplasm, increase of a combination of malignant and benign neoplasms, or marked increase of benign neoplasms if these progress to malignancy (4).

Teratogenicity and reproductive effects

TD_{Lo} (8-day pregnant) intraperitoneal rat 70 mg kg⁻¹ caused effects on fertility including post-implantation mortality (5).

TD_{Lo} (8-day pregnant) intraperitoneal rat 200 mg kg⁻¹ effect on embryo and foetus (6).

Genotoxicity

Salmonella typhimurium TA98, TA100, TA1535, TA1537 with and without metabolic activation negative (7).

Chinese hamster ovary cells sister chromatid exchanges and chromosomal aberrations with or without metabolic activation negative (8).

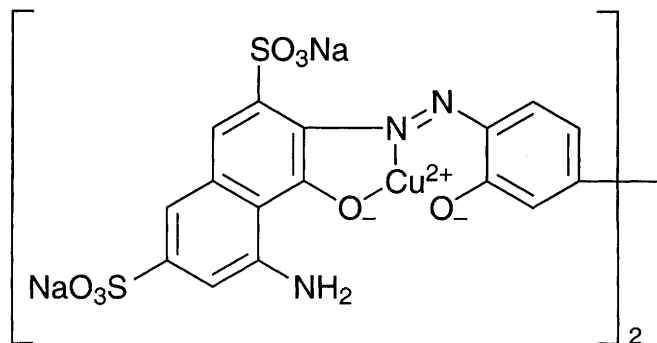
Other comments

Reviews on human health effects, experimental toxicology and environmental effects listed (9).

Fish toxicity, biodegradation and bioaccumulation reviewed (10).

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$C_{32}H_{16}Cu_2N_6Na_4O_{16}S_4$

Mol. Wt. 1087.82

CAS Registry No. 28407-37-6

Synonyms (μ -((3,3'-((3,3'-dihydroxy(1,1'-biphenyl)-4,4'-diyl)bis(azo)bis(5-amino-4-hydroxy-2,7-naphthalenedisulfonate))(8-)))dicuprate(4-), tetrasodium; C.I. 24401; Pontamine Fast Blue 7GLN; Dynarect Blue 2AH

EINECS No. 249-008-8

RTECS No. GS 2169000

Uses Stain for silk and wool.

Mammalian & avian toxicity

Acute data

LD₅₀ oral rabbit, rat 3290 mg kg⁻¹ (1).

LD_{Lo} dermal rabbit 8 g kg⁻¹ (1).

Carcinogenicity and chronic effects

National Toxicology Program tested rats and mice via feed. Some evidence for carcinogenicity in ♂ rats, no evidence for carcinogenicity in ♀ rats. Clear evidence for carcinogenicity in both ♂ and ♀ mice (2).

Computer-Optimised Molecular Parametric Analysis of Chemical Toxicity (COMPACT) procedure, evaluating carcinogenicity/toxicity based on interaction with active site of cytochrome P450I or binding site of Ah receptor, positive (3).

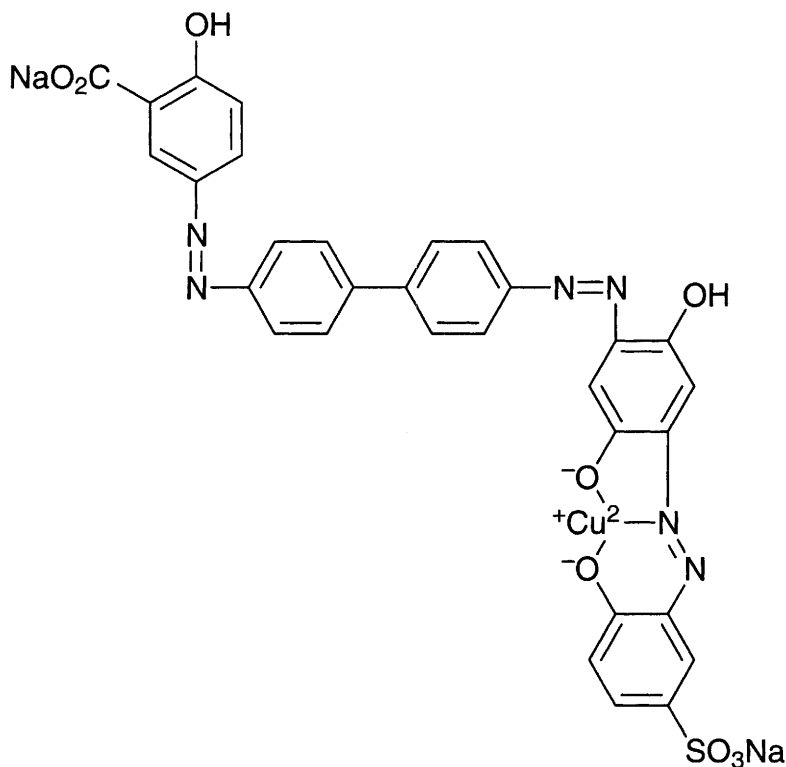
Genotoxicity

Salmonella typhimurium TA98, TA100, TA1535, TA1537 with and without metabolic activation negative (4).

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C407 C.I. Direct Brown 95



$C_{31}H_{18}CuN_6Na_2O_9S$

Mol. Wt. 760.11

CAS Registry No. 16071-86-6

Synonyms [5-[4'-[[[2,6-dihydroxy-3-[(2-hydroxy-5-sulfophenyl)azo]phenyl]azo][1,1'-biphenyl]-4-yl]azo-2-hydroxybenzoato, (4-)]cuprate(2-), disodium; 5-[[4'-[[[2,6-dihydroxy-3-[(2-hydroxy-5-sulfophenyl)-azo][1,1'-biphenyl]-4-yl]azo]-2-hydroxybenzoic acid, copper complex; Direct Brown 95; Direct Fast Brown BRL; C.I. 30145

EINECS No. 240-221-1

RTECS No. GL 7375000

Uses Dye stuff for cellulose, silk, wool, acetate, nylon, leather, paper and casein-formaldehyde plastics.

Physical properties

Solubility. Organic solvents: ethanol

Occupational exposure

Supply classification toxic

Risk phrases May cause cancer (R45)

Safety phrases Restricted to professional users – Avoid exposure – obtain special instruction before use – In case of accident or if you feel unwell, seek medical advice immediately (show label where possible) (S53, S45)

Ecotoxicity

Fish toxicity

LC₅₀ (96 hr) fathead minnow >180 mg l⁻¹ (1).

Invertebrate toxicity

Selenastrum capricornutum (7, 14 day) incubated at 24°C, dyes tested at 1 mg l⁻¹ and 10 mg l⁻¹. Direct Brown 95 did not inhibit algal growth (1).

Environmental fate

Anaerobic effects

Gradual feeding of C.I. Direct Brown 95 to an active sludge digester, resulting in a final concentration of 140 mg dye l⁻¹ in the digester after 45 days, had no significant effect upon the anaerobic digestion of added sludge over this period. During the course of the experiment some decolorisation was observed. It is suggested that some physical adsorption accompanied by biodegradation and chemical reduction could account for this (1).

Degradation studies

To study the effect on stream oxidative processes, dye-sewage sludge systems (dye concentration to yield 25 mg l⁻¹ organic carbon) diluted to 1:10 and 1:100 in river water. Inhibition was observed at dilution 1:10 69% oxygen consumed, 1:100 61% oxygen consumed (1).

A dye solution was added to provide a concentration of 25 mg l⁻¹ of organic carbon to an activated sludge 1500 mg l⁻¹ in settled domestic sewage. Oxygen uptake of the system was followed for 7 hr. Oxygen uptake at least 10% lower than control. Acclimated sludge (14 day) 25 mg l⁻¹ (organic carbon) before acclimatisation 84.5%, after acclimatisation 84.1% oxygen consumed. However, it should be kept in mind that the dye concentration of 25 mg l⁻¹ (organic carbon) is significantly higher than concentrations likely to be encountered in real life biological oxidation systems (1).

Mammalian & avian toxicity

Acute data

LD₅₀ oral rat >12 g kg⁻¹ (2).

LD_{Lo} oral rabbit 2000 mg kg⁻¹ (2).

Sub-acute and sub-chronic data

Effects on liver, spleen, thymus, lymph nodes and bone marrow reported in rats fed diets containing 190-3000 mg kg⁻¹ and mice 375-12500 mg kg⁻¹ for 13 wk (3).

Carcinogenicity and chronic effects

Inadequate evidence for carcinogenicity to humans, sufficient evidence for (technical-grade) carcinogenicity to animals, IARC classification group 2A (4).

National Toxicology Program investigated rat, mouse via feed. Designated carcinogen in ♀ rats, non-carcinogen in ♂ rats (5).

TD_{Lo} (5 wk) oral rat 2625 mg kg⁻¹ induced liver tumours (5).

Metabolism and toxicokinetics

Benzidine and monoacetylbenzidine found in urine of rats in 13-wk sub-chronic toxicity studies (3).

Genotoxicity

Salmonella typhimurium TA1538 with metabolic activation positive (6).

Salmonella typhimurium TA98, TA100, TA1535, TA1537 with and without metabolic activation equivocal (7).

Salmonella typhimurium TA98, TA1538 with or without metabolic activation negative (8).

In vivo/in vitro unscheduled DNA synthesis assay in primary rat hepatocytes positive (8).

Chinese hamster ovary cells chromosomal aberrations with or without metabolic activation negative; sister chromatid exchanges without metabolic activation negative; with metabolic activation slight but inconsistent positive (9).

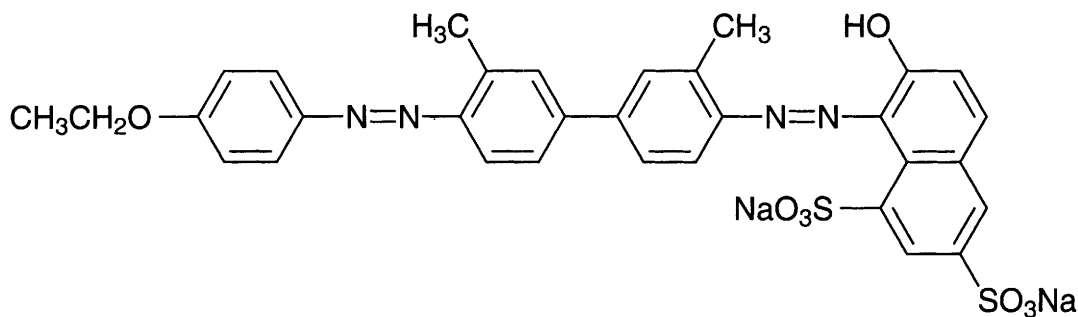
Other comments

Reviews on human health effects and physico-chemical properties, experimental toxicology listed (10).

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C408 C.I. Direct Red 39



$C_{32}H_{26}N_4Na_2O_8S_2$

Mol. Wt. 704.69

CAS Registry No. 6358-29-8

Synonyms 8-[[4'-[(4-ethoxyphenyl)azo]-3,3'-dimethyl[1,1'-biphenyl]-4-yl]azo]-7-hydroxy-1,3-naphthalenedisulfonic acid, disodium salt; C.I. 23630; Direct Red 39; Direct Fast Scarlet 3B; Phenamine Scarlet 3B

EINECS No. 228-766-3

RTECS No. QJ 6476000

Uses Dyestuff for silk and wool, acetate stain.

Physical properties

Solubility. Organic solvents: acetone, ethanol

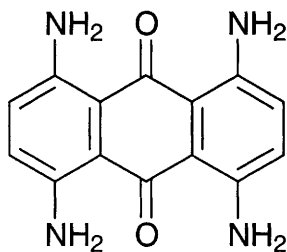
Genotoxicity

Salmonella typhimurium TA98, TA100, TA1535, TA1537 with and without metabolic activation negative (1,2).

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c409 C.I. Disperse Blue 1



$C_{14}H_{12}N_4O_2$

Mol. Wt. 268.28

CAS Registry No. 2475-45-8

Synonyms 1,4,5,8-tetraamino-9,10-anthracenedione; acetoquinone blue L; 1,4,5,8-tetraminoanthraquinone; C.I. 64500

EINECS No. 219-603-7

RTECS No. CB 0540000

Uses Dyestuff in semipermanent hair colorants, for nylon, cellulose acetate and triacetate, polyester and acrylate fibres, and thermoplastics.

Physical properties

M. Pt. 332°C **Partition coefficient** $\log P_{ow}$ -0.96 **Volatility** v.p. 1.37×10^{-5} mmHg

Solubility Water: 30 $\mu\text{g l}^{-1}$ at 25°C. Organic solvents: acetone, benzene, ethanol

Ecotoxicity

Bioaccumulation

Solubility data suggest the potential for a 30- to 150-fold concentration enhancement in sediments and bioconcentration of about 1,000 times in the absence of metabolism (1).

Mammalian & avian toxicity

Acute data

LD₅₀ oral rat 1.2 – >6.3 g kg⁻¹ (2).

Carcinogenicity and chronic effects

No adequate data for carcinogenicity to humans, sufficient evidence for carcinogenicity to animals, IARC classification group 2B (3).

Given in feed at 5000 ppm to F344/N rats and at 2500 ppm to B6C3F1 mice for 104 wk. Clear evidence of carcinogenicity in ♂ and ♀ rats (increased incidence of transitional cell papilloma and carcinoma, leiomyoma, leiomyosarcoma, squamous cell papilloma and carcinoma of the bladder, and adenoma and carcinoma of pancreatic islet cells). Equivocal results in ♂ mice, no evidence of carcinogenicity in ♀ mice (4).

A dermal carcinogenesis study in mice proved negative (5).

Teratogenicity and reproductive effects

Oral administration of a commercial product containing 0.61% Disperse Blue 1 had no effect on fertility, gestation, lactation or viability indices in rats, and was not teratogenic in rats or rabbits (3).

Metabolism and toxicokinetics

In vitro dermal penetration studies on skin from miniature pigs indicate that C.I. Disperse Blue 1 is poorly absorbed (5).

Irritancy

C.I. Disperse Blue 1 at concentrations up to 10% did not cause skin irritation in guinea pigs (5).

Sensitisation

No allergic response in 100 adult humans within 3 days after 24 hr contact with a 0.5% solution (2).

C.I. Disperse Blue 1 is a moderate sensitiser in guinea pigs (5).

Genotoxicity

Salmonella typhimurium TA98 with or without metabolic activation positive; TA1535 without metabolic activation negative, with metabolic activation positive; TA100 without metabolic activation negative, with metabolic activation equivocal; TA97 without metabolic activation positive, with metabolic activation equivocal (6).

L5178Y mouse lymphoma cell forward mutation assay without metabolic activation positive (7).

Chinese hamster ovary cell chromosomal aberration and sister chromatid exchange with and without metabolic activation positive (8).

Other comments

The American College of Toxicology report on the safety assessment of C.I. Disperse Blue 1 concluded that it was safe to use in hair dyes at concentrations up to 1% (5).

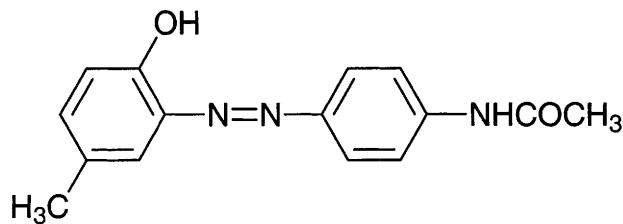
Human safety of C.I. Disperse Blue 1 assessed (9).

Reviews on human health effects and experimental toxicology listed (10).

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c410 C.I. Disperse Yellow 3



C₁₅H₁₅N₃O₂

Mol. Wt. 269.30

CAS Registry No. 2832-40-8

Synonyms N-(4-((2-hydroxy-5-methylphenyl)azo)phenyl)acetamide; Acetamine Yellow CG; Dispensol Printing Yellow G; 4'-((6-hydroxy-*m*-tolyl)azo)acetanilide; Estone Yellow GN; Hispacet Fast Yellow G; C.I. 11855; C.I. Solvent Yellow 77; Chemacet Yellow G; Duracet Yellow G

EINECS No. 220-600-8

RTECS No. AC 3662000

Uses Dyestuff for nylon, polyvinyl chloride and acrylic fibres, wools and furs, cellulose acetate, polystyrene and other thermoplastics.

Physical properties

M. Pt. 268-270°C

Solubility Water: 1.5-6.1 mg l⁻¹ at 60°C. Organic solvents: acetone, benzene, ethanol

Ecotoxicity

Fish toxicity

LC₅₀ (96 hr) fathead minnow >180 mg l⁻¹ (1).

Invertebrate toxicity

Selenastrum capricornutum (7, 14 day) incubated at 24°C, dyes tested at 1 mg l⁻¹ and 10 mg l⁻¹. Concentrations of 10 mg l⁻¹ inhibited algal growth by >80% after 7 days (1).

Environmental fate

Degradation studies

A dye solution was added to provide a concentration of 25 mg l⁻¹ of organic carbon to an activated sludge 1500 mg l⁻¹ in settled domestic sewage. Oxygen uptake <10% lower than control (1).

To study the effect on stream oxidative processes, dye-sewage sludge systems (dye concentration to yield 25 mg l⁻¹ organic carbon) diluted to 1:10 and 1:100 in river water. No inhibition was observed (1).

C.I. Disperse Yellow 3 is mineralised by the white rot basidiomycete *Phanerochaete chrysosporium* under nitrogen-limiting, ligninolytic conditions (2).

Mammalian & avian toxicity

Acute data

LD₅₀ intraperitoneal mouse, rat 8080-8190 mg kg⁻¹ (3).

Carcinogenicity and chronic effects

No adequate evidence for carcinogenicity to humans, limited evidence for carcinogenicity to animals, IARC classification group 3 (4).

National Toxicology Program tested rats and mice via feed. Carcinogen in ♂ rats and ♀ mice (liver adenomas and carcinomas), not carcinogenic in ♀ rats and ♂ mice (5).

Sensitisation

No allergic response in 100 adult humans within 3 days after 24 hr contact with a 0.5% solution (6).

Allergic contact-type dermatitis reported from textiles coloured with Disperse Yellow 3 (4).

Contact allergen in skin tests (4).

Genotoxicity

Salmonella typhimurium TA97, TA98, TA100 with and without metabolic activation positive (7).

Salmonella typhimurium TA100, TA1537, TA1538 with and without metabolic activation positive (8).

L5178Y mouse lymphoma cell forward mutation assay with metabolic activation positive (9).

In vitro Chinese hamster ovary cells sister chromatid exchanges without metabolic activation positive; with metabolic activation negative; chromosomal aberrations with and without metabolic activation negative (10).

In vivo mouse bone marrow micronucleus test negative (11), chromosomal aberration test negative (12).

Drosophila melanogaster sex-linked recessive lethal mutations assay negative (13).

Other comments

Report on the safety assessment of C.I. Disperse Yellow 3 (14).

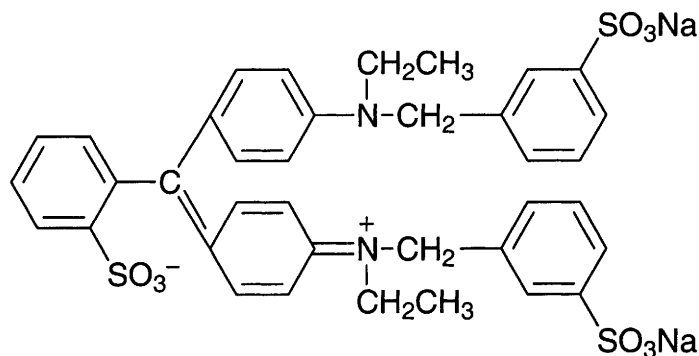
Genotoxicity reviewed (15).

Reviews on human health effects and experimental toxicology listed (16).

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C411 C.I. Food Blue 2



$C_{37}H_{34}N_2Na_2O_9S_3$

Mol. Wt. 792.86

CAS Registry No. 3844-45-9

Synonyms (ethyl)[(4-(p-[(ethyl-*m*-sulfobenzyl)amino]- α -(*o*-sulfophenyl)benzylidene)2,5-cyclohexadien-1-ylidene)](*m*-sulfobenzyl)ammonium hydroxide, inner salt, disodium salt; C.I. 42090; Acid Sky Blue A; Brilliant Blue; C.I. Acid Blue 9, disodium salt; Dever Brilliant Blue FCF; Edicol FD&C Blue No.1 Lake

EINECS No. 223-339-8

RTECS No. BQ 4725000

Uses Dyestuff for wool, silk, nylon, paper, leather, soap and wood stains. Indicator. Biological stain.

Physical properties

M. Pt. 283°C (decomp.)

Solubility. Organic solvents: ethanol

Mammalian & avian toxicity

Acute data

LD₅₀ subcutaneous mouse 4600 mg kg⁻¹ (1).

Carcinogenicity and chronic effects

No adequate data for carcinogenicity to humans, limited evidence for carcinogenicity to animals, IARC classification group 3 (2).

TD_{Lo} (62 wk) parenteral rat 6580 mg kg⁻¹ intermittent doses caused gastro-intestinal tumours (3,4).

No significant increase in tumour incidence in ♀ and ♂ ASH/CS1 mice fed 20-2000 mg kg⁻¹ for 80 wk (5).

Injection site fibrosarcomas developed in rats subcutaneously injected with 7.4 or 20 mg of the dye (37% or >90% pure) 2 × wk⁻¹ for 54-82 wk (5).

Metabolism and toxicokinetics

After oral administration to rats, rabbits and dogs <5% was absorbed. Excretion occurred via faeces. Intravenous rats >90% excreted in bile within 4 hr (6).

Genotoxicity

Salmonella typhimurium TA98, TA100, TA1537 with and without metabolic activation negative (5).

In vitro Chinese hamster lung cells chromosomal aberrations with and without metabolic activation positive (5).

Legislation

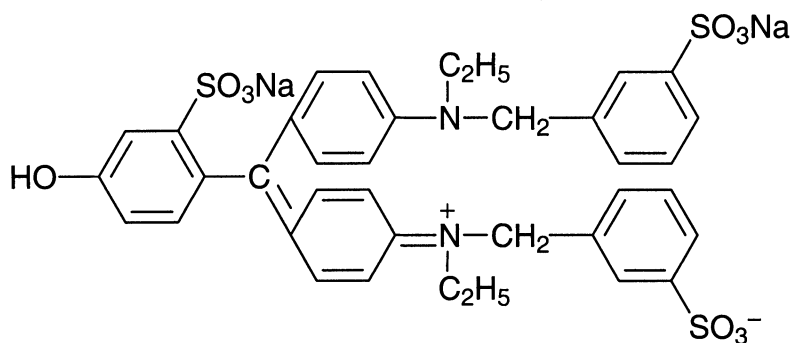
Acceptable Daily Intake 0-125 mg kg⁻¹ body weight (7).

Other comments

Toxicological data on C.I. Food Blue 2 in relation to its suitability for use as an environmental tracer dye reviewed (8).

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$C_{37}H_{34}N_2Na_2O_{10}S_3$

Mol. Wt. 808.86

CAS Registry No. 2353-45-9

Synonyms N-ethyl-N-[4-[[4-[ethyl[(3-sulfophenyl)methyl]amino]phenyl](4-hydroxy-2-sulfophenyl)-methylene]-2,5-cyclohexadien-1-ylidene]-3-sulfobenzenemethanaminium hydroxide inner salt, disodium salt; FD&C Green No. 3; Fast Green FCF; C.I. 42053

EINECS No. 219-091-5

RTECS No. BQ 4425000

Uses As a biological stain; in food, drugs and cosmetics.

Physical properties

M. Pt. 290°C (decomp.)

Solubility Water: very soluble. Organic solvents: ethanol

Mammalian & avian toxicity

Acute data

LD₅₀ oral rats >2.0 g kg⁻¹ (1).

Sub-acute and sub-chronic data

Oral beagle dogs (groups of 2 ♂ and 2 ♀, 6-9 months old) 0, 1.0 or 2.0% C.I. Food Green 3 in diet for 2 years (daily amounts of 258-288 and 512-781 mg kg⁻¹ at the 1% and 2% level, respectively). No toxic effects were observed (2).
Dermal mouse 0.1 ml of a 1% solution applied to a 6 cm² area once weekly. During the 18-month period, no significant effects of treatment were observed, but reduced survival was seen in the treated group (3).

Carcinogenicity and chronic effects

No adequate data for carcinogenicity to humans, limited evidence for carcinogenicity to animals, IARC classification group 3 (4).

Subcutaneous injection to two groups of 16 ♀ Fischer rats (~1 month old) 0.5 ml of a 3% or 6% aqueous solution of C.I. Food Green 3 twice weekly for 17 weeks, then injection of 3% solution to both groups twice weekly for a further 9 wk. 13/16 rats initially in the 6% solution group, and 10/14 rats in the other group developed fibrosarcomas at the injection site. The first tumours were observed after 7 months; no tumours were seen in 10 control rats injected with distilled water (5).

Metabolism and toxicokinetics

Studies in rats and dogs found that <5% of orally administered C.I. Food Green 3 is absorbed; it is mainly eliminated in the faeces (6).

In rats, 90% of dye given by intravenous injection was excreted in the bile within 4 hr (7).

C.I. food Green 3 binds to plasma protein (7,8).

Genotoxicity

Salmonella typhimurium TA98, TA100, TA1535, TA1537, TA1538 with and without metabolic activation negative (9).

In vitro mouse lymphoma L5178Y TK+/- assay negative (9).

In vivo and *in vitro* rat hepatocytes induction of unscheduled DNA synthesis negative (10).

In vitro Chinese hamster fibroblasts chromosomal aberration test without metabolic activation positive (crude sample) (11).

Legislation

Acceptable Daily Intake up to 25 mg kg⁻¹ (12).

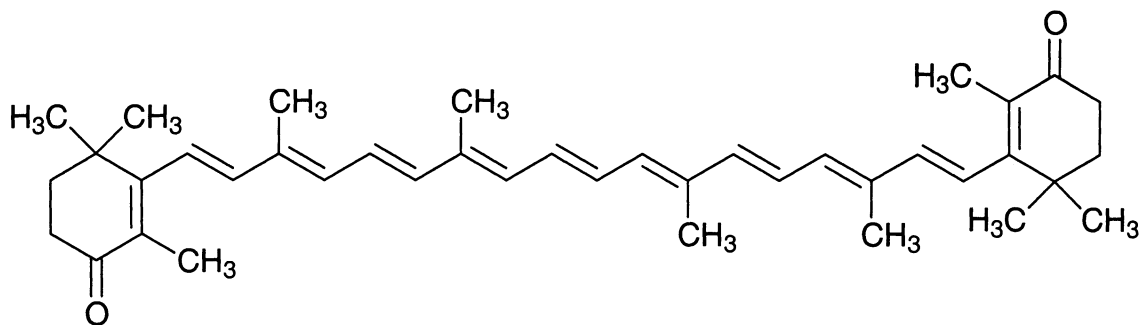
Other comments

Human health effects and experimental toxicology reviewed (13).

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c413 C.I. Food Orange 8



C₄₀H₅₂O₂

Mol. Wt. 564.85

CAS Registry No. 514-78-3

Synonyms β,β-carotene-4,4'-dione; 4,4'-dioxo-β-carotene; Canthaxanthin; Carophyll Red; Orobronze; Roxanthin Red 10; Carotaben Plus; C.I. 40850

EINECS No. 208-187-2

RTECS No. FI 0330000

Uses Colour additive for food and drugs. Oral suntanning agent.

Occurrence Widely distributed in nature. Isolated from the edible mushroom *Cantharellus cinnabarinus*. Isolated from flamingo feathers.

Physical properties

M. Pt. 217°C (decomp.)

Solubility. Organic solvents: chloroform

Ecotoxicity

Bioaccumulation

One force-fed meal containing 3H-C.I. Food Orange 8 was given to mature ♀ rainbow trout. At 96 hr C.I. Food Orange 8 had accumulated in the liver, skin, muscle and ovaries. It appears that 3H-C.I. Food Orange 8 is a precursor of astaxanthin which was found in the liver of all trout (1).

Environmental fate

Nitrification inhibition

Chlorella emersonii grown under high light intensity and low nitrogen degrades its chlorophyll and synthesises C.I. Food Orange 8 as the major carotenoid. Nitrogen starvation or high light alone does not induce C.I. Food Orange 8 production. Norflurazon, a carotene inhibitor at the level of phytoene desaturation inhibits production of C.I. Food Orange 8 with no accumulation of phytoene. *Chlorella vulgaris* exposed under similar conditions do not respond in the same way (2).

Mammalian & avian toxicity

Acute data

LD₅₀ oral mouse 10 g kg⁻¹ (3).

Sub-acute and sub-chronic data

TD_{Lo} (15 wk) oral man 86 mg kg⁻¹ intermittently retinal changes were observed (4).

Other effects

Any other adverse effects

Induces cytochrome P 4501A in rat liver (5).

Legislation

ADI 0-0.03 mg kg⁻¹ body weight (6).

Other comments

Carotenoid compounds react with nitrogen dioxide in the dark to form nitrosating agents. Under light conditions this reaction is limited and NO₂ is reduced by carotenoids to nitric oxide; this mechanism may be important in plants to prevent damage from NO₂ exposure (7).

Experimental toxicology and human health effects reviewed (8).

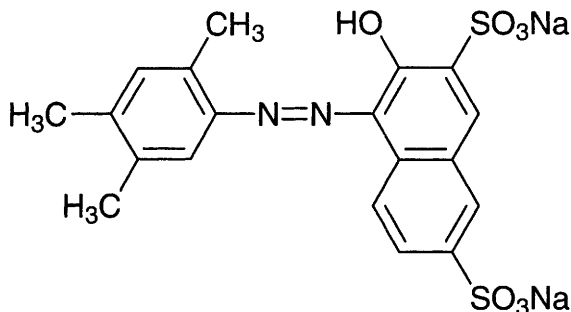
Detected in the thalli of ten Italian lichen species (9).

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C414 C.I. Food Red 6



$C_{19}H_{16}N_2Na_2O_7S_2$

Mol. Wt. 494.46

CAS Registry No. 3564-09-8

Synonyms Ponceau 3R; D&C Red No.15; C.I. Acid Dye; C.I. 16155; Dolkwal Ponceau 3R; FD&C Red No. 1; 3-hydroxy-4-[(2,4,5-trimethylphenyl)azo]-2,7-naphthalenedisulfonic acid, disodium salt; sodium cumeneazo- β -naphthol disulfonate

EINECS No. 222-638-0

RTECS No. QJ 6650000

Uses Dye. Biological stain.

Physical properties

Solubility Water: miscible. Organic solvents: ammonium acetate, ethanol

Mammalian & avian toxicity

Carcinogenicity and chronic effects

No adequate evidence for carcinogenicity to humans, sufficient evidence for carcinogenicity to animals, IARC classification group 2B (1).

Oral mouse 10 or 20 g kg⁻¹ diet. None of the mice survived longer than 68 wk. 36/67 high-dose animals had hepatic adenomas and 16/67 had hepatic carcinomas, four of which metastasised to the lungs. 9/217 untreated mice developed liver tumours (2,3).

Oral rat 0, 5, 10, 20 or 50 g kg⁻¹ diet for 2 yr. Hepatic carcinomas and benign hepatomas were induced in a dose-dependent manner. Nodular hyperplasia of the liver was also observed in treated animals compared to none in controls. Treated animals developed enlarged livers and kidneys, reduced body weight gain and high mortality (3).

Oral rat 0, 3, 10 or 30 mg kg⁻¹ diet for 65 wk. Bile duct adenomas were observed in 0/90, 1/20, 5/24 and 7/23 animals in control and treated groups, respectively, and hepatic carcinomas in 0/90, 0/20, 2/24 and 7/23 animals in control and treated groups, respectively (4).

Bladder implantation mouse (25 wk) single 15-17 mg pellet of 12.5% suspension in paraffin wax. 5/33 animals developed carcinoma of the bladder compared to 1/82 controls (5).

Metabolism and toxicokinetics

Following oral administration to rabbits, 0.4% unchanged dye and 44% 2,4,5-trimethylaniline were excreted in the urine. 2,4,5-Trimethylaniline was oxidised to dimethylaminobenzoic acids (6,7).

Genotoxicity

Salmonella typhimurium TA97, TA98, TA100, TA1535, TA1537, TA1538 (metabolic activation unspecified) negative (8).

Salmonella typhimurium TA98, TA100, TA1535, TA1537, TA1538 with and without metabolic activation positive (9).

In vitro mouse lymphoma cells, tk⁺/tk⁻ forward mutation assay without metabolic activation positive (9).

Legislation

Removed from approved list of substances, US Food and Drug Act, in 1966 (10).

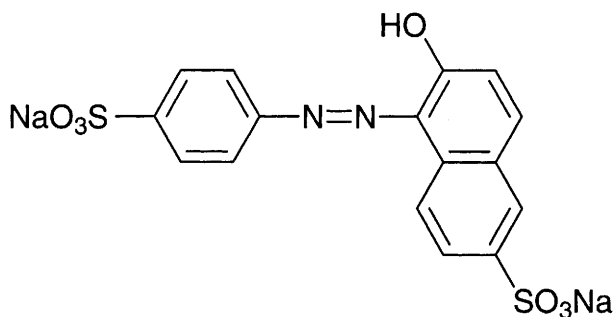
Other comments

Physical properties, uses, carcinogenicity and mammalian toxicity reviewed (10).

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3. Hanson, W. H. et al *Toxicol. Appl. Pharmacol.* 1963, **5**, 105-118.
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8. Klopman, G. et al *Mutat. Res.* 1990, **228**(1), 1-50.
9. Cameron, T. P. et al *Mutat. Res.* 1987, **189**(3), 223-261.
10. IARC Monograph 1975, **8**, 199-206

c415 C.I. Food Yellow 3



C₁₆H₁₀N₂Na₂O₇S₂

Mol. Wt. 452.38

CAS Registry No. 2783-94-0

Synonyms Sunset Yellow FCF; 6-hydroxy-5-[(4-sulfophenyl)azo]-2-naphthalenesulfonic acid, disodium salt; FD & C Yellow No. 6; C.I. 15985

EINECS No. 220-491-7

RTECS No. QK 2450000

Uses Provisionally listed for use in food, drugs and cosmetics.

Physical properties

Solubility Organic solvents: slightly soluble in ethanol

Environmental fate

Degradation studies

Escherichia coli, *Klebsiella aerogenes*, *Proteus vulgaris*, *Shigella dysenteriae*, *Shigella flexneri* and *Salmonella typhimurium* all reduced the azo bond of the dyes and converted them into corresponding amines. The azo dyes were also utilised by the organisms as sole amines and as sole source of carbon and nitrogen, indicating further degradation (1).

Mammalian & avian toxicity

Carcinogenicity and chronic effects

An evaluation of two reports of an increased incidence of adrenal medullary adenomas in rats given C.I. Food Yellow 3 for 2 yr as well as other studies in which there were no effects, concluded that the findings in the two reports were not attributable to the treatment (2).

Genotoxicity

After oral administration to rodents bile, excreta and bone marrow were negative in the Ames test. *Salmonella typhimurium* TA100 with metabolic activation positive only in faecal extract of treated animals (3).

Oral rat and mice 200 mg kg⁻¹ gave a negative result in bone marrow micronucleus tests (4).

Other effects

Any other adverse effects

Addition *in vitro* to rat hepatic microsomes resulted in a decrease of cytochrome P₄₅₀ and cytochrome b₅ levels and azo reductase activity (5).

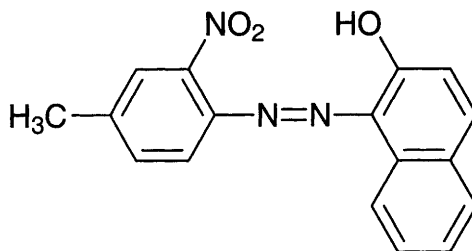
Legislation

ADI humans <2.5 mg kg⁻¹ (6).

References

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3. Westmoreland, C. et al *Carcinogenesis (London)* 1991, **12**(8), 14-3-1407.
4. Wever, J. et al *Environ. Mol. Mutagen.* 1989, **13**(3), 271-276.
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6. *Tech. Rep. Ser. Wld. Health Org.* 1982, **683**

C416 C.I. Pigment Red 3



$C_{17}H_{13}N_3O_3$

Mol. Wt. 307.31

CAS Registry No. 2425-85-6

Synonyms 1-[(4-methyl-2-nitrophenyl)azo]-2-naphthalenol; C.I. 12120; D & C Red No. 35; Fast Red A (pigment); Hansa red G; Pigment Red 3; Toluidine Red; COLO Pigment Scarlet RN

EINECS No. 219-372-2

RTECS No. QK 4247000

Uses Widely used pigment in paints, printing inks, synthetic resin lacquers and leather finishes. Pigment used in inks for foil and tinplate printing, paper coating and dyeing. Colorant used in wallpapers, linoleum, carbon papers, typewriter ribbon, student-grade artist materials, celluloid, cellulose acetate, styrene, protein plastics and cement.

Physical properties

M. Pt. 270-272°C

Solubility Organic solvents: acetone, benzene, ethanol

Mammalian & avian toxicity

Acute data

LD₅₀ oral rat >5 g kg⁻¹ (1).

Sub-acute and sub-chronic data

Oral rat, mouse 10% and 0.3% in diet for 14 and 90 days, respectively, caused haemolytic anaemia, spleen lesions, liver, bone marrow and kidney effects (2).

Carcinogenicity and chronic effects

National Toxicology Program tested rats and mice via feed. Some evidence of carcinogenicity in ♀ and ♂ rats, and ♂ mice. No evidence of carcinogenicity in ♀ mice. Demonstrated by chemically-related increase in neoplasms (malignant, benign or combined) (3).

Computer-Optimised Molecular Parametric Analysis of Chemical Toxicity (COMPACT) procedure, evaluating carcinogenicity/toxicity based on interaction with active site of cytochrome P450I or binding site of Ah receptor, positive (4).

Irritancy

5% in polyethylene glycol irritant in humans in 48 hr closed patch test (5).

1% non-irritant (6).

Sensitisation

Sensitisation and photosensitisation reported in humans; cosmetic related dermatitis observed after 48 hr closed patch test with 5% in polyethylene glycol (5).

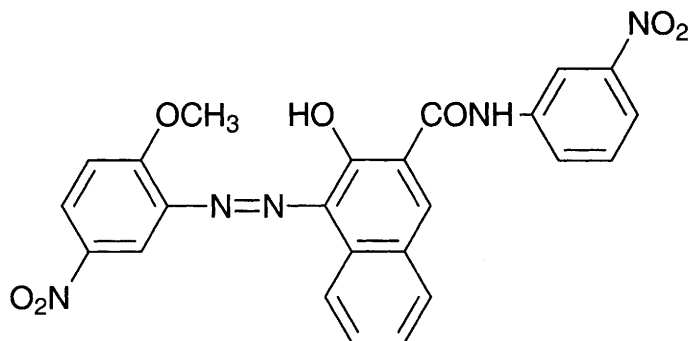
Genotoxicity

Salmonella typhimurium TA1535 with metabolic activation weakly positive (7).

References

1. National Toxicology Program Division of Toxicology Research and Testing MRT-005, NIEHS, Research Triangle Park, NC 27709, USA.
2. Morgan, D. L. et al *Food Chem. Toxicol.* 1989, 27(12), 793-800.
3. National Toxicology Program Research and Testing Division 1997, Report No. TR-407, NIEHS, Research Triangle Park, NC 27709, USA.
4. Lewis, D. F. V. et al *Mutagenesis* 1990, 5(5), 433-435.
5. *J. Dermatol.* 1978, 5, 291.
6. Kgzuka, T. et al *Contact Dermatitis* 1980, 6, 330.
7. Mortelmans, K. et al *Environ. Mutagen.* 1986, 8(Suppl. 7), 1-119

c417 C.I. Pigment Red 23



$C_{24}H_{17}N_5O_7$

Mol. Wt. 487.43

CAS Registry No. 6471-49-4

Synonyms 3-hydroxy-4-[(2-methoxy-5-nitrophenyl)azo]-N-(3-nitrophenyl)-2-naphthalenecarboxamide;
C.I. 12355; Pigment Red 23; Textile Red WD-263

EINECS No. 229-313-2

RTECS No. QJ 1897000

Uses Dyestuff in paints, printing inks, for linoleum, textile printing, rubber, plastic, lacquers, emulsions and paper.

Mammalian & avian toxicity

Carcinogenicity and chronic effects

National Toxicology Program tested rats and mice via feed. Equivocal evidence of carcinogenicity in ♂ rats. No evidence of carcinogenicity in ♀ rats, ♂ and ♀ mice (1).

Computer-Optimised Molecular Parametric Analysis of Chemical Toxicity (COMPACT) procedure, evaluating carcinogenicity/toxicity based on interaction with active site of P450I or binding site of Ah receptor positive (2).

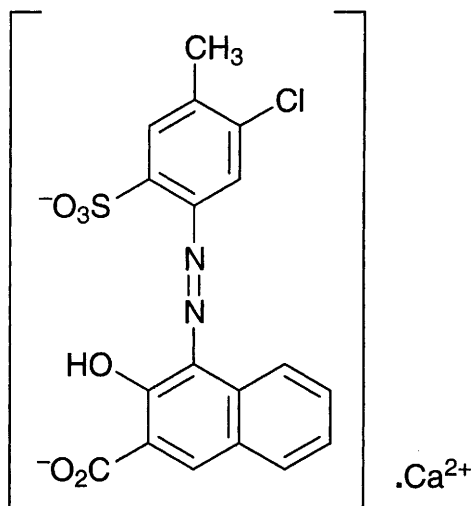
Genotoxicity

Salmonella typhimurium TA100 without metabolic activation positive (3).

References

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2. Lewis, D. F. V. et al *Mutagenesis* 1990, 5(5), 433-435.
3. Mortelmans, K. et al *Environ. Mol. Mutagen.* 1986, 8(Suppl. 7), 1-119

C418 C.I. Pigment Red 48:2



C₁₈H₁₂CaClN₂O₆S

Mol. Wt. 459.90

CAS Registry No. 7023-61-2

Synonyms C.I. 15865:2; 4-[(5-chloro-4-methyl-2-sulfophenyl)azo]-3-hydroxy-2-naphthalenecarboxylic acid, calcium salt; Radiant Red Lake; Rubine Toner 2BS; Sico Red WRC

EINECS No. 230-303-5

Uses Pigment in printing inks, paints, alkyd resin enamels and lacquers, rubber, paper, linoleum, book cloth, leather cloth, inks for wrapper and tinplate printing, PVC, cosmetics and textile printing.

Mammalian & avian toxicity

Acute data

LD₅₀ oral rat >5 g kg⁻¹ (1).

Irritancy

Caused no ulceration, corneal opacity, iris inflammation, redness or swelling in rabbits' eyes (1).

Not irritating to abraded or intact skin in rabbits after 24 hr covered contact (1).

Sensitisation

Positive patch test response to 10% in paraffin reported in a teacher with eczema from red chalk exposure (2).

Genotoxicity

Salmonella typhimurium TA98, TA1535, TA1538 with or without metabolic activation negative (3).

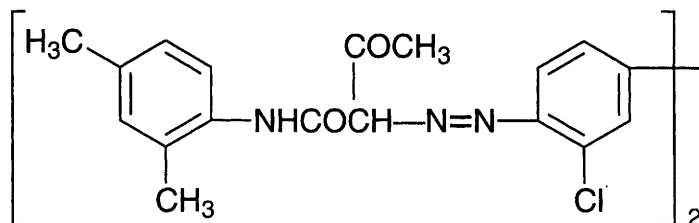
Other comments

Reviews on human health effects and experimental toxicology listed (4).

References

1. *Raw Materials Data Handbook* 1983, 4, 24, National Printing Ink Research Institute, New York, USA.
2. Lovell, C. R. et al *Contact Dermatitis* 1981, 7, 345.
3. Milvy, P. et al *J. Toxicol. Environ. Health* 1978, 4, 31-36.
4. *ECETOC Technical Report No. 71* 1996, European Centre for Ecotoxicology and Toxicology of Chemicals, 4 Avenue E. Van Nieuwenhuysse (Bte 6), B-1160 Brussels, Belgium

c419 C.I. Pigment Yellow 13



$C_{36}H_{34}Cl_2N_6O_4$

Mol. Wt. 685.61

CAS Registry No. 5102-83-0

Synonyms 2,2'-[(3,3'-dichloro[1,1'-biphenyl]-4,4'-diyl)bis(azo)]bis[N-(2,4-dimethylphenyl)-3-oxobutanamide; C.I. 21100

EINECS No. 225-822-9

RTECS No. EJ 3512000

Uses Colorant for printing inks, interior paints, textiles, rubber and plastics.

Physical properties

M. Pt. 344°C

Solubility Organic solvents: ethanol

Environmental fate

Anaerobic effects

50% inhibition of respiration in (unidentified) waste water organisms >100 mg l⁻¹ (1).

Mammalian & avian toxicity

Acute data

LD₅₀ oral rat >5 g kg⁻¹ (2).

Metabolism and toxicokinetics

Earlier inadequately reported research stated 0.05% of oral dose of 20 mg kg⁻¹ (purity unspecified) was excreted in urine as the animal carcinogen 3,3'-dichlorobenzidine (DCB) (3).

DCB was not detected (sensitivity 0.01 ppm DCB) in urine of rats or monkeys given 400 mg kg⁻¹ orally, or rabbits given 50 mg kg⁻¹ orally. DCB was not detected in urine of rabbits given 20 mg kg⁻¹ pigment yellow; contains <2 ppm DCB (sensitivity 0.3 ppm DCB) (4).

Irritancy

Not irritating to skin or eyes (5).

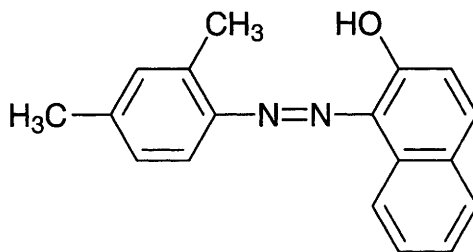
Other comments

Reviews on human health effects and experimental toxicology listed (6).

References

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3. Akiyama, T. *Jikei Med.* 1970, 17, 1.
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5. Cowley, A. C. D. *Polymers Paint Colour J.* 1985, 175, 580.
6. *ECETOC Technical Report No. 71* 1996, European Centre for Ecotoxicology and Toxicology of Chemicals, 4 Avenue E. Van Nieuwenhuysse (Bte 6), B-1160 Brussels, Belgium

c420 C.I. Solvent Orange 7



C₁₈H₁₆N₂O

Mol. Wt. 276.34

CAS Registry No. 3118-97-6

Synonyms 1-(2,4-xylylazo)-2-naphthol; 1-(*m*-xylylazo)-2-naphthol; C.I. 12140; Oil orange R; Oil red O; Oil scarlet BL; Sudan II; Sudan Orange

EINECS No. 221-490-4

RTECS No. QL 5850000

Uses Colouring agent for oils, waxes and hydrocarbon solvents. Used in polishes, candles and polystyrene resins. In Japan, used to colour petroleum products, plastics and shoe polish. Used in cosmetics and drugs applied externally.

Physical properties

M. Pt. 156-158°C

Solubility Organic solvents: acetone, benzene, ethanol, ether

Mammalian & avian toxicity

Sub-acute and sub-chronic data

Oral rat 200-400 mg kg⁻¹ (duration unspecified) caused a decline in haemoglobin levels (1).

Carcinogenicity and chronic effects

No adequate data for carcinogenicity to humans, limited evidence for carcinogenicity to animals, IARC classification group 3 (2).

TD_{Lo} implantation mice 80 mg kg⁻¹ induced bladder carcinomas (3).

Genotoxicity

Salmonella typhimurium TA1538 with and without metabolic activation negative (4).

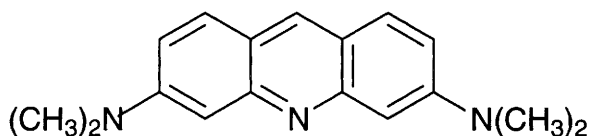
Salmonella typhimurium TA98, TA100, TA1535, TA1537, TA1538 with and without metabolic activation positive (5).

L5178Y tk⁺/tk⁻ mouse lymphoma assay with and without metabolic activation negative (5).

References

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2. IARC Monograph 1987, **Suppl. 7**, 72.
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4. Garner, R. C. et al *Mutat. Res.* 1977, **44**, 9-19.
5. Cameron, T. P. et al *Mutat. Res.* 1987, **189**, 223-261

C421 C.I. Solvent Orange 15



C₁₇H₁₉N₃

Mol. Wt. 265.36

CAS Registry No. 494-38-2

Synonyms *N,N,N',N'*-tetramethyl-3,6-acridinediamine; 3,6-bis(dimethylamino)acridine; Acridine Orange Base; Basic Orange 3RN; Rhoduline Orange; C.I. 46005B; **RTECS No. AR 7600000**

Uses Used to colour fats, oils and waxes a bright orange. Used as a diagnostic stain in microbiology.

Physical properties

M. Pt. 165°C (decomp.) (1). 181-182°C (2)

Solubility Organic solvents: acetone, benzene, ethanol

Ecotoxicity

Fish toxicity

5 ppm (24 hr) was not acutely toxic to fish (1).

Mammalian & avian toxicity

Acute data

LD₅₀ subcutaneous mouse 250 mg kg⁻¹ (2).

LD₅₀ gavage redwinged blackbird >100 mg kg⁻¹ (3).

Sub-acute and sub-chronic data

TD_{Lo} dermal mouse 6630 mg kg⁻¹, equivocal tumorigenic agent (4).

Carcinogenicity and chronic effects

No adequate data for carcinogenicity to humans, inadequate evidence for carcinogenicity to animals, IARC classification group 3 (5).

Genotoxicity

Salmonella typhimurium TA98, TA100, TA1537 with metabolic activation positive (6).

Saccharomyces cerevisiae mitotic gene conversion induced (7).

Rat liver unscheduled DNA synthesis 1 mmol l⁻¹ (8).

Hamster embryo oncogenic transformation 1μg l⁻¹ (9).

Other comments

Incompatible with strong oxidising agents.

Light-sensitive and forms radicals upon exposure to visible light.

Powerful inhibitor of RNA, DNA and protein synthesis. Forms non-covalent, tightly bound complexes with DNA by intercalation of the bases in the double-stranded DNA (10,11).

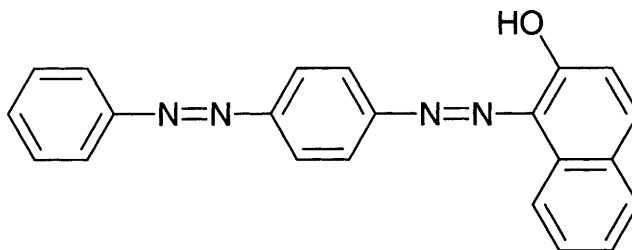
Carcinogenic risk to man reviewed (12).

References

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11. Zelenin, A. V. et al *Nature* 1964, **204**, 45-46.
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c422 C.I. Solvent Red 23



C₂₂H₁₆N₄O

Mol. Wt. 352.40

CAS Registry No. 85-86-9

Synonyms 1-[[4-(phenylazo)phenyl]azo]-2-naphthalenol; 1-(*p*-phenylazophenylazo)-2-naphthol; tetrazobenzene- β -naphthol; C.I. 26100; Oil Red; Sudan III

EINECS No. 201-638-4

Uses Stain for zoological, botanical, pathological specimens. Used for colouring oils, spirit lacquers.

Physical properties

M. Pt. 199°C (decomp.)

Solubility Water: insoluble in water. Organic solvents: acetic acid, chloroform

Mammalian & avian toxicity

Acute data

LD_{Lo} subcutaneous rabbit 1000 mg kg⁻¹ (1).

LD_{Lo} intraperitoneal rabbit 250 mg kg⁻¹ (1).

LD_{Lo} intrapleural rabbit 500 mg kg⁻¹ (1).

Carcinogenicity and chronic effects

No adequate data for carcinogenicity to humans, inadequate evidence for carcinogenicity to animals, IARC classification group 3 (2).

Teratogenicity and reproductive effects

Oral pregnant mice dosed on days 8-12 of gestation. Testes of 45-50 day-old postpubertal ♂ offspring examined.

No effect on germ cells was seen (3).

Genotoxicity

Salmonella typhimurium TA98, TA100 with and without activation negative for the pure compound, 3/5 commercial samples were mutagenic with metabolic activation (4).

Salmonella typhimurium mammalian microsome test negative (5).

Following reduction of C.I. Solvent Red 23 by azoreductase-producing bacteria isolated from the human intestinal tract no mutagenic compounds were detected by the umu test (6).

Clastogenic in CHO assay at 20 µM (7).

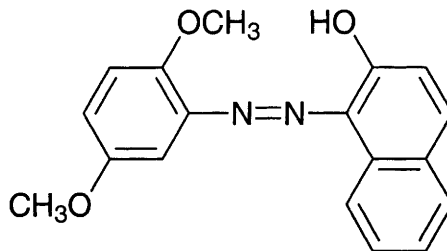
Other comments

C.I. Solvent Red 23 prevents benzo[a]pyrene-induced carcinogenesis in the rat due to an accelerated elimination of the carcinogen through the induction of cytochrome P448 and detoxifying enzymes (8).

References

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2. *IARC Monograph* 1987, **Suppl. 7**, 72.
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C423 C.I. Solvent Red 80



C₁₈H₁₆N₂O₃

Mol. Wt. 308.34

CAS Registry No. 6358-53-8

Synonyms 2,5-dimethoxybenzeneazo-β-naphthol; 1-[(2,5-dimethoxyphenyl)azo]-2-naphthalenol;

C.I. 12156; Citrus Red No. 2

EINECS No. 228-778-9

RTECS No. QL 3675000

Uses Colorant for inks.

Physical properties

M. Pt. 155-157°C

Solubility Water: miscible. Organic solvents: ethanol, vegetable oils

Mammalian & avian toxicity

Carcinogenicity and chronic effects

No adequate evidence for carcinogenicity to humans, sufficient evidence for carcinogenicity to animals, IARC classification group 2B (1).

Mice were fed a diet containing 0, 500 or 2500 mg kg⁻¹ diet for up to 2 yr. In the treated groups, 6/20 mice developed hyperplasia of the bladder wall, 2 had bladder papillomas and 1 ♂ receiving the highest dose had a papillary carcinoma of the bladder. No changes were reported in controls. In rats administered the same doses, papillomas of the urinary bladder were observed in 4/28 rats and hyperplasia of the bladder in 10/28 rats. No changes were reported in controls (2).

Mice were fed a diet containing 0, 100, 300 or 1000 mg kg⁻¹ diet for 80 wk. The total number of benign and malignant tumours found were 16 in controls compared with 22, 15 and 9 in the treated groups, respectively. The tumours were mainly adenocarcinomas of the lung and lymphosarcomas. A small number of malignant tumours occurred in the ureter, kidney, thyroid and colon of treated rats and rat in controls, but the increase was not significant. In mice given wkly subcutaneous injections of 0.1 ml of a 10% suspension for 35 wk, followed by 15 further injections every 3 wk, 37/100 developed benign and malignant tumours compared to 24/100 in controls. The incidence of malignant tumours (mainly adenocarcinomas of the lung and lymphosarcomas) was higher in ♀ mice (3).

Pellets weighing 15-17 mg, containing 12.5% Citrus Red No. 2 in paraffin wax were implanted in the bladder of mice. Bladder carcinomas developed in 7/50 mice compared with 6/142 controls (4).

Metabolism and toxicokinetics

Citrus Red No. 2 is reduced by azoreductase activity in intestinal microflora of rats, rabbits or dogs. After oral administration to rats, small amounts of the colour were detected in fat but not other tissues. When administered in corn oil only small amounts were found in faeces, however when administered in a dry diet, 26% was found in the faeces (5).

Urinary metabolites in rats included two red-coloured metabolites; one was identified as 2,5-dimethoxyphenylazo-2-naphthol glucuronide. Two other metabolites were 1-amino-2-naphthol glucuronide and 1-amino-2-naphthol sulfate. 1-Amino-2-naphthyl glucuronide has been identified as a metabolite in humans (6).

Genotoxicity

Salmonella typhimurium TA97, TA98, TA100, TA1535, TA1537, TA1538 without metabolic activation positive (7).

Salmonella typhimurium TA98, TA100 without metabolic activation negative, with metabolic activation positive (8).

Legislation

US Code of Fed. Rep. 1974, specify a minimum purity of 98%.

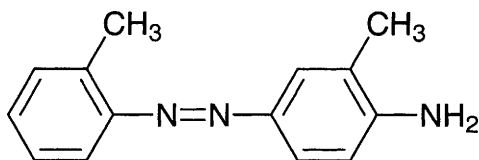
Other comments

The joint FAO/WHO Expert Committee on Food Additives considers Citrus Red No. 2 unsafe for use in food (9).

References

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9. *Summary of the Evaluations Performed by the Joint FAO/WHO Expert Committee on Food Additives (JECFA)* 1996, Food and Agriculture Organisation of the United Nations, Rome and the World Health Organization, Geneva, Switzerland

c424 C.I. Solvent Yellow 3



$C_{14}H_{15}N_3$

Mol. Wt. 225.29

CAS Registry No. 97-56-3

Synonyms o-aminoazotoluene; 4'-amino-2,3'-azotoluene; 2-amino-5-azotoluene; Butter Yellow; C.I. 11160; toluazotoluidine; 4-(o-tolylazo)-o-toluidine; Fast Garnet GBC Base

EINECS No. 202-591-2

RTECS No. XU 8800000

Uses Colorant for oils, fats and waxes.

Physical properties

M. Pt. 101-102°C

Solubility Organic solvents: acetone, cellosolve, ethanol, toluene

Occupational exposure

Supply classification toxic

Risk phrases May cause cancer – May cause sensitisation by skin contact (R45, R43)

Safety phrases Restricted to professional users – Avoid exposure – obtain special instruction before use – In case of accident or if you feel unwell, seek medical advice immediately (show label where possible) (S53, S45)

Mammalian & avian toxicity

Acute data

LD_{Lo} oral mouse 800 mg kg⁻¹ (1).

LD_{Lo} subcutaneous mouse 1200 mg kg⁻¹ (1).

Carcinogenicity and chronic effects

No adequate evidence for carcinogenicity to humans, sufficient evidence for carcinogenicity to animals, IARC classification group 2B (2).

C57/IF hybrid mouse implant (40 wk) 80 mg kg⁻¹ induced squamous metaplasia and carcinoma in 11/60 animals (3).

The transplacental effect on the liver was studied in three generations of CBA mice by intragastric administration on days 17, 18 and 19 of pregnancy. F₁ generation ♂ and ♀ had high incidence of liver tumours. F₂ generation ♀ had a statistically higher incidence of liver tumours than controls. F₃ generation ♀ no significant difference from controls (4).

Target organ for carcinogenicity in rats is the liver (5).

Metabolism and toxicokinetics

The bile of rats dosed with aminoazotoluene contained *N*-glucuronide of 4-amino-2-hydroxymethyl-3'-methylazobenzene, the sulfate and glucuronides of 4-amino-4'-hydroxyazotoluene and *N*-glucuronide-*O*-sulfate of 4'-hydroxyazotoluene (6).

The compound was shown to be taken up by periportal areas of liver lobules (7).

Irritancy

In humans, allergic reactions include eczema of the hands and arms (8).

Genotoxicity

Salmonella typhimurium TA1535/pSK1002 umu test system negative (9).

Salmonella typhimurium TA98, TA100, TA1538 with metabolic activation positive (10-12).

In vitro rat/hamster hepatocytes DNA repair-inducing activity positive (13).

Other effects

Any other adverse effects

Induces rat hepatic cytochrome P450 1A activity (14).

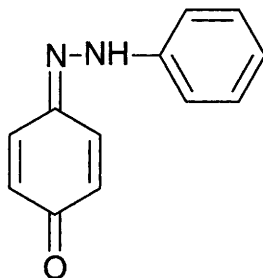
Other comments

Relationship between chemical toxicity, metabolism, mutagenicity, carcinogenicity and cocarcinogenicity is discussed (15).

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c425 C.I. Solvent Yellow 7



$C_{12}H_{10}N_2O$

Mol. Wt. 198.22

CAS Registry No. 1689-82-3

Synonyms *p*-benzoquinone monophenylhydrazone; 4-(phenylazo)phenol; *p*-benzeneazophenol; 4-hydroxyazobenzene

EINECS No. 216-880-6

RTECS No. SM 8300000

Uses Dyestuff.

Physical properties

M. Pt. 155-157°C B. Pt. 220-230°C at 20 mmHg

Solubility Organic solvents: diethyl ether

Ecotoxicity

Fish toxicity

LC₅₀ (96 hr) fathead minnow 1.1 mg l⁻¹ (1).

Invertebrate toxicity

EC₅₀ (30 min) *Photobacterium phosphoreum* 0.927 mg l⁻¹ Microtox test (2).

Environmental fate

Degradation studies

Under nitrogen-limiting, secondary metabolic conditions, the white rot basidiomycete *Phanerochaete chrysosporium* mineralises C.I Solvent Yellow 7. Extent of mineralisation 12 days after substrate addition to low-nitrogen culture was 28.4-38.2%, to high-nitrogen culture was 6.9-21.9% (3).

Mammalian & avian toxicity

Acute data

LD₅₀ intraperitoneal mouse 75 mg kg⁻¹ (4).

Sub-acute and sub-chronic data

Oral Sprague-Dawley rats (9 month) ≥ 53 mg kg⁻¹ no adverse effects reported (5).

Carcinogenicity and chronic effects

No adequate data for carcinogenicity to humans, inadequate evidence for carcinogenicity to animals, IARC classification group 3 (6).

Metabolism and toxicokinetics

In mice metabolised to 2-acetamidophenol, 4-acetamidophenol, conjugated 4-aminophenol, conjugated 2-aminophenol. Doses of 500 and 700 mg, which did not produce toxic effects, were completely absorbed from the diet of rabbits and were excreted mainly in the urine as glucuronide (7).

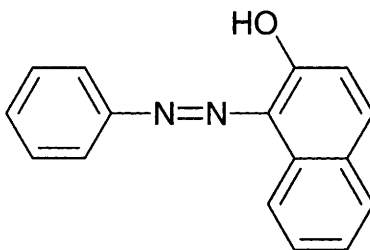
Other comments

Reviews on experimental toxicology and human health effects listed (8).

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c426 C.I. Solvent Yellow 14



$C_{16}H_{12}N_2O$

Mol. Wt. 248.28

CAS Registry No. 842-07-9

Synonyms benzene-1-azo-2-naphthol; 1-(phenylazo)-2-naphthalenol; 1-phenylazo- β -naphthol; C.I. 12055; Oil Orange; Sudan I; Sudan Orange R; Detectas Orange 201

EINECS No. 212-668-2

RTECS No. QL 4900000

Uses Colorant for hydrocarbon solvents, oils, fats, waxes, shoe and floor polishes, cellulose ether varnishes, styrene resins, petrol and soap. Colorant for plastics.

Physical properties

M. Pt. 131-133°C

Solubility Organic solvents: acetone, benzene, ethanol

Environmental fate

Degradation studies

C.I. Solvent Yellow 14 is mineralised by the white rot basidiomycete *Phanerochaete chrysosporium* under nitrogen-limiting, ligninolytic conditions (1).

Mammalian & avian toxicity

Acute data

LD₅₀ subcutaneous rabbit <500 mg kg⁻¹ (2).

Carcinogenicity and chronic effects

No adequate data for carcinogenicity to humans, inadequate evidence for carcinogenicity to animals, IARC classification group 3 (3).

TD_{Lo} (duration unspecified) bladder implantation mouse 80 mg kg⁻¹ induced tumours of kidney, ureter and bladder (4).

Oral rat (2 yr) 500 ppm in feed 30/50 animals developed liver neoplastic nodules, however it was non-carcinogenic in mice (5).

Metabolism and toxicokinetics

Oral rabbits (unspecified dose) metabolites detected 44% free and conjugated *p*-aminophenol, 24% as *p*-aminophenylglucuronide. Excreted via urine (6).

In vitro rat liver enzymes converted solvent yellow 14 into ring-hydroxy derivatives of benzene and naphthalene.

The benzenediazonium ion considered to be active in the subsequent development of cancer was detected (7).

The benzenediazonium ion reacts with DNA *in vitro* to form the stable 8-(phenylazo)guanine adduct (8).

C.I. Solvent Yellow 14 is metabolised by rat liver microsomes *in vitro* to 1-(3,4-dihydroxyphenylazo)-2-hydroxynaphthalene (9).

1-Phenylazo-2,6-dihydroxynaphthalene and 1-(4-hydroxyphenylazo)-2-hydroxynaphthalene are detoxication products of C.I. Solvent Yellow 14 (10).

Sensitisation

Positive in guinea pig sensitisation test. Investigations into the sensitisation and allergenic potential of Solvent Yellow 14 showed that the metabolite 4'-hydroxy-1-phenylazo-2-naphthol may be the causative agent. It was concluded that *p*-hydroxylation of the phenol group in Solvent Yellow 14 may play an important role in its allergenicity (11).

Dermal guinea pigs Magnusson/Kligman maximisation test, 1 to 25% concentrations of Solvent Yellow 14 caused inflammation and red spots on the skin (12).

Genotoxicity

Salmonella typhimurium TA97, TA98, TA100, TA1535, TA1537 with and without metabolic activation positive (13).

In vitro Chinese hamster ovary with and without activation sister chromatid exchange positive; chromosomal aberrations negative (14).

In vitro rat hepatocyte assay negative; *in vivo/in vitro* DNA repair assay, response equivocal (15).

In vitro mouse lymphoma L5178Y tk⁺/tk⁻ with metabolic activation positive (16).

In vivo rat bone marrow induced micronuclei after a single oral dose of >250 mg kg⁻¹ (17).

In vivo mice bone marrow single oral dose 2000 mg kg⁻¹ failed to induce micronuclei (17).

Drosophila melanogaster sex-linked recessive lethal mutation assay negative (18).

Rat and mouse (oral gavage, limit values of 5000 and 2000 mg kg⁻¹) *in vivo* bone marrow micronucleus assay.

Clear evidence of clastogenic activity in rat, weak effect in mouse. No evidence of DNA repair in the rat liver unscheduled DNA synthesis assay (19).

Other comments

Peroxidase-catalysed oxidation in the presence of NADH results in the formation of NAD⁺. The oxidation is thought to be caused by the reduction of reactive metabolites. Under certain conditions (not specified) NADH acts as the agent protecting the cellular nucleophilic compounds against modification by reactive metabolites formed by the peroxidase/H₂O₂ system. The physiological significances of NADH in the initiation of chemical carcinogenesis is discussed (20).

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CAS Registry No. 8003-22-3

Synonyms D & C Yellow 11; C.I. 47000; Quinoline Yellow Spirit Soluble; Quinoline Yellow Base; Quinoline Yellow A; Nitro Fast Yellow SL; Oil Yellow; Solvent Yellow 33

EINECS No. 232-318-2

RTECS No. WJ 6125000

Uses In spirit lacquers, colorant in polystyrene, polycarbonates, polyamides and acrylic resin products. In coloured smokes. In externally applied drugs and cosmetics.

Physical properties

Solubility Water: 0.17 mg l⁻¹ at 22°C. Organic solvents: acetone, benzene, chloroform, ethanol, linseed oil, mineral oil, oleic acid, paraffin wax, stearic acid, turpentine, toluene

Ecotoxicity

Fish toxicity

Not acutely toxic to fathead minnow, bluegill sunfish, channel catfish, rainbow trout, water flea, midge larvae and mayfly larvae exposed to the solubility limit for 96 hr (1).

Mammalian & avian toxicity

Acute data

LD₅₀ oral rat >13,650 mg kg⁻¹ (2).

LD₅₀ subcutaneous rat >13,650 mg kg⁻¹ (2).

Sub-acute and sub-chronic data

Rats were exposed to aerosols at average concentrations of 10, 51 or 230 mg m⁻³ for 6 hr daily, 5 days wk⁻¹ for 4 wk, or 1.0, 10.8 or 100 mg m⁻³ for 6 hr day⁻¹, 5 days wk⁻¹ for 13 wk. In the 4-wk highest concentration group body weights were ≈8% lower than their controls. In the 13-wk study, animals exposed to the highest concentration had body weights 5% lower than their controls, and an accumulation of vacuolated alveolar macrophages in the lungs. Very little of the substance was found in the lungs after exposure, indicating rapid clearance (3).

Rats and mice were fed 500-50,000 ppm for 13 wk. Minimum to mild toxicity was observed. Compound-related effects were evident at all intake levels. The liver was the target site in both rats and mice and the kidney in rats. With the exception of a minimal amount of pigment accumulation, the toxic effects in the kidney and liver of rats were reversible within 14 days of withdrawal of the chemical from the diet (4).

Teratogenicity and reproductive effects

TD_{Lo} oral ♀ rat (4 wk prior to mating/1-21 days of pregnancy/4 wk post-gestation) reproductive effects, 67 mg kg⁻¹ (5).

TD_{Lo} oral ♂ mouse (13 wk) reproductive effects 5384 mg kg⁻¹ (5).

Metabolism and toxicokinetics

Following oral administration of ¹⁴C-labelled substance at 0.00044-0.41% of diet, recovery of radioactivity during the 24-hr dosing period and 72-hr period thereafter was 89.1-93.9% in faeces, and 4.98-6.25% in urine. Tissues contained only trace amounts. Following intraperitoneal administration at 0.93 mg kg⁻¹, radioactivity was distributed evenly in most tissues. Maximum amounts were present at 5 min, the earliest time of assay. Maximum radioactivity in fat, skin and gut tissue, however, was found at 30 min after dosing. Within 24 hr intraperitoneal dosing rats excreted 81.1% of the dose in the faeces and 16.0% in the urine. For rats fitted with biliary cannulas, 54.5% of the dose, all of which was as metabolites, was recovered in the bile in 4 hr. Associated with this biliary excretion of metabolites was the appearance of large amounts of radioactivity in the faeces and also, at intermediate time points, in the liver, gut contents and gut tissue (6).

Genotoxicity

Salmonella typhimurium TA102, TA104 with and without metabolic activation positive (7).

Salmonella typhimurium TA98, TA1535, TA1538 with and without metabolic activation negative (7).

Salmonella typhimurium TA97, TA98, TA100, TA1535, TA1537 with and without metabolic activation weakly positive (8).

Induced mutation in L5178Y tk⁺/tk⁻ mouse lymphoma assay (7).

In vivo intraperitoneal mouse sister chromatid exchanges in bone marrow negative (7).

Legislation

Approved by the FDA for use in externally applied drugs and cosmetics.

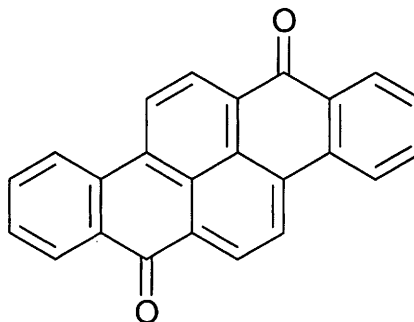
Other comments

A synthetic dyestuff consisting principally of quinophthalone (2-(2-quinolinyl)-1*H*-indene-1,3-(2*H*)-dione).

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c428 C.I. Vat Yellow 4



C₂₄H₁₂O₂

Mol. Wt. 332.36

CAS Registry No. 128-66-5

Synonyms dibenzo[*b,def*]chrysene-7,14-dione; 1',2',6',7'-dibenzpyrene-7,14-quinone; C.I. Vat Yellow; C.I. 59100; Amanthrene Golden Yellow; Benzadone Golden Yellow

EINECS No. 204-903-2

Uses Used to dye cellulose fibres including wool, silk and paper. In smoke screen preparation for military use.

Physical properties

M. Pt. 385-390°C

Solubility Organic solvents: nitrobenzene, tetrahydronaphthalene, xylene

Mammalian & avian toxicity

Carcinogenicity and chronic effects

No adequate evidence for carcinogenicity to humans, limited evidence for carcinogenicity to animals, IARC classification group 3 (1).

Tumours found in haematopoietic system of ♂ mice when administered in diet (2).

TD_{Lo} (2 yr) oral mouse 7420 g kg⁻¹ induced lymphoma tumours including Hodgkin's disease (3).

Oral 50 ♂ B6C3F mice 25,000 or 50,000 mg kg⁻¹ diet and oral 50 ♀ B6C3F mice 12,500 or 25,000 diet (106 wk) commercial formulation containing 18% dibenzo[*b,def*]chrysene-7,14-dione. A significant increase in the incidence of lymphomas was observed in ♂ mice. The incidences of hepatocellular carcinomas were not significant in either sex (3).

Oral ♂, ♀ Fischer 344 rats (104 wk) 3500 or 7000 mg kg⁻¹ in diet (commercial formulation containing 18% dibenzo[*b,def*]chrysene-7,14-dione. Mean body weights were lower than controls but survival was not affected by treatment. No significant incidence of tumours observed (3).

Genotoxicity

Salmonella typhimurium TA98, TA100, TA1535, TA1538 with and without metabolic activation negative (4).

In vitro mouse lymphoma L5178Y tk⁺/tk⁻ with metabolic activation positive (5).

Other comments

Commercial product is a mixture of chemicals including dibenzochrysenedione, benzanthrone, 3-benzoylbenzanthrone and 1,5-dibenzoylnaphthalene (6).

Detected as pollutant in air samples (7).

Physical/chemical properties, toxicology and environmental fate reviewed (8).

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c429 copper

Cu

Cu

Mol. Wt. 63.55

CAS Registry No. 7440-50-8

Synonyms bronze powder; copper-airborne; copper bronze; copper-milled; raney copper; gold bronze

EINECS No. 231-159-6

RTECS No. GL 5325000

Uses Largely used in the electrical industry for electroplating. Copper compounds are used in agriculture, especially as fungicides and insecticides. Pigments. Mordants in dyeing. Catalysts. Manufacture of bronzes, brass, other copper alloys. Ammunition. Copper salts. Works of art.

Occurrence Vast amounts of copper are present in the Earth's crust (70 ppm); also present in seawater (0.001-0.02 ppm). Copper minerals include chalcopyrite, chalcocite, bornite, tetrahedrite, enargite and anthlerite. Occurs in biological complexes such as pheophytin (analogue of chlorophyll), haemocyanin, tyrosinase and ceruloplasmin.

Physical properties

M. Pt. 1083°C **B. Pt.** 2595°C **Specific gravity** 8.94 at 20°C

Occupational exposure

DE-MAK 0.1 mg m⁻³ (fume); 1 mg m⁻³ (inhalable fraction of aerosol)

FR-VME 0.2 mg m⁻³ (fume); 1 mg m⁻³ (dust)

FR-VLE 2 mg m⁻³ (dust)

SE-LEVL 1 mg m⁻³ (total dust); 0.2 mg m⁻³ (respirable dust)

UK-LTEL 0.2 mg m⁻³ (fume)

UK-STEL 2 mg m⁻³ (dusts and mists) (as Cu)

US-TWA 0.2 mg m⁻³ (fume); 1 mg m⁻³ (dusts and mists as Cu)

Ecotoxicity

Fish toxicity

Chronic, partial chronic and early life stage toxicity tests were carried out on a number of species, king salmon, brook trout, bluegill sunfish, fathead minnow and bluntnose minnow. Study period was 30-60 days post-hatch. Under hard water conditions the lowest-observed-effect concentration (LOEC) – no observed effect concentration (NOEC) for fathead minnow was 33-15 µg l⁻¹ and bluntnose minnow 18-4 µg l⁻¹, respectively, with the reproduction part of the life cycle the most sensitive response (1).

A chronic study (30/60 day post-hatch) bluegill sunfish, fathead minnow in soft water conditions LOEC-NOEC range 40-11 µg l⁻¹, fry survival most sensitive response (1).

Partial chronic study (30/60 day post-hatch) brook trout LOEC-NOEC 17-9 µg l⁻¹, fry survival and fry growth most sensitive responses (1).

Early life stage toxicity test (60 day post-hatch) king salmon LOEC-NOEC 21-<21 µg l⁻¹, fry survival and growth most sensitive responses (1).

LC₅₀ (48 hr) larvae of flat fish *Paralichthys olivaceus* 0.36 mg l⁻¹ (Cu²⁺) (2).

LC₅₀ (96 hr) *Oreochromis niloticus* 1.06 mg l⁻¹ (3).

LC₅₀ (96 hr) rainbow trout 0.253 mg l⁻¹ (4).

Fertilised eggs of *Cyprinus carpio* (108 hr) 10, 50, 70 and 100 ppb Cu. Survival of developing eggs and hatchlings, hatchability and hatching % decreased with increasing concentration. Deformities observed were stunted growth, curved tail, enlargement of the pericardial sac, circulatory failure, deformed vertebral column, underdeveloped fins, deformed head region and formation of blisters (5).

Freshly fertilised ova of brown trout were exposed to Cu²⁺ at 5 µg l⁻¹ in flowing artificial soft-water media at pH5.6 [Ca] 800 µg l⁻¹ and 10°C. Mortalities were high in fry subjected to mixtures containing Cu (6).

Rainbow trout exposed to a number of combinations of copper, pH and hardness exhibited reduced growth rate during the first 10 days, followed by partial or complete recovery (7).

The lethal concentration of copper to rainbow trout was unaffected by alkalinity from 10-50 ppm in soft water, but the toxicity doubled by the same alkalinity change in hard water. Some synergism between pH value and copper toxicity noted (8).

Intraperitoneal injection of 500 ng g⁻¹ copper into sea bass caused a reduction in liver metallothionein content (9).

In preference-avoidance response determinations under uniform illumination in a countercurrent trough, lake whitefish *Coregonus clupeaformis* avoided copper ion concentrations of ≥ 1 µg l⁻¹ (10).

Invertebrate toxicity

EC₅₀ (48 hr) *Daphnia magna* 0.093 mg l⁻¹ (11).

IC₅₀ cell division *Chlorella pyrenoidosa* 16 µg l⁻¹ in synthetic salt water (12).

LC₅₀ (96 hr) *Perna viridis* 620 µg l⁻¹ (13).

Asellus aquaticus chronic exposure to 5 µg l⁻¹ juvenile development most sensitive response (14).

Using a refined microcosm technique the toxicity of copper to trophic groups of soil nematodes was investigated.

Nematode abundance was reduced after exposure to copper at 100 $\mu\text{g g}^{-1}$, with fungivore, bacteriovore, and omnivore-predator nematodes being the most sensitive groups (15).

LC₅₀ estuarine copepod *Eurytemora affinis* (48hr) 83.0, (96 hr) 69.4, (8 day) 64 $\mu\text{g l}^{-1}$ dissolved copper. CuCO_3 accounted for $\approx 78\%$ of the total copper (16).

Glochidia contained within the marsupia of gravid unionid mussels *Villosa iris* exposed to copper levels up to 19.1 $\mu\text{g l}^{-1}$ for 30 days exhibited no observable effects. However, released glochidia were sensitive to copper at comparatively low concentrations: median lethal concentration (24 hr) 36-80 $\mu\text{g l}^{-1}$. Length of exposure, water temperature, and water hardness all affected the sensitivity (17).

Toxicity to other species

Four-year-old Scots pine (*Pinus sylvestris* L.) saplings did not survive in quartz sand treated with > 150 ppm Cu (as copper sulfate). A copper sulfate/nickel sulfate combination was lethal at 15 ppm Cu + 15 ppm Ni (18). Copper (0.7, 1.4, and 2.8 mg l^{-1}) caused ultrastructural changes in plastids and heavy staining of the cell walls and mucilage of vegetative cells of the seaweed *Ceramium ciliatum*. Carpospores remained unmodified (19).

Bioaccumulation

The protectiveness of USEPA ambient water quality criteria for copper and zinc was tested using the snail *Leptoxis praerosa* in short- and long-term artificial stream tests. Significant bioconcentration of both Cu and Zn occurred within 40 days and significant cellulolytic enzyme activity impairment within 54 days for both metals at the respective chronic criteria concentrations. Approximately additive effects were seen in combination treatment of Cu and Zn. Survival was much higher in the Cu-exposed snails. The authors concluded that the USEPA criteria based upon abbreviated chronic tests may be underprotective for some sensitive taxa when exposures are prolonged (20).

Increasing copper levels in the seawater was matched by copper accumulation in mussel and crab tissues. Lethal concentration *Labeo rohita* 1.2 mg l^{-1} (accumulation in the order: gill > brain > muscle > liver) (21).

Clarias anguillanis was exposed to copper at concentrations of 0.027, 0.055 and 0.11 mg l^{-1} for 8 wk. Tissue residues were 15.7, 21.8 and 31.17 mg kg^{-1} dry weight respectively. The bioaccumulation factors were 117-581 (22).

Oreochromis niloticus were exposed to 0.05, 0.10 and 0.20 mg l^{-1} for 8 wk. The tissue residues were 34.7, 36.1 and 81.0 mg kg^{-1} dry weight, respectively. The bioconcentration factors were 176-694 (22).

The barnacle *Balanus amphitrite* exposed to 0.001-0.011 mg l^{-1} in tropical estuarine water, was found to accumulate up to 865 $\mu\text{g g}^{-1}$ dry weight (23).

Penaeus orientalis (unspecified concentration) dissolved in seawater, accumulated in intestine, gills and hepatopancreas. After 7 days exposure the prawn molt was seriously affected and mortality occurred (24).

Palaemon elegans regulates copper concentrations at a constant level ($\sim 129 \mu\text{g Cu g}^{-1}$) over a range of dissolved copper availabilities until regulation breaks down at high copper concentrations (25).

Echinogammarus pirlotii and *Elminius modestus* accumulate copper at all dissolved copper exposures with no evidence of regulation (25).

Bioconcentration and uptake of copper by carp is reduced by EDTA and histidine (26).

Environmental fate

Nitrification inhibition

Copper inhibition/denitrification – rotating disc – threshold at 20 mg l^{-1} ; inhibition of nitrification/denitrification – activated sludge – threshold at 20.0 mg l^{-1} . Toxicity to *Nitrosomonas* sp. threshold at 0.400 mg l^{-1} ; reduction of growth of *Nitrosomonas* no effect at 0.560 mg l^{-1} ; effect on growth of *Nitrosomonas* stimulation at 0.500 mg l^{-1} ; inhibition of nitrification *Nitrosomonas* 75% inhibition at 4 mg l^{-1} ; inhibition of nitrification – activated sludge – 75% at 200 mg l^{-1} ; inhibition of nitrification – activated sludge – 76% inhibition at 17.1 mg l^{-1} ; inhibition of nitrification – threshold at 5 $\mu\text{g l}^{-1}$ (27).

Carbonaceous inhibition

At pH 7.1 both aerobic and anaerobic carbon dioxide evolution were unaffected by 5000 $\mu\text{g (Cu) g}^{-1}$ sediment in 40 days at 15°C. However, after 40 days, a significant reduction, 28% was observed (28).

Mammalian & avian toxicity

Acute data

LD₅₀ chick embryo 58 µg egg⁻¹ (29).

TD_{Lo} oral human 0.120 mg kg⁻¹ (gastro-intestinal effects) (30).

LD₅₀ intraperitoneal mouse 3.5 mg kg⁻¹ (31).

Carcinogenicity and chronic effects

Oral rat (1 yr) 1 mg kg⁻¹ daily in drinking water was found to cause reduced serum concentrations of lipids, cholesterol, proteins and glycoprotein hexoses compared to controls. The content of hexosamines in the aorta was above that in controls. The collagen content was normal. Apparently, the fibrillar proteins of the aorta are not affected. Weak dystrophic changes were observed in the liver, kidney, heart and aorta tissues. No changes were found in rats administered 0.01 mg kg⁻¹ (i.e. the maximum permissible concentration in former USSR drinking water) (32).

Intratracheal instillation 20 mg (single dose) to ♂ rats of primary copper slag and secondary copper slag. Minimal to slight alveolar wall fibrosis was seen in the two copper slag groups. Significant numbers of primary lung tumours principally adenocarcinomas and adenomas were observed (33).

Teratogenicity and reproductive effects

Ten days after copper iontophoresis into the vas deferens of rats and rabbits, the animals were mated with fertile ♀. In spite of their normal mating behaviour, live spermatozoa were not detected in vaginal smears. Six months after copper deposition, vasal spermatozoal motility was normal towards the epididymal site but all sperm beyond the copper site were dead. The vasal lumen was patent and copper was detected at the site of deposition (34).

Copper solutions were injected into the airsacs on day 2 of the incubation of chicken eggs. Gross malformations observed on removal of live embryos included reduced body size, micromelia, twisted neck, haemorrhage, everted viscera and microphthalmia. A lethal dose (LD₅₀) of 58 µg egg⁻¹ was established (29).

When administered to rats in drinking water at a concentration of 0.05 mg kg⁻¹, embryo instability of the F₁ offsprings of treated ♂ rats was observed (35).

Whole rat embryos of 9.5 gestational days were cultured for 2 days on sera taken from rats fed diets deficient in copper 0.6 µg Cu g⁻¹ diet or fed a control diet containing 10 µg Cu g⁻¹. Head malformations were observed (36).

Metabolism and toxicokinetics

Generally, <30% of the copper consumed is absorbed in any species, and its absorption and retention are greatly affected by the chemical forms in which the metal is ingested; by the dietary levels of other minerals and organic substances; and by the acidity of the intestinal contents in the absorptive area. Copper is either stored in parenchymal cells and intracellularly in mitochondria, microsomes and nuclei or incorporated into erythrocuprein, or ceruloplasmin, or the various copper-containing enzymes. Hepatic copper is secreted into bile and smaller amounts of plasma copper is also excreted into the urine (37).

Six ♂ volunteers were monitored (78 days) for copper absorption by consuming a constant diet containing 3 mg copper day⁻¹. Serum copper levels were within the normal range for all subjects (38).

Genotoxicity

Salmonella typhimurium TA98, TA102, TA1535, TA1537 with metabolic activation negative (39).

Induced sister chromatid exchanges in human peripheral lymphocytes, but gave negative results in micronucleus and sperm teratogenicity tests (40).

Other effects

Other adverse effects (human)

Among ♂ Japanese copper smelter workers, squamous cell carcinomas have been found to be very frequent (41). Adverse effects have tended to arise following absorption of the metal from cooking utensils and during dialysis, causing hepatotoxicity. Adverse effects have been reported in women with copper-containing intra-uterine devices, including allergy and endometrial changes. Ingestion of copper salts can produce severe gastro-intestinal effects. The symptoms of Wilson's disease (hepatolenticular degeneration) are due to the accumulation of copper in various parts of the body (42).

A condition similar to metal fume fever in workers exposed to metallic copper dust has been reported (43). A type of chronic copper poisoning in humans, recognised in the form of Wilson's disease, may be fatal (44). 133 Cases of cancer identified between 1974 and 1984 among 5000 members of north-west Western Australia state employee cohort from whom serum specimen had been obtained. Risk of subsequent diagnosis of cancer was positively associated with serum copper levels but only with serum copper levels prior to diagnosis. The findings are less supportive of the hypothesis that serum copper levels affect cancer risk (45). In ten agricultural regions with similar climatic conditions and demographic composition, the incidence of cardiovascular diseases was positively correlated with drinking water concentrations of copper and titanium. Other trace metals (Mn, Ni, Cr, V, Mo, Ag, Zn and Br) may have protective effects and their deficiency may increase the toxic effects of the other two elements (46).

Any other adverse effects

Seven Cattle fed on a copper-deficient pasture experienced a lower weight gain and increased morbidity (47). Rats fed a diet deficient in copper were found to have lesions in the cortex, medulla and papilla of the kidney. The cause is suggested to be due to vascular underperfusion or could be secondary to the other cardiovascular lesions that are known to occur in copper deficiency (48).

Legislation

UK maximum admissible concentration in drinking water 3000 $\mu\text{g l}^{-1}$. EC advisory level for drinking water, 100 $\mu\text{g l}^{-1}$ at source of supply; 3000 $\mu\text{g l}^{-1}$ after standing in piping for 12 hr (49). Included in Schedule 4 (Release into Air: Prescribed Substances) Statutory Instrument No. 472, 1991 (50). WHO revised guidelines for drinking water quality: copper guide level 2 mg l^{-1} (51). UK National Environmental Quality Standards for List II Substances which includes copper (WRC Report Ref. TR210). Fresh water: direct – 20 $\mu\text{g Cu l}^{-1}$ total; abstraction to potable supply – 50 $\mu\text{g Cu l}^{-1}$ (95% of samples must comply). For the protection of sensitive and other aquatic life the dissolved annual average should not exceed: 1 $\mu\text{g Cu l}^{-1}$ (0-50 $\text{mg l}^{-1} \text{CaCO}_3$) and 95% of samples must not exceed 5 $\mu\text{g Cu l}^{-1}$; 6 $\mu\text{g Cu l}^{-1}$ (50-100 $\text{mg l}^{-1} \text{CaCO}_3$) and 95% of samples must not exceed 22 $\mu\text{g Cu l}^{-1}$; 10 $\mu\text{g Cu l}^{-1}$ (100-250 $\text{mg l}^{-1} \text{CaCO}_3$) and 95% of samples must not exceed 40 $\mu\text{g Cu l}^{-1}$; 28 $\mu\text{g Cu l}^{-1}$ (250+ $\text{mg l}^{-1} \text{CaCO}_3$) and 95% of samples must not exceed 112 $\mu\text{g Cu l}^{-1}$. For the protection of salt-water life the dissolved annual average should not exceed: 5 $\mu\text{g Cu l}^{-1}$ (52). FAO/WHO Acceptable Daily Intake 5-500 $\mu\text{g kg}^{-1}$ (53).

Other comments

Copper may be present in polluted surface fresh waters both associated with suspended solids and in different soluble chemical states. The most likely soluble forms of copper are its complexes with carbonate, cyanide, amino acids and polypeptides and humic substances, as well as the free Cu^{2+} ion. Copper is more dangerous in soft waters than in hard waters, the ionic form Cu^{2+} being the most toxic. In hard water the final precipitation product is the basic carbonate, malachite, $\text{CuCO}_3 \cdot \text{Cu(OH)}_2$. In the short term, copper behaves synergistically with zinc in fish toxicology.

Copper bracelets have been worn as a folk remedy for rheumatic disorders; there is no good evidence to justify such a practice (40).

Reviews on experimental toxicology and human health effects listed (54).

Adverse effects to human health, environment and ecological systems have been extensively reviewed (55-60).

Nutritional requirements for copper in humans and animals reviewed (61-64).

The effects of copper exposure on species reproduction is discussed (65).

Copper toxicity to the freshwater cichlid fish *Oreochromis mossambicus* can be removed by an optimum dosage of 0.5 g EDTA l^{-1} contaminated water (66).

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C430 copper acetate



$\text{C}_4\text{H}_6\text{CuO}_4$

Mol. Wt. 181.64

CAS Registry No. 142-71-2

Synonyms acetic acid, copper(2+) salt; cupric acetate; crystallised verdigris; neutralised verdigris; copper diacetate; Verdet

EINECS No. 205-553-3

RTECS No. AG 3480000

Uses Fungicide. Intermediate in the manufacture of Paris green. Catalyst. Textile dyestuff. Pigment for ceramics.

Physical properties

M. Pt. 115°C Specific gravity 1.882 at 20°C

Solubility Water: miscible. Organic solvents: diethyl ether, ethanol, glycerol

Occupational exposure

DE-MAK 1 mg m⁻³ (inhalable fraction of aerosol)

Ecotoxicity

Fish toxicity

LC₅₀ (96 hr) fathead minnow 0.39 mg l⁻¹ (1).

Invertebrate toxicity

LC₅₀ (96 hr) grass shrimp 37 mg l⁻¹ (1).

Bioaccumulation

Copper acetate was added to a corn silage-based diet, containing 35.7 mg kg⁻¹ copper and fed to sheep during an 87-day experiment. The liver concentration of copper had increased from 569 to 1038 mg kg⁻¹ dry weight representing ~2% of the ingested copper. In the kidneys the copper concentration increased from 16 to 59 mg kg⁻¹ dry weight. These levels have been encountered at the haemolytic stage of chronic copper poisoning (2).

Mammalian & avian toxicity

Acute data

LD₅₀ oral rat 710 mg kg⁻¹ (3).

LD₅₀ subcutaneous rat 350 kg⁻¹ (4).

Sub-acute and sub-chronic data

Oral, subcutaneous, intravenous calves (5 month) 2-6 mg kg⁻¹ Cu²⁺ day⁻¹. The copper level of the liver increased rapidly after subcutaneous administration (5).

Legislation

Limited under EC Directive on Drinking Water Quality 80/778/EEC. Copper: guide level $100\text{ }\mu\text{g l}^{-1}$ at outlets of pumping and/or treatment works and their substations and $3000\text{ }\mu\text{g l}^{-1}$ after the water has been standing for 12 hr in the piping and at the point where the water is made available to the consumer (6).

Included in Schedule 6 (Release into Land: Prescribed Substances) Regulations Statutory Instrument No. 472, 1991 (7).

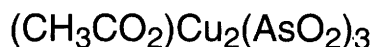
Other comments

Copper is more dangerous in soft waters than in hard waters; the ionic form Cu^{2+} being the most toxic. In hard water the final precipitation product is the basic carbonate, malachite, $\text{CuCO}_3\cdot\text{Cu}(\text{OH})_2$.

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C431 copper acetoarsenite



$\text{C}_2\text{H}_3\text{As}_3\text{Cu}_2\text{O}_8$

Mol. Wt. 506.90

CAS Registry No. 12310-22-4

Synonyms copper(II) acetoarsenite; cupric acetoarsenite; Paris Green; French Green; Emerald Green; (acetato)tris(arsenito)dicropper; copper acetate arsenite; C.I. 77410; bis(acetato)hexametaarsenitetetracopper
Uses Insecticide. Wood preservative. Paint pigment. Veterinary anthelmintic.

Physical properties

Specific gravity 1.1 at 20°C with respect to water at 4°C

Solubility Water: $20\text{--}30\text{ g l}^{-1}$

Occupational exposure

DE-MAK 1 mg m^{-3} (inhalable fraction of aerosol)

SE-LEVL 0.03 mg m^{-3} (as As)

UK-LTEL MEL 0.1 mg m^{-3} (as As)

US-TWA 0.01 mg m^{-3} (as As)

UN No. 1585 HAZCHEM Code 2Z Conveyance classification toxic substance

Environmental fate

Degradation studies

Arsenic compounds are oxidised by *Pseudomonas putida* and *Alcaligenes eutrophus* (1).

Mammalian & avian toxicity

Acute data

LD₅₀ oral ♀ rat 100 mg kg⁻¹ (2).

LD₅₀ oral rabbit, rat 13, 22 mg kg⁻¹, respectively (3,4).

LD₅₀ dermal rat 2400 mg kg⁻¹ (5).

Irritancy

Irritating to skin, eyes and mucous membranes (species unspecified) (6).

Sensitisation

Industrial exposure may cause dermatitis (7).

Genotoxicity

Salmonella typhimurium TA98, TA100, TA1535, TA1537 with and without metabolic activation negative (8).

Other effects

Any other adverse effects

Arsenites act by uncoupling oxidative mitochondrial phosphorylation by substituting for inorganic phosphorus (9).

Legislation

Limited under EC Directive on Drinking Water Quality 80/778/EEC. Copper: guide level 100 µg l⁻¹ at outlets of pumping and/or treatment works and their substations and 3000 µg l⁻¹ after the water has been standing for 12 hr in the piping and at the point where the water is made available to the consumer. Arsenic: maximum admissible concentration 50 µg l⁻¹ (10).

Included in Schedule 6 (Release into Land: Prescribed Substances) Statutory Instrument No. 472, 1991 (11).

Other comments

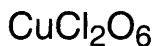
Toxicity relates primarily to arsenic content (12).

Soluble in ammonium hydroxide solution.

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c432 copper chlorate



Cl_2CuO_6

Mol. Wt. 147.00

CAS Registry No. 14721-21-2

Synonyms chloric acid, copper salt; copper(II) chlorate

Uses Mordant in printing and dyeing of textiles.

Physical properties

M. Pt. 65°C B. Pt. 100°C (decomp.)

Solubility Water: very soluble. Organic solvents: ethanol

Occupational exposure

DE-MAK 1 mg m⁻³ (inhalable fraction of aerosol)

SE-LEVL 1 mg m⁻³ (as Cu) (total dust); 0.2 mg m⁻³ (as Cu) (respirable dust)

UN No. 2721 HAZCHEM Code 1YE Conveyance classification oxidising substance

Environmental fate

Nitrification inhibition

Chlorates inhibit bacterial oxidation of nitrite to nitrate (1).

Abiotic removal

Chlorates can be removed from water by combined use of chlorine dioxide and granular activated carbon (2).

Legislation

Limited under EC Directive on Drinking Water Quality 80/778/EEC. Copper: guide level 100 µg l⁻¹ at pumping outlets/treatment works; 3 mg l⁻¹ after the water has been standing for 12 hr in the pipes (3).

World Health Organisation revised guidelines for drinking water quality. Copper: guide level 1 mg l⁻¹ (4).

Included in Schedule 4 (Release into Air: Prescribed Substances) Statutory Instrument No. 472, 1991 (5).

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c433 copper(I) chloride



ClCu

Mol. Wt. 99.00

CAS Registry No. 7758-89-6

Synonyms cuprous chloride; copper monochloride

EINECS No. 231-842-9

RTECS No. GL 6990000

Uses Catalyst for organic reactions. Catalyst, decoloriser, desulfurising agent in petroleum industry. Denitration

of cellulose. Condensing agent for soaps, fats and oils. In gas analysis to absorb carbon monoxide. Condensing agent for soaps.

Occurrence Occurs in nature as the mineral Nantokite.

Physical properties

M. Pt. 430°C **Specific gravity** 4.140 at 25°C with respect to water at 4°C **Volatility** v.p. 1.3 mmHg at 540°C

Solubility Water: sparingly soluble in water with partial decomposition

Occupational exposure

DE-MAK 1 mg m⁻³ (total dust)

SE-LEVL 1 mg m⁻³ (as Cu) (total dust); 0.2 mg m⁻³ (as Cu) (respirable dust)

UN No. 2802 **HAZCHEM Code** 2Z **Conveyance classification** corrosive substance

Supply classification harmful

Risk phrases Harmful if swallowed (R22)

Safety phrases Keep out of reach of children (if sold to general public) – Do not breathe dust (S2, S22)

Environmental fate

Abiotic removal

In soil, copper is partly leached to lower levels, partly bound by soil components and partly oxidatively transformed (1).

Mammalian & avian toxicity

Acute data

LD₅₀ oral rat 140 mg kg⁻¹ (2).

LD₅₀ subcutaneous guinea pig 100 mg kg⁻¹ (2).

Other effects

Any other adverse effects

Blood disorders may occur. Damage to the liver, kidney and other organs can occur (species unspecified) (3).

Legislation

Limited under EC Directive on Drinking Water Quality 80/778/EEC. Copper: guide level 100 µg l⁻¹ at outlets of pumping and/or treatment works and their substations and 3000 µg l⁻¹ after the water has been standing for 12 hr in the piping and at the point where the water is made available to the consumer (4).

Other comments

Copper is more dangerous in soft waters than in hard waters; the ionic form Cu²⁺ being the most toxic. In hard water the final precipitation product is the basic carbonate, malachite, CuCO₃·Cu(OH)₂.

Reviews on experimental toxicology and human health effects listed (5).

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C434 copper(II) chloride



Cl_2Cu

Mol. Wt. 134.45

CAS Registry No. 7447-39-4

Synonyms copper bichloride; cupric chloride; copper chloride

EINECS No. 231-210-2

RTECS No. GL 7000000

Uses Catalyst. Deodorising and desulfurising agent for the petroleum industry. Adsorbent for carbon monoxide. Mordant for dyeing and printing textiles. Oxidising agent for aniline dyestuffs. Used in indelible, invisible and laundry marking inks. Used in refining of copper, silver and gold ores. Electroplating baths for plating copper and aluminium. In photography as a fixer, desensitiser and reagent. To produce colour in pyrotechnic compositions. Manufacture of acrylonitrile and melanin. Pigment for glass and ceramics. Feed additive. Wood preservative and disinfectant. In hair dyes.

Physical properties

M. Pt. 620°C **B. Pt.** 993°C **Specific gravity** 3.386 at 25°C with respect to water at 4°C

Solubility Water: freely soluble. Organic solvents: acetone, ethanol, diethyl ether

Occupational exposure

DE-MAK 1 mg m⁻³ (total dust)

SE-LEVL 1 mg m⁻³ (as Cu) (total dust); 0.2 mg m⁻³ (as Cu) (respirable dust)

UN No. 2802 **HAZCHEM Code** 2Z **Conveyance classification** oxidising substance

Ecotoxicity

Fish toxicity

Stickleback exposed to 2 mg l⁻¹ (CuCl_2) died within 16-24 hr, and steelhead trout and sockeye salmon died in 12-16 hr. Bridgeline sucker exposed to 3 mg l⁻¹ died within 12-18 hr (1).

Invertebrate toxicity

The crab *Scylla serrata* was exposed to 10, 50 and 100 mg l⁻¹ (Cu^{2+}) for 14 days. The mortality rates were 60, 100 and 100%, respectively. Crabs exposed to 50 mg l⁻¹ Cu^{2+} for 48 hr had increased concentrations of copper in the haemolymph, hepatopancreas and gills suggesting entry of copper into the animal (2).

Mammalian & avian toxicity

Acute data

LD₅₀ intraperitoneal mouse 7.4 mg kg⁻¹ (3).

LD₅₀ intravenous mouse 17.5 mg kg⁻¹ (4).

Sub-acute and sub-chronic data

Following daily subcutaneous injections to calves of copper(II) chloride at doses of 0.1-0.3 mg kg⁻¹ of copper for six months, the copper content of the liver reached 5292 ppm. No symptoms of chronic copper poisoning were observed, but an increase in the plasma copper level and a decrease in the plasma alkaline phosphatase and plasma urea nitrogen levels were observed (5).

Teratogenicity and reproductive effects

Inhalation rat (3 month) 7.5-20 µg CuCl_2 m⁻³ (exposure duration unspecified) induced testis and prostate weight reduction, increased RNA concentration in the testis, sclerosis of Leydig cells and increased the number of abnormal spermatozoa (6).

Metabolism and toxicokinetics

Intravenous single dose ♀ Wistar rats 0.8 mg kg⁻¹ Cu^{2+} , copper was taken up by liver and kidney and excreted in

bile and urine. Serum copper levels decreased rapidly within 30 min and returned to normal 3 hr post injection, hepatic levels returned to normal after 4 hr (7).

Oral sheep (87 day) $6.7 \text{ mg kg}^{-1} \text{ day}^{-1} \text{ Cu}^{2+}$ dry matter. Liver copper concentration (mg kg^{-1} dry matter) increased from an initial value of 569 to 1174, kidney concentration increased from 16 to 114. These levels are equivalent to levels encountered at the haemolytic stage of chronic copper poisoning (8).

Sensitisation

Inhalation guinea pig (3 month) $7.5\text{--}20 \text{ }\mu\text{g CuCl}_2 \text{ m}^{-3}$ (exposure duration unspecified) induced weak allergic reaction. The maximum non-toxic concentration was $4 \text{ }\mu\text{g CuCl}_2 \text{ m}^{-3}$ (6).

Other effects

Any other adverse effects

In vitro human lymphocytes inhibited erythrocyte rosette formation; recovery from cytotoxic effects was not observed after washing (9).

Legislation

Limited under EC Directive on Drinking Water Quality 80/778/EEC. Copper: guide level $100 \text{ }\mu\text{g l}^{-1}$ at outlets of pumping and/or treatment works and their substations and $3000 \text{ }\mu\text{g l}^{-1}$ after the water has been standing for 12 hr in the piping and at the point where the water is made available to the consumer (10).

Other comments

Copper is more dangerous in soft waters than in hard waters; the ionic form Cu^{2+} being the most toxic. In hard water the final precipitation product is the basic carbonate, malachite, $\text{CuCO}_3 \cdot \text{Cu}(\text{OH})_2$.

References

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2. Arumugam, M. et al *Bull. Environ. Contam. Toxicol.* 1987, **39**(4), 708-715.
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9. Nagashima, S. *Igaku to Seibutsugaku* 1986, **113**(1), 31-33 (Japan.) (*Chem. Abstr.* **106**, 79968k).
10. *EC Directive Relating to the Quality of Water Intended for Human Consumption* 1982, 80/778/EEC, Office for Official Publications of the European Communities, 2 rue Mercier, L-2985 Luxembourg

c435 copper(I) cyanide

CuCN

CCuN

Mol. Wt. 89.56

CAS Registry No. 544-92-3

Synonyms cuprous cyanide; cupricin

EINECS No. 208-883-6

RTECS No. GL 7150000

Uses Catalyst. Cyanation agent. Electroplating of copper and iron. Insecticide. Fungicide. Antifouling agent in marine paints.

Physical properties

M. Pt. 474°C **Specific gravity** 2.920 at 20°C with respect to water at 4°C

Solubility Organic solvents: ethanol

Occupational exposure

DE-MAK 1 mg m⁻³ (inhalable dust fraction)

FR-VME 5 mg m⁻³ (as HCN)

SE-CEIL 5 mg m⁻³ (as CN)

UK-LTEL 5 mg m⁻³ (as CN)

UN No. 1587 **HAZCHEM Code** 4X **Conveyance classification** toxic substance

Supply classification very toxic

Risk phrases Very toxic by inhalation, in contact with skin and if swallowed – Contact with acids liberates very toxic gas (R26/27/28, R32)

Safety phrases Keep locked up and out of the reach of children (if sold to general public) – Keep container tightly closed – After contact with skin, wash immediately with plenty of water – Do not empty into drains – In case of accident or if you feel unwell, seek medical advice immediately (show label where possible) (S1/2, S7, S28, S29, S45)

Environmental fate

Nitrification inhibition

Threshold concentration for inhibition of nitrification and denitrification, rotating disc and activated sludge, 0.10 mg l⁻¹ (1).

Degradation studies

Cyanides converted into formamide by cyanide hydratase in *Stemphylium loti* (2).

Abiotic removal

Wastewater containing up to 15 mg l⁻¹ copper and up to 25 mg l⁻¹ cyanide was treated with activated carbon to yield an effluent containing <1 mg l⁻¹ copper and <0.5 mg l⁻¹ cyanide (3).

Adsorption of cyano complexes including copper(I) on activated carbon was investigated as a function of pH. Activated carbon was selective to metals that preferentially form neutral and singly charged cyano-complexes, namely gold and silver (4).

Mammalian & avian toxicity

Metabolism and toxicokinetics

Cyanide acts by inhibiting cytochrome oxidase with consequent inhibition of mitochondrial electron transport and oxidative phosphorylation (5).

Irritancy

Mucous membrane and upper respiratory tract irritant (species unspecified) (6).

Legislation

World Health Organisation revised guidelines for drinking water quality guide level: copper 1 mg l⁻¹; cyanide 0.1 mg l⁻¹ (7).

Limited under EC Directive on Drinking Water Quality 80/778/EEC. Copper: guide level 100 µg l⁻¹ at outlets of pumping and/or treatment works and their substations; 3 mg l⁻¹ after water has been standing for 12 hr in the piping and at the point where water is made available to the consumer. Cyanide: maximum admissible concentration 50 µg l⁻¹ (8).

Included in Schedule 6 (Release into Land: Prescribed Substances) Statutory Instrument No. 472, 1991 (9).

Other comments

Hazardous properties of copper cyanide reviewed (10).
Soluble in ammonium hydroxide and hydrochloric acid.

References

1. Knoetze, C. *Water Res.* 1979, (9), 5-6.
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6. Lenga, R. E. *Sigma-Aldrich Library of Chemical Safety Data* 2nd ed., 1988, 1, 913, Sigma-Aldrich, Milwaukee, USA.
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8. *EC Directive Relating to the Quality of Water Intended for Human Consumption* 1982, 80/778/EEC, Office for Official Publications of the European Communities, 2 rue Mercier, L-2985 Luxembourg.
9. *S. I. 1991 No. 472 The Environmental Protection (Prescribed Processes and Substances) Regulations* 1991, HMSO, London, UK.
10. *Dangerous Prop. Ind. Mater. Rep.* 1991, 11(1), 37-45

C436 copper EDTA

$C_{10}H_{14}CuN_2Na_2O_9$

Mol. Wt. 415.75

CAS Registry No. 51395-10-9

Synonyms disodium copper(II) EDTA; aqua[[N,N'-1,2-ethanediylbis[(N-(carboxymethyl)glycinato)]-(4-)-N,N',O,O',O N]cuprate(2-), disodium; dihydrogen disodium ethylenedinitrilo(tetraacetate)cuprate(2-)

Uses Molluscicide. Algicide. Plating baths. Fertiliser formulations.

Physical properties

M. Pt. 135°C (loses water *in vacuo*)

Occupational exposure

DE-MAK 1 mg m⁻³ (inhalable fraction of aerosol)

Ecotoxicity

Fish toxicity

LC₅₀ (96 hr) bluegill sunfish 555 mg l⁻¹. No-adverse-effect level 320 mg l⁻¹ (1).

Invertebrate toxicity

LC_{Lo} oral *Biomphalaria glabrata* >2.5-20 ppm. No effects observed at this concentration on the respiration of this mollusc, therefore deemed non-lethal (2).

LC₅₀ (144 hr) *Macoma balthica* 8 mg l⁻¹, *Nereis virens* >30 mg l⁻¹. *Crangon septemspiroso* and *Pandalus montagui* no effects observed at copper concentrations of 30 mg l⁻¹ (3).

Environmental fate

Anaerobic effects

Saccharomyces cerevisiae 0.415-4.15 mg l⁻¹ inhibits nicotinamide adenine dinucleotide dependent dehydrogenases, stimulates glycolysis; no effect on cell respiration. High concentrations block both processes (4).

Abiotic removal

Removal from wastewater effected by hydroxide coprecipitation, coagulation and activated carbon adsorption (5).

Mammalian & avian toxicity

Acute data

LD₅₀ intraperitoneal mouse 2.09 mg Cu kg⁻¹ (6).

Other effects

Any other adverse effects

Oral cows 100 mg late January, 6 wk before calving, or to 6-wk-old calves, 50 mg; no weight gain (7).

Intravenous (8 hr) rabbit 13.3 mg kg⁻¹ blood serum K increased, serum Ca decreased, serum Na unchanged (8).

Intravenous (8 hr) rabbit, rat 13.3 mg kg⁻¹ blood glucose decreased (8).

Intravenous (8 hr) guinea pigs 13.3 mg kg⁻¹ transient hyperglycaemia, then hypoglycaemia (8).

Legislation

Limited under EC Directive on Drinking Water Quality 80/778/EEC. Copper: guide level 100 µg l⁻¹ at pumping outlets/treatment works; 3 mg l⁻¹ after the water has been standing for 12 hr in the pipes (9).

World Health Organisation revised guidelines for drinking water quality. Copper: guide level 1 mg l⁻¹ (10).

Included in Schedule 4 (Release into Air: Prescribed Substances) Statutory Instrument No. 472, 1991 (11).

Other comments

Used in admixtures to attain higher pregnancy rates by artificial insemination compared with frozen, untreated bovine, rabbit sperm (12).

Is not toxic to boar, bull or rabbit semen (13).

References

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3. McLeese, D. W. et al *Bull. Environ. Contam. Toxicol.* 1986, **36**(5), 749-755.
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9. *EC Directive Relating to the Quality of Water Intended for Human Consumption* 1982, 80/778/EEC, Office for Official Publications of the European Communities, 2 rue Mercier, L-2985 Luxembourg.
10. *Guidelines for Drinking Water Quality* 1984, **1**, 7, WHO, Geneva, Switzerland.
11. *S. I.* 1991 No. 472 *The Environmental Protection (Prescribed Processes and Substances) Regulations* 1991, HMSO, London, UK.
12. Zhil'tsova, L. S. et al *Dokl. Vses. Akad. S-kh. Nauk im V.I. Lenina* 1985, (1), 33-34 (*Chem. Abstr.* **102**, 129513y).
13. Milovanov, V. K. et al *Vestn. S-kh. Nauki (Moscow)* 1982, (2), 58-66 (Russ.) (*Chem. Abstr.* **96**, 140522d).

c437 copper naphthenate

CAS Registry No. 1338-02-9

Synonyms naphthenic acid, copper salt; copper uversol; Usol Copper Green; Aseptaborex

EINECS No. 215-657-0

RTECS No. QK 9100000

Uses Used for prevention of rotting in wood, fabric, rope and fishing nets. Disinfectant and preservative for wooden seed boxes, fence posts. Tree wound dressing to prevent canker and as an animal repellent to reduce damage to deciduous and coniferous forest trees.

Physical properties

Specific gravity 1.055 at 20°C **Volatility** v.p. $<1.0 \times 10^{-3}$ mmHg at 100°C
Solubility Organic solvents: most organic solvents, petroleum oils

Occupational exposure

DE-MAK 1 mg m⁻³ (inhalable fraction of aerosol)
Supply classification harmful
Risk phrases Flammable – Harmful if swallowed (R10, R22)
Safety phrases Keep out of reach of children (if sold to general public) (S2)

Mammalian & avian toxicity

Acute data
LD₅₀ oral mouse 6400-7200 mg kg⁻¹ (1).
LD₅₀ oral rat 110 mg kg⁻¹ (1).
LC₅₀ (1 hr) inhalation rat >5.5 mg kg⁻¹ (1).
LD₅₀ dermal rabbit >2000 mg kg⁻¹ (1).

Legislation

Limited under EC Directive on Drinking Water Quality 80/778/EEC. Copper: guide level 100 µg l⁻¹ at pumping outlets/treatment works; 3 mg l⁻¹ after the water has been standing for 12 hr in the pipes. Pesticides and related products: maximum admissible concentration 0.1 µg l⁻¹ (2).

Other comments

Experimental toxicology and human health effects reviewed (3,4).
Phytotoxic to growing plants (1).
Usually contains ≈8% copper.

References

1. *The Agrochemicals Handbook* 3rd ed., 1991, The Royal Society of Chemistry, London, UK.
2. *EC Directive Relating to the Quality of Water Intended for Human Consumption* 1982, 80/778/EEC, Office for Official Publications of the European Communities, 2 rue Mercier, L-2985 Luxembourg.
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c438 copper nitrate



CuN₂O₆

Mol. Wt. 187.56

CAS Registry No. 3251-23-8

Synonyms nitric acid, copper(2+) salt; copper dinitrate; cupric nitrate

EINECS No. 221-838-5

RTECS No. QU 7400000

Uses Fungicide. Herbicide. Catalyst component in solid rocket fuel. In light-sensitive reproductive papers. Ceramic colour. Mordant and oxidising agent in textile dyeing and printing. Reagent for burnishing iron, copper and zinc. In nickel-plating baths. In aluminium brighteners. Wood preservative. In pyrotechnic compositions.

Physical properties

M. Pt. 255-256°C B. Pt. 150-225°C (sublimes) Specific gravity 2.047 at 20°C
Solubility Water: miscible. Organic solvents: diethyl ether, dioxane, ethyl acetate

Occupational exposure

DE-MAK 1 mg m⁻³ (inhalable fraction or aerosol)

SE-LEVL 1 mg m⁻³ (as Cu) (total dust); 0.2 mg m⁻³ (as Cu) (respirable dust)

UN No. 1477

UN No. 3218 (aqueous solution) HAZCHEM Code 1 $\frac{1}{2}$ HAZCHEM Code 2 $\frac{1}{2}$ (aqueous solution)

Conveyance classification oxidising substance

Ecotoxicity

Fish toxicity

Steelhead trout and sockeye salmon exposed to 2 mg l⁻¹ (Cu(NO₃)₂) died within 16-24 hr; 24 hr static bioassay. Test conditions: fish were acclimated for at least 60 hr before testing; temperature 15°C; total hardness 67-120 mg l⁻¹; alkalinity 151-183 mg l⁻¹ (methyl orange); total dissolved solids 160-175 mg l⁻¹; pH 7.1 (1).
Bridgelip exposed to 2 mg l⁻¹ (Cu(NO₃)₂) died within 3-4 hr (2).
Trout and yellow perch exposed to 5 ppm (Cu(NO₃)₂) died within 22 hr (3).

Mammalian & avian toxicity

Acute data

LD₅₀ oral rat 940 mg kg⁻¹ (4).

Irritancy

Dermal rabbit (duration unspecified) 500 mg caused severe irritation and 100 mg instilled into rabbit eye caused severe irritation (5).

Legislation

Limited under EC Directive on Drinking Water Quality 80/778/EEC. Copper: guide level 100 µg l⁻¹ at outlets of pumping and/or treatment works under their substations and 3000 µg l⁻¹ after the water has been standing for 12 hr in the piping and at the point where the water is made available to the consumer (6).
Included in Schedule 6 (Release into Land: Prescribed Substances) Regulations Statutory Instrument No. 472, 1991 (7).

Other comments

Copper is more dangerous in soft waters than in hard waters; the ionic form Cu²⁺ being the most toxic. In hard water the final precipitation product is the basic carbonate, malachite, CuCO₃.Cu(OH)₂.

References

1. Macphee, C. et al *Fish Toxicity Screening Data. Part I Lethal Effects of 964 Chemicals Upon Steelhead Trout and Bridgelip Sucker* 1989, Part 1, US EPA560/6-89-001, PB-89-156715, Washington, DC, USA.
2. Macphee, C. et al *Fish Toxicity Screening Data. Part II Lethal Effects of 2014 Chemicals Upon Sockeye Salmon, Steelhead Trout and Threespine Stickleback* 1989, Part 2, US EPA560/6-89-001, PB-89-156715, Washington, DC, USA.
3. *The Toxicity of 3400 Chemicals to Fish* 1987, Part 1, US EPA560/6-87-002, PB 87-200-275, Washington, DC, USA.
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6. *EC Directive Relating to the Quality of Water Intended for Human Consumption* 1982, 80/778/EEC, Office for Official Publications of the European Communities, 2 rue Mercier, L-2985 Luxembourg.
7. S. I. 1991 No. 472 *The Environmental Protection (Prescribed Processes and Substances) Regulations* 1991, HMSO, London, UK

C439 copper oxalate



C_2CuO_4

Mol. Wt. 151.57

CAS Registry No. 814-91-5

Synonyms cupric oxalate; oxalic acid, copper(II) salt (1:1); ethanedioic acid, copper(2+) salt (1:1), hemihydrate

Physical properties

M. Pt. 310°C (decomp.)

Occupational exposure

DE-MAK 1 mg m⁻³ (inhalable fraction or aerosol)

UN No. 2449

Legislation

Limited under EC Directive on Drinking Water Quality 80/778/EEC. Copper: guide level 100 µg l⁻¹ at outlets of pumping and/or treatment works and their substations and 3000 µg l⁻¹ after the water has been standing for 12 hr in the piping and at the point where the water is made available to the consumer (1).

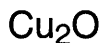
Other comments

Copper is more dangerous in soft waters than in hard waters; the ionic form Cu²⁺ being the most toxic. In hard water the final precipitation product is the basic carbonate, malachite, CuCO₃·Cu(OH)₂.

References

1. EC Directive Relating to the Quality of Water Intended for Human Consumption 1982, 80/778/EEC, Office for Official Publications of the European Communities, 2 rue Mercier, L-2985 Luxembourg

C440 copper(I) oxide



Cu_2O

Mol. Wt. 143.09

CAS Registry No. 1317-39-1

Synonyms dicopper oxide; cuprous oxide; brown copper oxide; red copper oxide; copper suboxide; C.I. 77402; Cupridan; Cuprox

EINECS No. 215-270-7

RTECS No. GL 8050000

Uses Fungicide. Catalyst. Antifouling agent in marine paints. In photoelectric cells. Red pigment for glass and ceramic glazes. In brazing pastes. In rectifiers.

Occurrence As the mineral cuprite.

Physical properties

M. Pt. 1232°C B. Pt. 1800°C Specific gravity 6.0 at 25°C with respect to water at 4°C

Occupational exposure

DE-MAK 1 mg m⁻³ (total dust)

SE-LEVL 1 mg m⁻³ (as Cu) (total dust); 0.2 mg m⁻³ (as Cu) (respirable dust)

Supply classification harmful

Risk phrases Harmful if swallowed (R22)

Safety phrases Keep out of reach of children (if sold to general public) – Do not breathe dust (S2, S22)

Ecotoxicity

Invertebrate toxicity

Non-toxic to honey bees (1).

Mammalian & avian toxicity

Acute data

LD₅₀ oral rat 470 mg kg⁻¹ (2).

LD₅₀ dermal rat >2000 mg kg⁻¹ (1).

Genotoxicity

Induced sister chromatid exchanges in human peripheral lymphocytes, but gave negative results in the Ames test and micronucleus test (3).

Legislation

Limited under EC Directive on Drinking Water Quality 80/778/EEC. Copper: guide level 100 µg l⁻¹ at outlets of pumping and/or treatment works and their substations and 3000 µg l⁻¹ after the water has been standing for 12 hr in the piping and at the point where the water is made available to the consumer (4).

Included in Schedule 6 (Release into Land: Prescribed Substances) Regulations Statutory Instrument No. 472, 1991 (5).

Other comments

Reviews on experimental toxicology and human health effects listed (6).

Data on the aquatic behaviour and ecotoxicological effects of antifouling commonly used in the world are present (7).

The oxidation of ammonium to nitrite is particularly sensitive to chemicals. A test method to detect potential nitrification is discussed (8).

The ban of tributyltin compounds in antifouling paints has increased the use cuprous oxide ten-fold since 1982.

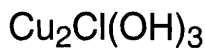
Despite this, statistical analysis of data monitored between 1979-1985 showed stable copper levels in oysters (9).

Soluble in ammonium hydroxide and hydrochloric acid.

References

1. *The Pesticide Manual* 11th ed., 1997, The British Crop Protection Council, Farnham, UK.
2. Smyth, H. F. et al *Am. Ind. Hyg. Assoc. J.* 1969, **30**(5), 470-476.
3. Shi, R. et al *Gongye Weisheng Yu Zhiyebing* 1988, **14**(2), 110-111 (Ch.) (*Chem. Abstr.* **111**, 210246w).
4. *EC Directive Relating to the Quality of Water Intended for Human Consumption* 1982, 80/778/EEC, Office for Official Publications of the European Communities, 2 rue Mercier, L-2985 Luxembourg.
5. S. I. 1991 No. 472 *The Environmental Protection (Prescribed Processes and Substances) Regulations* 1991, HMSO, London, UK.
6. *ECETOC Technical Report No. 71* 1996, European Centre for Ecotoxicology and Toxicology of Chemicals, 4 Avenue E. Van Nieuwenhuysse (Bte 6), B-1160 Brussels, Belgium.
7. Miniero, R. et al *Rapp. ISTISAN* 1989, 1-57 (Ital.) (*Chem. Abstr.* **113**, 120400s).
8. Hansson, G. B. et al *Environ. Toxicol. Water Qual.* 1991, **6**(3), 351-360.
9. Alzieu, C. et al *Oceanol. Acta* 1987, **10**(4), 463-468 (Fr.) (*Chem. Abstr.* **109** 33368y)

C441 copper oxychloride



$\text{ClCu}_2\text{H}_3\text{O}_3$

Mol. Wt. 213.57

CAS Registry No. 1332-40-7

Synonyms copper(II) chloride oxide hydrate; dicopper chloride trihydroxide; blue copper; copper chloride oxide; cupric oxide chloride; Miedzian; **RECS No.** GL 7020000

Uses Foliar fungicide. Antifouling agent. Catalyst.

Physical properties

M. Pt. 220°C (decomp.)

Solubility Water: $<10^{-5}$ mg l⁻¹ at 20°C

Occupational exposure

DE-MAK 1 mg m⁻³ (inhalable fraction of aerosol)

SE-LEVL 1 mg m⁻³ (as Cu) (total dust); 0.2 mg m⁻³ (as Cu) (respirable dust)

Ecotoxicity

Fish toxicity

LC₅₀ (48 hr) carp 2.2 mg l⁻¹ (1).

Invertebrate toxicity

Minimum toxicity observed when *Pleurotus ostreatus* were exposed to 1000 mg l⁻¹ (duration unspecified) (2).

Non-toxic to bees (1).

LC₅₀ (24 hr) *Daphnia* 3.5 mg l⁻¹ (1).

Environmental fate

Adsorption and retention

Leaching experiments and testing groundwater under treated ploughland showed that copper oxychloride did not pollute groundwater because of strong adsorption, virtually immobile in soil and(or) rapid decomposition (3).

Mammalian & avian toxicity

Acute data

LD₅₀ oral ♂ rat 1440 mg kg⁻¹ (1).

Genotoxicity

Salmonella typhimurium TA98, TA100 without metabolic activation positive (4).

Other effects

Any other adverse effects

Oral mammal (unspecified) 3-5 g caused gastroenteritis without affecting absorption. The active substance is almost completely eliminated by vomiting. Doses of 5-8 g damaged the capillaries and digestive tract mucous membranes, signs of heavy-metal poisoning, and loss of water and electrolytes. Death may occur at doses of 8-12 g (1).

Legislation

Limited under EC Directive on Drinking Water Quality 80/778/EEC. Copper: guide level 100 µg l⁻¹ at pumping outlets/treatment works; 3 mg l⁻¹ after the water has been standing for 12 hr in the pipes (5).

World Health Organisation revised guidelines for drinking water quality. Copper: guide level 1 mg l⁻¹ (6).
WHO Toxicity Class III (7).
EPA Toxicity Class (formulation) III (1).

Other comments

Data on the aquatic behaviour and ectotoxicological effects of commonly used antifouling agents are presented (8).
Soluble in dilute acids and ammonium hydroxide solutions.

References

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c442 copper sulfate



CuO₄S

Mol. Wt. 159.61

CAS Registry No. 7758-98-7

Synonyms copper(II) sulfate; sulfuric acid, copper(2+) salt (1:1); cupric sulfate

EINECS No. 231-847-6

RTECS No. GL 8800000

RTECS No. GL 8900000

Uses Antidote to phosphorus poisoning. Topical antifungal agent. Veterinary antihelmintic and fungicide. Treating copper deficiency in ruminants. The pentahydrate is used as an agricultural fungicide, herbicide, algicide and bactericide. Fertiliser additive. Mordant in textile dyeing. Preparation of azo dyestuffs. Preserving hides and wood. Tanning leather. Electroplating solution, battery electrolyte. Laundry and metal making inks. Pigment in paints. Mordant baths for intensifying photographic negatives. Anti-rusting compositions in heat exchangers. Anhydrous salt is used for detecting and removing trace amounts of water from alcohols and other organic compounds.

Occurrence Copper sulfate occurs in nature as the mineral hydrocyanite while the pentahydrate form occurs as the chalcantite minerals. The commercial preparation is the pentahydrate commonly called Bluestone, Blue vitriol, Roman vitriol, Salzburg vitriol.

Physical properties

M. Pt. 560°C (decomp.) **Specific gravity** 3.603 at 20°C with respect to water at 4°C (anhydrous)

Solubility Water: monohydrate soluble, pentahydrate very soluble. Organic solvents: (pentahydrate) ethanol, glycerol, methanol

Occupational exposure

DE-MAK 1 mg m⁻³ (inhalable fraction of aerosol)

SE-LEVL 1 mg m⁻³ (as Cu) (total dust); 0.2 mg m⁻³ (as Cu) (respirable dust)

Supply classification harmful

Risk phrases Harmful if swallowed – Irritating to eyes and skin (R22, R36/38)

Safety phrases Keep out of reach of children (if sold to general public) – Do not breathe dust (S2, S22)

Ecotoxicity

Fish toxicity

Considerable acetylcholinesterase inhibition in carp was manifested at 5 ppm copper sulfate treatment for 2 wk. Levels returned to normal after treatment (1).

Indian catfish exposed to 0.25 mg l⁻¹ for up to 30 days, became lethargic and began surfacing frequently to gulp air. Numerous immature erythrocytes and broken fragments of blood corpuscles were evident (2).

Threespine stickleback exposed to 10 mg l⁻¹ died within 16-24 hr (3).

LC₅₀ (96 hr) rainbow trout, harlequin fish, goldfish, eel 0.1-2.5 mg l⁻¹ (4-6).

Exposed carp (concentration and duration unspecified) had increased serum cholinesterase and transaminase activities, and adrenaline and noradrenaline levels. The long lasting effect could be due to a decrease in γ -globulin level, which lowers resistance to infectious diseases (7).

A static bioassay was conducted on Indian carp using low doses (0.05 ppm) of copper sulfate. Erythrocyte count and haematocrit value decreased 34.1% and 14.6%, respectively, whereas haemoglobin concentration increased to 7.6%. Morphological study of erythrocytes showed slight erythroanisocytosis, degenerating red cell membrane and clumping of red blood cells. Thus copper sulfate caused a direct or indirect effect on the cell membrane leading to haemolysis (8).

The order of the concentrations of copper sulfate taken up by carp organs was skeletal muscle > liver > gills > intestine > kidney > heart > brain. With the exception of the brain, greater copper accumulation was measurable in every organ at 20°C compared to 4°C. Carp exposed to 5 ppm for 2 wk exhibited considerable acetylcholinesterase inhibition but this could only be measured in the first 24 hr (1).

Invertebrate toxicity

EC₅₀ (48 hr) *Daphnia magna* 24 μ g l⁻¹ (9).

EC₅₀ (4 hr) *Scenedesmus quadricauda* 0.1 mg l⁻¹ (10).

EC₅₀ (96 hr) *Asellus aquaticus*, *Crangonyx pseudogracilis* 1.3-9.2 mg l⁻¹ (11).

Scylla serrata (14 day) 10, 50 and 100 mg l⁻¹ caused 40, 80 or 100% mortality, respectively. Exposure to 50 mg l⁻¹ copper over 48 hr increased the concentration of copper in the haemolymph, hepatopancreas and gills (12).

LC₅₀ (96 hr) freshwater snail *Viviparus bergalensis* 2.40 mg l⁻¹ (13).

The effect of pH on the biological availability of copper to the brine shrimp *Artemia franciscana* was studied with acclimated and non-acclimated individuals for the pH range 5.5-8.5. Copper was absorbed across the gut epithelium proportional to time over a 2-hr period. The biological availability of copper decreased with decrease in pH and a concomitant increase of the cupric ion concentration. Acclimation to the experimental pH had a marked effect on the uptake process and was dependent on the buffer used (14).

Environmental fate

Nitrification inhibition

Standard Aquatic Microcosm Protocol (SAM) showed low copper sulfate concentrations were associated with temporary reduction in *Daphnia* sp. populations and concurrent algal blooms (15).

Mammalian & avian toxicity

Acute data

LD₅₀ ♂ domestic chicken 693 mg kg⁻¹ (16).

LD₅₀ oral rat 300 mg kg⁻¹ (17).

LD₅₀ oral rat 960 mg kg⁻¹ (as pentahydrate) (18).

LD₅₀ subcutaneous rat 43 mg kg⁻¹ (19).

LD₅₀ intraperitoneal mouse 18 mg kg⁻¹ (20).

LD₅₀ intravenous rabbit 10 mg kg⁻¹ (21).

LD_{Lo} oral human 50 mg kg⁻¹ (22).

Sub-acute and sub-chronic data

Rats fed copper sulfate 25 mg kg⁻¹ day⁻¹ for 4 wk showed slightly decreased food intake and a slight decrease in growth rate (23).

Pigs exposed to 5-25 mg in the diet for 54-88 days experienced reductions in haemoglobin and haematocrit and reduced weight gain (23).

Following oral administration at doses of 12-51 mg kg⁻¹ as copper for 2-3 months to calves, the concentration of copper in the liver did not exceed 1000 ppm. No clinical changes were seen and the average daily body weight gain was 1036 g during the experimental period. A calf given 255 mg kg⁻¹ copper (copper sulfate) orally died two days after the last administration. After subcutaneous administration of 51 mg kg⁻¹ copper calves died 9 hr after injection (24).

Carcinogenicity and chronic effects

National Toxicology Program short term toxicity studies on copper sulfate in rats and mice are currently scheduled for peer review (25).

Teratogenicity and reproductive effects

An investigation was carried out on 12 couples (25-40 yrs old) who routinely handled pesticides, including copper sulfate, in the vineyards of Andhra Pradesh. Couples were examined clinically and data on their health, previous illnesses, nature of work and reproductive performance were recorded. In these workers a high percentage (43.75%) of abortions was recorded compared to 7.5% in control group. One stillbirth was noted compared to none in controls. No abortions or stillbirths were recorded in the reproductive histories of the exposed couples prior to their employment in the vineyards (26).

Metabolism and toxicokinetics

After an oral dose absorption occurs in the upper gastro-intestinal tract in mammals. Absorbed copper is predominantly bound to albumin and transported to liver. Faecal excretion via secretion in bile is greater than urinary excretion (27).

Corn silage-based diet containing copper sulfate at a concentration of 35.7 mg kg⁻¹ copper was fed to sheep. After 87 days the liver concentration of copper had increased from 569 to 1050 mg kg⁻¹ dry weight, representing ≈2% of the ingested copper. In the kidneys the copper concentration increased from 16 to 23 mg kg⁻¹ dry weight. These levels have been encountered at the haemolytic stage of chronic copper poisoning (28).

Sensitisation

95 patients were epicutaneously patch-tested in order to detect the prevalence of sensitivity to compounds of dental alloys. 17 individuals (17.9%) developed allergic reactions, which were caused by: mercury (10.5%); copper (2.1%); nickel, cobalt, tin, gold and zinc (1.1%). 8/17 allergic responders had a history of dermatitis from metal contact (29).

Genotoxicity

Escherichia coli PQ37, PQ35 SOS chromotest negative (30).

In vivo mouse bone marrow micronuclei test negative (31).

Other effects

Other adverse effects (human)

Accidental and suicidal ingestions are not uncommon in India (32).

Individual with glucose-6-phosphate dehydrogenase deficient red cells developed intense methaemoglobinemia and intravascular haemolysis after ingesting 50 gm of copper sulfate (33).

A disease known as Indian childhood cirrhosis has been associated with high intakes of copper (34).

Copper sulfate corrosion and necrosis of the oesophagus and stomach after ingestion reported (35).

Copper poisoning has occurred from the application of copper sulfate to extensive areas of burned skin (36).

Any other adverse effects

Copper sulfate produced a concentration-dependent inhibition of histamine release in rat peritoneal mast cells *in vitro* (37).

Legislation

Limited under EC Directive on Drinking Water Quality 80/778/EEC. Copper: guide level 100 µg l⁻¹ at pumping/substations outlets; 3 mg l⁻¹ after water has been standing 12 hr in the piping (38).

World Health Organisation revised guidelines for drinking water quality: copper guide level 1 mg l⁻¹ (39).

Other comments

Copper is more dangerous in soft waters than in hard waters; the ionic form Cu²⁺ being the most toxic. In hard water the final precipitation product is the basic carbonate, malachite, CuCO₃. Cu(OH)₂. In the short term, copper behaves synergistically with zinc in fish toxicology.

Effects on ecosystems and algal toxicity reviewed (40).

Effects on oxygen demand during nitrification discussed (41).

It is generally believed that milk stored in brass containers leads to high copper intakes in children (35).

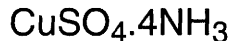
Copper sulfate 0.3 ppm day⁻¹ is used to control algal blooms in fish ponds (8).

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c443 copper sulfate, ammoniated



$\text{CuH}_{12}\text{N}_4\text{O}_4\text{S}$

Mol. Wt. 227.73

CAS Registry No. 10380-29-7

Synonyms tetraamminecopper(II) sulfate; tetraamminecopper(2+) sulfate (1:1); sulfuric acid, copper(II) salt, ammoniated

Occupational exposure

DE-MAK 1 mg m⁻³ (inhalable fraction of aerosol)

SE-LEVL 1 mg m⁻³ (as Cu) (total dust); 0.2 mg m⁻³ (as Cu) (respirable dust)

Legislation

Limited under EC Directive on Drinking Water Quality 80/778/EEC. Copper: guide level 100 µg l⁻¹ at outlets of pumping and/or treatment works and their substations 3000 µg l⁻¹ after the water has been standing for 12 hr in the piping and at the point where the water is made available to the consumer (1).

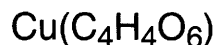
Other comments

Copper is more dangerous in soft waters than in hard waters; the ionic form Cu²⁺ being the most toxic. In hard water the final precipitation product is the basic carbonate, malachite, CuCO₃·Cu(OH)₂. At neutral pH ammonia exists in its ionic form which is less toxic than ammonia.

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c444 copper tartrate



$\text{C}_4\text{H}_4\text{CuO}_6$

Mol. Wt. 211.62

CAS Registry No. 815-82-7

Synonyms cupric tartrate; 2,3-dihydroxy-[R-(R')]-butanedioic acid, copper(II) salt

EINECS No. 212-425-0

Uses Analytical chemistry. Biuret agent. In baths for copper plating.

Physical properties

Solubility Water: slightly soluble

Occupational exposure

DE-MAK 1 mg m⁻³ (inhalable fraction of aerosol)

Legislation

Limited under EC Directive on Drinking Water Quality 80/778/EEC. Copper: guide level 100 µg l⁻¹ at outlets of pumping and/or treatment works and their substations and 3000 µg l⁻¹ after the water has been standing for 12 hr in the piping and at the point where the water is made available to the consumer (1).

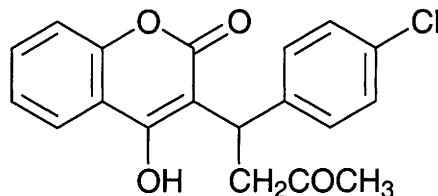
Other comments

Copper is more dangerous in soft waters than in hard waters; the ionic form Cu²⁺ being the most toxic. In hard water the final precipitation product is the basic carbonate, malachite, CuCO₃.Cu(OH)₂. Soluble in acid and alkaline solutions.

References

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C445 coumachlor



C₁₉H₁₅ClO₄

Mol. Wt. 342.78

CAS Registry No. 81-82-3

Synonyms 4-hydroxy-3-[3-oxo-1-(4-chlorophenyl)-butyl]coumarin; 3-(α-acetonyl-*p*-chlorobenzyl)-4-hydroxycoumarin; 3-(α-*p*-chlorophenyl-β-acetylethyl)-4-hydroxycoumarin; 3-[1-(4-chlorophenyl)-3-oxobutyl]-4-hydroxy-2*H*-1-benzopyran-2-one; 3-[1-(4-chlorophenyl)-3-oxobutyl]-4-hydroxycoumarin; Ratilan; Tomorin

EINECS No. 201-378-1

RTECS No. GN 4830000

Uses Superseded anticoagulant and rodenticide.

Physical properties

M. Pt. 169-171°C **Volatility** v.p. <7.5 × 10⁻⁵ mmHg at 20°C

Solubility Water: 0.5 mg l⁻¹ at 20°C at pH 4.5. Organic solvents: dimethylformamide, acetone, methanol, octan-1-ol, chloroform, benzene, diethyl ether, petroleum ether

Occupational exposure

Supply classification harmful

Risk phrases Harmful: danger of serious damage to health by prolonged exposure if swallowed (R48/22)

Safety phrases Keep out of reach of children (if sold to general public) – Wear suitable gloves (S2, S37)

Mammalian & avian toxicity

Acute data

LD₅₀ oral rat 900-1200 mg kg⁻¹ (1).

LD₅₀ dermal rat 33 mg kg⁻¹ (1).

Sub-acute and sub-chronic data

LD₅₀ oral rat for 4 or 5 doses 150 mg kg⁻¹, and for repeated doses 0.1-1.0 mg kg⁻¹ day⁻¹ (1).

Irritancy

Non-irritating to skin and eyes of rabbit (1,2).

Legislation

EC and UK maximum admissible concentration for individual pesticides in drinking water 0.1 µg l⁻¹ (3).

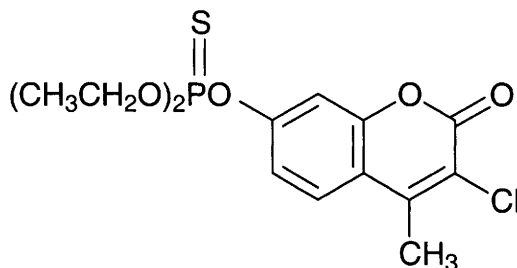
Other comments

Mode of action as a rodenticide – anticoagulant. It does not induce bait shyness (1).

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C446 coumaphos



C₁₄H₁₆ClO₅PS

Mol. Wt. 362.77

CAS Registry No. 56-72-4

Synonyms O-(3-chloro-4-methylcoumarin-7-yl) O,O-diethyl phosphorothioate; 3-chloro-7-hydroxy-4-methylcoumarin, O,O-diethylphosphorothioato-; O-(3-chloro-4-methyl-2-oxo-2H-1-benzopyran-7-yl) O,O-diethyl phosphorothioate; O-3-chloro-4-methyl-2-oxo-2H-chromen-7-yl O,O-diethyl phosphorothioate; 3-chloro-7-diethoxyphosphinothioyl-4-methylcoumarin; Asuntol; Co-Ral; Perizin

EINECS No. 200-285-3

RTECS No. GN 6300000

Uses Livestock insecticide. Nematicide. Therapeutically as (veterinary) antihelmintic.

Physical properties

M. Pt. 95°C (90-92°C, tech.) **Specific gravity** 1.474 at 20°C **Partition coefficient** log P_{ow} 4.13

Volatility v.p. 0.0975 × 10⁻⁶ mmHg

Solubility Water: 1.5 mg l⁻¹ at 20deg.C. Organic solvents: acetone, chloroform, dimethyl sulfoxide, ethanol

Occupational exposure

Supply classification very toxic, dangerous for the environment

Risk phrases Harmful in contact with skin – Very toxic if swallowed – Very toxic to aquatic organisms, may cause long-term adverse effects in the aquatic environment (R21, R28, R50/53)

Safety phrases Keep locked up and out of the reach of children (if sold to general public) – After contact with skin, wash immediately with plenty of water – Wear suitable protective clothing and gloves – In case of accident or if you feel unwell, seek medical advice immediately (show label where possible) – This material and/or its container must be disposed of as hazardous waste – Avoid release to the environment. Refer to special instructions/safety data sheet (S1/2, S28, S36/37, S45, S60, S61)

Ecotoxicity

Fish toxicity

LC₅₀ (96 hr) coho salmon, fathead minnow 15-18 mg l⁻¹ (1).

LC₅₀ (96 hr) bluegill sunfish 0.18 mg l⁻¹ (1).

LC₅₀ (96 hr) rainbow trout 1.5 mg l⁻¹ (1).

Invertebrate toxicity

LC₅₀ (96 hr) *Gammarus fasciatus* 0.15 mg l⁻¹ (2).

EC₅₀ (48 hr) *Daphnia magna* 1.0 µg l⁻¹ (3).

Environmental fate

Degradation studies

Bacteriological degradation was shown to be responsible for loss of activity in cattle-dips (4).

Abiotic removal

Has been demonstrated to degrade faster in wool under UV irradiation; t_{1/2} for irradiated wool at 24-32°C was 12 hr compared to 15 days for a control (5).

Coumaphos was irradiated at 313 nm in chloroform. The coumarin ring was the most reactive part of the molecule leading to dimerisation. A dehalodimerisation product was also identified (6).

Mammalian & avian toxicity

Acute data

LD₅₀ oral redwing blackbird 2-10 mg kg⁻¹ (7).

LD₅₀ oral starling, house sparrow, pigeon, house finch 75-316 mg kg⁻¹ (7).

LD₅₀ oral Japanese quail 13 mg kg⁻¹ (7).

LD₅₀ oral rat 16-41 mg kg⁻¹ (8).

LC₅₀ (duration unspecified) inhalation rat 303 mg m⁻³ (9).

LD₅₀ dermal rat 860 mg kg⁻¹ (10).

LD₅₀ intraperitoneal mouse 50 mg kg⁻¹ (11).

Carcinogenicity and chronic effects

No evidence for carcinogenicity when administered in feed to rats and mice at concentrations of 10 or 20 ppm for 103 wk (12).

Oral rat (2 yr) 100 ppm in diet, no adverse effects reported (13).

Metabolism and toxicokinetics

When fed to rabbits and cattle at 50 and 75 mg kg⁻¹, coumaphos appeared in the blood after 30 min (max 48-96 hr) and in the internal organs after 3-24 hr (max 48-96 hr); >50% excreted in the urine and faeces was unchanged.

Metabolites detected included 3-chloro-4-methyl-7-hydroxycoumarin and coroxon (3-chloro-7-hydroxy-4-methylcoumarin diethyl phosphate) (14).

Dermal treatment of lactating goats with 14 mg kg⁻¹. ¹⁴C-coumaphos resulted in an average of <0.1, 4.7 and 1% of the administered dose being eliminated in the milk, urine and faeces, respectively, within seven days of initial treatment. ≈45% of the administered ¹⁴C-labelled compound remained in the hair and skin as intact coumaphos.

Residues in selected tissues were in every case $<1 \text{ mg kg}^{-1}$, with the highest residues in adipose tissue, followed by the kidney and liver. In milk, residual amounts plateaued after \approx two days and remained relatively constant at $\approx 0.1 \text{ mg kg}^{-1}$. Residues in milk, adipose tissue and faeces consisted mainly of intact coumaphos. In urine most of the radiolabelled coumaphos was present as metabolites. Coumaphos was absorbed slowly and at a constant rate after dermal application as a pour-on application (15).

Genotoxicity

Salmonella typhimurium TA98, TA100, TA1535, TA1538 with and without metabolic activation negative (16,17).

Mouse lymphoma L5178Y tk⁺/tk⁻ cell forward mutation assay negative (18).

Chinese hamster ovary cells sister chromatid exchange and chromosome aberrations negative (19).

Other effects

Other adverse effects (human)

Veterinarians treating grub infestations in cattle with pour-on application of the chemical in poorly ventilated areas experienced nausea, headaches and irritation of the throat and skin (20).

Any other adverse effects

A cholinesterase inhibitor. Repeated or prolonged exposure may result in delayed neuropathy (13).

Legislation

Limited under EC Directive on Drinking Water Quality 80/778/EEC. Pesticides: maximum admissible concentration $0.1 \mu\text{g l}^{-1}$ (21).

Included in Schedule 6 (Release into Land: Prescribed Substances) Statutory Instrument No. 472, 1991 (22).

WHO Toxicity Class Ia (23).

Partition coefficient exceeds EC limit.

Other comments

Toxicity and health hazards reviewed (24,25).

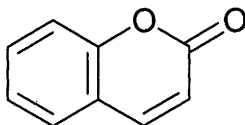
Metabolism by soil bacteria and biological degradation in waste disposal situations reviewed (26).

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C447 coumarin



C₉H₆O₂

Mol. Wt. 146.15

CAS Registry No. 91-64-5

Synonyms 2H-1-benzopyran-2-one; 1-benzo- α -pyrone; 1,2-benzopyrone; *cis-o*-coumarinic acid lactone; coumarinic anhydride; Tonka bean camphor; *o*-hydroxycinnamic acid lactone

EINECS No. 202-086-7

RTECS No. GN 4200000

Uses Flavouring agent. Fixatives and enhancing agent for essential oil odours in perfumes. Tobacco products. Cosmetics.

Occurrence Angelica, Tonka beans, lavender oil, woodruff (*Asperula spp.*), sweet clover (*Melilotis*), Cassia, Peru Balsam, other plants of Orchidaceae and lavender families, parsnip, fruits, cinnamon oil and other essential oils.

Physical properties

M. Pt. 68-70°C **B. Pt.** 297-299°C **Specific gravity** 0.935 at 20°C with respect to water at 4°C

Partition coefficient log P_{ow} 1.39 (1) **Volatility** v.p. 1 mmHg at 106°C

Solubility Water: 2.5 g l⁻¹ at 20°C. Organic solvents: chloroform, ethanol, diethyl ether

Ecotoxicity

Fish toxicity

Not toxic to brown trout, bluegill sunfish, yellow perch or goldfish, when exposed to 5 mg l⁻¹ for 24 hr (2).

Invertebrate toxicity

EC₅₀ (48 hr) *Daphnia pulex* 30.6 mg l⁻¹ (3).

Toxicity to other species

Small cell *Xenopus laevis* blastulae were tested under the frog embryo teratogenic assay. Coumarin was found to have a moderate positive teratogenic potential *in vitro* (4).

Mammalian & avian toxicity

Acute data

LD₅₀ oral mouse, guinea pig, rat 196-680 mg kg⁻¹ (5-7).

LD₅₀ intraperitoneal mouse 220 mg kg⁻¹ (8).

LD₅₀ subcutaneous mouse 310 mg kg⁻¹ (7).

Sub-acute and sub-chronic data

Oral ♂, ♀ baboon (3 wk) 50 ppm in diet when liver biopsies were taken. Animals were then maintained on a coumarin-free diet for 3 months, after which the dose was increased to 100 ppm for a further 3 wk. A second liver biopsy was performed and animals were given a coumarin-free diet for another 3 months. No histological abnormalities were observed, however histochemically, the lysosomes were larger than normal and dispersed throughout the liver cells, indicative of a hepatotoxic effect (9).

Carcinogenicity and chronic effects

No adequate evidence for carcinogenicity to humans, limited evidence for carcinogenicity to animals, IARC classification group 3 (10).

Oral rat (18 month) 5000 ppm caused 33% of animals to develop liver carcinomas (11).

Rats were fed diets containing 0, 1000, 2500 or 5000 mg kg⁻¹ for 2 yr. Of 24 rats fed 5000 mg kg⁻¹ diet, 12/24 (11 ♂, 1 ♀) developed bile duct carcinomas. In a subsidiary experiment bile duct carcinomas occurred in 4/25 ♂ and 1/8 ♀ fed 3500 mg kg⁻¹ diet. A few bile duct adenomas were found in rats fed 1000 and 2500 mg kg⁻¹ diet. None were reported in controls (12).

Teratogenicity and reproductive effects

TD_{Lo} oral mouse (6-17 day of pregnancy) 3600 mg kg⁻¹ positive teratogen caused delay of development (13).

Metabolism and toxicokinetics

o-Hydroxyphenylacetaldehyde was the major metabolite formed by rat, hamster and gerbil liver microsomes *in vitro*, while human liver microsomes metabolised coumarin to 7-hydroxy coumarin and 3-hydroxycoumarin. Its formation was NADPH dependent (14).

In rats, following oral administration, the compound was rapidly absorbed and widely distributed in serum, liver and kidney within 5 min, serum levels reaching a maximum after ≈30 min. Up to 80% was excreted in the urine, mainly as 2-hydroxyphenylacetic acid, 3-, 4-, 7- and 8-hydroxycoumarins, *o*-coumaric acid and only small amounts of 2-hydroxyphenylpropionic acid (15).

Coumarin compounds have been found to bind to α-1-acid glycoprotein and to human serum albumin.

Hydrophobic interaction was found to be important in binding to both proteins. The size of the 3'-substituent also influenced binding to α-1-acid glycoprotein. Binding sites, therefore, are located within the hydrophobic crevices of the proteins (16).

Eight volunteers (4♂, 4♀) were each given 200 mg coumarin in capsule form. Metabolites detected in 24 hr urine samples were *o*-hydroxyphenylacetic acid (1-6%) and 7-hydroxycoumarin (68-92%). This suggests that coumarin is quickly absorbed in the human gut and that any enterohepatic circulation is unlikely (17).

Human populations are thought to metabolise coumarin almost exclusively by 7-hydroxylation mediated by the cytochrome P-450 isozyme CYP2A6. An individual was identified to be homozygous for a single amino acid substitution (Leu160His) in the cytochrome P-450 CYP2A6 arising from the variant CYP2A6*2 allele. On administering 2 mg orally, no detectable 7-hydroxycoumarin was excreted in the 0-8 hr urine, rather, 50% approximately of the dose was eliminated as 2-hydroxyphenylacetic acid, the end product of coumarin 3-hydroxylation. Persons homozygous for the CYP2A6*2 allele may constitute 1-25% of various human populations (18).

Absorption and metabolism of radiolabelled coumarin in rat and human skin was measured using flow-through 3 and pH 7.4 buffered Hank's salt solution as a receptor fluid. Skin absorption was greater from the emulsion vehicle than the ethanol in both human and rat skin. Penetration was rapid with >75% (rat) and >95% (human) of the absorbed dose found in the receptor fluid within 6 hr. No evidence of coumarin metabolism was observed (19).

Sensitisation

Sensitising capacity negative (species unspecified) (20).

Genotoxicity

Salmonella typhimurium TA98, TA100, TA1535, TA1537 with metabolic activation positive; without metabolic activation negative (21).

Negative in the sex-linked recessive lethal test in *Drosophila melanogaster* (22).

Did not induce sister chromatid exchanges in Chinese hamster ovary cells *in vitro* (23).

Other effects

Any other adverse effects

Coumarin and some of its metabolites have been shown to inhibit glucose-6-phosphatase activity in rat liver and in liver microsomal preparations (24,25).

Single intraperitoneal doses of 125 mg kg⁻¹ to σ^7 rats induced a depletion of hepatic non-protein sulfhydryl groups (mainly reduced glutathione) after 2 hr, and increased liver weight and produced hepatic centrilobular necrosis after 24 hr (26).

Legislation

EC and UK maximum admissible concentration for individual pesticides in drinking water 0.1 $\mu\text{g l}^{-1}$ (27).

Other comments

Bacteriostatic to extensive concentration of *Escherichia coli* at >146 mg l⁻¹ (28).

Inhibited the growth of cancer cells (HeLa-S 3) *in vitro* at concentrations >5 $\mu\text{g ml}^{-1}$ (29).

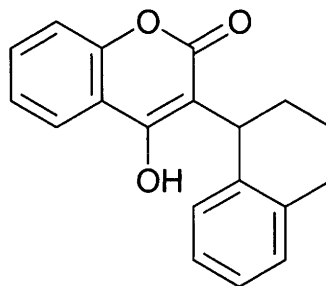
Threshold odour detection limit in air ~10 mg m⁻³ and in water ~5 $\times 10^{-2}$ mg l⁻¹ (1).

Reviews on experimental toxicology and human health effects are listed (30).

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C448 coumatetralyl



C₁₉H₁₆O₃

Mol. Wt. 292.33

CAS Registry No. 5836-29-3

Synonyms 4-hydroxy-3-(1,2,3,4-tetrahydro-1-naphthyl)coumarin; 4-hydroxy-3-(1,2,3,4-tetrahydro-1-naphthalenyl)-2*H*-1-benzopyran-2-one; 4-hydroxy-3-(α -tetralyl)coumarin; Endocide; Rodentin; Aragon; Bio Racumin; Cumirat; Integral Rat

EINECS No. 227-424-0

RTECS No. GN 6300000

Uses Rodenticide.

Physical properties

M. Pt. 172-176°C **Partition coefficient** log P_{ow} 3.346 **Volatility** v.p. <1.43 mmHg at 20°C

Solubility Water: 425 mg l⁻¹ at 20°C at pH 7.0. Organic solvents: acetone, benzene, dichloromethane, diethyl ether, ethanol, propan-2-ol, toluene

Occupational exposure

Supply classification very toxic

Risk phrases Very toxic in contact with skin and if swallowed – Toxic: danger of serious damage to health by prolonged exposure in contact with skin and if swallowed – Harmful to aquatic organisms, may cause long-term adverse effects in the aquatic environment (R27/28, R48/24/25, R52/53)

Safety phrases Keep locked up and out of the reach of children (if sold to general public) – Wear suitable protective clothing and gloves – In case of accident or if you feel unwell, seek medical advice immediately (show label where possible) – Avoid release to the environment. Refer to special instructions/safety data sheet (S1/2, S28, S36/37, S45, S61)

Ecotoxicity

Fish toxicity

LC₅₀ (96 hr) guppy \approx 1000 mg l⁻¹ (1).

Environmental fate

Abiotic removal

Exposure to sun or UV light, $t_{1/2}$ 1.0-6.6 hr (aqueous solution) (2).

Mammalian & avian toxicity

Acute data

LD₅₀ oral rat 16.5 mg kg⁻¹ (1,2).

LD_{Lo} oral cat 20 mg kg⁻¹ (3).

LD₅₀ dermal rat 25-50 mg kg⁻¹ (1,2).

Sub-acute and sub-chronic data

LC₅₀ (8 day) oral hen >50 mg kg⁻¹ in diet (1).

Coumatetralyl was administered to dogs at 1/7th the LD₅₀ (route unspecified). It caused subcutaneous and thoracic cavity haemorrhage, a distended gall bladder and a shrunken spleen. The liver, lung, heart and urinary bladder all showed evidence of pathological changes (4).

Legislation

Limited under EC Directive on Drinking Water Quality 80/778/EEC. Pesticides: maximum admissible concentration $0.1 \mu\text{g l}^{-1}$ (5).

WHO Toxicity Class Ib (6).

EPA Toxicity Class I (formulation) (2).

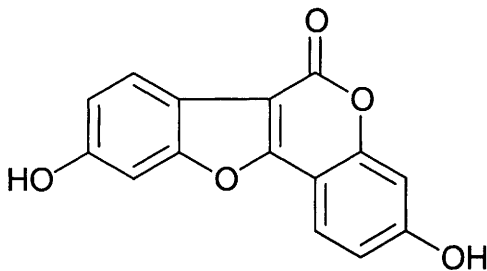
Other comments

Mode of action as a rodenticide – inhibits blood coagulation by blocking prothrombin formation in the liver. Does not induce bait shyness (1).

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C449 coumestrol


$$\text{C}_{15}\text{H}_8\text{O}_5$$

Mol. Wt. 268.23

CAS Registry No. 479-13-0

Synonyms 3,9-dihydroxy-6*H*-benzofuro[3,2-*c*][1]benzopyran-6-one; 3-benzofurancarboxylic acid, 2-(2,4-dihydroxyphenyl)-6-hydroxy-, δ -lactone; coumestrol; cumoestrol; cumostrol

EINECS No. 207-525-6

Occurrence An oestrogenic factor which occurs in forage crops, especially in ladino clover (*Trifolium repens* L.), strawberry clover (*Trifolium fragiferum* L.) and alfalfa (*Medicago sativa* L.)

Physical properties

M. Pt. 385°C (crystals) sublimes at 325°C

Solubility Water: practically insoluble neutral and acid pH, sparingly soluble pH 11-12. Organic solvents: slightly soluble in chloroform, ether, methanol; very slightly soluble in carbon tetrachloride

Mammalian & avian toxicity

Sub-acute and sub-chronic data

A diet containing 50 ppm coumestrol fed to White Mountain chicks for three weeks caused a reduction in plasma cholesterol levels. This may have been due to increased faecal losses and (or) reduced endogenous synthesis of cholesterol (1).

Newborn ♀ mice were given daily subcutaneous injections of 0.08 µg diethylstilbestrol or 100 µg coumestrol in 0.005 ml DMSO, or DMSO alone, or were untreated, for the first five days of life. (The doses chosen were equivalent in biological activity based on published uterine bioassay data for young adult mice.) Diethylstilbestrol and coumestrol significantly advanced the time of complete vaginal opening and induced a comparable degree of ovary-independent persistent vaginal cornification. Coumestrol also caused the occurrence of haemorrhagic ovarian follicles (2).

Teratogenicity and reproductive effects

TD_{Lo} (teratogenic and reproductive effects) oral ♀ mice 35 g kg⁻¹ over a period of 14 days prior to mating (3). Dietary coumestrol fed to strain B6D2F1 ♀ mice (150-300 ppb) resulted in a reduction of ovulation rates (50-66%) and an increase in the incidence of degenerate embryos (26-81% against 4% for controls). The corresponding values for strain ICR ♀ mice fed 50-400 ppb in their diet were a reduction of ovulation rates of 30-54% and an increase in the incidence of degenerate embryos to 46% (for animals fed 400 ppb) from the control level of 3%. The fertilisation rate of strain B6D2F1 mice was not affected by dietary coumestrol but that of strain ICR mice was reduced. Maternal weights of strain B6D2F1 mice were not affected by 900 ppb coumestrol in the diet, but 400 ppb reduced the maternal weights of strain ICR mice (4).

Genotoxicity

Salmonella typhimurium TA98, TA100, TA1538 with and without metabolic activation negative (5).

Subcutaneous mouse 400 mg kg⁻¹ unscheduled DNA synthesis assay positive (6).

Other effects

Any other adverse effects

Coumestrol was effective in developing the reproductive tract and endocrine glands in immature ♀ mice but did not cause any significant change in the weight of adrenal or pituitary glands (7).

Coumestrol and oestrone administered to ♀ rats via feed acted similarly on uterus weight but differently on insulin level and carbohydrate metabolism. Coumestrol feeding in young immature and ovariectomised adult rats lowered the insulin level, contrary to oestrone which either increased or had no effect on the insulin level. Coumestrol also decreased the liver and muscle glycogen content but these changes were dependent on the physiological state of the animals (8).

Coumestrol inhibited but did not abolish uterine gland genesis in a dose-dependent manner in the neonatal rat. The compound elicited uterine biochemistry and morphological toxicity much like diethylstilbestrol (9).

Coumestrol administration to ovariectomised rats effectively lowered the total serum cholesterol level and prevented ovariectomy-induced bone loss (10).

Intramuscular injection (7.5-25 mg day⁻¹) or intraruminal infusion (350 mg day⁻¹ of coumestrol to ovariectomised sheep gave plasma levels of 6-31 µg l⁻¹ and stimulated uterine growth to almost maximum extent. Oestrogenic activity was more closely related to the level of free coumestrol in the plasma than to the level of total coumestrol (11).

Sheep grazed in pastures high in coumestrol for one day showed significant oestrogenic activity in the cervical mucous bioassay. The response remained significant during 8-10 days of grazing (12).

Coumestrol and oestradiol were fed to prepubertal ewe lambs for 12 days. The level of coumestrol fed relative to oestradiol was established from the relative binding affinities of the uterine cytosol oestrogen receptors to be the biologically effective amount. The effects of coumestrol treatment were increased uterine weight and decreased ovarian weight and follicular development. There was a relation between uterine weight and exchanged tritiated oestradiol bound to the endometrial cell nuclear pellet. The dose of coumestrol as calculated from its affinity to the uterine oestrogen receptor is within the range which could be consumed in alfalfa (13).

Observations on a herd of dairy cattle over 26 years showed that symptoms of hyperoestrogenic syndrome appeared when the animals were fed alfalfa. Bioassay of alfalfa extracts taken from the farm showed oestrogenic activity. The most potent oestrogenic activity was due to coumestrol, which was identified in the milk and urine of cows fed alfalfa (14).

Other comments

Endocrine disrupting effects discussed (15).

The binding of coumestrol to the oestrogen receptor in human breast tumour cell line MCF-7 is approximately 10% as potent as oestradiol and about 3000 times less potent than diethylstilbestrol for inducing uterine growth in ovariectomised rodents (16).

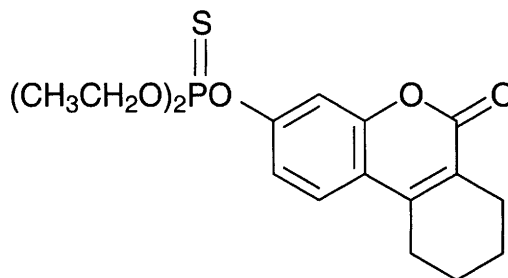
Coumestrol is approximately 900-100,000 times less potent than oestradiol in inducing oestrogen responsible cell proliferation or oestrogen-specific protein in human breast tumour cell line MCF-7 (17).

Phytochemical mimicry of reproductive hormones and modulation of herbivore fertility by phytoestrogens reviewed (18).

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C450 coumithoate



C₁₇H₂₁O₅PS

Mol. Wt. 368.39

CAS Registry No. 572-48-5

Synonyms *O,O*-diethyl *O*-(7,8,9,10-tetrahydro-6-oxobenzo[*c*]chromen-3-yl) phosphorothioate; *O,O*-diethyl 7-hydroxy-3,4-tetramethylenecoumarinyl phosphorothioate; 7-hydroxy-3,4-tetramethylenecoumarin *O,O*-diethyl thiophosphate; *O,O*-diethyl *O*-(7,8,9,10-tetrahydro-6-oxo-6*H*-dibenzo[*b,d*]pyran-3-yl) phosphorothioate

RTECS No. GW 4200000

Uses Superseded insecticide.

Physical properties

M. Pt. 88-88.5°C

Occupational exposure

Supply classification toxic

Risk phrases Toxic if swallowed (R25)

Safety phrases Keep locked up and out of the reach of children (if sold to general public) – After contact with skin, wash immediately with plenty of water – Wear suitable protective clothing and gloves – In case of accident or if you feel unwell, seek medical advice immediately (show label where possible) (S1/2, S28, S36/37, S45)

Mammalian & avian toxicity

Acute data

LD₅₀ oral rat 67 mg kg⁻¹ (1).

LD₅₀ oral guinea pig, dog, rabbit 200-500 mg kg⁻¹ (2).

LC₅₀ dermal rat >200 mg kg⁻¹ (1).

Other effects

Any other adverse effects

Cholinesterase inhibitor (3).

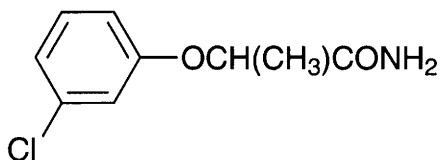
Legislation

EC and UK maximum admissible concentration for individual pesticides in drinking water 0.1 µg l⁻¹ (4).

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C451 3-CPA



$C_9H_{10}ClNO_2$

Mol. Wt. 199.64

CAS Registry No. 5825-87-6

Synonyms 2-(*m*-chlorophenoxy)propanamide; α -(3-chlorophenoxy)propionamide;
2-(3-chlorophenoxy)propionamide; 2-(3-chlorophenoxy)propanamide

EINECS No. 227-398-0

RTECS No. TX 1408500

Uses Plant growth regulator.

Physical properties

M. Pt. 108-110°C Partition coefficient $\log P_{ow}$ 2.03

Legislation

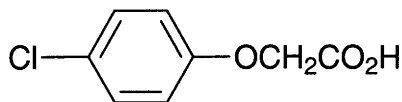
Limited under EC Directive on Drinking Water Quality 80/778/EEC. Pesticides: maximum admissible concentration 0.1 $\mu\text{g l}^{-1}$ (1).

Included in Schedule 6 (Release into Land: Prescribed Substances) Statutory Instrument No. 472, 1991 (2).

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C452 4-CPA



$C_8H_7ClO_3$

Mol. Wt. 186.59

CAS Registry No. 122-88-3

Synonyms *p*-chlorophenoxyacetic acid; 4-chlorophenoxyacetic acid; Tomatone; Tomatotone; 4-CP; PCPA

EINECS No. 204-581-3

RTECS No. AG 0175000

Uses A plant growth regulator used to improve tomato set.

Physical properties

M. Pt. 163-165°C Partition coefficient $\log P_{ow}$ 1.99 (1)

Solubility Organic solvents: readily soluble in most organic solvents

Occupational exposure

Supply classification harmful

Risk phrases Harmful if swallowed (R22)

Safety phrases Keep out of reach of children (if sold to general public) (S2)

Ecotoxicity

Fish toxicity

LC₅₀ (24 hr) brown trout 147 ppm (2).

Not toxic to brown trout, bluegill sunfish, yellow perch or goldfish exposed to 5 mg l⁻¹ for 24 hr (3).

Invertebrate toxicity

EC₅₀ (5, 15, 30 min) *Photobacterium phosphoreum* 97.9 ppm microtox test (4).

Non-toxic to bees (5).

Environmental fate

Degradation studies

Biodegradation 11 days for ring cleavage in soil suspension (6).

Soil microorganisms metabolise 4-CPA to 2-hydroxy-4-chlorophenoxyacetic acid, further degradation occurs via phenoxyacetic acid to yield the *o*- and *p*-hydroxy derivatives (7).

The following were identified in culture extracts from a *Pseudomonas* species isolated from soil: 4-chloro-2-hydroxyphenoxyacetate; 4-chlorocatechol; β-chloromuconolactone; γ-carboxyethylene-δ-α-β-butenolide. It was found that β-chloromuconolactone was unstable in aqueous solutions and hydrolysed to the corresponding β-hydroxy analogue (8).

t_{1/2} in clay loam soil 20 days (9).

Azotobacter chroococcum was able to utilise 4-CPA as sole carbon source (10).

Abiotic removal

Decomposed under UV or sunlight to *p*-chlorophenol, phenol, hydroquinone, *p*-chlorophenyl formate, phenoxyacetic acid, *p*-hydroxyphenoxyacetic acid and humic acids (11).

Mammalian & avian toxicity

Acute data

LD₅₀ oral redwing blackbird >104 mg kg⁻¹ (12).

LD₅₀ oral rat 850 mg kg⁻¹ (13).

LD₅₀ intraperitoneal mouse 680 mg kg⁻¹ (14).

Genotoxicity

Salmonella typhimurium TA98, TA100, TA1535, TA1537, TA1538, TA2637, TA94 with and without metabolic activation negative (15-17).

Escherichia coli WP2UVRA with and without metabolic activation negative (16).

Legislation

EC and UK maximum admissible concentration for individual pesticides in drinking water 0.1 µg l⁻¹ (18).

Included in Schedule 6 (Release into Land: Prescribed Substances) Statutory Instrument No. 472, 1991 (19).

WHO Toxicity Class III (20).

EPA Toxicity Class III (21).

Other comments

Degradation product of 2,4-dichlorophenoxyacetic acid (2,4-D).

Toxic syndrome associated with exposure to 4-CPA may be due in part to the presence of 2,4-D which is a common impurity (22).

Biodegradation pathways in soil have been reviewed (23).

In plants, 63.4% of the unchanged compound remained after two days. The substance is phloem mobile (24).

Metabolic pathways reviewed (25).

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C453 creosote

CAS Registry No. 8001-58-9

Synonyms brick oil; coal tar oil; heavy oil; liquid pitch oil; naphthalene oil; tar oil

EINECS No. 232-287-5

RTECS No. GF 8615000

Uses Wood preservative. Disinfectant. Insecticide. Veterinary antihelminthic. Frothing agent. Animal dips. Germicides.

Physical properties

B. Pt. Distillation range 195-400°C **Flash point** 74-75°C (open cup) **Specific gravity** 1.06 at 38°C with respect to water at 15.5°C

Ecotoxicity

Invertebrate toxicity

LC₅₀ (96 hr) *Homarus americanus* 1760 µg l⁻¹ at 10°C (1).

LC₅₀ (96 hr) *Homarus americanus* larvae 20 µg l⁻¹ at 20°C (1).
LC₅₀ (96 hr) *Crangon* sp. 130 and 110 µg l⁻¹ at 10 and 20°C, respectively (1).

Mammalian & avian toxicity

Acute data

LD_{Lo} oral pigeon ≈0.1 g kg⁻¹ (2).
LD₅₀ oral mouse, rabbit, rat 435-725 mg kg⁻¹ (3-5).
LD_{Lo} (14-36 hr after ingestion) oral man ≈7 g (adult), 1-2 g (child) (2).

Carcinogenicity and chronic effects

Sufficient evidence for carcinogenicity to humans, sufficient evidence for carcinogenicity to animals, IARC classification group 1 (coal tar) (6).
Human skin cancer positive (hands, forearm, scrotum, penis, face, neck) (7-9).
A study in the US investigating human scrotal cancer mortality rate found 29 cases per million men; national average 4.2 per million men (7,10).

Metabolism and toxicokinetics

In rabbits, almost completely metabolised in a conjugated form (11).

Irritancy

Contact with skin or condensation on skin or mucous membranes leads to erythema, grey-yellow-to-bronze pigmentation and papular and vesicular eruptions (species unspecified) (12-14).

Sensitisation

Photosensitisation reported (species unspecified) (15).

Genotoxicity

Salmonella typhimurium TA1537, TA1538, TA98, TA100 with metabolic activation positive (16).
Creosotes from four countries, Germany, Denmark, USSR and Poland were tested for mutagenic activity in the Ames Test (*Salmonella typhimurium*), SOS chromotest (*Escherichia coli*), Chinese hamster ovary sister chromatid test, with and without metabolic activation. Components of distillation fractions have been identified where possible. One common feature seemed to be that mutagenicity occurred in fractions having the highest boiling ranges (>290°C) (17).

Other effects

Other adverse effects (human)

Excessive industrial exposure produces symptoms including melanoderma, papules, hyperkeratoses, warts, telangiectases. Acute symptoms include burns, gangrene, human keratitis, conjunctivitis, corneal abrasions and permanent visual impairment in humans (5,18,19).
Chronic symptoms include salivation, vomiting, respiratory difficulties, vertigo, headache, cyanosis, hypothermia, mild convulsions (5).
Oral and dermal exposure can cause loss of pupil reflexes, thready pulse, digestive disturbances (increased peristalsis and faecal excretion), hypertension and cardiovascular collapse (18).

Legislation

Banned in the USA (20).

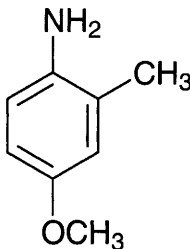
Other comments

Fatal to cattle licking creosoted telegraph poles. Inflammation and congestion of whole gastrointestinal tract on post-mortem (21).
Reviews on experimental toxicology and human health effects listed (22).

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C454 *m*-cresidine



C₈H₁₁NO

Mol. Wt. 137.18

CAS Registry No. 102-50-1

Synonyms 3-cresidine; 2-methyl-*p*-anisidine; 4-methoxy-2-methylaniline; 4-methoxy-2-methylbenzenamine; 2-methyl-4-methoxyaniline; NCI-CO2993

EINECS No. 203-036-7

RTECS No. BZ 6730000

Uses Intermediate in synthesis of azo dyestuffs, inks and pigments. Stabiliser for polyketones.

Physical properties

M. Pt. 13-14°C **B. Pt.** 248-249°C **Flash point** >110°C **Specific gravity** 1.065 at 20°C with respect to water at 4°C **Partition coefficient** log P_{ow} 1.44

Solubility Organic solvents: ethanol, hot petroleum ether

Occupational exposure

UN No. 2431 HAZCHEM Code 3X Conveyance classification toxic substance

Mammalian & avian toxicity

Carcinogenicity and chronic effects

Inadequate evidence for carcinogenicity to humans and animals, IARC classification group 3 (1).

TD_{Lo} (77 wk intermittent) oral rat 62 g kg⁻¹ positive urinary-bladder carcinogen (2,3).

Genotoxicity

Salmonella typhimurium TA1537, TA1538, TA98, TA100 with and without metabolic activation negative (4,5).

Escherichia coli WP2uvrA with and without metabolic activation negative (4,5).

Lowest toxic dose causing oncogene transformation to rat embryo cells was 51.5 µg plate⁻¹ (6).

Oral ♂ CD-1 mice (8-wk-old) 595 mg kg⁻¹. Statistically significant DNA damage in bladder mucosa was seen at 3 and 24 hr after dosing. No significant effects were seen in kidney, brain, bone marrow, or mucosa of stomach and colon at 3 and 24 hr (7).

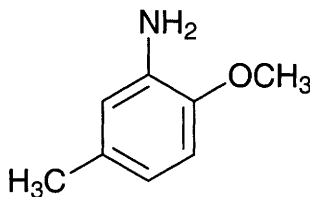
Other comments

Reviews on experimental toxicology and human health effects listed (8).

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C455 *p*-cresidine



C₈H₁₁NO

Mol. Wt. 137.18

CAS Registry No. 120-71-8

Synonyms 2-methoxy-5-methylaniline; 1-amino-2-methoxy-5-methylbenzene; 5-methyl-*o*-anisidine; 3-amino-*p*-cresol, methyl ether; 3-amino-4-methoxytoluene; 2-amino-4-methylanisole; 2-methoxy-5-methylbenzenamine

EINECS No. 204-419-1

RTECS No. BZ 6720000

Uses Dyestuff intermediate for cotton, chemical intermediate.

Physical properties

M. Pt. 51.5°C B. Pt. 235°C Flash point >112°C

Solubility Organic solvents: benzene, diethyl ether, ethanol, hot petroleum ether

Ecotoxicity

Bioaccumulation

Non-accumulative or low accumulative (1).

Mammalian & avian toxicity

Acute data

LD₅₀ oral rat 1450 mg kg⁻¹ (2,3).

Carcinogenicity and chronic effects

No adequate data for evidence of carcinogenicity to humans, sufficient evidence for carcinogenicity in animals, IARC classification group 2B (4,5).

Target organs of carcinogenicity: mouse and rat liver, mouse and rat urinary bladder/urethra (6).

The National Toxicology Program tested ♀ and ♂ mice and rats via dosed-feed. Positive evidence of carcinogenicity was seen with all animals (7).

Oral ♂, ♀ rat (104 wk) 0.5% or 1% in feed induced adenomas, adenocarcinomas and squamous cell carcinomas of the nasal cavity. Poorly differentiated adenocarcinomas infiltrating the skull and brain were observed in 49% of ♂ animals (8).

Genotoxicity

Salmonella typhimurium TA98, TA100, TA1538 with and without metabolic activation positive (9).

Other effects

Any other adverse effects

Induced methaemoglobinaemia in rodents indicating that the compound is absorbed and metabolically oxidised (10).

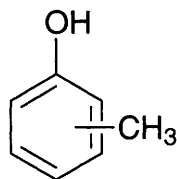
Other comments

Human health effects, epidemiology, workplace experience and experimental toxicology reviewed (4,11).

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C456 cresol



C₇H₈O

Mol. Wt. 108.14

CAS Registry No. 1319-77-3

Synonyms methylphenol; hydroxytoluene; cresylic acid; tricresol; RCRA waste number U052; Hetoxide MPC; Productol; Bray's Emulsion

EINECS No. 215-293-2

RTECS No. GO 5950000

Uses Disinfectant. Local antiseptic. Parasiticide. Manufacture of synthetic resins. Solvent.

Occurrence Obtained from coal tar.

Physical properties

M. Pt. 10.9-35.5°C **B. Pt.** 191-203°C **Flash point** 81°C **Specific gravity** 1.030-1.038 at 25°C with respect to water at 25°C **Volatility** v.p. 1 mmHg at 38-53°C ; v.den. 3.72

Solubility Water: ~20 g l⁻¹

Occupational exposure

DE-MAK 5 ppm (22 mg m⁻³)

FR-VME 5 ppm (22 mg m⁻³)

JP-OEL 5 ppm (22 mg m⁻³)

UK-LTEL 5 ppm (22 mg m⁻³)

US-TWA 5 ppm (22 mg m⁻³)

UN No. 2076 **HAZCHEM Code** 2X **Conveyance classification** toxic substance, corrosive

Supply classification toxic

Risk phrases Toxic in contact with skin and if swallowed – Causes burns (R24/25, R34)

Safety phrases Keep locked up and out of the reach of children (if sold to general public) – Wear suitable protective clothing, gloves and eye/face protection – In case of accident or if you feel unwell, seek medical advice immediately (show label where possible) (S1/2, S36/37/39, S45)

Environmental fate

Degradation studies

Methanobacterium sp., *Methanobrevibacter* sp., *Methanococcus* sp., *Methanosarcina* sp. were able to degrade a sewage sludge mixture containing cresol, after a short time lag (1).

Confirmed biodegradable (2).

Mammalian & avian toxicity

Acute data

LD₅₀ oral rat 1450 mg kg⁻¹ (3).

LD₅₀ oral mouse 760 mg kg⁻¹ (4).

LD₅₀ dermal rabbit 2000 mg kg⁻¹ (5).

Gavage rat complex mixture (from wastestream containing cresol) 10 samples in total. Evaluation 24 hr later showed 7/10 samples caused death at dose 1-5 ml kg⁻¹. 8/10 samples were hepatotoxic (6 centrilobular) (2 periportal). 9/10 samples caused an increase in the ratio of liver to body weight (6).

Other effects

Other adverse effects (human)

Chronic oral or percutaneous absorption gives rise to digestive disturbance, nervous disorders, syncope, vertigo, mental changes, skin eruptions, jaundice, oligourea and uremia (7).

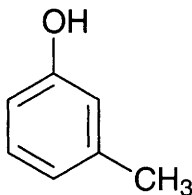
Other comments

Acute toxicity, skin corrosion data and hazards reviewed (5,8,9).

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C457 *m*-cresol



C₇H₈O

Mol. Wt. 108.14

CAS Registry No. 108-39-4

Synonyms 3-cresol; *m*-cresylic acid; 3-hydroxytoluene; 3-methylphenol; RCRA waste number U052; *m*-toluol

EINECS No. 203-577-9

RTECS No. GO 6125000

Uses In disinfectants, fumigants, photographic developers. Synthetic resins and varnishes.

Occurrence Constituent of coal tar.

Physical properties

M. Pt. 8-10°C **B. Pt.** 203°C **Flash point** 86°C **Specific gravity** 1.034-1.038 at 20°C with respect to water at 4°C **Partition coefficient** log P_{ow} 1.96-2.01 **Volatility** v.p. 0.04 mmHg at 20°C
Solubility Water: 23.5 g l⁻¹ at 20°C

Occupational exposure

DE-MAK 5 ppm (22 mg m⁻³)

JP-OEL 5 ppm (22 mg m⁻³)

UK-LTEL 5 ppm (22 mg m⁻³)

US-TWA 5 ppm (22 mg m⁻³)

UN No. 2076 HAZCHEM Code 2X Conveyance classification toxic substance, corrosive

Supply classification toxic

Risk phrases Toxic in contact with skin and if swallowed – Causes burns (R24/25, R34)

Safety phrases Keep locked up and out of the reach of children (if sold to general public) – Wear suitable protective clothing, gloves and eye/face protection – In case of accident or if you feel unwell, seek medical advice immediately (show label where possible) (S1/2, S36/37/39, S45)

Ecotoxicity

Fish toxicity

LC₅₀ (24-96 hr) mosquito fish 24 mg l⁻¹ (1).

LC₅₀ (96 hr) bluegill sunfish 10-13 mg l⁻¹ (1).

LC₅₀ (24 hr) tench, roach, goldfish 21-25 mg l⁻¹ (2).

LC₅₀ (24 hr) trout embryo 7 mg l⁻¹ (2).

Invertebrate toxicity

LC₁₀₀ (24 hr) *Tetrahymena pyriformis* 378 mg l⁻¹ (3).

Environmental fate

Nitrification inhibition

75% inhibition of ammonia oxidation by activated sludge at 11.4 mg l⁻¹ (4).

Carbonaceous inhibition

IC_{Lo} *Pseudomonas putida* 53 mg l⁻¹; *Entosiphon sulcatum* 31 mg l⁻¹; *Microcystis aeruginosa* 13 mg l⁻¹; *Uronema parduczi* 62 mg l⁻¹ (duration unspecified) (5-7).

Perturbation level *Vorticella campanula* 0.5 mg l⁻¹ (3).

Perturbation level *Paramecium caudatum* 0.9 mg l⁻¹ (3).

Degradation studies

Biodegradable (8).

A denitrifying *Pseudomonas* sp. strain oxidised *m*-cresol as the sole organic substrate to carbon dioxide, generation time 14 hr (9).

Anaerobic biodegradation was observed in anoxic aquifer slurries under both sulfate-reducing and nitrate-reducing but not methanogenic conditions. Initial concentration 32 mg l⁻¹ *m*-cresol, >85% parent substrate consumed in six days (10).

Methanogenic bacteria completely degraded *m*-cresol to methane and carbon dioxide (11).

Decomposition period soil microflora 1 day (12).

Adapted activated sludge 20°C, product sole carbon source, 95.5% COD, 55 mg COD g O₂ day inoculum⁻¹ hr⁻¹ (13).

BOD₅ 1.7 mg l⁻¹ O₂ standard diluted sewage (14).

BOD₅ standard diluted acclimated sewage 1.7-1.88 mg l⁻¹ O₂ (1).

BOD (24 hr) (30°C) 20 mg l⁻¹ O₂ 46% ThOD (15).

BOD(48 hr) (30°C) 20 mg l⁻¹ O₂ 62% ThOD (15).

BOD (120 hr) (30°C) 20 mg l⁻¹ O₂ 80% ThOD (15).

COD 2.4 mg l⁻¹ O₂ (1,14).

Acclimated activated sewage 250 mg l⁻¹, after 30 min, phenol, *o*-cresol, *m*-cresol, *p*-cresol, mandelic acid, ThOD 37, 41, 38, 2 and 13%, respectively (16).

Resistant to microbial degradation by *Pseudomonas aeruginosa* and *Pseudomonas putida* (17).

Mammalian & avian toxicity

Acute data

LD₅₀ oral redwing blackbird 113 mg kg⁻¹ (18).

LD₅₀ oral rat, mouse 242, 828 mg kg⁻¹, respectively (19,20).

LD₅₀ dermal rat, rabbit 1100, 2050 mg kg⁻¹, respectively (20,21).

LD_{Lo} intravenous mouse, rabbit 168, 280 mg kg⁻¹, respectively (21,22).

LD_{Lo} subcutaneous mouse, rabbit, guinea pig 300-500 mg kg⁻¹ (5,22).

Irritancy

Dermal rabbit (24 hr) 517 mg caused severe irritation and 103 mg instilled into rabbit eye caused severe irritation (20).

The irritant and corrosive effects of *o*-, *m*- and *p*-cresols were studied by Evan's blue test. Chemical soaked discs were placed on rabbit dorsal skin. No difference in intensity of either dye exudation or of skin corrosion was found for the three isomers. Irritation did occur (23).

Genotoxicity

In vitro mouse lung V79 cells cytotoxic dependent on concentration and time. DNA, RNA and protein synthesis also inhibited (24).

Legislation

Maximum permissible concentration in domestic water in former USSR 4 µg l⁻¹ (25).

Other comments

Reviews on toxicity and hazards listed (26,27).

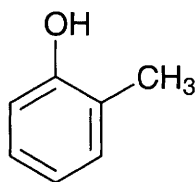
Bioaccumulation potential in terrestrial or aquatic organisms discussed (28).

Methanogenic metabolism reviewed (29).

Physical, chemical and hazardous properties of *m*-cresol reviewed (30).

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C₇H₈O

Mol. Wt. 108.14

CAS Registry No. 95-48-7

Synonyms 2-cresol; 2-methylphenol; *o*-cresylic acid; *o*-hydroxytoluene; RCRA waste number U052; *o*-toluol; 1-hydroxy-2-methylbenzene

EINECS No. 202-423-8

RTECS No. GO 6300000

Uses Solvent. Disinfectant. Food antioxidant. Organic intermediate for perfume, dyestuffs, plastics, resin and herbicide manufacture. Synthesis of salicylaldehyde, coumarin.

Occurrence From coal tar, petroleum, and wood-tar distillates.

Physical properties

M. Pt. 30-33.5°C **B. Pt.** 191-192°C **Flash point** 81-83°C **Specific gravity** 1.047 at 20°C with respect to water at 4°C **Volatility** v.p. 0.24 mmHg at 25°C

Solubility Water: 31 g l⁻¹ at 40°C

Occupational exposure

DE-MAK 5 ppm (22 mg m⁻³)

JP-OEL 5 ppm (22 mg m⁻³)

UK-LTEL 5 ppm (22 mg m⁻³)

US-TWA 5 ppm (22 mg m⁻³)

UN No. 2076 **HAZCHEM Code** 2X **Conveyance classification** toxic substance, corrosive

Supply classification toxic

Risk phrases Toxic in contact with skin and if swallowed – Causes burns (R24/25, R34)

Safety phrases Keep locked up and out of the reach of children (if sold to general public) – Wear suitable protective clothing, gloves and eye/face protection – In case of accident or if you feel unwell, seek medical advice immediately (show label where possible) (S1/2, S36/37/39, S45)

Ecotoxicity

Fish toxicity

LC₅₀ (24, 96 hr) goldfish 49 and 19 mg l⁻¹, respectively (1).

LC₅₀ (24, 96 hr) bluegill sunfish 22 and 20 mg l⁻¹ (1).

LC₅₀ (24, 96 hr) fathead minnow 18 and 13 mg l⁻¹ (1).

LC₅₀ (24 hr) crucian carp 30 mg l⁻¹ (2).

LC₅₀ (24 hr) tench 15 mg l⁻¹ (2).

Metabolism of *o*-cresol was studied in zebrafish after uptake from water (concentration and duration unspecified).

Metabolites identified were 2-cresyl glucuronide, 2-cresyl sulfate and 2-hydroxybenzoic acid in trace amounts (3).

Invertebrate toxicity

LC₁₀₀ (24 hr) *Tetrahymena pyriformis* 0.4 g l⁻¹ (4).

Toxicity to other species

LC₅₀ (48 hr) Mexican axolotl (3-4 wk old) 40 mg l⁻¹ (5).

LC₅₀ (48 hr) clawed toad (3-4 wk old) 38 mg l⁻¹ (6).

Environmental fate

Nitrification inhibition

Inhibition of nitrification in activated sludge, concentrations of 11-16 mg l⁻¹ caused 75% reduction (7).

Carbonaceous inhibition

Aspergillus flavus exposed to 500 ppm *o*-cresol, mycelial growth was inhibited by 90%. 700 ppm totally suppressed fungal growth (8).

IC_{Lo} *Pseudomonas putida* 33 mg l⁻¹ (9).

IC_{Lo} *Entosiphon sulcatum* 17 mg l⁻¹ (9).

IC_{Lo} *Uronema parduczi* 31 mg l⁻¹ (5).

Degradation studies

Confirmed biodegradable (10).

The metabolism of *o*-cresol under methanogenic conditions by an anaerobic consortium known to carboxylate phenol to benzoate was investigated. Incubation period 50 day at 29°C. *o*-Cresol was transformed to 3-methylbenzoic acid via carboxylation in the *p*-position relative to the phenolic hydroxyl group and dehydroxylated by the anaerobic consortium. Further degradation did not occur (11).

Ozone pretreatment studies were conducted to evaluate the effects of ozonisation on the anaerobic biodegradability and toxicity of the reaction products. Two types of batch studies, the biochemical, methane potential and the anaerobic toxicity assay were performed on samples with and without preozonisation. The ozonisation products were fermentable to methane, ≈60% COD or 32% dissolved organic carbon was achieved by ozonisation regardless of the initial concentration of *o*-cresol. Salicyclic acid, glyoxylic acid, oxalic acid, propionic acid, acetic acid and formic acid were the oxidation products identified (12).

Paracoccus sp. utilised *o*-cresol as sole organic substrate with a generation time of 11 hr. Degradation occurred via oxidation to carbon dioxide with nitrate being reduced to nitrogen (13).

Standard diluted sewage BOD₅ 1.69-1.74 mg l⁻¹ O₂ (14).

BOD (24 hr) 15 mg l⁻¹ O₂ at 30°C 53% ThOD (15).

BOD (48 hr) 15 mg l⁻¹ O₂ 61% ThOD (15).

BOD₅ 15 mg l⁻¹ O₂ 77% THOD (15).

o-Cresol in gasoline contaminated groundwater from a site in Zealand, Denmark, was degraded in 5-15 days, initial concentration ≈0.5 mg l⁻¹ (16).

Mammalian & avian toxicity

Acute data

LD_{Lo} oral rat, rabbit 940, 1350 mg kg⁻¹, respectively (17).

LD₅₀ oral rat, mouse 121, 344 mg kg⁻¹, respectively (18,19).

LC₅₀ (2 hr) inhalation mouse 179 mg m⁻³ (20).

LD₅₀ dermal rat, mouse 620 mg kg⁻¹ (19,20).

LD₅₀ dermal rabbit 890 mg kg⁻¹ (21).

LD_{Lo} intraperitoneal mouse 200 mg kg⁻¹ (22).

Irritancy

Dermal rabbit (24 hr) 524 mg caused severe irritation and 105 mg instilled into rabbit eyes caused severe irritation (18).

The irritant and corrosive effects of *m*-, *p*- and *o*-cresol were carried out by Evan's blue test. Chemical soaked disks were placed on rabbit dorsal skin. No difference in intensity of either the dye exudation or of skin corrosion occurred for the isomers, but irritation did occur (23).

Genotoxicity

In vitro human fibroblasts sister chromatid exchange positive (24).

Other comments

Constituent of domestic sewage.

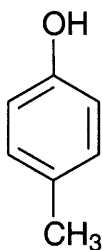
Physical/chemical properties, experimental toxicology and human health effects reviewed (25-27).

Heavy metal and organic compound emissions from sewage sludge incinerators reviewed (28).

Bioaccumulation potential in terrestrial and aquatic organisms discussed (29).

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C₇H₈O

Mol. Wt. 108.14

CAS Registry No. 106-44-5

Synonyms 4-cresol; *p*-methylphenol; *p*-cresylic acid; *p*-hydroxytoluene; RCRA waste number U052; *p*-toluol

EINECS No. 203-398-6

RTECS No. GO 6475000

Uses Disinfectant.

Occurrence In essential oils, including ylang-ylang and oil of jasmine. A constituent of coal tar.

Physical properties

M. Pt. 32-34°C **B. Pt.** 202°C **Flash point** 89°C **Specific gravity** 1.0341 at 20°C with respect to water at 4°C

Partition coefficient log *P*_{ow} 1.92-1.94 **Volatility** v.p. 1 mmHg at 53°C

Solubility Water: 25 g l⁻¹ 50°C

Occupational exposure

DE-MAK 5 ppm (22 mg m⁻³)

JP-OEL 5 ppm (22 mg m⁻³)

UK-LTEL 5 ppm (22 mg m⁻³)

US-TWA 5 ppm (22 mg m⁻³)

UN No. 2076 **HAZCHEM Code** 2X **Conveyance classification** toxic substance, corrosive

Supply classification toxic

Risk phrases Toxic in contact with skin and if swallowed – Causes burns (R24/25, R34)

Safety phrases Keep locked up and out of the reach of children (if sold to general public) – Wear suitable protective clothing, gloves and eye/face protection – In case of accident or if you feel unwell, seek medical advice immediately (show label where possible) (S1/2, S36/37/39, S45)

Ecotoxicity

Fish toxicity

Trout exposed to 5 ppm died within 22 hr (1).

LC₅₀ (24 hr) trout embryo 4 mg l⁻¹ (2).

LC₅₀ (24 hr) crucian carp, roach, tench 16-21 mg l⁻¹ (2).

Invertebrate toxicity

LC₁₀₀ (24 hr) *Tetrahymena pyriformis* 0.4 g l⁻¹ (3).

EC₅₀ (15 min) *Photobacterium phosphoreum* 1.6 mg l⁻¹ Microtox test (4).

Environmental fate

Nitrification inhibition

Inhibition of ammonia oxidation by activated sludge, 75% inhibition, 5.6-16.5 mg l⁻¹ (5).

Degradation studies

Degraded by soil microflora within 24 hr (6).

Adapted activated sludge at 20°C, product as sole carbon source, 96% COD, 55 mg COD g⁻¹ O₂ dry inoculum hr⁻¹ (7).

Anaerobic degradation studied under denitrifying, sulfidogenic, and methanogenic conditions. 100 mg l⁻¹ initial concentration was degraded in all systems within 3-4 wk. In acclimated cultures degradation occurred in <1 wk. *p*-Cresol was completely metabolised under denitrifying, sulfidogenic and methanogenic conditions with the formation of nitrogen, loss of sulfate, and formation of methane and carbon dioxide, respectively (8).

Paracoccus sp. utilised *p*-cresol as sole organic substrate, generation time 11 hr (9).

Methanogenic bacteria completely degraded *p*-cresol (10-12).

BOD₅ standard dilute acclimated sewage 1.4-1.76 mg l⁻¹ O₂ (13).

BOD (24 hr) 30°C 15 mg l⁻¹ O₂ 55% ThOD(14).

BOD₂ 15 mg l⁻¹ O₂ 61% ThOD (14).

BOD₅ 15 mg l⁻¹ O₂ 81% ThOD (14).

Activated sludges acclimated to *p*-cresol 250 mg l⁻¹; after 30 min phenol, *o*-cresol, *m*-cresol, *p*-cresol, mandelic acid were 33, 34, 35, 39, 20% ThOD, respectively (15).

Resistant to microbial degradation by *Pseudomonas aeruginosa* and *Pseudomonas putida* (16).

Mammalian & avian toxicity

Acute data

LD₅₀ oral redwing blackbird >96 mg kg⁻¹ (17).

LD₅₀ oral rabbit, rat 620, 1800 mg kg⁻¹, respectively (18).

LD₅₀ oral mouse 344 mg kg⁻¹ (19).

LD₅₀ dermal rabbit, rat 300, 750 mg kg⁻¹, respectively (19,20).

LD₅₀ intraperitoneal mouse 25 mg kg⁻¹ (13).

LD_{Lo} intravenous rabbit 180 mg kg⁻¹ (18).

LD_{Lo} subcutaneous mouse, rabbit, guinea pig 150-300 mg kg⁻¹ (21,22).

Sub-acute and sub-chronic data

Gavage rat (13 wk) 0, 50, 175 and 600 mg kg⁻¹ day⁻¹ three ♀ died during days 1-3 of the study. Signs of central nervous system depression were apparent in high-dose ♂ and ♀. Reductions in body weight gain were seen in ♂ and ♀ treated at high doses and to a lesser extent in the mid-dose ♂. *p*-cresol was hepatotoxic, nephrotoxic and induced a mild anaemic state (23).

Irritancy

Dermal rabbit (24 hr) 517 mg caused severe irritation and 103 mg instilled into rabbit eye caused severe irritation (20).

The irritant and corrosive effects of *o*-, *m*- and *p*-cresol were studied by Evan's blue test. Chemical soaked paper discs were placed on the rabbit dorsal skin. No difference in intensity of dye exudation or of skin corrosion were observed for the isomers. Irritation did occur (24).

Other effects

Other adverse effects (human)

p-Cresol is a microbial amino acid metabolite which shows cocarcinogenic or promoting activity in animal studies. Its involvement in the development of human bladder cancer has been detected by measuring the urinary excretion of indican and conjugated phenols. 32 patients (22 ♂, 10 ♀) with histological confirmed carcinoma of the urinary bladder and a similar number of age and sex matched controls took part in the study. The excretion of indican and *p*-cresol showed wide inter-individual variability, but did not differ significantly between the two groups. Thus, *p*-cresol does not contribute significantly to the development of human bladder cancer (25).

Legislation

Maximum permissible concentration in domestic water in former USSR 4 µg l⁻¹ (26).

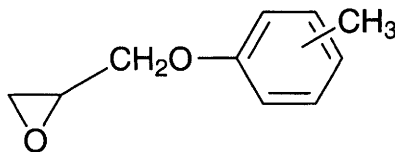
Other comments

Reviews on toxicity, hazards and human health effects listed (27,28).
Physical, chemical properties and hazards reviewed (29).
Bioaccumulation potential in terrestrial and aquatic organisms discussed (30).

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C460 cresyl glycidyl ether



$C_{10}H_{12}O_2$

Mol. Wt. 164.20

CAS Registry No. 26447-14-3

Synonyms 1,2-epoxy-3-(tolylloxy)propane; [(methylphenoxy)methyl]oxirane; tolyl glycidyl ether; cresol glycidyl ether; glycidyl methylphenyl ether

EINECS No. 247-711-4

RTECS No. TZ 3699000

Uses Cross-linking agent. Foam stabiliser. Manufacture of epoxy resin used in crack-resistant pavements. Artificial mortars.

Physical properties

B. Pt. 259°C Flash point 93.3°C (closed cup) Specific gravity 1.09 at 20°C

Occupational exposure

SE-LEVL 10 ppm (70 mg m⁻³)

SE-STEL 15 ppm (100 mg m⁻³)

Supply classification irritant

Risk phrases Irritating to the skin (R38)

Safety phrases Keep out of reach of children (if sold to general public) – In case of contact with eyes, rinse immediately with plenty of water and seek medical advice – After contact with skin, wash immediately with plenty of water followed by polyethylene glycol (mol. wt. 300) for at least 30 minutes (S2, S26, S28)

Mammalian & avian toxicity

Acute data

LD₅₀ oral guinea pig, mouse, rat 1650, 1700, 5140 mg kg⁻¹, respectively (1).

LC₅₀ (duration unspecified) inhalation rat, mouse 282, 310 mg m⁻³, respectively (1).

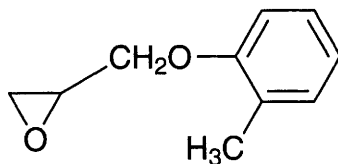
Other comments

Reviews on experimental toxicology and human health effects listed (2).

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C461 2-cresyl glycidyl ether



C₁₀H₁₂O₂

Mol. Wt. 164.20

CAS Registry No. 2210-79-9

Synonyms 2-[(2-methylphenoxy)methyl]oxirane; glycidyl 2-methylphenyl ether; glycidyl *o*-tolyl ether; 2-methylphenyl glycidyl ether; 1,2-epoxy-3-(2-methylphenoxy)propane; 1-(2,3-epoxypropoxy)-2-methylbenzene; *o*-cresyl glycidyl ether

EINECS No. 218-645-3

RTECS No. TZ 3700000

Uses Herbicide. Waterproofing agent. Manufacture of epoxides.

Physical properties

B. Pt. 134.5°C at 14 mmHg Flash point >110°C Specific gravity 1.0884 at 20°C with respect to water at 4°C

Occupational exposure

Supply classification irritant

Risk phrases Irritating to the skin (R38)

Safety phrases Keep locked up and out of the reach of children (if sold to general public) – In case of contact with eyes, rinse immediately with plenty of water and seek medical advice – After contact with skin, wash immediately with plenty of water followed by polyethylene glycol (mol. wt. 300) for at least 30 minutes (S1/2, S26, S28)

Genotoxicity

Salmonella typhimurium TA100, TA1535 without metabolic activation positive (1).

Other comments

EC (1 hr) human body louse 30°C 1% solution in acetone gives knockdown of body lice (2).

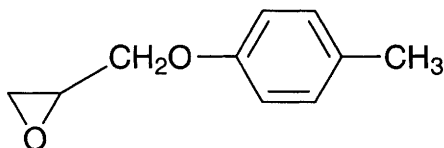
The bacteriostatic activity was determined at 2.2×10^5 moles ml⁻¹ in *Escherichia coli* B (3).

Toxicity and hazards reviewed (4).

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C462 4-cresyl glycidyl ether



$C_{10}H_{12}O_2$

Mol. Wt. 164.20

CAS Registry No. 2186-24-5

Synonyms [(4-methylphenoxy)methyl]oxirane; *p*-cresyl glycidyl ether

EINECS No. 218-574-8

RTECS No. TZ 3701000

Uses Manufactured heat-resistant and low-shrinkage polyamides. Stabilisers for methylene dichloride. Plastisers for PVC. Manufacture of epoxides resins.

Physical properties

B. Pt. 259-261°C **Specific gravity** 1.0496-1.0831 at 20°C with respect to water at 4°C

Occupational exposure

SE-LEVL 10 ppm (70 mg m⁻³)

SE-STEL 15 ppm (100 mg m⁻³)

Supply classification irritant

Risk phrases Irritating to the skin (R38)

Safety phrases Keep locked up and out of the reach of children (if sold to general public) – In case of contact with eyes, rinse immediately with plenty of water and seek medical advice – After contact with skin, wash immediately with plenty of water followed by polyethylene glycol (mol. wt. 300) for at least 30 minutes (S1/2, S26, S28)

Mammalian & avian toxicity

Sub-acute and sub-chronic data

Oral rat 10 mg kg⁻¹ day⁻¹ no oestrogenic properties and non-toxic at this dose level (duration of treatment unspecified) (1).

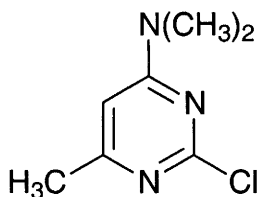
Genotoxicity

Salmonella typhimurium TA100, TA1535 without metabolic activation positive (2,3).

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C463 crimidine



C₇H₁₀ClN₃

Mol. Wt. 171.63

CAS Registry No. 535-89-7

Synonyms 2-chloro-*N,N*,6-trimethyl-4-pyrimidinamine; Castrix; 2-chloro-4-dimethylamino-6-methylpyrimidine

EINECS No. 208-622-6

RTECS No. UV 8050000

Uses Superseded rodenticide.

Physical properties

M. Pt. 87°C B. Pt. 140-147°C at 4 mmHg Volatility v.p. <10⁻⁵ mmHg at 20°C

Solubility Water: 9.36 g l⁻¹ at 20°C. Organic solvents: soluble in most organic solvents

Occupational exposure

Supply classification very toxic

Risk phrases Very toxic if swallowed (R28)

Safety phrases Keep locked up and out of the reach of children (if sold to general public) – Wear suitable protective clothing and gloves – In case of accident or if you feel unwell, seek medical advice immediately (show label where possible) (S1/2, S36/37, S45)

Ecotoxicity

Invertebrate toxicity

LC_{Lo} *Tubifex tubifex* >100 mg l⁻¹ (1).

Bioaccumulation

Exposure of carp, crucian carp, tench to 10 or 50 mg l⁻¹ was studied in short-term (6, 12, 24, 48 and 72 hr) and long-term (up to 6 wk) tests. Highest accumulation occurred in the kidney followed by muscle and gill. After 1-3 wk, tissue concentrations are reduced and after transfer to clean water there is a general sharp decline. Therefore crimidine is not firmly bound in body (2).

Mammalian & avian toxicity

Acute data

LD₅₀ oral chicken 22 mg kg⁻¹ (3).

LD₅₀ oral Japanese quail 20 mg kg⁻¹ (4).

LD₅₀ oral rat, mouse, guinea pig, rabbit 1.2-5 mg kg⁻¹ (5-9).

LD₅₀ dermal rat ~1.7 mg kg⁻¹ (6).

LD₅₀ intraperitoneal rat, mouse, guinea pig, rabbit 0.5-5 mg kg⁻¹ (5).

Other effects

Other adverse effects (human)

Oral human 75 mg death occurred ~16 hr after ingestion. Changes in many of the internal organs, petechial haemorrhage under epicardium and pleura pulmonalis, and coloration of duodenum and mucous membranes were found on autopsy (10).

Human clinical symptoms include serious central nervous system damage, convulsions, restlessness, apprehension, muscular stiffness, sensitivity to light, noise and contact, and cold sweats. No serious effects persist if patient survives (11).

Legislation

Limits under EC Directive on Drinking Water Quality 80/778/EEC. Pesticides: maximum admissible concentration $0.1 \mu\text{g l}^{-1}$ (12).

Other comments

Pyridoxine was found to be an excellent antidote for mice poisoned with crimidine (13).

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C464 cristobalite



CAS Registry No. 14464-46-1

Synonyms calcined diatomite

EINECS No. 238-455-4

RTECS No. VV 7325000

Uses Manufacture of glass, water glass, abrasives, cements, fillers. Dental investments, refractories. Fused form – ablative in rockets and re-entry vehicles, fibres in re-inforced plastics.

Occurrence In diatomite, kaolin, vitreous silica, zircon. A form of crystalline silica. Cristobalite is found in coastal and central parts of the oceans and occurs in ancient sediments (Cretaceous, Eocene).

Physical properties

M. Pt. 1696-1729°C **B. Pt.** 2230°C **Specific gravity** 2.325 at 27°C

Occupational exposure

DE-MAK 0.15 mg m^{-3} (respirable fraction or aerosol)

FR-VME 0.05 mg m^{-3} (respirable dust)

SE-LEVL 0.05 mg m^{-3} (respirable dust)

UK-LTEL MEL 0.4 mg m⁻³ (respirable dust)

US-TWA 0.05 mg m⁻³ (respirable fraction)

Mammalian & avian toxicity

Acute data

LD₅₀ oral rat 3160 mg kg⁻¹ (1).

LD_{Lo} intratracheal rat 200 mg kg⁻¹ (1).

LD₅₀ intravenous rat 15 mg kg⁻¹ (1).

Sub-acute and sub-chronic data

Inhalation (species unspecified) as dust, causes more silicosis than quartz dust (2).

Intratracheal rats 50 mg powdered brick ml⁻¹ physiological saline – *m*-cristobalite was less fibrogenic than quartz (fibrogenicity may be reduced by Fe₂O₃) (3).

Intratracheal rats (3 months) concentration unspecified caused silicosis, antibodies (partly specified) were found in blood (4).

Inhalation rat (8 day) unspecified concentration caused a rapid influx of neutrophils and macrophages into alveolar and tissue compartments of the lung followed by a more gradual accumulation of T-lymphocytes. This inflammatory response persisted throughout 52 wk following exposure (5).

Carcinogenicity and chronic effects

Limited evidence for carcinogenicity to humans, sufficient evidence for carcinogenicity to animals, IARC classification group 2A (6).

Single intrapleural injection Alderley Park rats (concentration unspecified) induced malignant lymphomas of histiocytic type (7,8).

Metabolism and toxicokinetics

Inhalation rats, cytopathogenic. 25% of retained material reached lymph nodes in six months (9).

Other effects

Other adverse effects (human)

Chronic (10-25 yr) exposure in humans caused dyspnoea, cough, pains in chest, decreased vital capacity and decreased chest expansion (10).

Found in lungs of humans with pneumoconiosis (11).

Acute silicosis has been described relatively infrequently, in response to very high, uncontrolled exposures to quartz or cristobalite. It is always fatal. Classical silicosis ranges from small opacities on the chest radiograph unassociated with clinical disablement to progressive massive fibrosis which may lead to premature death. The disease, once initiated is usually progressive and can occur for the first time after exposure has ceased (12).

Legislation

Recommendations for air pollution control (13,14).

Standard in France (15).

Other comments

Highly cytotoxic, highly fibrogenic in rat lungs but poor correlation between the two effects (16).

Intraperitoneal rats, vinylpyridine *N*-oxide 10-20 mg protects against simultaneous injection of cristobalite dust.

Interacts with dust, stabilises lysosomal and mitochondrial membranes (17).

In guinea pigs 4 mg l⁻¹ increased mucin secretion in tracheal implants while 20 mg l⁻¹ inhibited mucin secretion by bronchioles. Explants of trachea, bronchioles showed increased synthesis of leukotrienes C₄, D₄ and prostaglandin E. Hamster epithelial cells exposed 24 hr non-toxic dose: increase in synthesis of leukotrienes C₄, D₄ and prostaglandins E (18).

Reviews on experimental toxicology and human health effects listed (19).

Control of wastewater sludge by cristobalite reviewed (20).

Soluble in HF. Slowly attacked by hot concentrated H₃PO₄. Pulverised form is attacked by molten alkali.

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c465 crocidolite

CAS Registry No. 12001-28-4

Synonyms blue asbestos; NCI C 09007

RTECS No. CI 6479000

Uses Used in the manufacture of asbestos cement pipes, and in boards, tiles, corrugated sheets for roofing/guttering. In textiles for protective clothing, safety curtains and conveyor belts. In filtration cloths and filter pads, packing sand gaskets and spray insulation.

Occurrence Occurs as crossite, glaucophane, riebeckite and magnesio-riebeckite asbestiform minerals of amphibole family. Magnesio-riebeckite also occurs in non-fibrous prismatic crystals. Occurs in metamorphosed banded ironstones. Amphibole minerals comprise 8% of earth's crust, therefore a potential major source of asbestos exposure is in the mining industry. Major occurrence of crocidolite is in South Africa with minor amounts mined in Western Australia and Bolivia. Amphibole minerals are double chains of silica tetrahedra, cross-linked with bridging cations principally magnesium, iron, calcium and sodium.

Physical properties

Specific gravity 3.37

Occupational exposure

UK-LTEL 0.2 fibres ml⁻¹ (4 hr)

UK-STEL 0.6 fibres ml⁻¹ (10 min)

US-TWA 0.2 fibres cc⁻¹

UN No. 2212

Environmental fate

Abiotic removal

Mineral fibres are relatively stable and tend to persist under typical environmental conditions. However, asbestos fibres may undergo chemical alteration as well as changes in dimension. This occurs for chrysotile but to a lesser extent for crocidolite. Because of their high absorptive properties, it is thought that some mineral fibres may adsorb and carry various organic agents present in the environment (1).

Adsorption and retention

Long range transportation of asbestiform fibres in water has been reported. Asbestos is introduced into water by the dissolution of asbestos containing minerals and ores from industrial effluents, atmospheric pollution and asbestos-cement piping. Once liberated into the environment, asbestos persists for an unknown length of time (2). Airborne asbestos fibres have aerodynamic diameters $<0.3\ \mu\text{m}$, therefore their sedimentation velocities are very low. Studies indicate fibres are transported great distances from sources and fibres in ambient air are small in size requiring electronic beam instrumentation for detection (3).

Amphibole fibres detected in the municipal water supply of Duluth, Minnesota, had been transported over 96 km from a mining operation (4).

Mammalian & avian toxicity

Carcinogenicity and chronic effects

Sufficient evidence of carcinogenicity to humans, sufficient evidence of carcinogenicity to animals, IARC classification group 1 (5).

Sprague-Dawley rats single dose of 67 mg (route unspecified) induced mesotheliomas (6).

Intraleural rabbits (22-24 months) 16 mg induced mesotheliomas in two surviving animals (6).

National Toxicology Program tested rats via feed (2-yr study). Negative evidence of carcinogenic activity (7).

45.7% of human lung cancer cases due to crocidolite exposure were squamous-cell carcinomas, compared with 35.2% control cases (8).

Inhalation rat (2-yr) 49 mg m^{-3} 16 hr wk^{-1} . Two of 31 exposed animals which survived treatment had squamous cell carcinomas of the lung (6).

Inhalation rat (6-24 months) 50 mg m^{-3} 4 hr day^{-1} 4 day wk^{-1} caused lung carcinomas in 14% of exposed animals (9).

Studies on the effects of ingested asbestos on animal species have been reviewed. No conclusive evidence from the toxicological studies to date was available to suggest that ingested asbestos is carcinogenic (10).

Intraperitoneal C57B1/6 mice (concentration unspecified) wly injection for 30-50 wk produced mesotheliomas.

Initial histological response was a nodular lesion on the peritoneal lining composed of clusters of fibres, activated macrophages and proliferating mesenchymal cells. Earliest visible sign of angiogenesis was observed for around 7% of lesions within 14 days of a single 200 μg injection (11).

Inhalation rat (1 yr) 2.2-6.0 mg m^{-3} , 74% of the animals developed bronchiolalveolar hyperplasia (12).

Metabolism and toxicokinetics

Of 35% of inhaled crocidolite deposited onto respiratory tissues, $\approx 50\%$ lodged in the upper airways and was cleared to the gastro-intestinal tract within 1 hr. The remainder in lungs and trachea was reduced after 30 days to 73% of the initial value (13).

It is not possible to conclude with certainty that asbestos fibres do not cross the gastrointestinal wall. However, available evidence indicates that if penetration does occur it is extremely limited (14).

Genotoxicity

In vitro rat embryo cells induction of DNA strand breaks positive (15).

Hamster lung (24 hr) cytogenic 5 mg l^{-1} positive (16).

Sister chromatid exchange Chinese hamster ovary 10 mg plate^{-1} positive (17,18).

Mutation hamster somatic lung 10 mg l^{-1} positive (19).

Other effects

Other adverse effects (human)

Human occupational exposure to crocidolite causes asbestosis, pleural plaques, diffuse pleural thickening (fibrosis), benign asbestos pleurisy, mesothelioma, lung cancer, squamous cell carcinoma and adenocarcinoma of lung. Other adverse effects are anorexia, cough dyspnoea, weight loss, euphoria, weakness, cyanosis and decreased vital capacity (20).

Epidemiological evidence showed that a ten-fold excess risk of lung cancer in UK asbestos textile workers who had been employed before 1930 and for 10 yr or more (21).

Mesotheliomas were reported to occur in miners of crocidolite and in non-mining populations in the vicinity of the mines. Asbestos fibres were detected in the lungs in 8 of 33 cases. The latent period between first exposure and clinical recognition of the tumour was long, a mean of 40 yr (22).

In persons occupationally exposed to asbestos, smaller numbers of asbestos bodies or fibres than are seen in lung tissue have been found in extra-pulmonary tissues, including tonsils, thoracic and abdominal lymph nodes, pleura, peritoneum, liver, spleen, kidney and small intestine (23).

In a study of 7098 employees in two asbestos cement producing plants in New Orleans, 10 mesotheliomas had occurred in 1984. In one plant a case-control analysis found a relation between risk of mesothelioma developing and duration of employment and proportion of time spent in the plant area, thus adding to the evidence of a greater risk of mesothelioma from crocidolite than from chrysotile asbestos (24).

A case study was reported in which a woman developed malignant mesothelioma from secondary exposure to asbestos through laundering her husband's asbestos-contaminated work clothes. At necropsy, the patient's lung asbestos fibre content was similar to cases of mesothelioma associated with occupational exposure (25).

The lungs of 36 past workers at an east London asbestos factory who had died from asbestos-related disease were compared with lung tissue from 56 matched control patients with carcinoma of the lung. Asbestosis was associated with far heavier fibre burdens than mesothelioma. Crocidolite was strongly associated with asbestosis (26).

Any other adverse effects

Following intraperitoneal injection of crocidolite asbestos fibres in mice a dose-response relationship exists between the number of fibres delivered to the parietal lining and the resulting inflammatory and proliferative responses. Biopersistent fibres are thought to cause persistent inflammation and chronic mesothelial cell proliferation (27).

Legislation

UK Health & Safety at Work Act 1974; Control of Asbestos at Work Regulation [1987]; Asbestos (Licensing) Regulations [1983]; Asbestos (Prohibitions) Regulations [1985]; Asbestos (Prohibitions) (Amendments) Regulations [1988] (28).

Other comments

Carcinogenicity and toxicology reviewed (29).

Crystal structure has been determined (30).

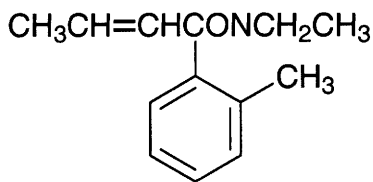
The toxicity and carcinogenicity of asbestos and other natural mineral fibres have been extensively reviewed (2,31,32). Crocidolite is no longer used in developed countries, but building products containing it remain in place and in use (33).

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C466 crotamiton



C₁₃H₁₇NO

Mol. Wt. 203.28

CAS Registry No. 483-63-6

Synonyms *N*-ethyl-*N*-(2-methylphenyl)-2-butenamide; *N*-ethyl-*N*-(2-methylphenyl)crotonamide; *N*-ethyl-*o*-crotonotoluidide; Crotamitex; Eurax; Euraxil

EINECS No. 207-596-3

RTECS No. GQ 7000000

Uses Fungicide. Insecticide. Veterinary scabicide. Bacteriostat. Disinfectant. Insect repellent. Antipruritic in steroidal anti-inflammatory creams.

Physical properties

B. Pt. 153-155°C at 10 mmHg

Solubility Organic solvents: ethanol, methanol

Mammalian & avian toxicity

Acute data

LD₅₀ oral rat, mouse 1500-1600 mg kg⁻¹ (1).

Sensitisation

Crotamiton was found to be an extremely weak sensitiser in guinea pigs (2).

Legislation

Limited under EC Directive on Drinking Water Quality 80/778/EEC. Pesticide: maximum admissible concentration 0.1 µg l⁻¹ (3).

Other comments

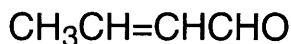
Acute toxicity, primary skin irritation, cumulative skin irritation and sensitisation of a cream containing crotamiton, urea, menthol and azunol was studied in laboratory animals. The main sign of acute toxicity in rats and mice was a decrease in spontaneous movement. No treatment-related changes were seen in body weights or gross pathology. The cream showed mild primary and accumulative irritation in rabbits. No changes observed in skin sensitisation tests in guinea pigs (4).

Bacteriostatic against *Streptococci*, *Staphylococci*, *Diphtheria bacillus* (1).

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C467 crotonaldehyde



C₄H₆O

Mol. Wt. 70.09

CAS Registry No. 123-73-9

Synonyms *trans*-2-butenal; β-methylacrolein; propylenealdehyde; crotonic aldehyde

EINECS No. 224-030-0

RTECS No. GP 9625000

Uses Used in the manufacture of butyl alcohol, butyraldehyde, resins, rubber antioxidants and insecticides. Solvent, used in the purification of mineral oils. Warning agent in fuel gases and in chemical warfare.

Physical properties

M. Pt. -76.5°C **B. Pt.** 104°C **Flash point** 13°C (open cup) (anhydrous) **Specific gravity** 0.853 at 20°C with respect to water at 20°C **Partition coefficient** log P_{ow} 0.20 (1) **Volatility** v.p. 30 mmHg at 20°C ; v.den. 2.41 **Solubility** Water: 181 g l⁻¹ at 20°C. Organic solvents: benzene, diethyl ether, ethanol, gasoline, kerosene, solvent naphtha, toluene

Occupational exposure

FR-VME 2 ppm (6 mg m⁻³)

US-STEL Ceiling limit 0.3 ppm

UN No. 1143 **HAZCHEM Code** 2WE **Conveyance classification** toxic substance, danger of fire (flammable liquid)

Supply classification flammable, toxic, dangerous for the environment

Risk phrases Highly flammable – Toxic by inhalation – Irritating to eyes, respiratory system and skin – Very toxic to aquatic organisms, may cause long-term adverse effects in the aquatic environment (R11, R23, R36/37/38, R50/53)

Safety phrases Keep locked up and out of the reach of children (if sold to general public) – Do not empty into drains – Take precautionary measures against static discharges – In case of accident or if you feel unwell, seek medical advice immediately (show label where possible) – This material and/or its container instructions/safety data sheet (S1/2, S29, S33, S45, S60, S61)

Ecotoxicity

Fish toxicity

LC₅₀ (14 day) guppy 556 mg l⁻¹ (1).

LC₅₀ (96 hr) bluegill sunfish 3.5 ppm, static fresh water bioassay, 23°C mild aeration applied after 24 hr (2).

LC₅₀ (96 hr) inland silverside 1.3 ppm, static synthetic seawater bioassay, 23°C mild aeration applied after 24 hr (2).

Bioaccumulation

The calculated bioconcentration factor of 0.7 indicates environmental accumulation is unlikely (3).

Environmental fate

Degradation studies

BOD₅ 37% reduction of dissolved oxygen concentration using AFNOR 90 test protocol. COD 97% oxygen consumed, standard dilute sewage (4,5).

Abiotic removal

Evaporation from environmental waters may be significant, estimated t_{1/2} 18 days (3).

Photolytic t_{1/2} 11-12 hr (calc.) (6).

Activated carbon adsorbability 92 mg l⁻¹ carbon, 45.6% reduction, influent 1 g l⁻¹, effluent 544 mg l⁻¹ (7,8).

Mammalian & avian toxicity

Acute data

LD₅₀ oral mouse 240 mg kg⁻¹ (9).

LD₅₀ dermal rabbit, guinea pig 255-380 mg kg⁻¹ (10,11).

LD₅₀ subcutaneous rat 140 mg kg⁻¹ (12).

Inhalation rat (10 min) 1650 ppm was lethal: respiratory distress, convulsions, bronchiolar damage and pulmonary oedema side-effects (13).

Carcinogenicity and chronic effects

Administration of 42 mg l⁻¹ of crotonaldehyde in drinking water to rats for 113 wk induced hepatocellular carcinoma and neoplastic nodules in the liver (14).

Irritancy

Human volunteers exposed to 41 ppm for 15 min reported extreme irritation of the nose and upper respiratory tract with lachrymation in 30 sec (15).

Sensitisation

Apparent sensitisation has been reported by workers handling small amounts of crotonaldehyde (16).

Investigated by the National Toxicology Program in an immunology study carried out in 1989. In a study for hypersensitivity crotonaldehyde demonstrated weak to no potential for causing skin sensitisation (17).

Genotoxicity

Salmonella typhimurium TA104 with and without metabolic activation positive, TA100 without metabolic activation and following special treatment positive (18).

Escherichia coli PQ37 with and without metabolic activation negative (19).

In vitro Chinese hamster ovary cells with and without metabolic activation sister chromatid exchange positive (20).

Drosophila melanogaster lethal mutations and reciprocal translocations positive (21).

The shuttle vector plasmid p2189 was treated with varying concentrations of crotonaldehyde at 37°C for 2 hr and transfected into human lymphoblast cells. After 2.5 days replicated plasmids were purified from the cells. Plasmid survival (quantified by transformation ability) showed a significant decrease with increased crotonaldehyde concentration, reflecting the genotoxicity of the DNA damage to the plasmids (22).

Other effects

Any other adverse effects

Can cause burns to cornea (23).

In vitro exposure of rat pulmonary macrophage to crotonaldehyde decreased membrane fluidity (24).

Other comments

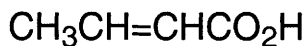
Commercial product is the *trans* isomer (CAS RN 123-73-9) and is stabilised with water; a solid phase separates at -5°C. Has been detected in wastewater effluent, petrol and diesel engine exhausts.

Toxicity reviewed (25).

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C468 crotonic acid



C₄H₆O₂

Mol. Wt. 86.09

CAS Registry No. 3724-65-0

Synonyms (Z)-2-butenic acid; 3-methylacrylic acid; α-butenic acid; α-crotonic acid; solid crotonic acid

EINECS No. 223-077-4

RTECS No. GQ 2800000

Uses Manufacture of copolymers, softening agents, pharmaceuticals, synthetic resins, fungicides, surface coatings, plasticisers. Used in the manufacture of threonine, vitamin A.

Occurrence Found in some Texan oils.

Physical properties

M. Pt. 71.6-72°C **B. Pt.** 189°C **Flash point** 87.7°C (closed cup) **Specific gravity** 1.018 at 15°C with respect to water at 4°C **Volatility** v.p. 0.18-0.19 mmHg at 20°C

Solubility Water: 76.1 g l⁻¹ at 25°C. Organic solvents: acetone, ethanol, toluene

Occupational exposure

UN No. 2823 **HAZCHEM Code** 2X **Conveyance classification** corrosive substance

Environmental fate

Degradation studies

Pseudomonas sp. CLA-1 isolated from soil degraded crotonic acid (1).

Mammalian & avian toxicity

Acute data

LD₅₀ oral rat, mouse 1000, 4800 mg kg⁻¹, respectively (2,3).

LD₅₀ dermal guinea pig 616 mg kg⁻¹ (2).

LD₅₀ intraperitoneal guinea pig, rat 60, 100 mg kg⁻¹, respectively (4).

LD₅₀ subcutaneous mouse 3590 mg kg⁻¹ (5).

Sub-acute and sub-chronic data

Oral rat (41 days) 1% in diet – no effect (6).

Irritancy

Dermal rabbit (24 hr) 10 mg caused irritation on open application (2).

Other effects

Any other adverse effects

Corrosive, irritant. Poison by intraperitoneal administration. Moderately toxic by ingestion, skin adsorption, subcutaneous administration. Harmful when inhaled or swallowed. Extremely destructive to mucous membranes and upper respiratory tract, eyes and skin. Inhalation: fatal spasm, inflammation, oedema of larynx, bronchi. Chemical pneumonitis, pulmonary oedema. Ingestion: sore throat, abdominal pain, vomiting. Skin: burning sensation, redness. Eye: pain, redness, watering, blurred vision. Respiratory tract: sore throat, cough, dyspnoea, wheeze, laryngitis, headache (2).

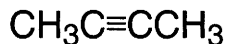
Other comments

Chemical structure/biological activity relationships are discussed in relation to water pollution and wastewater treatment (7).

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C469 crotonylene



C₄H₆

Mol. Wt. 54.09

CAS Registry No. 503-17-3

Synonyms 2-butyne; dimethylacetylene; 2-butine

EINECS No. 207-962-2

RTECS No. GQ 7210000

Uses Odourant for liquefied petroleum gas.

Physical properties

M. Pt. -24°C B. Pt. 27-27.6°C Flash point < -34°C (closed cup) Specific gravity 0.6913 at 20°C with respect to water at 4°C

Occupational exposure

UN No. 1144 HAZCHEM Code 3WE Conveyance classification flammable liquid

Ecotoxicity

Invertebrate toxicity

EC₅₀ (5, 15, 30 min) *Photobacterium phosphoreum* 48.2 ppm Microtox test (1).

Mammalian & avian toxicity

Acute data

Effective dose (10 min) inhalation mice, dogs 4.1% in air – surgical anaesthesia (2).

Total dose (10 min) inhalation mice, dogs 4.6% in air – respiratory arrest (2).

Other effects

Any other adverse effects

Anaesthetic index 1-1 (poor); induction leads to greater state of agitation compared with ethylene; induced involuntary leg movement (2).

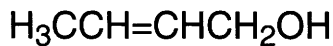
Other comments

Occurs in jet-engine exhausts.

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C470 crotyl alcohol



C₄H₈O

Mol. Wt. 72.11

CAS Registry No. 6117-91-5

Synonyms but-2-en-1-ol; crotonyl alcohol; 1-hydroxy-2-butene; 3-methylallyl alcohol; Δ^2 -1-butenol; 2-buten-1-ol

EINECS No. 228-086-7

RTECS No. EM 9275000

Uses Catalyst for polymerisation of ketones (1).

Shortens dough-mixing time (2).

Occurrence Natural occurrence in Victoria plums *Prunus domestica*, lemon juice, colza oil and wood-alcohol oil (3-5).

Physical properties

M. Pt. $<-30^\circ\text{C}$ **B. Pt.** $118-122^\circ\text{C}$ **Flash point** $33-37^\circ\text{C}$ **Specific gravity** 0.8532 at 20°C with respect to water at 4°C **Partition coefficient** $\log P_{\text{ow}}$ 0.54 (6)

Solubility Water: 166 g l⁻¹ at 20°C . Organic solvents: miscible with ethanol

Environmental fate

Abiotic removal

Wastewater treatment by reverse osmosis, 40°C , 600 psi. 18.3% rejection rate from a 0.72 g l⁻¹ aqueous solution (7).

Mammalian & avian toxicity

Acute data

LD₅₀ oral rat 790 mg kg⁻¹ (8).

Inhalation (4 hr) 6 rats 1000 ppm caused 0/6 mortality, 2000 ppm caused 6/6 mortality (8).

LD₅₀ dermal rabbit 1083 mg kg⁻¹ (8).

Irritancy

Dermal rabbit (24 hr) 0.01 ml caused no irritation, 0.005 ml caused severe burns to rabbit eyes (8).

Genotoxicity

Salmonella typhimurium TA100 with and without metabolic activation positive (9,10).

Other effects

Other adverse effects (human)

Ingestion can cause nausea, vomiting, symptoms of drunkenness. Inhalation systemic effects cough, tight chest and throat irritation. Exposure to high concentrations is destructive to mucous membranes, upper respiratory tract, skin, and eyes. Causes burning sensation, cough, wheeze, laryngitis, dyspnoea, nausea, vomiting and unconsciousness (11).

Other comments

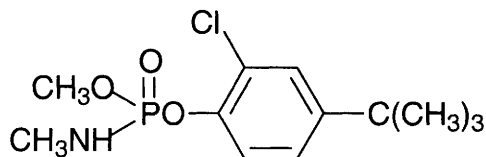
Pollutant from gasoline exhaust (0.1-3.6 ppm). Metabolised by *Saccharomyces cerevisiae* 30% starved yeast in 6.8 g l⁻¹ phosphoric acid, monopotassium salt solution consumed 1392 $\mu\text{g O}_2 \text{ min}^{-1}$ (12).

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C471 crufomate



$C_{12}H_{19}ClNO_3P$

Mol. Wt. 291.71

CAS Registry No. 299-86-5

Synonyms 4-*tert*-butyl-2-chlorophenyl *N*-methyl *O*-methylphosphoramidate; *O*-methyl-*O*-2-chloro-4-*tert*-butylphenyl *N*-methyamidophosphate; phosphoramidic acid, methyl-, 2-chloro-4-(1,1-dimethylethyl)phenylmethyl ester; Ruelene; Rulene

EINECS No. 206-083-1

RTECS No. TB 3850000

Uses Insecticide. Veterinary medicine as anthelmintic.

Physical properties

M. Pt. 60-60.5°C **B. Pt.** 117-118°C at 0.01 mmHg **Specific gravity** 1.1618 **Volatility** v.p. 0.01 mmHg at 117°C
Solubility Water: 5g l⁻¹. Organic solvents: acetone, benzene, carbon tetrachloride, diethyl ether, cyclohexane

Occupational exposure

FR-VME 5 mg m⁻³

US-TWA 5 mg m⁻³

Supply classification harmful, dangerous for the environment

Risk phrases Harmful in contact with skin and if swallowed – Very toxic to aquatic organisms, may cause long-term adverse effects in the aquatic environment (R21/22, R50/53)

Safety phrases Keep out of reach of children (if sold to general public) – Wear suitable protective clothing and gloves – This material and/or its container must be disposed of as hazardous waste – Avoid release to the environment. Refer to special instructions/safety data sheet (S2, S36/37, S60, S61)

Mammalian & avian toxicity

Acute data

LD₅₀ oral redwing blackbird, starling 100 mg kg⁻¹ (1).

LD₅₀ oral rabbit, rat 400, 460 mg kg⁻¹, respectively (2,3).

LD₅₀ oral guinea pig 1000 mg kg⁻¹ (4).

LC_{Lo} (4 hr) inhalation rat 12 mg m⁻³ (5).

LD₅₀ dermal rabbit 2000 mg kg⁻¹ (6).

Teratogenicity and reproductive effects

Dermal mice (35 and 21 days prior to mating) 50 or 100 mg kg⁻¹. No clinical toxicity was observed in treated animals. Reduced mating response and conception rate, reduced progeny weight reported (7).

Dermal mice (prior to copulation) 50 or 100 mg kg⁻¹. No signs of toxicity but cholinesterase activity was inhibited in 46-54% of treated animals. High-dose reduced conception rate, numbers of litters and live birth. The authors conclude crufomate adversely effects reproduction and growth of progeny (8).

At mid incubation chick (10 and 13 day) showed marked mortality within 24 hr of injection with crufomate to embryos, congenital food deformities observed (9,10).

Other effects

Any other adverse effects

Cholinesterase activity inhibitor in sheep and cattle, symptoms include profuse salivation, ataxia, dyspnoea, dullness, and muscle twitching (11).

Goats (duration unspecified) treated with 40 mg kg⁻¹ showed no significant morphological or histochemical abnormalities in their organs and tissues. Local hair loss was observed (12).

Systemic effects include nausea, vomiting, diarrhoea, cramp, central nervous system and neuromuscular effects, pulmonary oedema and cardiac arrest possible (13).

Legislation

Limited under EC Directive on Drinking Water Quality 80/778/EEC. Pesticides: maximum admissible concentration 0.1 µg l⁻¹ (14).

Included in Schedule 6 (Release into Land: Prescribed Substances) Statutory Instrument No. 472, 1991 (15).

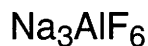
Other comments

Toxicity reviewed (16).

From 1979-1984, investigations were conducted into 311 events of suspected contamination of wells with pesticides. Contaminations were caused by spills of pesticide solutions, back-siphoning of spray solutions, and/or spills from overfilling, emptying or rinsing spray equipment. The pesticides either entered directly into the wells, or contaminated the area in the vicinity of the wells. In spite of clean-up attempts, difficulty was experienced in decontaminating most well waters and some had to be abandoned. The longest period of monitoring a contaminated well was 1117 days; during the time the decline in residue was slow (17).

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AlF₆Na₃

Mol. Wt. 209.94

CAS Registry No. 15096-52-3

Synonyms kryolith; ice spar; sodium aluminium fluoride; sodium hexafluoroaluminate; ice stone; greenland spar; Monterey Kryocide; Synkrolith

EINECS No. 239-148-8

RTECS No. WA 9625000

Uses Electrolyte in the production of aluminium from alumina (electrolytic flux). Used in ceramics, polishes, abrasives and the fireproofing of polycarbonates.

Occurrence A mineral; large deposits exist in Greenland and the Urals.

Physical properties

M. Pt. 975-1014°C **Specific gravity** 2.90 at 20°C with respect to water at 4°C **Volatility** v.p. 3.7 mmHg at 1000°C

Solubility Water: 0.34 g l⁻¹ at 15°C

Occupational exposure

UK-LTEL 2 mg m⁻³

Supply classification toxic, dangerous for the environment

Risk phrases Harmful by inhalation and if swallowed – Toxic: danger of serious damage to health by prolonged exposure through inhalation and if swallowed – Toxic to aquatic organisms, may cause long-term adverse effects in the aquatic environment (R20/22, R48/23/25, R51/53)

Safety phrases Keep locked up and out of the reach of children (if sold to general public) – Do not breathe dust – Wear suitable gloves – In case of accident or if you feel unwell, seek medical advice immediately (show label where possible) – Avoid release to the environment. Refer to special instructions/safety data sheet (S1/2, S22, S37, S45, S61)

Ecotoxicity

Invertebrate toxicity

EC₅₀ (48 hr) *Daphnia pulex* 5 mg l⁻¹ (at 30°C) (1).

EC₅₀ (48 hr) *Simocephalus serrulatus* 10 mg l⁻¹ (30°C) (1).

Mammalian & avian toxicity

Acute data

LD₅₀ oral redwing blackbird, starling >100 mg kg⁻¹ (2).

LD_{Lo} oral rabbit 9 g kg⁻¹ (3).

Sub-acute and sub-chronic data

LD_{Lo} inhalation rat (5 month) 0.5 mg m⁻³ 6 hr day⁻¹ 6 day wk⁻¹ caused no effect to central nervous system (4).

Inhalation rat (5 month) mg m⁻³ (6 hr day⁻¹) (as cryolite) exerted general and specific toxic reactions, central nervous system disruption, motor coordination impaired, carbohydrate metabolism and acetylcholinesterase activity reduced, osteocyte lysis increased (5).

Metabolism and toxicokinetics

Oral rat (7 day) 0.37 g kg⁻¹ in diet. Fluoride disposition was analysed: apparent absorption 85% of dietary input, faecal excretion 15%. Of apparent absorption, 30% of input was excreted in urine and 54% retained. Ratio of retained F⁻ versus absorbed F⁻ 64%. Plots of log tissue F⁻ (g kg⁻¹ dry wt) versus amount F⁻ retained in body (mg F⁻ over 7 days), correlation coefficient *r* 0.65 (*p* <0.01) for kidney, (0.75) for femur. Amount F⁻ available 46% of original F⁻ in cryolite (6).

Genotoxicity

Inhalation rat (5 month) 0.5-3 mg m⁻³ cryolite increased the frequency of chromosome aberration in bone marrow cells; no effect on mitotic activity in corneal epithelial cells (7).

Inhalation rat (5 month) 3 mg m⁻³ 6 hr day⁻¹ 6 day wk⁻¹ increased the number of chromosome aberrations in bone marrow cells (8).

Other effects

Other adverse effects (human)

Workers in the cryolite industry showed early symptoms of F⁻ poisoning which included blood vessel dystonia (mainly hypertonia) and decreased rate and intensity of blood circulation (9).

Ninety 30-50 yr old men employed in the cryolite industry with 10-30 yr exposure to fluorine compounds including hydrogen fluoride, sodium fluoride and cryolite 72/90 had 1- and 2-degree chronic 'S' poisoning and 18/90 had suspected fluorosis, 59/90 had liver damage (10).

The concentrations of thyrotropin and thyroid hormones in the blood of workers occupationally exposed to hydrogen fluoride, sodium fluoride and cryolite were studied. Moderate changes in the functional state of the pituitary gland – thyroid system were found. No clinical manifestations of hypo- or hyperthyrosis were found. Increased levels of calcitonin in the blood indicated the stimulation of parafollicular cells of the thyroid gland (11).

Any other adverse effects

Inhalation rat (5 month) 0.5 mg m⁻³ 6 hr day⁻¹ (cryolite) and 0.35 mg m⁻³ 6 hr day⁻¹ (HF) caused decreased phagocytic activity by white cells. Activity restored after exposure ceased (12).

Legislation

Maximum allowable concentration 0.5 mg (F⁻) m⁻³ wk⁻¹ in air in (5).

Limited under EC Directive on Drinking Water Quality 80/778/EEC. Pesticides: maximum admissible concentration 0.1 µg l⁻¹ (13).

Included in Schedule 6 (Release into Land: Prescribed Substances) Statutory Instrument No. 472, 1991 (14).

Other comments

Occupational exposure and health hazards in USA reviewed (15).

Reviews on experimental toxicology and human health effects listed (16).

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C473 cufraneb

CAS Registry No. 11096-18-7

Synonyms ethylene bis(dithiocarbamate), mixed metal complex containing $\geq 8.15\%$ (*m/m*) zinc, 8.05% (*m/m*) magnesium, 5.5% (*m/m*) copper and 1.0% (*m/m*) iron; **RTECS No.** GR 7903000

Uses Superseded foliar fungicide with secondary acaricidal activity.

Ecotoxicity

Invertebrate toxicity

Non-toxic to bees (1).

Mammalian & avian toxicity

Acute data

LD₅₀ oral rat 2700 mg kg⁻¹ (1).

Irritancy

Skin, eye and respiratory system irritant (species unspecified) (2).

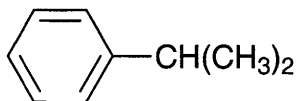
Legislation

Limited under EC Directive on Drinking Water Quality 80/778/EEC. Pesticide: maximum admissible concentration 0.1 µg l⁻¹ (3).

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C474 cumene



C₉H₁₂

Mol. Wt. 120.19

CAS Registry No. 98-82-8

Synonyms isopropylbenzene; cumol; 2-phenylpropane; (1-methylethyl)benzene; RCRA Waste Number U055

EINECS No. 202-704-5

RTECS No. GR 8575000

Uses High octane blending component in aviation fuel. Thinner for cellulose and paints. Constituent of many commercial petroleum solvents and a good solvent for fats. Major use in the synthesis of organic chemicals, especially styrene, phenol and acetone. Used in the perfume industry.

Occurrence Crude petroleum. Coal tar.

Physical properties

M. Pt. -96°C B. Pt. $152\text{--}154^{\circ}\text{C}$ Flash point 46°C Specific gravity 0.862–0.864 at 20°C with respect to water at 4°C Partition coefficient $\log P_{\text{ow}}$ 3.66 Volatility v.p. 3.2 mmHg at 20°C ; v.den. 4.1
Solubility Water: 50 mg l^{-1} at 20°C . Organic solvents: benzene, chlorinated solvents, diethyl ether, ethanol

Occupational exposure

DE-MAK 50 ppm (250 mg m^{-3}) FR-VLE 50 ppm (245 mg m^{-3})
SE-LEVL 25 ppm (120 mg m^{-3}) SE-STEEL 35 ppm (170 mg m^{-3})
UK-LTEL 25 ppm (125 mg m^{-3}) UK-STEEL 75 ppm (375 mg m^{-3})
US-TWA 50 ppm
UN No. 1918 HAZCHEM Code 3 $\frac{+}{-}$ Conveyance classification flammable liquid
Supply classification irritant
Risk phrases Flammable – Irritating to the respiratory system (R10, R37)
Safety phrases Keep out of reach of children (if sold to general public) (S2)

Ecotoxicity

Invertebrate toxicity
EC_{Lo} bay mussel larvae 1–50 ppm no significant alteration in growth rate (duration unspecified) (1).
EC₅₀ (5, 15, 30 min) *Photobacterium phosphoreum* 1.48 ppm Microtox test (2).
LC₅₀ (24 hr) *Artemia* sp. 0.39 mol m^{-3} , *Tetrahymena elliotti* 0.95 mol m^{-3} (3).

Environmental fate

Abiotic removal
Evaporation rate relative to n-butyl-acetate which has been assigned a value of 1 and at 25°C is 0.43 (4).
Extraction efficiency of macroreticular resins, sample flow 20 ml min^{-1} at pH5.7, concentration 10 ppm XAD-2 67%, XAD-7 67% (5).

Mammalian & avian toxicity

Acute data
LD₅₀ oral redwing blackbird $>98\text{ mg kg}^{-1}$ (6).
LD₅₀ oral rat 1.4 g kg^{-1} (7).
LC₅₀ (4 hr) inhalation rat 8000 ppm (8).
LC₅₀ (7 hr) inhalation mouse 2000 ppm (9).
LC₅₀ (2 hr) inhalation mouse 24.7 g m^{-3} (10).
LD₅₀ dermal rabbit 12.3 g kg^{-1} (8).

Metabolism and toxicokinetics

Gavage Chinchilla rabbits 0.45 g kg^{-1} (in water) metabolised to hydratropyl glucuronide, 2-phenylisopropyl glucosiduronic acid and hydratropylglucuronide which were excreted in the urine. Further analysis showed cumene was oxidised to 2-phenylpropan-2-ol (40%), hydratropic alcohol (25%) and hydratropic acid (25%) (11). Ten human volunteers inhaled cumene vapours at concentrations of 240, 480 or 720 mg m^{-3} under controlled conditions. Average retention of cumene was ~50%, which tended to diminish at the end of each exposure (12).

Irritancy

86 mg instilled into rabbit eye (24 hr) caused mild irritation (7).
Dermal rabbit (24 hr) 10 mg (open) caused mild irritation (8).
TC_{Lo} inhalation human 200 ppm, nose irritant, pulmonary irritant, central nervous system effects (13).

Other effects

Other adverse effects (human)

Human systemic effects by inhalation: an antipsychotic; unspecified changes in sense of smell and respiratory system. Central nervous system depressant. Chronic exposure: damage to lungs, liver, kidneys. At high concentrations vapour causes headaches, dizziness loss of coordination and loss of consciousness. Cumene has caused lung damage in experimental animals, but this has not been observed in humans (14).

Any other adverse effects

The effects of pretreatment with cumene on hepatic and pulmonary microsomal enzymes were studied in σ rats (duration and concentrations unspecified). Lung cytochrome P450 concentration and 7-ethoxycoumarin O-deethylase activity decreased. Liver cytochrome P450 and enzyme activity was increased (15).

Legislation

The log P_{ow} value exceeds the European Community recommended level 3.0 (6th and 7th amendments) (16).

Other comments

Cumene is a narcotic, characterised by slow induction and long duration relative to benzene or toluene (14).

Not mutagenic in a study of components of tobacco smoke (14).

Reviews on experimental toxicology and human health effects listed (17).

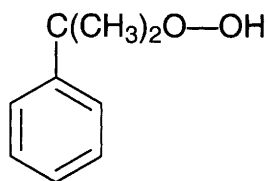
Pathways used by 16 bacterial strains isolated from soil and water and capable of degrading alkylbenzenes are discussed (18).

Non-empirical model to predict soil sorption coefficient bioconcentration factors and acute fish toxicity described (19).

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C475 cumene hydroperoxide



C₉H₁₂O₂

Mol. Wt. 152.19

CAS Registry No. 80-15-9

Synonyms α-cumene hydroperoxide; cumenyl hydroperoxide; α-cumyl hydroperoxide; 7-cumyl hydroperoxide; isopropylbenzene hydroperoxide; dimethylbenzyl hydroperoxide; Aztec CHP-80; Trigonox 239A

EINECS No. 201-254-7

RTECS No. MX 2450000

Uses Manufacture of acrylic polymers and adhesives, catalyst.

Physical properties

B. Pt. 153°C **Flash point** 79°C **Specific gravity** 1.023 at 20°C **Volatility** v.p. <0.03 mmHg at 20°C
Solubility Water: <1 g l⁻¹ at 18°C. Organic solvents: acetone, diethyl ether, dimethyl sulfoxide, ethanol

Occupational exposure

Supply classification oxidising, corrosive

Risk phrases May cause fire – Harmful by inhalation and if swallowed – Causes burns (R7, R20/22, R34)

Safety phrases Keep locked up and out of the reach of children (if sold to general public) – Keep container tightly closed in a cool place – Keep away from acids – Wear suitable protective clothing, gloves and eye/face protection – In case of accident or if you feel unwell, seek medical advice immediately (show label where possible) – Do not mix with oxidisable materials (S1/2, S3/7, S14, S36/37/39, S45, S50)

Mammalian & avian toxicity

Acute data

LD₅₀ oral rat 382 mg kg⁻¹ (1).

LC₅₀ (4 hr) inhalation mouse, rat 200, 220 ppm, respectively (1).

LD₅₀ dermal rat 500 mg kg⁻¹ (2).

LD₅₀ subcutaneous mouse 490 mg kg⁻¹ (3).

Metabolism and toxicokinetics

Metabolised to form methyl radical adducts by human carcinoma skin keratinocytes. The free radicals are believed to be involved in the tumour promotion associated with human cancer risk from hydroperoxides (4).

Irritancy

Dermal rabbit, 500 mg caused mild irritation (period of exposure unspecified) (5).

Genotoxicity

Salmonella typhimurium TA97, TA98, TA100, TA102, TA1535, with and without metabolic activation positive (6).

Induced DNA strand breaks in human cells *in vitro* (cell type unspecified) (7).

Other effects

Any other adverse effects

In vitro rat liver biliary epithelial cells induced cytotoxic injury including a strong depletion of GSH, depletion of protein thiols and increase in cell death (8).

Legislation

Included in Schedule 6 (Release into Land: Prescribed Substances) Statutory Instrument No. 472, 1991 (9).

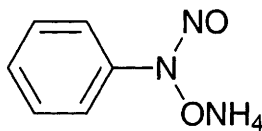
Other comments

Contact with NaI in 2-propanol caused violent decomposition (10).
Autoignition temperature 221°C.

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C476 cupferron



$C_6H_{10}N_3O_2$

Mol. Wt. 156.16

CAS Registry No. 135-20-6

Synonyms ammonium *N*-nitrosophenylhydroxylamine; *N*-hydroxy-*N*-nitrosobenzeneamine, ammonium salt; NCI-C05258; *N*-nitrosophenylhydroxylamine, ammonium salt

EINECS No. 205-183-2

RTECS No. NC 4725000

Uses Reagent for separating copper and iron from other metals.

Physical properties

M. Pt. 163-164°C

Solubility Water: freely soluble. Organic solvents: ethanol

Ecotoxicity

Fish toxicity

LD₅₀ (16-24 hr) threespine stickleback 10 mg l⁻¹ (1).

Invertebrate toxicity

Cytogenic effects grasshopper 1 µg m⁻³ (2).

Mammalian & avian toxicity

Acute data

LD₅₀ oral redwing blackbird >96 mg kg⁻¹ (3).

LD₅₀ oral rat 199 mg kg⁻¹ (4).
LD₅₀ intravenous mouse 180 mg kg⁻¹ (5).

Carcinogenicity and chronic effects

Oral rat, mouse (78 wk) 0.3% and 0.4% in food, respectively, positive for carcinogenicity. In ♂ rats tumours found in circulatory system, liver and stomach. In ♀ rats tumours found in circulatory system, liver, stomach and Zymbal gland. In ♀ mice tumours in circulatory system, Harderian gland, liver and Zymbal gland (6,7).

Irritancy

20 mg instilled into rabbit eye (24 hr) caused severe irritation (8).

Genotoxicity

Salmonella typhimurium TA98, with and without metabolic activation positive (9).

Escherichia coli WP2 uvrA with and without metabolic activation positive (10).

Oral gerbil 1 ppm produced cytogenic effects (2).

Other comments

Reviews on experimental toxicology and human health effects listed (11).

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c477 cupriethylenediamine



C₄H₁₄CuN₄

Mol. Wt. 181.73

CAS Registry No. 13426-91-0

Synonyms bis(1,2-ethanediamine-*N,N'*-copper(II)); 1,2-diaminoethane copper complex

RTECS No. KH 8660000

Uses Cellulose solvent.

Occupational exposure

DE-MAK 1 mg m⁻³ (total dust)

UN No. 1761 HAZCHEM Code 2X **Conveyance classification** corrosive substance, toxic

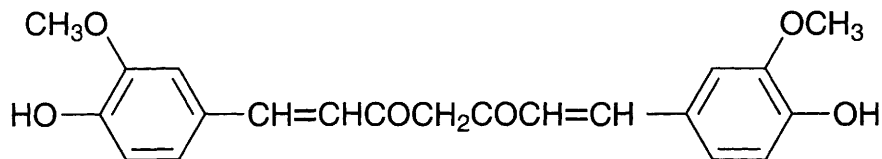
Other comments

Activated sludge from a bench-scale plant was incubated with cupriethylenediamine, high toxicity threshold demonstrated due to its stability (1).

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C478 curcumin



$C_{21}H_{20}O_6$

Mol. Wt. 368.39

CAS Registry No. 458-37-7

Synonyms C.I. 75300; C.I. Natural Yellow 3; diferuloylmethane; Indian saffron; NCI-C61325; 1,7-bis(4-hydroxy-3-methoxyphenyl)-1,6-heptadiene-3,5-dione; Naturchrom Turmeric

EINECS No. 207-280-5

RTECS No. MI 5230000

Uses Preparation of curcuma paper. In the detection of boron.

Occurrence Natural dye obtained from root of *Curcuma longa* L., L. Zingiberaceae.

Physical properties

M. Pt. 183°C

Solubility Organic solvents: methanol

Mammalian & avian toxicity

Acute data

LD₅₀ intraperitoneal mouse 1500 mg kg⁻¹ (1).

Sub-acute and sub-chronic data

Oral ♂, ♀ pigs (102-109 days) 60, 296, 1551 mg kg⁻¹ of turmeric oleoresin (which contains curcumin) in the diet. Highest dosed animals showed a reduction in weight gain and in feed-conversion efficiency. Statistically significant dose-related increases in the weight of the liver and the thyroid were recorded at all dose levels. Pericholangitis, hyperplasia of the thyroid and epithelial changes in the kidney and urinary bladder were observed in two of the higher dose groups (2).

Irritancy

Dermal rabbit (24 hr) 500 mg caused mild irritation (3).

Genotoxicity

Salmonella typhimurium TA98, TA100, TA1535, TA1537 with and without metabolic activation negative (4).

Curcumin had no discernible effect on the frequency of mitotic irregularities in bovine papillomavirus DNA-carrying cells (5).

Other effects

Any other adverse effects

Oral rats (single dose) 100, 200 and 400 mg kg⁻¹ paracetamol caused liver damage. Curcumin protected animals from paracetamol-induced liver lesions (6).

Other comments

Pharmacological effects including anti-inflammatory, antitumour, antioxidant, photodynamic and cardiovascular effects reviewed (7).

When illuminated curcumin exerted potent phototoxic effects in bacteria. Gram-negative bacteria displayed greater resistance. Oxygen was required for phototoxicity, mechanism of toxicity may involve hydrogen peroxide production. Singlet excited oxygen was not detected (8).

The water solubility, photostability, heat endurance, toxicity are discussed (9).

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c479 cyanamide



CH₂N₂

Mol. Wt. 42.04

CAS Registry No. 420-04-2

Synonyms carbamonitrile; carbimide; carbodiimide; cyanogen nitride; USAF EK 1995; cyanoamine; hydrogen cyanamide; Stabilizer 2013-P; Hi-Cane; Alzodef; Dormex; Luxan Alzodef

EINECS No. 206-992-3

RTECS No. GS 5950000

Uses Chemical intermediate. Dyestuff. Used as an inhibitor of aldehyde dehydrogenase in the treatment of chronic alcoholism.

Physical properties

M. Pt. 44-46°C **B. Pt.** 83°C at 380 mmHg **Flash point** >110°C **Specific gravity** 1.285 **Volatility** v.den. 1.45
Solubility Water: 775 g l⁻¹ at 15°C. Organic solvents: (sparingly) alcohols, benzene, ethyl acetate

Occupational exposure

FR-VME 2 mg m⁻³

UK-LTEL 2 mg m⁻³

US-TWA 2 mg m⁻³

Supply classification toxic

Risk phrases Harmful in contact with skin – Toxic if swallowed – Irritating to eyes and skin – May cause sensitisation by skin contact (R21, R25, R36/38, R43)

Safety phrases Keep locked up and out of the reach of children (if sold to general public) – Keep in a cool place – Do not breathe dust – Wear suitable protective clothing and gloves – In case of accident or if you feel unwell, seek medical advice immediately (show label where possible) (S1/2, S3, S22, S36/37, S45)

Environmental fate

Nitrification inhibition

Some inhibition of nitrification in activated sludge at 10 mg l⁻¹ (1).

Mammalian & avian toxicity

Acute data

LD₅₀ oral rat 125 mg kg⁻¹ (2).

LD₅₀ dermal rat 84 mg kg⁻¹ (3).

LD₅₀ intravenous rat 56 mg kg⁻¹ (3).

LD_{Lo} intraperitoneal rat 200 mg kg⁻¹ (4).

LD₅₀ intraperitoneal mouse 200 mg kg⁻¹ (5).

Sub-acute and sub-chronic data

Oral rat (6 month) 2-25 mg kg⁻¹ day⁻¹ no significant histological changes in the liver (6).

Teratogenicity and reproductive effects

Oral rat (duration unspecified) in a two generation reproduction-fertility study. Rats were given 2, 7 and 25 mg kg⁻¹ day⁻¹. High-dose animals exhibited decreased weight, decreased number of corpora lutea, number of implantations and decreased numbers of neonates. ♂ Rats showed reduced fertility rate and decreases in weight of reproductive organs. Changes related to cyanamide treatment were not observed in F₁ generation (7).

Metabolism and toxicokinetics

Intravenous human volunteers 0.1, 0.3, 0.6 and 1 mg kg⁻¹ elimination t_{1/2} 42-52 min and total plasma clearance values 14.4 to 20.5 ml kg⁻¹. After oral administration of 1 and 1.5 mg kg⁻¹ elimination t_{1/2} were 75 and 61 min. Rapid absorption was indicated by t_{max} values ranging from 10.5-15.5 min. Absorption was not complete, the oral bioavailability was 53% and 70% (8).

Intravenous dog single dose 1, 2 and 4 mg kg⁻¹ significant changes were recorded in plasma clearance values (12.6 to 19.7 ml kg⁻¹ min⁻¹), t_{1/2} 39 to 61 min and mean residence times 50 to 79 min. Peak plasma concentrations after oral administration of 4 mg kg⁻¹ were achieved after 30 min and oral bioavailability was ≈ 65% (9).

Other effects

Any other adverse effects

Aldehyde dehydrogenase inhibitor (10).

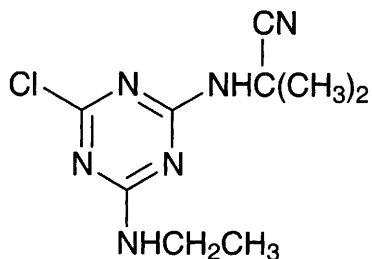
Other comments

Experimental toxicology and human health effects reviewed (11,12).

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C480 cyanazine



C₉H₁₃ClN₆

Mol. Wt. 240.70

CAS Registry No. 21725-46-2

Synonyms 2-[[4-chloro-6-(ethylamino)-1,3,5-triazin-2-yl]amino]-2-methylpropanenitrile; 2-[[4-chloro-6-(ethylamino)-s-triazin-2-yl]amino]-2-methylpropionitrile; 2-chloro-4-(1-cyano-1-methylethylamino)-6-ethylamino-1,3,5-triazine; Bladex; Match; Radeks; Reply; Urlac

EINECS No. 244-544-9

RTECS No. UG 1490000

Uses Herbicide.

Physical properties

M. Pt. 166-167°C **Specific gravity** 1.29 kg l⁻¹ at 20°C **Partition coefficient** log P_{ow} 2.10

Volatility v.p. 1.6 × 10⁻⁹ mmHg at 20°C

Solubility Water: 171 mg l⁻¹ 20°C. Organic solvents: benzene, chloroform, ethanol, hexane

Occupational exposure

Supply classification harmful

Risk phrases Harmful if swallowed (R22)

Safety phrases Keep out of reach of children (if sold to general public) – Wear suitable gloves (S2, S37)

Ecotoxicity

Fish toxicity

LC₅₀ (96 hr) *Sarotherodon aureus*, *Sarotherodon galilaeus*, *Sarotherodon mossambicus* 1.3 mg l⁻¹ (1).

LC₅₀ (96 hr) *Cirrhina mrigala* 6.3 mg l⁻¹ (1).

LC₅₀ (48 hr) harlequin fish, sheepshead minnow 10-18 mg l⁻¹ (2).

Nemoria esthamus acclimated to cyanazine were exposed to 1.0-10 mg l⁻¹. Adverse effects to gills and oxygen consumption. The opercular beats min⁻¹ substantially increased at high concentration levels (3).

Invertebrate toxicity

Non-toxic to bees (2).

LC₅₀ (24, 48, 96 hr) *Myxus vittatus* 62.6, 45.7 and 30.8 mg l⁻¹, respectively (4).

LC₅₀ (48 hr) *Chironomus tentans* larvae 6.6 mg l⁻¹ (4).

EC₅₀ (48 hr) *Daphnia magna* (age 14 hr to 6 days) 53-106 µg l⁻¹ (5).

LC₅₀ (24, 48, 96 hr) *Labeo rohita* 19.5, 8.6 and 4.8 mg l⁻¹, respectively (4).

LC₁₀₀ (duration unspecified) *Scenedesmus* sp. 0.5 mg l⁻¹ (6).

Bioaccumulation

Scenedesmus quadricauda exposed to an algal toxicity bioassay using a continuous culture showed the alga could overcome the inhibitory effects of the herbicide. Values for the accumulation factor tended to increase proportionally with the exposure time of algal cell, but decreased as the concentration of herbicides increased (7).

Environmental fate

Degradation studies

Decomposes within 10 wk in top 20 cm soil at 35°C (8).

$t_{1/2}$ 3 wk in non-sterile soil (9).

The nitrile group is hydrolysed to carboxylic acid and the chlorine is replaced by a hydroxy group (10).

Mammalian & avian toxicity

Acute data

LC₅₀ oral redwing blackbird 1.33 g l⁻¹ (11).

LD₅₀ oral mallard duck >2000 mg kg⁻¹ (2).

LD₅₀ oral quail 400 mg kg⁻¹ (2).

LD₅₀ oral rat 182 mg kg⁻¹ (12).

LD₅₀ dermal rat >1200 mg kg⁻¹ (2).

Carcinogenicity and chronic effects

In a 2-yr feeding trials the no-effect level for rats was 12 mg kg⁻¹ and for dogs 25 mg kg⁻¹ (2).

Teratogenicity and reproductive effects

TD_{Lo} (6-15 day pregnant) oral rat 25 mg kg⁻¹; decreased carcass weight, significantly increased skeletal variation but was non-teratogenic (13).

Metabolism and toxicokinetics

In rats metabolism occurs via *N*-demethylation and conjugation to give *N*-acetylcysteiny derivatives in the urine. Major metabolites include *N*-acetyl-S-[4-amino-6-(1-cyano-1-methylethylamino)-s-triazin-2-yl]cysteine; 2-chloro-4-amino-6-(1-cyano-1-methylethylamino)-s-triazine; *N*-acetyl-S-[4-ethylamino-6-(1-cyano-1-methylethylamine)-s-triazin-2-yl]cysteine; and 2-chloro-4-ethylamino-6-(1-amido-1-methylethyl(amino)-s-triazine (14).

Genotoxicity

Escherichia coli SOS Chromotest with and without metabolic activation negative (15).

Neurospora crassa sex chromosome loss and non-disjunction positive (16).

Drosophila melanogaster 79 mg l⁻¹ positive parental effects in dominant lethal test (17).

Legislation

Limited under EC Directive on Drinking Water Quality 80/778/EEC. Pesticides: maximum admissible concentration 0.1 mg l⁻¹ (18).

Other comments

Pollutant in lakes and river waters (19,20).

The behaviour of cyanazine in soils described (21).

Has been detected in treated water supplies from US public water utilities using surface water resources (22).

Metabolic pathways reviewed (23).

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c481 cyanide

CN⁻

CN

Mol. Wt. 26.02

CAS Registry No. 57-12-5

Synonyms carbon nitride ion; isocyanide; cyanide anion; RCRA waste number P030

RTECS No. GS 7175000

Uses Extraction of gold and silver from ores. Electroplating, case hardening of steel. Chemical synthesis. Fumigant.

Occupational exposure

DE-MAK 5 mg m⁻³ (inhalable dust fraction)

SE-CEIL 5 mg m⁻³ (as CN)

UK-LTEL 5 mg m⁻³

UN No. 1935 (solution) **HAZCHEM Code** 2X **Conveyance classification** toxic substance

Ecotoxicity

Fish toxicity

Early life stage toxicity test Atlantic salmon exposed to hydrocyanic acid (HCN) 0.01-0.10 mg l⁻¹. Newly fertilised eggs were continually exposed to the end of the sac-fry stage. At 0.08 and 0.10 mg l⁻¹ cyanide delayed hatching by 6-9 days but all concentrations reduced hatching by 15-40% (1).

LC₅₀ (20 day) rainbow trout 0.005-0.045 mg (HCN) l⁻¹ significantly reduced growth weight in flow-through assay temperature range 6-18°C (2).

LC₅₀ (24 hr) common sunfish 0.18 mg (HCN) l⁻¹ (3).

LC₅₀ (96 hr) rainbow trout, yellow perch, Arctic char 0.053-0.076 mg (HCN) l⁻¹ (4).

Changes in heart rate, ventilatory activity and oxygen consumption were detected in trout and brown bullhead catfish exposed to a steadily increasing concentration of waterborne cyanide (HCN) selected to produce death 8-9 hr. Trout developed an immediate and gradually increasing bradycardia throughout the exposure period. In bullheads tachycardia was the initial response followed by bradycardia as the concentration increased. Cardiac and ventilatory response were attributed to stimulation of central- and chemoreceptors by cyanide in both species. The trout response to cyanide was similar to that produced by environmental hypoxia, while bullheads

experienced a gustatory stimulus which masked the hypoxia-like response (5). Bluegill sunfish was exposed to various concentrations of HCN to determine the effects on long-term survival, growth, egg production and egg hatchability. Intermittent-flow experiments were conducted using adults, juveniles and newly hatched eggs. Egg production was the most sensitive response, no adverse effect concentration $< 5.2 \mu\text{g (HCN) l}^{-1}$. No-adverse-effect concentration in fry survival (through first 6 wk) was $15.6\text{--}19.4 \mu\text{g (HCN) l}^{-1}$ (6).

Environmental fate

Nitrification inhibition

Nitrification and denitrification inhibition, rotating disc threshold at 0.1 mg l^{-1} ; inhibition of nitrification/denitrification, activated sludge, threshold 0.1 mg l^{-1} (7).

Degradation studies

Klebsiella planticola converted cyanide into ammonia under anaerobic conditions (concentration and duration unspecified) (8).

Pseudomonas acidovorans isolated from soil was able to degrade cyanide (concentration and duration unspecified) (9).

A Gram-positive endospore-forming bacterium *Bacillus pumilus* rapidly degraded 100 mg l^{-1} free cyanide in the absence of added organic/inorganic substances. The ability to degrade cyanide was linked to the growth phase and required $\geq 0.002 \text{ mg Mn}^{2+} \text{ l}^{-1}$. Cyanide-degrading activity was intracellular and free cell extracts rapidly degraded cyanide (10).

Abiotic removal

Hydrolysis of complex cyanides to lethal simple cyanides is caused by solar irradiation. $\sim 1 \text{ mg (CN}^{-}) \text{ l}^{-1}$ was formed from 5 mg l^{-1} ferrocyanide (CN^{-}) during summer solar irradiation for 1 hr equivalent to $\sim 20\%$ photolysis (11).

Mammalian & avian toxicity

Acute data

LD_{50} intraperitoneal mouse 3 mg kg^{-1} (as CN^{-}) (12).

Sub-acute and sub-chronic data

Oral mice chronic study (duration and concentration unspecified). Intoxication was confirmed by inhibition of cytochrome oxidase activity in liver, brain, heart and blood. Results support the fundamental role of the enzyme rhodanese in detoxifying cyanide (13).

Other effects

Other adverse effects (human)

In humans, systemic effects include constriction of the throat, nausea, vomiting, giddiness, headache, palpitation, hypernoea then dyspnoea, bradycardia, unconsciousness, convulsions and death. The fatal dose of HCN in humans is $\approx 50 \text{ mg}$ and of the cyanides 250 mg (14).

Any other adverse effects

Cyanides interfere with the oxygen uptake of cells by inhibition of cytochrome oxidase, an enzyme necessary for cellular oxygen transport (14).

Legislation

Maximum permissible concentration in domestic water in former USSR 0.1 mg l^{-1} (15).

World Health Organisation revised guideline for drinking water quality: guide level 0.1 mg l^{-1} (16).

Limited under EC Directive on Drinking Water Quality 80/778/EEC. Cyanides: maximum admissible concentration $50 \mu\text{g l}^{-1}$ (17).

Other comments

In solution, the toxicity of cyanides is dependent on the pH value. The cyanide anion CN^- is of low toxicity; the free acid HCN is lethal.

Human poisoning by cyanides may occur from inhalation of the vapour, ingestion or absorption through the skin. Poisoning may arise from cyanide pesticides, industrial accidental exposure of the inhalation of fumes from some burning plastics. Poisoning may also occur from cyanide-containing plants or fruits (14).

Experimental toxicology and human health effects reviewed (18,19).

Mechanism of cyanide neurotoxicity described (20).

Microbial cyanide and nitrile metabolism reviewed (21).

The solution equilibria of cyanide chemistry is comprehensively discussed (22).

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C_2N_2

Mol. Wt. 52.04

CAS Registry No. 460-19-5

Synonyms oxalonitrile; carbon nitride; dicyanogen; ethanedinitrile; oxalyl cyanide

EINECS No. 207-306-5

RTECS No. GT 1925000

Uses Intermediate in chemical synthesis.

Physical propertiesM. Pt. $-27.9^{\circ}C$ B. Pt. $-21^{\circ}C$ Specific gravity 0.9537 at $21^{\circ}C$ with respect to water at $4^{\circ}C$

Solubility Water: 1 volume water dissolves 4 volumes cyanogen gas. Organic solvents: diethyl ether, ethanol

Occupational exposureDE-MAK 10 ppm (22 mg m^{-3})FR-VME 2 ppm (4 mg m^{-3})FR-VLE 10 ppm (20 mg m^{-3})UK-LTEL 10 ppm (22 mg m^{-3})US-TWA 10 ppm (21 mg m^{-3})

UN No. 1026 (liquified) Conveyance classification toxic gas, danger of fire (flammable gas) (liquified)

Supply classification highly flammable, toxic

Risk phrases Highly flammable – Toxic by inhalation (R11, R23)

Safety phrases Keep locked up and out of the reach of children (if sold to general public) – Do not breathe vapour – In case of accident or if you feel unwell, seek medical advice immediately (show label where possible) (S1/2, S23, S45)

Ecotoxicity

Toxicity to other species

LD_{Lo} subcutaneous frog 45 mg kg^{-1} (1).**Mammalian & avian toxicity**

Acute data

LD_{Lo} subcutaneous pigeon 9 mg kg^{-1} (1).LC₅₀ (1 hr) inhalation rat 350 $\mu g m^{-3}$ (2).LD_{Lo} subcutaneous rabbit 13 mg kg^{-1} (1).

Irritancy

16 ppm was irritating to human eye after 6 min (2).

Other effects

Other adverse effects (human)

In humans, systemic effects include constriction of the throat, nausea, vomiting, giddiness, headache, palpitation, hypernoea then dyspnoea, bradycardia, unconsciousness, convulsions and death. The fatal dose of HCN in humans is ~ 50 mg and of the cyanides 250 mg (3).

Any other adverse effects

Cyanides interfere with the oxygen uptake of cells by inhibition of cytochrome oxidase, an enzyme necessary for cellular oxygen transport (3).

Legislation

Limited under EC Directive on Drinking Water Quality 80/778/EEC. Cyanides: maximum admissible concentration 50 µg l⁻¹ (4).

World Health Organisation guidelines for drinking water quality cyanide: guide level 0.1 mg l⁻¹ (5).

Other comments

In solution, the toxicity of cyanides is dependent on the pH value. The cyanide anion CN⁻ is of low toxicity; the free acid HCN is lethal.

Human poisoning by cyanides may occur from inhalation of the vapour, ingestion or absorption through the skin. Poisoning may arise from cyanide pesticides, industrial accidental exposure or the inhalation of fumes from some burning plastics. Poisoning may also occur from cyanide-containing plants or fruits (3).

Reviews on experimental toxicology and human health effects listed (6).

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C483 cyanogen bromide



CBrN

Mol. Wt. 105.92

CAS Registry No. 506-68-3

Synonyms bromine cyanide; bromocyan; bromocyanogen; cyanobromide

EINECS No. 208-051-2

RTECS No. GT 2100000

Uses Immobilisation of enzymes. Fumigant.

Physical properties

M. Pt. 50-53°C **B. Pt.** 61-62°C **Specific gravity** 2.015 at 20°C with respect to water at 4°C

Volatility v.p. 92 mmHg at 20°C

Solubility Water: freely soluble. Organic solvents: acetonitrile, diethyl ether, dichloromethane, ethanol

Occupational exposure

SE-CEIL 5 mg m⁻³ (as CN)

UK-LTEL 5 mg m⁻³ (as CN)

UN No. 1889 **HAZCHEM Code** 2XE **Conveyance classification** toxic substance, corrosive

Ecotoxicity

Fish toxicity

LC₅₀ (96 hr) bluegill sunfish 0.24 mg l⁻¹ (1).

LC₅₀ (96 hr) inland silverside 0.47 mg l⁻¹ (1).

Environmental fate

Degradation studies

Cyanides converted into formamide by cyanide hydratase in *Stemphylium loti* (2).

Mammalian & avian toxicity

Acute data

Probable oral lethal dose in humans $<5 \text{ mg kg}^{-1}$ (3).

LC_{Lo} (10 min) inhalation human 92 ppm (4).

LC_{Lo} (10 min) inhalation mouse 500 mg m^{-3} (5).

Metabolism and toxicokinetics

$t_{1/2}$ for conversion of cyanide into thiocyanate in humans between 20-60 min (6).

Mode of action of cyanides is by inhibition of cytochrome oxidase with consequent inhibition of mitochondrial electron transport and oxidative phosphorylation (7).

Irritancy

Eye, skin, mucous membranes and upper respiratory tract irritant (species unspecified) (8).

Other effects

Other adverse effects (human)

In humans, systemic effects include constriction of the throat, nausea, vomiting, giddiness, headache, palpitation, hypernoea then dyspnoea, bradycardia, unconsciousness, convulsions and death. The fatal dose of HCN in humans is $\approx 50 \text{ mg}$ and of the cyanides 250 mg (9).

Other comments

In solution, the toxicity of cyanides is dependent on pH value. The cyanide anion CN^- is of low toxicity; the free acid HCN is lethal.

Human poisoning by cyanides may occur from inhalation of the vapour, ingestion or absorption through the skin. Poisoning may arise from cyanide pesticides, industrial accidental exposure or the inhalation of fumes from some burning plastics. Poisoning may also occur from cyanide-containing plants or fruits (9).

Toxic effect similar to hydrogen cyanide (10).

Lachrymatory.

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C484 cyanogen chloride

CICN

CCIN

Mol. Wt. 61.47

CAS Registry No. 506-77-4

Synonyms chlorine cyanide; chlorocyan; Mauguinite

EINECS No. 208-052-8

RTECS No. GT 2275000

Uses Chemical intermediate. Insecticide. Military poison gas (Mauguinite). Warning gas in fumigants.

Physical properties

M. Pt. -6.5°C B. Pt. 13.1°C Specific gravity 1.218 at 4°C with respect to water at 4°C

Partition coefficient $\log P_{ow}$ 0.64 Volatility v.p. 1000 mmHg at 20°C ; v.den. 1.98

Solubility Water: 30 g l⁻¹. Organic solvents: diethyl ether, ethanol

Occupational exposure

FR-VLE 0.3 ppm (0.6 mg m⁻³)

SE-LEVL 0.1 ppm (0.3 mg m⁻³)

SE-STEEL 0.3 ppm (0.8 mg m⁻³)

UK-STEEL 0.3 ppm (0.77 mg m⁻³)

US-STEEL ceiling limit 0.3 ppm (0.75 mg m⁻³)

UN No. 1589 (inhibited) HAZCHEM Code 2X (inhibited) Conveyance classification toxic gas, corrosive (inhibited)

Ecotoxicity

Invertebrate toxicity

Cyanogen chloride toxicity to *Daphnia magna* neonates (1-5 days old) at CN⁻ concentrations between 18 and 262 $\mu\text{g l}^{-1}$. LC₅₀ (24, 48 hr) 86 and 65 $\mu\text{g l}^{-1}$, respectively. Cyanogen chloride rapidly decomposes in water; toxicity may therefore result from parent compound and its decomposition products (1).

Environmental fate

Abiotic removal

Undergoes photolysis (2).

Mammalian & avian toxicity

Acute data

LD_{Lo} subcutaneous pigeon 8.7 mg kg⁻¹ (3).

LD₅₀ oral cat 6 mg kg⁻¹ (4).

LC₅₀ (3 min) inhalation rat 5400 mg m⁻³ (1).

LC₅₀ (1 min) inhalation monkey, dog 3800-4400 mg m⁻³ (1).

LD₅₀ subcutaneous rabbit 20 mg kg⁻¹ (3).

In man, inhalation fatal after 10 min at 159 ppm, after 30 min at 48 ppm (5).

Metabolism and toxicokinetics

Converted into the cyanide ion *in vivo* by a reaction with haemoglobin and glutathione (5).

Irritancy

Lowest human irritant concentration 1 ppm for 10 min (5).

Human eye (2 min) 100 mg m⁻³ caused severe irritation (6).

Other effects

Other adverse effects (human)

Repeated inhalation of small amounts reported to cause dizziness, congestion of the lungs, loss of appetite, weight loss and mental deterioration (7).

Any other adverse effects

Cyanides interfere with the oxygen uptake of cells by inhibition of cytochrome oxidase, an enzyme necessary for cellular oxygen transport (8).

Legislation

Limited under EC Directive on Drinking Water Quality 80/778/EEC. Cyanides: maximum admissible concentration 50 µg l⁻¹ (9).

World Health Organisation revised guidelines for drinking water quality cyanides: guide level 0.1 mg l⁻¹ (10).

Other comments

By-product of disinfection of water supplies using chlorine (11).

In solution, the toxicity of cyanides is dependent on the pH value. The anion CN⁻ is of low toxicity; the free acid HCN is lethal.

Human poisoning by cyanides may occur from inhalation of the vapour, ingestion or absorption through the skin. Poisoning may arise from cyanide pesticides, industrial accidental exposure or the inhalation of fumes from some burning plastics. Poisoning may also occur from cyanide-containing plants or fruits (8).

Absorbed from atmosphere by carbon impregnated with various metal compounds (12).

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c485 cyanogen iodide

ICN

CIN

Mol. Wt. 152.92

CAS Registry No. 506-78-5

Synonyms iodine cyanide; Jodcyan

EINECS No. 208-053-3

RTECS No. NN 1750000

Uses In taxidermy for preserving insects.

Physical properties

M. Pt. 147-149°C **Specific gravity** 2.84 at 18°C **Volatility** v.p. 1 mmHg at 25.2°C
Solubility Water: soluble. Organic solvents: diethyl ether, ethanol

Occupational exposure

SE-CEIL 5 mg m⁻³ (as CN)

UK-LTEL 5 mg m⁻³ (as CN)

UN No. 1588 **HAZCHEM Code** 4X **Conveyance classification** toxic substance

Mammalian & avian toxicity

Acute data

LD_{Lo} oral cat 18 mg kg⁻¹ (1).

LD_{Lo} subcutaneous rat 44 mg kg⁻¹ (2).

Metabolism and toxicokinetics

t_{1/2} for conversion of cyanide into thiocyanide in man is 20-60 min (3).

Mode of action of cyanides is by inhibition of cytochrome oxidase with consequent inhibition of mitochondrial electron transport and oxidative phosphorylation (4).

Irritancy

Eye, skin, mucous membranes and upper respiratory tract irritant (species unspecified) (5).

Other effects

Other adverse effects (human)

In humans, systemic effects include constriction of the throat, nausea, vomiting, giddiness, headache, palpitation, hyperventilation then dyspnoea, bradycardia, unconsciousness, convulsions and death. The fatal dose of HCN in humans is ≈50 mg and of the cyanides 250 mg (6).

Legislation

Limited under EC Directive on Drinking Water Quality 80/778/EEC. Cyanides: maximum admissible concentration 50 µg l⁻¹ (7).

Other comments

In solution, the toxicity of cyanides is dependent on the pH value. The cyanide anion CN⁻ is of low toxicity; the free acid HCN is lethal.

Human poisoning by cyanides may occur from inhalation of the vapour, ingestion or absorption through the skin.

Poisoning may arise from cyanide pesticides, industrial accidental exposure or the inhalation of fumes from some burning plastics. Poisoning may also occur from cyanide-containing plants or fruits (6).

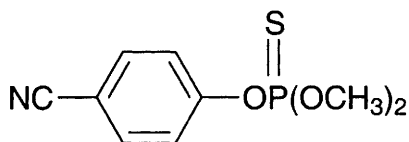
Lacks inhalation hazard of some cyanides (8).

Strongly inhibits xanthine oxidase (9).

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C486 cyanophos



C₉H₁₀NO₃PS

Mol. Wt. 243.22

CAS Registry No. 2636-26-2

Synonyms O-(4-cyanophenyl) O,O-dimethyl phosphorothioate; O,O-dimethyl O-(4-cyanophenyl) phosphorothioate; phosphorothioic acid, O-(4-cyanophenyl) O,O-dimethyl ester; Cyanox; Cynock

EINECS No. 220-130-3

RTECS No. TF 7600000

Uses Insecticide.

Physical properties

M. Pt. 14-15°C **B. Pt.** 119-20°C (decomp.) **Flash point** 104°C **Specific gravity** 1.255-1.265 at 25°C

Partition coefficient log P_{ow} 2.65 at room temp. **Volatility** v.p. 7.88 × 10⁻⁴ mmHg

Solubility Water: 46 mg l⁻¹ at 30deg;C. Organic solvents: acetone, chloroform, methanol

Occupational exposure

Supply classification harmful, dangerous for the environment

Risk phrases Harmful in contact with skin and if swallowed – Very toxic to aquatic organisms, may cause long-term adverse effects in the aquatic environment (R21/22, R50/53)

Safety phrases Keep out of reach of children (if sold to general public) – Wear suitable protective clothing and gloves – This material and/or its container must be disposed of as hazardous waste – Avoid release to the environment. Refer to special instructions/safety data sheet (S2, S36/37, S60, S61)

Ecotoxicity

Fish toxicity

LC₅₀ (48 hr) carp 5 mg l⁻¹ (1,2).

LC₅₀ (24, 48 hr) harlequin fish 14.4 and 5.6 mg l⁻¹, respectively. These values are extrapolated from the LC₅₀ (24 and 48 hr tests) on harlequin fish using the 40% formulation Cyanox. LC₅₀ (24, 48 hr) harlequin fish 36 mg cyanox l⁻¹ and 14 mg cyanox l⁻¹ (3).

Invertebrate toxicity

Toxic to honey bees (2).

Bioaccumulation

Guppies were exposed to a mixture of organophosphorus compounds containing cyanophos for 0-264 hr, elimination period was 420 hr. Other compounds in the mixture were methylparathion, ronnel, fenitrothion, dicapthion, iodofenphos and 1,2,3,5-tetrachlorobenzene as an internal standard. Exposure was carried out in a continuous flow-through system: temperature 25°C, pH 7.5-8.0 and oxygen content 6.5-8.5 mg O₂ l⁻¹. Bioconcentration factor 203-275 µg l⁻¹ increasing with exposure duration (4).

Environmental fate

Degradation studies

Agrobacterium sp. isolated from soil hydrolysed the CN group in cyanophos to the carboxylic acid via the intermediate amide (5).

Abiotic removal

Rapidly decomposed upon exposure to light (1).

Mammalian & avian toxicity

Acute data

LD₅₀ oral chicken 24 mg kg⁻¹ (6).

LD₅₀ oral rat 610 mg kg⁻¹ (1,2).

LD₅₀ oral guinea pig 324 mg kg⁻¹ (7).

LD₅₀ dermal rat 800 mg kg⁻¹ (8).

Metabolism and toxicokinetics

¹⁴C-labelled cyanophos administered orally to ♂ Wistar rats had its maximum distribution within 1 hr post-administration in the kidney and adrenal gland but was comparatively low in the brain. Within 96 hr, ≈90% and 10% of the total radioactivity was excreted in the urine and faeces, respectively. Radioactivity in expired carbon dioxide was negligible. Urinary degradation products include demethylcyanox, demethylcyanoxon, *p*-cyanophenol and *p*-cyanophenylsulfate (9).

Irritancy

Mild skin and mild local irritation on the eye mucosa (animal type unspecified) (7).

Other effects

Any other adverse effects

Chronic administration (2 months) (unspecified species) 1 mg kg⁻¹ increased haemoglobin levels and this increase persisted. Erythrocyte and leukocyte numbers also increased. Cholinesterase inhibitor in erythrocytes, kidney, plasma and whole blood and brain (7).

Legislation

Limited under EC Directive on Drinking Water Quality 80/778/EEC. Pesticide: maximum admissible concentration 0.1 µg l⁻¹ (10).

Included in Schedule 6 (Release into Land: Prescribed Substances) Statutory Instrument No. 472, 1991 (11).

Recommended maximum permissible concentration in water reservoirs 0.05 mg l⁻¹ in former USSR (7).

WHO Toxicity Class II (12).

EPA Toxicity Class (formulation) III (1).

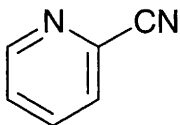
Other comments

Insecticide action is through cholinesterase inhibition (2).

References

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C487 2-cyanopyridine



C₆H₄N₂

Mol. Wt. 104.11

CAS Registry No. 100-70-9

Synonyms picolinonitrile; 2-pyridinecarbonitrile; 2-azobenzonitrile

EINECS No. 202-880-3

Uses Chemical intermediate.

Physical properties

M. Pt. 26-28°C B. Pt. 212-215°C Flash point 89°C Specific gravity 1.0810 at 25°C with respect to water at 4°C Partition coefficient log P_{ow} 0.50 Volatility v.p. 0.5 mmHg at 25°C

Solubility Organic solvents: benzene, carbon tetrachloride, diethyl ether, ethanol

Ecotoxicity

Fish toxicity

LC₅₀ (96 hr) fathead minnow 726 mg l⁻¹ (1).

Invertebrate toxicity

EC₅₀ (60 hr) *Tetrahymena pyriformis* 646.7 mg l⁻¹ (2).

EC₅₀ (5, 15, 30 min) *Photobacterium phosphoreum* 88.6 ppm Microtox test (3).

Environmental fate

Nitrification inhibition

Nocardia rhodochrous LL100-21 utilised 2-cyanopyridine as source of nitrogen for growth. Studies with intact bacteria and cell-free extracts indicated that cyanopyridine was hydrolysed directly to nicotinic acid by an inducible nitrilase and that the organism also possessed a separate inducible nicotinamidase (4).

Mammalian & avian toxicity

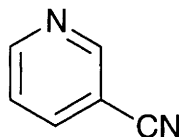
Irritancy

Eye, skin, mucous membranes and upper respiratory tract irritant (species unspecified) (5).

References

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C488 3-cyanopyridine



C₆H₄N₂

Mol. Wt. 104.11

CAS Registry No. 100-54-9

Synonyms nicotinitrile; 3-pyridinecarbonitrile; 3-azobenzonitrile

EINECS No. 202-863-0

RTECS No. QT 3030000

Uses Prevention and treatment of pellagra-like disease in dogs. Chemical intermediate.

Physical properties

M. Pt. 50-52°C B. Pt. 201°C Flash point 84°C Partition coefficient log P_{ow} 0.36

Volatility v.p. 0.4 mmHg at 25°C

Solubility Organic solvents: benzene, chloroform, diethyl ether, ethanol

Ecotoxicity

Invertebrate toxicity

EC₅₀ (5, 15, 30 min) *Photobacterium phosphoreum* 657 ppm Microtox test (1).

EC₅₀ (60 hr) *Tetrahymena pyriformis* 581.6 mg l⁻¹ (2).

Environmental fate

Nitrification inhibition

Nocardia rhodochrous LL100-21 utilised 3-cyanopyridine as sources of nitrogen for growth. Studies with intact bacteria and cell-free extracts indicated that 3-cyanopyridine was hydrolysed to form ammonia which was utilised for growth; and nicotinic acid which was not further metabolised and accumulated in the culture medium (3).

Mammalian & avian toxicity

Acute data

LD₅₀ oral rat 1190 mg kg⁻¹ (4).

LD_{Lo} dermal rabbit 4000 mg kg⁻¹ (4).

LD₂₅ intraperitoneal mouse 810 mg kg⁻¹ (5).

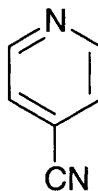
Irritancy

Eye, skin, mucous membranes and upper respiratory tract irritant (species unspecified) (6).

References

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c489 4-cyanopyridine



$C_6H_4N_2$

Mol. Wt. 104.11

CAS Registry No. 100-48-1

Synonyms isonicotinonitrile; 4-pyridinecarbonitrile; 4-azobenzonitrile

EINECS No. 202-856-2

Physical properties

M. Pt. 78-80°C

Solubility Organic solvents: benzene, chloroform, diethyl ether, ethanol

Ecotoxicity

Invertebrate toxicity

EC₅₀ (60 hr) *Tetrahymena pyriformis* 830 mg l⁻¹ (1).

EC₅₀ (5, 15, 30 min) *Photobacterium phosphoreum* 396-487 (2).

Environmental fate

Nitrification inhibition

Nocardia rhodochrous LL100-21 utilised 4-cyanopyridine as sources of nitrogen for growth. Studies with intact bacteria and cell-free extracts indicated that cyanopyridine was hydrolysed directly to nicotinic acid by an inducible nitrilase and that the organism also possessed a separate inducible nicotinamidase (3).

Mammalian & avian toxicity

Irritancy

Eye, skin, mucous membranes and upper respiratory tract irritant (species unspecified) (4).

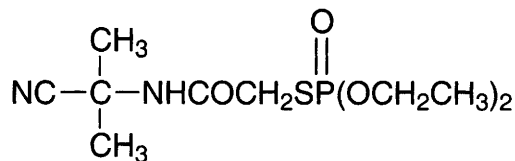
Genotoxicity

Salmonella typhimurium TA1537, TA2637, TA98, TA100 with and without metabolic activation negative (5).

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2. Kaiser, K. L. E. et al *Water Pollut. Res. J. Can.* 1991, 26(3), 361-431.
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C490 cyanthoate



$C_{10}H_{19}N_2O_4PS$

Mol. Wt. 294.31

CAS Registry No. 3734-95-0

Synonyms phosphorothioic acid, *S*-[2-[(1-cyano-1-methylethyl)amino]-2-oxoethyl] *O,O*-diethyl ester; acetamide, *N*-(1-cyano-1-methylethyl)-2-mercapto-, *S*-ester with *O,O*-diethyl phosphorothioate; phosphorothioic acid, *O,O*-diethyl ester, *S*-ester with *N*-(1-cyano-1-methylethyl)-2-mercaptoacetamide; Tartan; M 1586

EINECS No. 223-099-4

RTECS No. TE 8750000

Uses Superseded and insecticide and acaricide.

Physical properties

Specific gravity 1.19 at 19°C with respect to water at 4°C

Occupational exposure

Supply classification very toxic

Risk phrases Toxic in contact with skin – Very toxic if swallowed (R24, R28)

Safety phrases Keep locked up and out of the reach of children (if sold to general public) – Wear suitable protective clothing and gloves – In case of accident or if you feel unwell, seek medical advice immediately (show label where possible) (S1/2, S36/37, S45)

Mammalian & avian toxicity

Acute data

LD₅₀ oral rat, mouse 4-12 mg kg⁻¹ (1,2).

LD₅₀ dermal rat 105 mg kg⁻¹ (3).

Legislation

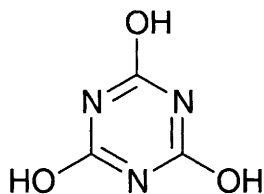
Included in Schedule 6 (Release into Land: Prescribed Substances) Statutory Instrument No. 472, 1991 (4).

Limited under EC Directive on Drinking Water Quality 80/778/EEC. Pesticide: maximum admissible concentration 0.1 µg l⁻¹ (5).

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5. *EC Directive Relating to the Quality of Water Intended for Human Consumption* 1982, 80/778/EEC, Office for Official Publications of the European Communities, 2 rue Mercier, L-2985 Luxembourg

C491 cyanuric acid



$C_3H_3N_3O_3$

Mol. Wt. 129.08

CAS Registry No. 108-80-5

Synonyms isocyanuric acid; *s*-triazinetriol; trihydroxycyanidine; pseudocyanuric acid; *s*-triazine-2,4,6-(1*H*,3*H*,5*H*)-trione; 2,4,6-trihydroxy-1,3,5-triazine

EINECS No. 203-618-0

RTECS No. XZ 1800000

Uses Herbicide. Used in plastics. Laboratory source of cyanic acid (vapour).

Physical properties

M. Pt. >360°C **Specific gravity** 2.5 at 20°C with respect to water at 4°C

Solubility Water: 5 g l⁻¹. Organic solvents: hot ethanol, pyridine

Ecotoxicity

Fish toxicity

Rainbow trout survived for 5 days in 1000 mg cyanuric acid l⁻¹. The acid was solubilised as the sodium salt (1).

Environmental fate

Degradation studies

Pseudomonas sp. NRRL B-12228 and *Achromobacter* sp. utilised cyanuric acid as sole nitrogen source and degraded the compound completely to carbon dioxide and ammonia. Optimal temperature for utilisation was 35°C (2).

Mammalian & avian toxicity

Acute data

LD₅₀ oral mouse, rat 3400, 7700 mg kg⁻¹, respectively (3).

Irritancy

Dermal rabbit (24 hr) 500 mg caused mild irritation and 20 mg instilled into rabbit eye caused mild irritation (4,5).

Other effects

Other adverse effects (human)

A case of acute occupational intoxication occurred in plant producing herbicides (atrazine, simazine and propazine). The worker was exposed to cyanuric acid in the production process. Brief exposure caused immediate irritation of skin, eyes and pharynx followed later by serious obstructive pulmonary syndrome with impairment of alveolar capillary exchanges. The patient fully recovered from skin, eye and lung disorders in 3 wk (6).

Legislation

Maximum permissible concentration in domestic water in former USSR 6.0 mg l⁻¹ (7).

Limited under EC Directive on Drinking Water Quality 80/778/EEC. Herbicides: maximum admissible concentration 0.1 µg l⁻¹ (8).

Other comments

Reviews on experimental toxicology and human health effects listed (9).

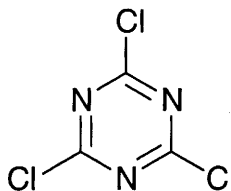
Chemical, bacterial and toxicological properties of cyanuric acid and chlorinated isocyanurates as applied to swimming pool disinfection reviewed (10).

Toxicity of cyanuric acid and its chlorinated derivatives reviewed (11).

References

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c492 cyanuric chloride



$C_3Cl_3N_3$

Mol. Wt. 184.41

CAS Registry No. 108-77-0

Synonyms 2,4,6-trichloro-1,3,5-triazine; chlorotriazine; cyanurchloride; cyanuric acid chloride; cyanuric trichloride; tricyanogen chloride; 2,4,6-trichlorotriazine

EINECS No. 203-614-9

RTECS No. XZ 1400000

Uses Chemical intermediate for polymers. Used in the synthesis of pesticides, dyes and optical bleaches.

Physical properties

M. Pt. 145.5-148.5°C **B. Pt.** 190°C **Specific gravity** 1.32 at 20°C with respect to water at 4°C

Volatility v.p. 2 mmHg at 70°C

Solubility Organic solvents: diethyl ether, ethanol

Occupational exposure

UN No. 2670 **HAZCHEM Code** 2X **Conveyance classification** corrosive substance

Supply classification irritant

Risk phrases Irritating to eyes, respiratory system and skin (R36/37/38)

Safety phrases Keep out of reach of children (if sold to general public) – After contact with skin, wash immediately with plenty of water (S2, S28)

Ecotoxicity

Fish toxicity

Exposure of trout, bluegill sunfish, yellow perch and goldfish to 5 ppm resulted in no fatalities within 24 hr (1).

Mammalian & avian toxicity

Acute data

LD₅₀ oral mouse, rat 350, 485 mg kg⁻¹, respectively (2).

LC_{Lo} (2 hr) inhalation mouse 10 mg m⁻³ (2).

LD₅₀ intravenous mouse 18 mg kg⁻¹ (3).

Irritancy

Dermal rabbit (24 hr) 500 mg caused moderate irritation and 50 µg instilled into rabbit eye caused severe irritation (4).

Caused irritation of the mucous membranes and disturbance of heart rhythm in humans (5).

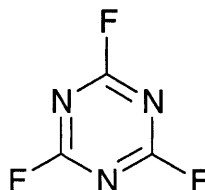
Other comments

Reviews on experimental toxicology and human health effects listed (6).

References

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2. Izmerov, N. F. et al *Toxicometric Parameters of Industrial Toxic Chemicals Under Single Exposure* 1982, 114, CIP, Moscow, USSR.
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5. Catenacci, G. *Med. Lav.* 1987, **78**(2), 155-161 (Ital.) (*Chem. Abstr.* 107, 120368c).
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C493 cyanuric fluoride



C₃F₃N₃

Mol. Wt. 135.05

CAS Registry No. 675-14-9

Synonyms 2,4,6-trifluoro-1,3,5-triazine; 2,4,6-trifluoro-s-triazine

EINECS No. 211-620-8

RTECS No. XZ 1750000

Uses Preparation of fibre-reactive dyestuffs.

Physical properties

M. Pt. -40 to -41°C B. Pt. 72.4°C Specific gravity 1.574 at 20°C with respect to water at 4°C

Occupational exposure

FR-VME 2.5 mg m⁻³ (as F)

UK-LTEL 2.5 mg m⁻³ (as F)

US-TWA 2.5 mg m⁻³ (as F)

Mammalian & avian toxicity

Acute data

LC₅₀ (4 hr) inhalation rat 17 µg l⁻¹ (1).

LD₅₀ dermal rabbit 160 mg kg⁻¹ (1).

Irritancy

Causes burns. Extremely destructive to eyes, skin, mucous membranes and upper respiratory tract (species unspecified) (2).

Legislation

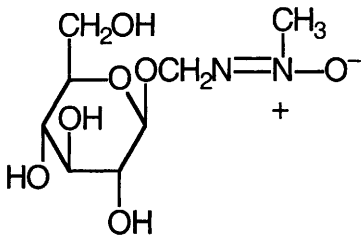
Limited under EC Directive on Drinking Water Quality 80/778/EEC. Fluorides: maximum admissible concentration 1500 µg l⁻¹ at 8-12°C and 700 µg l⁻¹ 25-30°C (3).

World Health Organisation revised guidelines for drinking water quality: guide level fluoride 1.5 mg l⁻¹. Natural or deliberately added; local or climatic conditions may necessitate adaptation(4).

References

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2. Lenga, R. E. *The Sigma-Aldrich Library of Chemical Safety Data* 2nd ed., 1988, 1, 947, Sigma-Aldrich, Milwaukee, USA.
3. *EC Directive Relating to the Quality of Water Intended for Human Consumption* 1982, 80/778/EEC, Office for Official Publications of the European Communities, 2 rue Mercier, L-2985 Luxembourg.
4. *Guidelines for Drinking Water Quality* 1984, 1, 6, WHO, Geneva, Switzerland

C494 cycasin



C₈H₁₆N₂O₇

Mol. Wt. 252.22

CAS Registry No. 14901-08-7

Synonyms β -D-glucosyloxymethylazoxymethane; methylazoxymethanol β -D-glucoside; (methyl-ONN-azoxy)methyl β -D-glucopyranoside; methylazoxymethanol β -D-glucoside

RECS No. LZ 5982000

Occurrence Obtained from seeds of *Cycas circinalis* and *Cycas revoluta* (the sago palm).

Physical properties

M. Pt. 154°C (decomp.)

Solubility Organic solvents: ethanol

Mammalian & avian toxicity

Acute data

LD₅₀ oral rat, mouse 270, 500 mg kg⁻¹, respectively (1,2).

LD₅₀ oral rabbit 30 mg kg⁻¹ (2).

Carcinogenicity and chronic effects

Inadequate evidence for carcinogenicity to humans, sufficient evidence for carcinogenicity to animals, IARC classification group 2B (3).

Carcinogenic to mice, rats, hamsters, guinea pigs, rabbits and fish following oral administration, producing a variety of malignant tumours, mainly in the liver, kidney and intestine. Skin tumours also induced. It is active in new-born mice and suckling rats and hamsters after subcutaneous injection both in single doses and prenatal exposure. The carcinogenicity of its aglycone methylazoxymethanol derivative has also been demonstrated in rats following intraperitoneal administration and in hamsters following intraperitoneal and intravenous administration (4,5).

Metabolism and toxicokinetics

Converted into methylazoxymethanol by glucosidases in intestinal microflora (6).

Enzymatic hydrolysis has been demonstrated in subcutaneous tissues of newborn mice and rats (4).

Genotoxicity

Salmonella typhimurium TA97, TA98, TA100, TA1535, TA1538, TA1537 without metabolic activation positive (7).

In vivo mouse DNA-repair host-mediated assay positive. Highest genotoxic activity observed in liver, followed by intestine and stomach and kidneys. *In vitro* *Escherichia coli* without metabolic activation positive (8).

Other comments

A study in a community where the *Cycas* sp. forms a major part of the diet showed no appreciable increase in cancer mortality after 2 to 7 yr (4).

Cycasin and its mutagenic metabolites reviewed and discussed (9).

Activity of this substance is linked to its conversion into methylazoxymethanol (5).

Biological effects, metabolism and mechanism of action of cycasin and its aglycone are discussed (10).

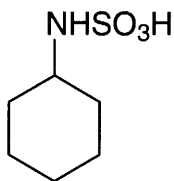
Toxicity and carcinogenicity of cycasin from *Cycas* sp. used as food sources reviewed (11).

Reviews on experimental toxicology and human health effects listed (12).

References

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C495 cyclamic acid



$C_6H_{13}NO_3S$

Mol. Wt. 179.24

CAS Registry No. 100-88-9

Synonyms cyclohexanesulfamic acid; cyclohexylsulfamic acid; hexamic acid; sucaryl; sucaryl acid

RTECS No. GV 6950000

Uses Non-nutritive sweetener.

Physical properties

M. Pt. 169-170°C

Solubility Water: very sparingly soluble

Mammalian & avian toxicity

Acute data

LD₅₀ oral rat 12 g kg⁻¹ (1).

LD₅₀ intravenous rat 4g kg⁻¹ (1).

LD₅₀ oral mouse 10 g kg⁻¹ (1).

LD₅₀ intravenous mouse 180 mg kg⁻¹ (2).

Carcinogenicity and chronic effects

Inadequate evidence for carcinogenicity to humans, limited evidence for carcinogenicity to animals, IARC classification group 3 (3).

Metabolism and toxicokinetics

In several human subjects up to 0.7% of an ingested dose of cyclamate was converted into cyclohexylamine, cyclohexanol, cyclohexanone and conjugated cyclohexanol, which were excreted in the urine (4).

Metabolic studies on over 1000 human subjects showed that 10-30% of subjects converted cyclamate into cyclohexylamine. Most of these converted < 0.1-8% of ingested dose, but a small number converted up to 60%. There is some evidence that conversion of cyclamate into cyclohexylamine is inversely related to the dose of cyclamate (5).

Rats fed cyclamate in their food were found to convert cyclamate into cyclohexylamine (6).

Cyclamate is not metabolised by the liver, spleen or kidney tissue or blood of rats or rabbits. However, cyclamate is converted into cyclohexylamine when incubated anaerobically with the contents of caecum, colon or rectum or with faeces from cyclamate-pretreated rats or rabbits. *Clostridia* in rats and *Enterobacteria* in rabbits converted cyclamate into cyclohexylamine (7).

Genotoxicity

The *Drosophila melanogaster* sex-linked recessive lethal assay, *in vitro* rat hepatocyte unscheduled DNA synthesis assay, and an *in vitro* mammalian cell assay for gene mutation all negative (8).

Bone marrow cells from Chinese hamsters administered 1-10 g kg⁻¹ cyclamate showed no sister chromatid exchanges (9).

Chromosome breaks were observed in lymphocytes from human patients with chronic liver and kidney diseases who were dosed with 2-5 g cyclamates day⁻¹ for 1-3 years. Significant differences were mainly between patients and controls, rather than dosed and non-dosed patients (5).

Legislation

In 1980 cyclamates were denied approval as safe food additives by the US Federal Food, Drug, and Cosmetic Act because evidence failed to show that they did not cause cancer and did not cause heritable genetic damage (10). The use of cyclamates as artificial sweeteners in food, soft drinks and artificial sweetening tablets is no longer permitted in Great Britain because of fears over their metabolite cyclohexylamine. The US ban on cyclamates has been reappraised since doubt exists over their carcinogenicity (11).

Acceptable daily intake 0-11 mg kg⁻¹ body weight (expressed as cyclamic acid) (12).

Other comments

Fairly strong acid. Slowly hydrolysed by hot water.

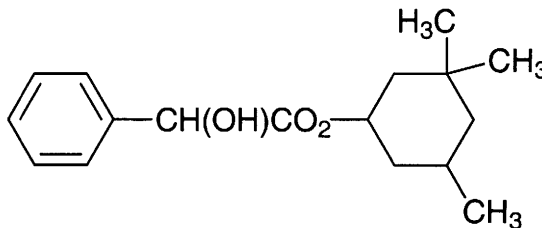
The mutagenicity of cyclamates and their metabolites reviewed (13).

Carcinogenicity of cyclamates reviewed (14).

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c496 cyclandelate



C₁₇H₂₄O₃

Mol. Wt. 276.38

CAS Registry No. 456-59-7

Synonyms α-hydroxybenzeneacetic acid, 3,3,5-trimethylcyclohexyl ester; mandelic acid, 3,3,5-trimethylcyclohexyl ester; 3,3,5-trimethylcyclohexyl mandelate; Dilatin

EINECS No. 207-271-6

RTECS No. OO 8200000

Uses Antispasmodic. Vasodilator. Used in treatment of cerebrovascular and peripheral vascular disorders.

Physical properties

M. Pt. 50-53°C B. Pt. 192-194°C at 14 mmHg

Solubility Organic solvents: acetone, diethyl ether, ethanol, petroleum ether

Mammalian & avian toxicity

Acute data

LD₅₀ oral rat 5 g kg⁻¹ (1).

LD₅₀ intraperitoneal rat, mouse 2570, 3780 mg kg⁻¹, respectively (2).

Metabolism and toxicokinetics

t_{1/2} various rat tissues 2.8-4.1 days (3).

In humans, the major metabolite of cyclandelate is mandelic acid which is excreted in the urine (4).

Other effects

Any other adverse effects

In vitro rat hepatocytes accumulated cyclandelate rapidly, hydrolysing the ester and excreting trimethylhexanol into the medium. This compound re-entered the cells and was converted into glucuronide prior to excretion (5).

The vasodilatory effects of cyclandelate metabolites were studied in rats. Cyclandelate was rapidly hydrolysed in the blood to yield mandelic acid (no cardiovascular effects) and *cis*-3,3,5-trimethylcyclohexanol which had a hypotensive effect, inhibiting phosphodiesterase (6).

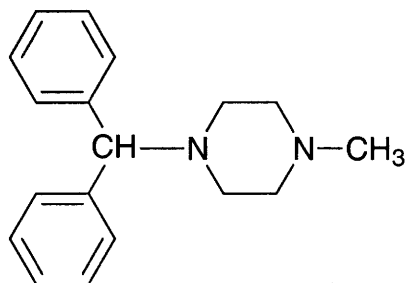
Other comments

Mode of action via selective phosphodiesterase inhibition and inhibition of aldose reductase (7).

References

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C497 cyclizine



C₁₈H₂₂N₂

Mol. Wt. 266.39

CAS Registry No. 82-92-8

Synonyms (*N*-benzhydryl)(*N'*-methyl)diethylenediamine; *N*-benzhydryl-*N'*-methylpiperazine; 1-(diphenylmethyl)-4-methylpiperazine; Marezine

EINECS No. 201-445-5

RTECS No. TL 6475000

Uses Anti-travel sickness preparations. Antiemetic. Antihistamine.

Physical properties

M. Pt. 105.5-107.5°C

Solubility Water: <0.001 g ml⁻¹ at 25°C. Organic solvents: chloroform, diethyl ether, ethanol

Mammalian & avian toxicity

Acute data

LD₅₀ oral mouse 147 mg kg⁻¹ (1).

Sub-acute and sub-chronic data

TD_{Lo} (6 wk intermittently) oral woman 126 mg kg⁻¹ blood effects including agranulocytosis (2).

Metabolism and toxicokinetics

Phase I *N*-demethylation (species unspecified) (3).

Sensitisation

A 26-yr-old ♂ with no previous history of skin disorder, sought advice about a sore and inflamed patch on the shaft of his penis. Initial symptoms were irritation and soreness of the ventral surface of the penis becoming more severe over several hours, and followed by erythema, vesiculation and scaling. Diagnosed as fixed drug eruption to cyclizine. The patient had taken 50 mg orally to combat travel sickness (4).

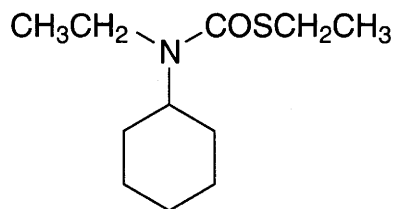
Other effects

Other adverse effects (human)

Can cause cholestatic jaundice, also been reported as a drug for abuse (5).

References

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C₁₁H₂₁NOS

Mol. Wt. 215.36

CAS Registry No. 1134-23-2

Synonyms S-ethyl cyclohexyl(ethyl)thiocarbamate; S-ethyl N-cyclohexyl-N-ethyl(thiocarbamate); hexylthiocarbam; carbamothioic acid, cyclohexylethyl-, S-ethyl ester; cyclohexanecarbamic acid, N-ethylthio-, S-ethyl ester; Buranit; Cikloherb; Cybet; Cyclobet; Cyclor; Tiolent; Ro-Neet

EINECS No. 214-482-7

Uses Selective systemic herbicide.

Physical properties

M. Pt. 11.5°C **B. Pt.** 145°C at 10 mmHg **Flash point** 139°C **Specific gravity** 1.024 at 20°C with respect to water at 4°C **Partition coefficient** log P_{ow} 3.88 **Volatility** v.p. 6.2 × 10⁻³ mmHg at 25°C

Solubility Water: 75 mg l⁻¹ at 20°C. Organic solvents: acetone, benzene, ethanol, isopropanol, kerosene, methanol, xylene

Ecotoxicity

Fish toxicity

LC₅₀ (96 hr) rainbow trout 4.5 mg l⁻¹ (1).

Invertebrate toxicity

Physa fontinalis and *Lymnaea stagnalis* showed diminished motility in the presence of cycloate. Concentrations of cycloate (lower than in practical use) delayed egg-maturing and increased the total number of dead embryos in *Lymnaea stagnalis* (2).

Environmental fate

Degradation studies

Principal mode of degradation via microbial activity, t_{1/2} 4-8 wk (3).

Adsorption and retention

Adsorption and volatilisation of cycloate was studied on six soil types (unspecified) in the laboratory. Cycloate adsorbed strongly and was least volatile of the compounds tested (4).

Mammalian & avian toxicity

Acute data

LD₅₀ oral Japanese quail >2000 mg kg⁻¹ (5).

LD₅₀ oral ♂, ♀ rat 2710 mg kg⁻¹ (5).

LC₅₀ (1 hr) inhalation ♀ rat 90 mg l⁻¹ (1).

LD₅₀ dermal rabbit >4640 mg kg⁻¹ (3).

Sub-acute and sub-chronic data

LC₅₀ (7 day) oral bobwhite quail >56 g kg⁻¹ diet (3).

In 90-day feeding trial, rats receiving 55 mg kg⁻¹ day⁻¹ and dogs receiving 240 mg kg⁻¹ showed no ill-effects (3).

Metabolism and toxicokinetics

In animals converted into the sulfoxide by microsomal enzymes and then cleared rapidly by the liver as glutathione conjugate (1).

Irritancy

Eyes, skin, nose and mouth (in some cases) irritant (species unspecified) (6).

0.1 ml instilled into rabbit eye produced moderate reversible conjunctivitis (1).

Genotoxicity

Salmonella typhimurium TA92, TA98, TA100, TA1535, TA1537, TA2637 with and without metabolic activation negative (7).

Legislation

Included in Schedule 6 (Release into Land: Prescribed Substances) Statutory Instrument No. 472, 1991 (8).

Limited under EC Directive on Drinking Water Quality 80/778/EEC. Herbicides: maximum admissible concentration 0.1 µg l⁻¹ (9).

The log P_{ow} suggests the compound may be a bioconcentrator hazard. The given value log P_{ow} 3.88 exceeds the European Community recommended level of 3.0 (6th and 7th amendments) (10).

WHO Toxicity Class III (11).

EPA Toxicity Class (formulation) III (5).

Other comments

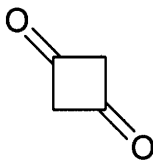
Mode of action as herbicide, inhibits growth in meristematic region of leaves (1).

In plants metabolites include ethyl cyclohexylamine, carbon dioxide, amino acids and sugars (1).

References

1. Stauffer Chemical Co. 1970, Technical Information A-10104 R-71.
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11. *The WHO Recommended Classification of Pesticides by Hazard and Guidelines to Classification* 1998-1999 WHO/PCS/98.21

c499 cyclobutane-1,3-dione



$C_4H_4O_2$

Mol. Wt. 84.07

CAS Registry No. 15506-53-3

Synonyms

Uses Intermediate in chemical synthesis.

Physical properties

M. Pt. 119-120°C (decomp.)

Occupational exposure

Supply classification highly flammable

Risk phrases Highly flammable (R11)

Safety phrases Keep out of reach of children (if sold to general public) – Keep container in a well ventilated place – Keep away from sources of ignition – No smoking – Take precautionary measures against static discharges (S2, S9, S16, S33)

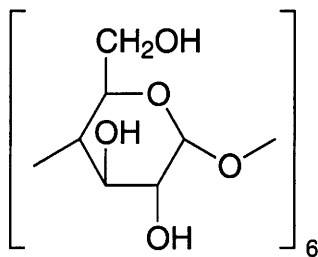
Other comments

Reviews on experimental toxicology and human health effects listed (1).

References

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c500 α -cyclodextrin



$C_{36}H_{60}O_{30}$

Mol. Wt. 972.85

CAS Registry No. 10016-20-3

Synonyms cyclohexaamylose; α -Schardinger dextrin; α -cycloamylose; α -cyclodextrin hydrate; Alpha W6 Pharma Grade

EINECS No. 233-007-4

RTECS No. GU 2292000

Uses Used as a stabiliser in foods. Can be used to increase water solubility of vitamins. Used as a complexing agent in the study of enzyme action and as a carrier molecule for drug delivery systems.

Physical properties

M. Pt. 278°C (decomp.)

Solubility Organic solvents: ethanol

Mammalian & avian toxicity

Acute data

LD₅₀ intraperitoneal rat 1000 mg kg⁻¹ (1).

LD₅₀ intravenous rat 788 mg kg⁻¹ (2).

Metabolism and toxicokinetics

Cyclodextrin is relatively inert metabolically. It is broken down by gut bacteria into absorbable sugars such as glucose and malto-oligosaccharides (3).

Very little intestinal absorption was observed in ligated rat bile duct. Absorption did occur when bile was present; intact α -cyclodextrin then entered systemic circulation. Results indicate that internal absorption occurs through the paracellular pathway (4).

Other comments

Enhances activity of some fungicides by acting as a fungistatic and by increasing the fungicide solubility (5).

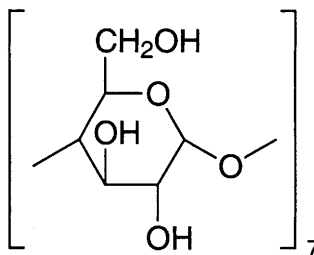
Experimental toxicology and human health effects reviewed (6).

Formed when starch is degraded by *Bacillus macerans*.

References

1. *Pharmacometrics* 1983, **26**, 287, Oyo Yakuri, Japan.
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6. *BIBRA Toxicity Profiles* 1986, British Industrial Biological Research Association, Carshalton, UK

C501 β -cyclodextrin



C₄₂H₇₀O₃₅

Mol. Wt. 1135.00

CAS Registry No. 7585-39-9

Synonyms cycloheptaamylose; β -Schardinger dextrin; β -cycloamylose

EINECS No. 231-493-2

RTECS No. GU 2293000

Uses Complexing agent in study of enzyme action. Carrier molecule for drug delivery systems.

Mammalian & avian toxicity

Acute data

LD₅₀ intraperitoneal rat, mouse 330-356 mg kg⁻¹ (1).

LD₅₀ subcutaneous mouse 412 mg kg⁻¹ (1).

LD₅₀ intravenous rat 1008 mg kg⁻¹ (2).

Sub-acute and sub-chronic data

Injection rat (route unspecified) (12 day) ≥50 mg kg⁻¹ accumulated in rat kidney and caused dose-related glomerular necrosis (3).

Oral Sprague-Dawley rats (90 day) 1.25% in diet, no dose-related adverse effects pertaining to haematology, blood or urine chemistry (4).

Carcinogenicity and chronic effects

Oral Fischer 344 rats (104 wk) 0, 2.5, or 5% β-cyclodextrin in diet. Surviving rats were given a basal diet for a further 5 wk and killed at 109 wk. A variety of tumours developed in all groups, including the control group, but all the neoplastic lesions were histologically similar to those known to occur spontaneously in this strain of rat, and no significant increase in the incidence of any tumour was found for either sex of the treated groups. Thus, the high dose, ~340-400 × higher than the current daily human intake from ingestion as a food additive and from pharmaceutical use, does not have any carcinogenic potential in F344 rats (5).

Metabolism and toxicokinetics

Biodegradation by *Bacteroides* sp. in human colon. Different species possess different cyclodextrinases which produce glucose or malto-oligomers (6).

Irritancy

Anti-inflammatory eye preparations incorporating β-cyclodextrin produce no irritation (7).

Other comments

Three day old seedlings grown from seeds treated with β-cyclodextrin showed 60-70% growth retardation while at 4 wk an 18-30% growth enhancement was observed (8).

Enhances activity of some fungicides acting as a fungistatic and by increasing the fungicide solubility (9).

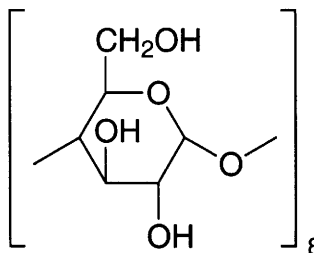
Experimental toxicology and human health effects reviewed (10).

Formed when starch is degraded by *Bacillus macerans*.

References

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C502 γ -cyclodextrin



$\text{C}_{48}\text{H}_{80}\text{O}_{40}$

Mol. Wt. 1297.14

CAS Registry No. 17465-86-0

Synonyms cyclooctaamylose; cyclooctapentylose; γ -Schardinger dextrin; Gamma W8

EINECS No. 241-482-4

Uses Complexing agent in study of enzyme action. Carrier molecule for drug delivery systems.

Physical properties

M. Pt. 267°C (decomp.)

Environmental fate

Degradation studies

Degradation by *Aspergillus oryzae*, yielding all of the malto-oligomers from maltose to malto-octaose (1).

Mammalian & avian toxicity

Acute data

LD_{50} oral rat 8000 mg kg^{-1} (2).

LD_{50} oral mouse >16,000 mg kg^{-1} (2).

LD_{50} intravenous, subcutaneous rat, mouse 2400-4000 mg kg^{-1} (2).

Irritancy

Anti-inflammatory eye preparations incorporating γ -cyclodextrin produce no irritation (3).

Other comments

Enhances activity of some fungicides, acting as a fungistatic and by increasing the fungicidal solubility (4).

Experimental toxicology and human health effects reviewed (5).

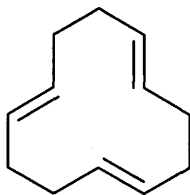
Main characteristics of cyclodextrins in analysis reviewed (6).

Formed when starch is degraded by *Bacillus macerans*.

References

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2. Matsuda, K. et al *Oyo Yakuri* 1983, 26(2), 287-291 (*Chem. Abstr.* 100, 699t).
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C503 (E,E,E)-1,5,9-cyclododecatriene



C₁₂H₁₈

Mol. Wt. 162.27

CAS Registry No. 676-22-2

Synonyms all-*trans*-1,5,9-cyclododecatriene

EINECS No. 211-626-0

Physical properties

M. Pt. 35-37°C B. Pt. 237-238°C Flash point 81°C

Occupational exposure

UN No. 2518 HAZCHEM Code 3X Conveyance classification toxic substance

Ecotoxicity

Bioaccumulation

Confirmed to accumulate at moderate levels (1).

Other effects

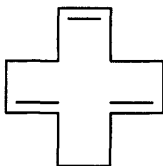
Any other adverse effects

Extremely destructive to eyes, skin, mucous membranes and upper respiratory tract (species unspecified) (2).

References

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C504 (E,E,Z)-1,5,9-cyclododecatriene



C₁₂H₁₈

Mol. Wt. 162.27

CAS Registry No. 2765-29-9

Synonyms *trans,trans,cis*-1,5,9-cyclododecatriene

EINECS No. 220-437-2

RTECS No. GU 2310000

Physical properties

M. Pt. -18°C B. Pt. 231°C Flash point 87°C Specific gravity 0.890 at 20°C with respect to water at 4°C

Occupational exposure

UN No. 2518 HAZCHEM Code 3X Conveyance classification toxic substance

Ecotoxicity

Fish toxicity

LC₅₀ (24 hr) goldfish 4 mg l⁻¹ (1).

Bioaccumulation

Confirmed to accumulate at moderate levels (2).

Mammalian & avian toxicity

Irritancy

Dermal mouse (12 day) 100% concentration caused severe irritation (3).

Dermal rabbit (duration unspecified) 2670 mg caused severe irritation and 89 mg instilled into rabbit eye caused mild irritation (3).

Other effects

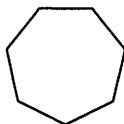
Any other adverse effects

Extremely destructive to eyes, skin, mucous membranes and upper respiratory tract (species unspecified) (3).

References

1. Shell Chemie *Shell Industrie Chemically Gids* 1975, '2 Gravenhague, Netherlands.
2. Ministry of International Trade and Industry (MITI) Report 1984, Japan.
3. Lenga, R. E. *The Sigma-Aldrich Library of Chemical Safety Data* 2nd ed., 1988, 1, 953, Sigma-Aldrich, Milwaukee, USA

c505 cycloheptane



C₇H₁₄

Mol. Wt. 98.19

CAS Registry No. 291-64-5

Synonyms

EINECS No. 206-030-2

Occurrence Petroleum fractions.

Physical properties

M. Pt. -12°C B. Pt. 118.5°C (98% pure) Flash point 6°C (98% pure) Specific gravity 0.81 at 20°C with respect to water at 4°C

Occupational exposure

UN No. 2241 HAZCHEM Code 3ME Conveyance classification flammable liquid

Ecotoxicity

Invertebrate toxicity

EC₅₀ (48 hr) *Daphnia magna* strauss 50 mg l⁻¹ (1).

Environmental fate

Degradation studies

<25% of theoretical BOD (2).

Mammalian & avian toxicity

Sub-acute and sub-chronic data

Intraperitoneal ♀ Sprague-Dawley rats (2 wk) ≥1.5 g kg⁻¹ caused renal tubular injury as evidenced by an increase in β₂-microglobulinuria. At highest dose the renal concentrating ability was depressed (3).

Irritancy

Changes epidermal arginase activity when applied to guinea pig skin (4).

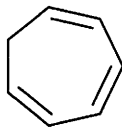
Other comments

Potential for degradation by gasoline degrading bacteria *Pseudomonas* spp., *Alcaligenes* spp., *Nocardia* spp. and *Micrococcus* spp. is discussed (5).

References

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c506 cycloheptatriene



C₇H₈

Mol. Wt. 92.14

CAS Registry No. 544-25-2

Synonyms 1,3,5-cycloheptatriene

EINECS No. 208-866-3

RTECS No. GU 3675000

Uses Chemical intermediate.

Physical properties

M. Pt. -79.5°C B. Pt. 117°C at 749 mmHg Flash point 26°C Specific gravity 0.888 at 18.5°C with respect to water at 4°C

Solubility Organic solvents: benzene, chloroform, diethyl ether, ethanol

Occupational exposure

UN No. 2603 HAZCHEM Code 3WE Conveyance classification flammable liquid, toxic

Ecotoxicity

Fish toxicity

LC₅₀ (24 hr) goldfish 15 mg l⁻¹ (1).

Environmental fate

Degradation studies

Non-biodegradable/qualified (2).

Mammalian & avian toxicity

Acute data

LD₅₀ oral rat, mouse 57, 171 mg kg⁻¹, respectively (3).

LD₅₀ dermal rat 442 mg kg⁻¹ (3).

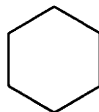
Other comments

Bactericidal activity observed for a variety of Gram-negative and Gram-positive microorganisms, but no sporicidal activity (4).

References

1. Shell Chemie *Shell Industrie Chemicalien Gids* 1975, 's Gravenhague, Netherlands.
2. *Ministry of International Trade and Industry (MITI) Report* 1984, Japan.
3. Brown, V. K. H. et al *Annals Occup. Hyg.* 1967, 10 123.
4. Trust, T. J. et al *Antimicrob. Agents Chemother.* 1975, 8(3), 381-383 (*Chem. Abstr.* 86, 115606v)

C507 cyclohexane



C₆H₁₂

Mol. Wt. 84.16

CAS Registry No. 110-82-7

Synonyms hexahydrobenzene; hexamethylene; hexanapthene

EINECS No. 203-806-2

RTECS No. GU 6300000

Uses Solvent for waxes, fats, resins, cellulose ethers, paint adhesives and natural rubber, often used in a mixture with other hydrocarbons such as toluene. Used in the manufacture of nylon. Intermediate in the production of benzene, cyclohexanol, caprolactam and hexamethylenediamine. Steroids are recrystallised from cyclohexane during industrial manufacture.

Physical properties

M. Pt. 6.5°C B. Pt. 80.7°C Flash point -18°C Specific gravity 0.775 at 20°C with respect to water at 4°C

Volatility v.p. 77 mmHg at 20°C ; v.den. 2.90

Solubility Water: 55 mg l⁻¹ at 20°C. Organic solvents: miscible in acetone, benzene, diethyl ether, ethanol

Occupational exposure

DE-MAK 200 ppm (700 mg m⁻³)

FR-VME 300 ppm (1050 mg m⁻³)

JP-OEL 150 ppm (520 mg m⁻³)

SE-LEVL 300 ppm (1000 mg m⁻³)

UK-LTEL 100 ppm (350 mg m⁻³)

US-TWA 300 ppm (1030 mg m⁻³)

FR-VLE 375 ppm (1300 mg m⁻³)

SE-STEL 370 ppm (1300 mg m⁻³)

UK-STEL 300 ppm (1050 mg m⁻³)

UN No. 1145 **HAZCHEM Code 3** **WE** Conveyance classification flammable liquid

Supply classification highly flammable

Risk phrases Highly flammable (R11)

Safety phrases Keep out of reach of children (if sold to general public) – Keep container in a well ventilated place – Keep away from sources of ignition – No smoking – Take precautionary measures against static discharges (S2, S9, S16, S33)

Ecotoxicity

Fish toxicity

LC₅₀ (7 day) guppy >84 mg l⁻¹ (1).

LC₅₀ (96 hr) fathead minnow 93 mg l⁻¹ static bioassay in Lake Superior water (2).

LC₅₀ (24-96 hr) bluegill sunfish 43-34 mg l⁻¹ (3).

Invertebrate toxicity

EC₅₀ (48 hr) *Daphnia magna* 400 mg l⁻¹ (4).

Threshold concentration cell multiplication inhibition test *Uronema parduczi* >50 mg l⁻¹, *Mytilus edulis* 10-20% increase in growth rate at 1-100 ppm (5).

EC₅₀ (48 hr) *Chlorella pyrenoidosa* 3.8 mg l⁻¹ (6).

EC₅₀ (5, 30 min) *Photobacterium phosphoreum* 227 ppm Microtox test (7).

Environmental fate

Nitrification inhibition

Inhibition of nitrification in Agar test, limit concentration 40 mg l⁻¹ (8).

Degradation studies

BOD₃₅₂₅ 2.39 in sea water (9).

Abiotic removal

Evaporation rate relative to *n*-butyl-acetate which has been assigned a value of 1 and at 25°C is 5.60 (10).

Mammalian & avian toxicity

Acute data

LD₅₀ oral mouse 813 mg kg⁻¹ (11).

LD_{Lo} oral rabbit 5500 mg kg⁻¹ (12).

LC_{Lo} (2 hr) inhalation mouse 70 g m⁻³ (13).

LD_{Lo} intravenous rabbit 77 mg kg⁻¹ (14).

LD₅₀ oral rat 8.0-39 mg kg⁻¹ depending on age, extrapolation to humans suggests a no-effect level of 0.016 ml kg⁻¹ (15).

Inhalation mouse (1 hr) 60, 70, 80 or 90 ml of an adhesive containing acetone, isopropyl acetate, 2, 3-dimethylbutane, 2-methylpentane mixture, 3-methylpentane, *n*-hexane, cyclohexane, methylcyclopentane and toluene. Number of deaths in 4-wk-old mice exposed to 60, 70 and 80 ml 0/10, 4/10 and 10/10, respectively and in 19-wk-old mice exposed to 70, 80 and 90 ml were 0/10, 3/10 and 10/10, respectively. Death was considered to be due to cyclohexane (16).

Metabolism and toxicokinetics

Metabolised to cyclohexanol, (excreted as sulfate and glucuronide) and cyclohexanone, (partially oxidised to adipic acid) (species unspecified) (17).

Irritancy

Skin irritant, to a greater extent than benzene or toluene, but to a lesser extent than xylene (18).

Genotoxicity

Salmonella typhimurium TA100, TA98, T1535, TA1537 with and without metabolic activation negative (18,19).

Escherichia coli 840 $\mu\text{g l}^{-1}$ DNA damage negative (20).

Other effects

Other adverse effects (human)

A safe solvent when used according to instructions but does act as an irritant and central nervous system depressant. Can cause nausea, dizziness, vomiting and depression. At high concentrations it is narcotic and can lead to coma and death from respiratory failure. Classed as having low chronic toxicity due to its efficient metabolism and excretion. It does not produce toxic changes to nerve cells and peripheral neuropathy associated with exposure to *n*-hexane (21).

Legislation

No-effect dose for domestic water as determined in former USSR from mammalian toxicity tests 0.005 mg kg^{-1} .

Maximum permissible concentration in domestic water in former USSR 0.1 mg l^{-1} (22).

Other comments

Reviews on experimental toxicology and human health effects reviewed (23).

Physical and chemical properties, hazards in its use and current French legislation listed (24).

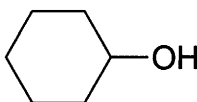
Potential for degradation by gasoline degrading bacteria *Pseudomonas* spp., *Alcaligenes* spp., *Nocardia* spp. and *Micrococcus* spp. is discussed (25).

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c508 cyclohexanol



$C_6H_{12}O$

Mol. Wt. 100.16

CAS Registry No. 108-93-0

Synonyms hexalin; hexahydrophenol; cyclohexyl alcohol; Hexalin

EINECS No. 203-630-6

RTECS No. GV 7875000

Uses Used in manufacture of adipic acid for the production of nylon 66. Used in production of lacquers, paints, varnishes, degreasing agents, plastics, plasticisers, soaps, detergents, rubber cements, textiles, dyes and insecticides.

Physical properties

M. Pt. 20-22°C (99% pure) **B. Pt.** 160-161°C (99% pure) **Flash point** 67°C (closed cup) (99% pure)

Specific gravity 0.959 at 25°C with respect to water at 4°C **Partition coefficient** $\log P_{ow}$ 1.23

Volatility v.p. 1 mmHg at 20°C ; v.den. 3.45

Solubility Water: 57 g l⁻¹ at 15°C. Organic solvents: miscible with aromatic hydrocarbons, ethanol, ethyl acetate, petroleum solvents

Occupational exposure

DE-MAK 50 ppm (210 mg m⁻³)

FR-VME 50 ppm (200 mg m⁻³)

FR-VLE 75 ppm (300 mg m⁻³)

JP-OEL 25 ppm (102 mg m⁻³)

SE-LEVL 50 ppm (200 mg m⁻³)

SE-STEL 75 ppm (300 mg m⁻³)

UK-LTEL 50 ppm (208 mg m⁻³)

US-TWA 50 ppm (206 mg m⁻³)

Supply classification harmful

Risk phrases Harmful by inhalation and if swallowed – Irritating to respiratory system and skin (R20/22, R37/38)

Safety phrases Keep out of reach of children (if sold to general public) – Avoid contact with skin and eyes (S2, S24/25)

Ecotoxicity

Fish toxicity

LC₅₀ (96 hr) bluegill sunfish 1100 mg l⁻¹ freshwater static bioassay, temperature 23°C (1).

LC₅₀ (96 hr) inland silverside 720 mg l⁻¹ synthetic seawater static bioassay, temperature 23°C (1).

Invertebrate toxicity

EC₅₀ (5 min) *Photobacterium phosphoreum* 115 ppm Microtox test (2).

Environmental fate

Degradation studies

Cyclohexanol was degraded aerobically and anaerobically by denitrifying *Pseudomonas* spp.. Complete oxidation occurred under aerobic conditions, while degradation under anaerobic conditions resulted in the production of phenol, 40% of which accumulated in the medium and 60% was completely degraded to carbon dioxide (3,4). Biodegradable (5).

Abiotic removal

Evaporation rate relative to *n*-butyl-acetate which has been assigned a value of 1 at 25°C is 0.05 (6).

Mammalian & avian toxicity

Acute data

LD₅₀ oral rat, rabbit 2060-2200 mg kg⁻¹ (7,8).

LD₅₀ subcutaneous mouse 2480 mg kg⁻¹ (9).

LD₅₀ intravenous mouse 272 mg kg⁻¹ (10).

LD₅₀ intramuscular mouse 1000 mg kg⁻¹ (11).

Sub-acute and sub-chronic data

Intraperitoneal ♀ Sprague-Dawley rats (2 wk) ≥1.5 g kg⁻¹ caused renal tubular injury as evidenced by an increase in β₂-microglobulinuria. Highest dose caused the renal concentrating ability to be depressed (12).

Teratogenicity and reproductive effects

Mice were dosed with 1% cyclohexanol in food. ♂ animals showed slightly inhibited growth and ♀ animals showed considerably inhibited growth (first generation). Growth curve for second generation mice was normal (13).

Irritancy

Produces moderate and severe irritation and reversible corneal injury in rabbit eyes (14).

Dermal rabbit (24 hr) 15 mg caused mild irritation (15).

2 mg instilled into rabbit eye caused severe irritation (16).

Other effects

Other adverse effects (human)

In man cyclohexanol produces narcotic effects, headaches and eye, nose and throat irritation. Contact with skin produces irritation and absorption sufficient to produce tremor and hypothermia. Can be absorbed through the skin in toxic amounts (17).

Any other adverse effects

Inhalation of high concentrations of cyclohexanol vapour produced intoxication, lachrymation, incoordination, narcosis and convulsions in rabbits, accompanied by degeneration of the brain, heart, liver and kidneys (17).

Legislation

Maximum permissible concentration in domestic water in former USSR 0.5 mg l⁻¹. No effect dose for domestic water as determined in former USSR from mammalian toxicity tests 0.025 mg kg⁻¹ (18).

Other comments

Metabolite of cyclamate (19).

Reviews on experimental toxicology and human health effects listed (20).

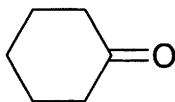
Potential for degradation by gasoline degrading bacteria *Pseudomonas* spp., *Alcaligenes* spp., *Nocardia* spp. and *Micrococcus* spp. is discussed (21).

Physical and chemical properties, toxicity and hazards of cyclohexanol and French regulations pertinent to its use (22).

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C509 cyclohexanone



C₆H₁₀O

Mol. Wt. 98.14

CAS Registry No. 108-94-1

Synonyms pimelic ketone; ketohexamethylene; Nadone; NCI-C55005

EINECS No. 203-631-1

RTECS No. GW 1050000

Uses Used in the manufacture of adipic acid and caprolactam, for the synthesis of nylon. Solvent for a number of substances including resins, nitrocellulose, rubber, shellac and waxes.

Physical properties

M. Pt. -47°C (99.8% pure) **B. Pt.** 155.6°C **Flash point** 46°C (closed cup) **Specific gravity** 0.943 at 20°C with respect to water at 4°C **Partition coefficient** log P_{ow} 0.81 **Volatility** v.p. 6.2 mmHg at 30°C ; v.den. 3.4 **Solubility** Water: 150 g l⁻¹ at 10°C; 50 g l⁻¹ at 30°C. Organic solvents: diethyl ether, ethanol and common organic solvents

Occupational exposure

FR-VME 25 ppm (100 mg m⁻³)

JP-OEL 25 ppm (100 mg m⁻³)

SE-LEVL 25 ppm (100 mg m⁻³)

UK-LTEL 25 ppm (102 mg m⁻³)

SE-STEL 50 ppm (200 mg m⁻³)

UK-STEL 100 ppm (408 mg m⁻³)

US-TWA 25 ppm (100 mg m⁻³)

UN No. 1915 HAZCHEM Code 3 $\frac{+}{+}$ Conveyance classification flammable liquid

Supply classification harmful

Risk phrases Flammable – Harmful by inhalation (R10, R20)

Safety phrases Keep out of reach of children (if sold to general public) – Avoid contact with the eyes (S2, S25)

Ecotoxicity

Fish toxicity

LC₅₀ (96 hr) fathead minnow 527 mg l⁻¹ (1).

Invertebrate toxicity

EC₅₀ (48 hr) *Daphnia magna* 820 mg l⁻¹ (2).

Cell multiplication inhibition test *Pseudomonas putida* 180 mg l⁻¹, *Scenedesmus quadricauda* 370 mg l⁻¹, *Entosiphon sulcatum* 545 mg l⁻¹ and *Microcystis aeruginosa* 52 mg l⁻¹ (3,4).

EC₅₀ (5 min) *Photobacterium phosphoreum* 18.7 ppm Microtox test (5).

Toxicity to other species

LD_{Lo} subcutaneous frog 1900 mg kg⁻¹ (6).

Environmental fate

Degradation studies

Adapted activated sludge, product as sole carbon source: COD 90%, 30.0 mg COD dry inoculum⁻¹ hr⁻¹ wastewater treatment (6).

Confirmed biodegradable (7).

Abiotic removal

Evaporation rate relative to *n*-butyl-acetate, which has been assigned a value of 1 at 25°C, is 0.30 (8).

Activated carbon adsorbability: 0.134 g g⁻¹C, 66.8% reduction, influent: 1000 mg l⁻¹ effluent 332 mg l⁻¹ (9).

Mammalian & avian toxicity

Acute data

LD₅₀ oral rat, mouse 1400, 1535 mg kg⁻¹, respectively (10,11).

LC₅₀ (4 hr) inhalation rat 8000 ppm (12).

LD₅₀ subcutaneous rat 2170 mg kg⁻¹ (13).

Carcinogenicity and chronic effects

Oral F344 rats, C57BL/6/C3H mice (2-yr) 3300 and 6500 ppm (rats); 6500 and 13,000 ppm (♂ mice); and 6500, 13,000 and 25,000 ppm (♀ mice) in drinking water. No statistically significant incidence of neoplasms in treated rats compared to controls. Mice had a statistically significant incidence of lymphomas-leukaemias in ♀ given 6500 ppm but not the higher dose. ♂ Mice given 6500 ppm had an increased incidence of hepatocellular adenomas and carcinomas (50% compared to 32% in controls). The incidence was 37% in ♂ mice given 13,000 ppm. Results indicate the evidence for carcinogenic activity is marginal and the effect if any is weak (14).

Teratogenicity and reproductive effects

Gavage pregnant ICR/SIM mice (gestation days 8-12). The toxic dose selected caused either up to 10% mortality or other sign of clinical toxicity, or was 10 g kg⁻¹, for compounds that produced no toxicity in preliminary tests. Chernoff/Kavlock developmental toxicity screen for teratogens and embryotoxins positive (15).

Inhalation pregnant rats (5 to 20 days gestation) 100, 250 or 500 ppm 7 hr day⁻¹. No significant differences between treated animals and controls for foetal weight, resorption site, foetal death or sex ratio. No significant incidence of malformations. Slight increase in numbers of rudimentary ribs. No significant incidence of skeletal malformations (16).

Metabolism and toxicokinetics

In rabbits and rats the major metabolic pathway is via reduction to cyclohexanol and conjugation to form glucuronides (17).

Irritancy

Severe skin and eye irritant. Irritation to human eyes has been observed after 3-5 min exposure to 50-75 ppm (13). Contact with the pure liquid to rabbits eyes caused marked irritation and corneal damage. Cyclohexanone is able to defat the skin and prolonged or repeated contact may cause irritation and dermatitis. Pure cyclohexanone liquid causes severe irritation to rabbit skin (18).

Sensitisation

Cyclohexanone has been implicated in causing allergic sensitisation in workers producing caprolactam (18).

Genotoxicity

Salmonella typhimurium equivocal results have been obtained. Other mutagenicity studies have proved negative with *Drosophila melanogaster*. In mammalian *in vitro* studies, cyclohexanone has been shown to damage DNA or chromosomes; other genotoxic assays have given negative results (18).

Salmonella typhimurium TA98 and TA100 with metabolic activation positive (19).

In vitro human peripheral lymphocytes induced chromatid and chromosomal aberrations and was cytogenic (20).

In vitro mouse lymphoma L-5178Y tk⁺/tk⁻ with and without metabolic activation negative (21).

Other effects

Other adverse effects (human)

A group of 75 Romanian workers exposed to cyclohexanone in a furniture factory and 85 matched controls submitted to a clinical examination and gave samples for the identification of biological exposure markers, underwent motor nerve conduction velocity and neurobehavioural tests, and completed a questionnaire which included questions about alcohol consumption. On the basis of the results it was proposed that the 6-hr permissible exposure limit for cyclohexanone be reduced to 150 mg m⁻³ (22).

Any other adverse effects

Rats and mice in acute studies (high doses) exhibit narcosis, anaesthesia and respiratory difficulties (18,23,24).

Legislation

Maximum permissible concentration in domestic water in former USSR 0.2 mg l⁻¹ (25).

Other comments

Experimental toxicology, hazards and human health effects reviewed (26,27).

Degradation and utilisation of cyclohexane by *Aureobasidium* sp. KUFI-6N has been reviewed (28).

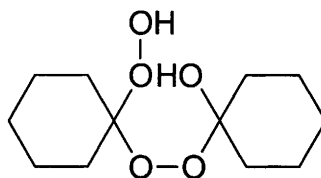
Physical and chemical properties, hazards and current French legislation reviewed (29).

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c510 cyclohexanone hydroperoxide



C₁₂H₂₂O₅

Mol. Wt. 246.30

CAS Registry No. 78-18-2

Synonyms 1-[(1-hydroperoxycyclohexyl)dioxy]-cyclohexanol, 1-hydroperoxycyclohexyl 1-hydroxycyclohexyl peroxide; 1-hydroxy-1'-hydroperoxydicyclohexyl peroxide

EINECS No. 201-091-1

RTECS No. GV 9570000

Uses Component of catalysts used for curing epoxy resin polyesters. Used in polyolefin blends to improve compatibility. In catalysts for polymerisation of fluorine-containing methacrylates. In catalysts for cross-linking unsaturated polyesters.

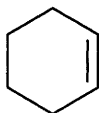
Other comments

Reviews on experimental toxicology and human health effects listed (1).

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C511 cyclohexene



C₆H₁₀

Mol. Wt. 82.15

CAS Registry No. 110-83-8

Synonyms benzenetetrahydride; hexanaphthylene; tetrahydrobenzene; 1,2,3,4-tetrahydrobenzene

EINECS No. 203-807-8

RTECS No. GW 2500000

Uses Alkylation component in the manufacture of adipic acid, maleic acid, hexahydrobenzoic acid and aldehyde. Used in the preparation of butadiene in laboratory. Used in oil extraction. Inorganic synthesis. Catalyst solvent.

Occurrence In coal tar.

Physical properties

M. Pt. -104°C B. Pt. 83°C Flash point -11.6°C Specific gravity 0.81 at 20°C with respect to water at 4°C

Volatility v.p. 160 mmHg at 38°C

Solubility Water: 213 mg l⁻¹ at 20°C. Organic solvents: acetone, benzene, diethyl ether, ethanol

Occupational exposure

DE-MAK 300 ppm (1000 mg m⁻³)

FR-VME 300 ppm (1015 mg m⁻³)

UK-LTEL 300 ppm (1020 mg m⁻³)

US-TWA 300 ppm (1010 mg m⁻³)

UN No. 2256 HAZCHEM Code 3/E Conveyance classification flammable liquid

Ecotoxicity

Fish toxicity

Young coho exposed to ≥100 ppm for 96 hr in artificial sea water at 8°C suffered no significant fatality (1).

Invertebrate toxicity

EC₅₀ (48 hr) *Daphnia magna strauss* 720 mg l⁻¹ (2).

Cell multiplication inhibition test *Pseudomonas putida* 17 mg l⁻¹ (3).

Environmental fate

Degradation studies

Readily biodegradable to cyclohexanone (4).

Mammalian & avian toxicity

Acute data

Laboratory animals are seriously affected after inhaling 8850 ppm cyclohexene; lethal dose 14,800 ppm in single exposure studies (duration unspecified) (5).

Metabolism and toxicokinetics

Hydroxylation of cyclohexene at the allylic position takes place in mammals. Small amounts of 2-cyclohexene-1-one metabolite was excreted by rats (6).

Genotoxicity

Escherichia coli loss of reproduction and breaks in the DNA (7).

Legislation

Maximum permissible concentration in domestic water in former USSR 0.02 mg l⁻¹ (8).

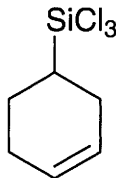
Other comments

Reviews on experimental toxicology and human health effects listed (9).

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8. *Russian Toxicological Data for Chemicals in Sources of Drinking Water* 1978, Technical Note No. 20, Central Water Planning Unit, Reading, UK.
9. *ECETOC Technical Report No. 71* 1996, European Centre for Ecotoxicology and Toxicology of Chemicals, 4 Avenue E. Van Nieuwenhuyse (Bte 6), B-1160 Brussels, Belgium

c512 3-cyclohexenyltrichlorosilane



C₆H₉Cl₃Si

Mol. Wt. 215.58

CAS Registry No. 10137-69-6

Synonyms trichloro-(3-cyclohexenyl)silane; 3-cyclohexenyltrichlorosilane

EINECS No. 233-377-7

RTECS No. VV 2800000

Physical properties

B. Pt. 202 °C Flash point 93 °C Specific gravity 1.263 at 25°C with respect to water at 25°C

Occupational exposure

UN No. 1762 HAZCHEM Code 4XE Conveyance classification corrosive substance

Mammalian & avian toxicity

Acute data

LD₅₀ oral rat 2830 mg kg⁻¹ (1).

LD₅₀ dermal rabbit 630 mg kg⁻¹(1).

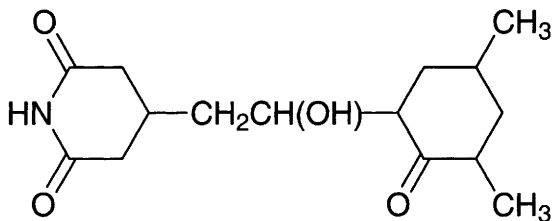
Irritancy

Dermal rabbit (24 hr) 5 mg caused severe irritation and 250 µg instilled into rabbit eye caused severe irritation (2).

References

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C513 cycloheximide



C₁₅H₂₃NO₄

Mol. Wt. 281.35

CAS Registry No. 66-81-9

Synonyms 4-[2-(3,5-dimethyl-2-oxocyclohexyl)-2-hydroxyethyl]-2,6-piperidinedione; 3-[2-(3,5-dimethyl-2-oxocyclohexyl)-2-hydroxyethyl]glutarimide; Acti-Dione

EINECS No. 200-636-0

RTECS No. MA 4375000

Uses Antibiotic and superseded plant pathogen fungicide.

Occurrence Obtainable from *Streptomyces griseus*.

Physical properties

M. Pt. 119.5-121°C **Partition coefficient** log P_{ow} 0.55

Solubility Water: 21 g l⁻¹ at 2 °C. Organic solvents: amyl acetate, chloroform, diethyl ether, ethanol, isopropanol

Mammalian & avian toxicity

Acute data

LD₅₀ oral rat 2 mg kg⁻¹ (1).

LD₅₀ oral mouse 133 mg kg⁻¹ (1).

LD₅₀ oral guinea pig 65 mg kg⁻¹ (1).

LD₅₀ oral monkey 60 mg kg⁻¹ (1).

LD₅₀ intravenous mouse 150 mg kg⁻¹ (2).

Irritancy

Dermal rabbit (24 hr) 5 mg caused irritation and 1% instilled into rabbit eye caused moderate irritation (3).

Sensitisation

Prolonged or repeated exposure may cause allergic reactions in certain sensitive individuals (3).

Genotoxicity

Inhibits DNA synthesis in human myeloblastic leukaemia cell line (ML-1) (4).

Legislation

Limited under EC Directive on Drinking Water Quality 80/778/EEC. Pesticides: maximum admissible concentration $0.1 \mu\text{g l}^{-1}$ (5).
WHO Toxicity Class Ia (6).

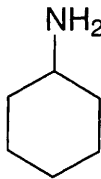
Other comments

Inhibits protein synthesis (2).

References

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2. *The Merck Index* 12th ed., 1996, Merck & Co., Inc., Whitehouse Station, NJ, USA.
3. Lenga, R. E. *The Sigma-Aldrich Library of Chemical Safety Data* 2nd ed., 1988, Sigma-Aldrich, Milwaukee, USA.
4. Craig, R. W. et al *Cancer Res.* 1984, **44**, 2421-2429.
5. *EC Directive Relating to the Quality of Water Intended for Human Consumption* 1982, 80/778/EEC, Office for Official Publications of the European Communities, 2 rue Mercier, L-2985 Luxembourg.
6. *The WHO Recommended Classification of Pesticides by Hazard and Guidelines to Classification* 1998-1999 WHO/PCS/98.21

C514 cyclohexylamine



$\text{C}_6\text{H}_{13}\text{N}$

Mol. Wt. 99.18

CAS Registry No. 108-91-8

Synonyms hexahydroaniline; aminocyclohexane; cyclohexanamine

EINECS No. 203-629-0

RTECS No. GX 0700000

Uses Used in organic synthesis. Manufacture of plasticisers, corrosion inhibitors, rubber chemicals, dyestuffs, emulsifying agents, dry cleaning soaps, acid gas absorbants and insecticides.

Physical properties

M. Pt. -17°C B. Pt. 134°C Flash point 32°C Specific gravity 0.863 at 20°C with respect to water at 4°C

Volatility v.den. 3.42

Solubility Water: miscible. Organic solvents: acetone, benzene, diethyl ether, ethanol

Occupational exposure

DE-MAK 10 ppm (41 mg m^{-3})

FR-VME 10 ppm (40 mg m^{-3})

SE-LEVL 5 ppm (20 mg m^{-3})

SE-STEL 10 ppm (40 mg m^{-3})

UK-LTEL 10 ppm (41 mg m^{-3})

US-TWA 10 ppm (41 mg m^{-3})

UN No. 2357 HAZCHEM Code 3WE Conveyance classification corrosive substance, danger of fire (flammable liquid)

Supply classification corrosive

Risk phrases Flammable – Harmful in contact with skin and if swallowed – Causes burns (R10, R21/22, R34)

Safety phrases Keep locked up and out of the reach of children (if sold to general public) – Wear suitable protective clothing, gloves and eye/face protection – In case of accident or if you feel unwell, seek medical advice immediately (show label where possible) (S1/2, S36/37/39, S45)

Ecotoxicity

Invertebrate toxicity

EC₅₀ *Daphnia magna* 49 mg l⁻¹ (1).

Toxicity threshold (cell multiplication inhibition test) *Pseudomonas putida* 420 mg l⁻¹ (1).

Environmental fate

Nitrification inhibition

75% inhibition NH₃ oxidation – activated sludge at 230 mg l⁻¹ (2).

Carbonaceous inhibition

1500 mg l⁻¹ completely inhibited growth of activated sludge bacteria; none of the strains were able to utilise cyclohexylamine as a carbon source (3).

Abiotic removal

Evaporation rate relative to *n*-butyl-acetate which has been assigned a value of 1 at 25°C is 0.734 (4).

Mammalian & avian toxicity

Acute data

LD₅₀ oral rat 400-800 mg kg⁻¹ (5% solution) (5).

LC₅₀ (16 hr) inhalation rat 1000 ppm (6).

LD₅₀ intraperitoneal rat 200 mg kg⁻¹ (6).

Teratogenicity and reproductive effects

0.5% cyclohexylamine in diet led to growth retardation and embryonal death in mice (the experiment included six generations). Growth retardation was more pronounced in ♀ mice (7).

No significant teratogenic or embryotoxic effects in rhesus monkeys treated with 25-75 mg kg⁻¹ (route unspecified) for various four-day periods during days 20-45 of gestation (8).

Metabolism and toxicokinetics

Anaerobic deamination of cyclohexylamine by the intestinal microorganisms in rabbits given 0.34% cyclohexylamine hydrochloride in drinking water (9).

Major metabolites in rats are 3- and 4-aminocyclohexanol (10).

Not readily metabolised because of its strong basicity. Hydroxylated and deaminated metabolites identified in urine of humans, rats, guinea pigs and rabbits include cyclohexanol, *trans*-cyclohexane-1,2-diol, *cis*-3-, *trans*-3-, *cis*-4- and *trans*-4-hydroxycyclohexylamine and *N*-cyclohexylhydroxylamine (11).

Cyclohexylamine, like hydroxylated compounds are retained *in vivo* as fatty acid conjugates in lipid containing tissues of rats (11).

Irritancy

One drop of a 50% aqueous solution instilled into the conjunctival sac of the rabbit eye caused complete destruction of the eye. 25% solution was severely irritating to skin of human volunteers (6).

Rats and guinea pigs exposed to 150 ppm for 70 hr suffered respiratory tract and eye irritation, and corneal opacities (5).

Sensitisation

25% solution caused slight sensitisation in human volunteers (6).

Genotoxicity

Salmonella typhimurium TA100, TA1535, TA1537, TA98 with and without metabolic activation negative (12).

In vitro unscheduled DNA synthesis assay in rat hepatocytes negative (13).

In vitro human lymphocytes sister chromatid exchange without metabolic activation positive; both positive and negative results reported for chromosomal aberrations. Syrian hamster embryo cell transformation without metabolic activation positive. Induced chromosomal aberrations in hamster lymphocytes but not bone marrow cells *in vivo*. Did not induce dominant lethal mutations in rats, equivocal results in mice (14).

Other effects

Other adverse effects (human)

Three non-fatal human exposures to cyclohexylamine vapour caused strong irritation, nausea and vomiting (6).

Other comments

Cyclohexylamine 10 g l⁻¹ inhibited the growth of various fungi in culture, including *Pythium ultimum*, *Alternaria radicina*, *Cylindrocarpum destructans*, *Gliocladium virens*, *Paecilomyces farinosus*, *Phomopsis sclerotoides*, *Trichoderma viride*, *Phytophthora citricola* and *Rhizoctonia solani* (15).

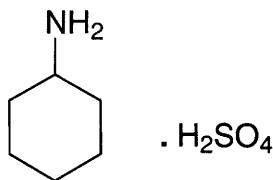
Toxicity reviewed (16).

Experimental toxicology and human health effects reviewed (17).

References

1. Bringmann, G. et al *Z. Wasser/Abwasser Forsch.* 1982, 15(1), 1-6.
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4. *Texaco Chemical UK* 1992, 195 Knightsbridge, London, UK.
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6. Mallette, F. S. et al *Arch. Ind. Hyg. Occup. Med.* 1952, 5, 311-317.
7. Kroes, R. et al *Toxicology* 1977, 8, 285.
8. *IARC Monograph* 1980, 22.
9. Takeida, T. et al *Agric. Biol.* 1979, 43, 25.
10. Roberts, A. et al *Toxicol. Appl. Pharmacol.* 1989, 98(2), 216-229.
11. Leighty, E. G. et al *Food Chem. Toxicol.* 1983, 21, 251-254.
12. Mortelmans, K. et al *Environ. Mutagen.* 1986, 8(Suppl. 7), 1-119.
13. Brusick, D. et al *Environ. Mol. Mutagen.* 1989, 14(3), 188-199.
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15. Gindrat, D. *Experientia* 1981, 37, 1163-1165.
16. Randall, D. J. *Acute Toxic. Data* 1990, 1(1), 65-66.
17. *BIBRA Toxicology Profiles* 1991, British Industrial Biological Research Association, Carshalton, UK

c515 cyclohexylamine sulfate



C₆H₁₅NSO₄

Mol. Wt. 197.26

CAS Registry No. 19834-02-7

Synonyms CHA-sulfate; CHS

EINECS No. 243-360-6

RTECS No. GX 1800000

Mammalian & avian toxicity

Acute data

TD_{Lo} oral rat 11 g kg⁻¹ (1).

TD_{Lo} oral mouse 42 g kg⁻¹ (2).

Teratogenicity and reproductive effects

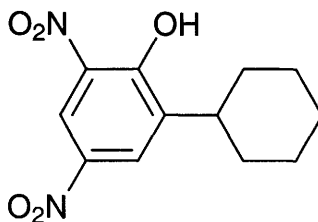
Oral administration of 22 to 178 mg kg⁻¹ day⁻¹ to Wistar rats did not adversely affect ♀ or ♂ fertility, and no embryotoxic effects were reported (3).

No dominant lethal mutation or pre-implantation effects observed in mice (4).

References

1. Price, J. M. et al *Science* 1970, **167**, 1131-1132.
2. *Toxicology* 1977, **8**, 285.
3. Khera, K. S. et al *Toxicol. Appl. Pharmacol.* 1971, **18**, 263-269.
4. Loreke, D. et al *Humangenetik* 1975, **26**(3), 199-205

c516 2-cyclohexyl-4,6-dinitrophenol



C₁₂H₁₄N₂O₅

Mol. Wt. 266.25

CAS Registry No. 131-89-5

Synonyms 2,4-dinitro-6-cyclohexylphenol; dinex

EINECS No. 205-042-5

RTECS No. SK 6650000

Uses Insecticide, especially in control of citrus red mite. Now superseded.

Physical properties

M. Pt. 106.5-107.5°C

Solubility Organic solvents: benzene, dimethylformamide, petroleum oils 2.5-6%

Occupational exposure

Supply classification toxic

Risk phrases Toxic by inhalation, in contact with skin and if swallowed (R23/24/25)

Safety phrases Keep out of reach of children (if sold to general public) – Keep away from food, drink and animal feeding stuffs – In case of accident or if you feel unwell, seek medical advice immediately (show label where possible) (S2, S13, S45)

Ecotoxicity

Invertebrate toxicity

An unidentified *Coccobacillus* isolated from a molluscicide test chamber containing *Australorbis glabratus* was capable of growing in medium containing 2-cyclohexyl-4,6-dinitrophenol as the sole nitrogen source (1).

Environmental fate

Abiotic removal

Reaction with photochemically generated hydroxyl radicals in the atmosphere (calc.) $t_{1/2}$ 6.8 hr (2).

Adsorption and retention

Release to the soil will result in strong adsorption and little leaching is expected. Estimated soil adsorption coefficient of 3.9 (3).

Expected to adsorb to sediments. Accumulation of un-ionised 2-cyclohexyl-4,6-dinitrophenol will be significant although the ionised species is not expected to accumulate (2).

Mammalian & avian toxicity

Acute data

LD₅₀ oral mouse, rat 50, 65 mg kg⁻¹, respectively (4,5).

LD_{Lo} dermal guinea pig 1000 mg kg⁻¹ (6).

LD₅₀ intraperitoneal mouse 25 mg kg⁻¹ (7).

LD_{Lo} intravenous pigeon 7 mg kg⁻¹ (8).

LD₅₀ intravenous dog 8 mg kg⁻¹ (8).

Metabolism and toxicokinetics

Toxicity mechanism is via stimulation of oxidative metabolism in cell mitochondria. Interferes with normal coupling of carbohydrate oxidation to phosphorylation (9).

Irritancy

Dermal rabbit (9 day) 105 mg intermittent dosing caused moderate irritation (10).

Other effects

Any other adverse effects

Toxic to liver, kidney and nervous system (9).

Legislation

Limited under EC Directive on Drinking Water Quality 80/778/EEC. Pesticides: maximum admissible concentration 0.1 µg l⁻¹ (11).

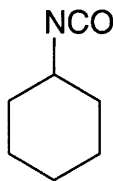
Other comments

Toxicity and hazards reviewed (12).

References

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2. GEMS: Graphical Exposure Modeling System Fate of Atmospheric Pollutants 1986, Office of Toxic Substances, USEPA, Washington, DC, USA.
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4. *Agric. Res. Serv.* 1966, **20**, 9, USDA Information Memorandum.
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6. *Pest. Chem. Off. Comp.* 1966, 417.
7. *Biochem. Pharmacol.* 1969, **18**, 1389.
8. *Arch. Int. Pharmacol. Ther.* 1935, **50**, 20.
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12. *Dangerous Prop. Ind. Mater. Rep.* 1987, **7**(1), 48-50

C517 cyclohexyl isocyanate



C₇H₁₁NO

Mol. Wt. 125.17

CAS Registry No. 3173-53-3

Synonyms

EINECS No. 221-639-3

RTECS No. NQ 8650000

Uses In preparation of the oral antidiabetic agent acetoexamide (1).

Physical properties

M. Pt. <-80°C B. Pt. 168-170°C Flash point 48°C Specific gravity 0.980 at 20°C with respect to water at 4°C
Volatility v.p. 2 mmHg at 25°C

Occupational exposure

SE-LEVL 0.005 ppm

SE-CEIL 0.01 ppm

UK-LTEL MEL 0.02 mg m⁻³ (as NCO)

UK-STEL MEL 0.07 mg m⁻³ (as NCO)

UN No. 2488 HAZCHEM Code 3W Conveyance classification toxic substance

Mammalian & avian toxicity

Acute data

LD₅₀ intravenous mouse 18 mg kg⁻¹ (2).

LD₅₀ intraperitoneal mouse 13 mg kg⁻¹ (3).

Other effects

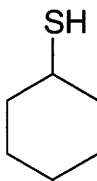
Any other adverse effects

Inhibits acetyl cholinesterase activity in humans (4).

References

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2. U.S. Army Armament Res. and Dev. Command, Chemical Systems Laboratory, (Aberdeen Proving Ground MD 21010, USA) NX#04502.
3. Natl. Cancer. Inst. Screening Program Data Summary, *Developmental Therapeutics Program* Jan 1986.
4. Baur, X. et al *Eur. J. Respiratory Diseases* 1982, 62(123), 128-129

C518 cyclohexyl mercaptan



$C_6H_{12}S$

Mol. Wt. 116.23

CAS Registry No. 1569-69-3

Synonyms cyclohexanethiol

EINECS No. 216-378-7

RTECS No. GV 7525000

Physical properties

B. Pt. 158-160°C Flash point 43°C Specific gravity 0.095

Occupational exposure

UN No. 3054 HAZCHEM Code 3WE Conveyance classification flammable liquid

Mammalian & avian toxicity

Acute data

LD₅₀ oral rat 558 mg kg⁻¹ (1).

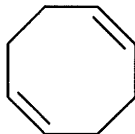
Irritancy

Dermal rabbit (24 hr) 500 mg caused severe irritation and 500 mg instilled into rabbit eye caused mild irritation (1). High concentrations are extremely destructive to tissues of the mucous membranes and upper respiratory tract, eyes and skin (1).

References

1. Lenga, R. E. *The Sigma-Aldrich Library of Chemical Safety Data* 2nd ed., 1988, Sigma-Aldrich, Milwaukee, USA

C519 1,5-cyclooctadiene



C_8H_{12}

Mol. Wt. 108.18

CAS Registry No. 111-78-4

Synonyms

EINECS No. 203-907-1

Physical properties

M. Pt. -69°C B. Pt. 149-150°C Specific gravity 0.8811 at 20°C with respect to water at 4°C
Partition coefficient log P_{ow} 3.384

Occupational exposure

UN No. 2520 HAZCHEM Code 3 **☒** Conveyance classification flammable liquid

Ecotoxicity

Fish toxicity

LC₅₀ (24 hr) goldfish 14 mg l⁻¹ (1).

Mammalian & avian toxicity

Metabolism and toxicokinetics

Metabolised to dihydroxycyclooctylmercapuric acids in rats and rabbits (2).

Genotoxicity

Salmonella typhimurium TA1538, TA98, TA100 with and without metabolic activation negative (3).

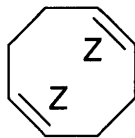
Escherichia coli WP₂, WP₂ uvrA with and without metabolic activation negative (3).

Saccharomyces cerevisiae with and without metabolic activation negative. Did not induce chromosome damage in rat liver cell lines (3).

References

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2. Waring, R. H. *Xenobiotica* 1971, **1**(3), 303-308.
3. Dean, B. J. et al *Mutat. Res.* 1985, **153**, 57-77

C520 (Z,Z)-1,5-cyclooctadiene



C₈H₁₂

Mol. Wt. 108.18

CAS Registry No. 1552-12-1

Synonyms *cis,cis*-1,5-cyclooctadiene

EINECS No. 216-291-4

RTECS No. GX 9620000

Uses Preparation of flame retardants.

Physical properties

M. Pt. -70°C B. Pt. 151-152°C Specific gravity 0.8818 at 25°C with respect to water at 4°C

Volatility v.p. 5 mmHg at 25°C

Solubility Organic solvents: benzene, carbon tetrachloride

Occupational exposure

UN No. 2520 HAZCHEM Code 3 **☒** Conveyance classification flammable liquid

Ecotoxicity

Fish toxicity

LC₅₀ (24 hr) goldfish 14 mg l⁻¹ (1).

Mammalian & avian toxicity

Acute data

LD₅₀ oral rat 2.7 mg kg⁻¹ (1).

Metabolism and toxicokinetics

Metabolised in rats and rabbits to dihydrocyclooctylmercapturic acid (2).

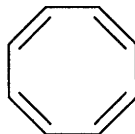
Irritancy

Dermal rabbit (duration unspecified) 2640 mg caused severe irritation. Dermal rabbit (31 day) 20 g (total dose) intermittent exposure caused severe irritation; dermal mouse (12 day) 100% solution caused severe irritation; and 88 mg instilled into rabbit eye caused mild irritation (3).

References

1. *Shell Industrie Chemicalien Gids* 1975, Shell Netherlands Chemie, Wasseraarseweg 80, Netherlands.
2. Waring, R. H. *Xenobiotica* 1971, 1(3), 303.
3. *Br. J. Ind. Med.* 1968, 25, 75

c521 cyclooctatetraene



C₈H₈

Mol. Wt. 104.15

CAS Registry No. 629-20-9

Synonyms

EINECS No. 211-080-3

Physical properties

M. Pt. -7°C B. Pt. 140.6°C Flash point <22°C Volatility v.p. 7.9 mmHg at 25°C

Occupational exposure

UN No. 2358 HAZCHEM Code 3ME Conveyance classification flammable liquid

Ecotoxicity

Bioaccumulation

Soil sorption coefficient K_{oc} at 20°C is estimated to be 5.19E + 02 (1).

References

1. Jeng, C. Y. et al *Pollut. Eng.* 1992, 24(12), 54-60

c522 cyclopentane



C₅H₁₀

Mol. Wt. 70.13

CAS Registry No. 287-92-3

Synonyms pentamethylene

EINECS No. 206-016-6

RTECS No. GY 2390000

Uses Laboratory reagent.

Occurrence Occurs in petroleum, found in petroleum ether fractions.

Physical properties

M. Pt. 94.4°C B. Pt. 49.3°C Flash point -7°C Specific gravity 0.746 at 20°C with respect to water at 4°C

Volatility v.p. 400 mmHg at 31°C ; v.den. 2.42

Solubility Organic solvents: acetone, benzene, diethyl ether, ethanol

Occupational exposure

FR-VME 600 ppm (1720 mg m⁻³)

US-TWA 600 ppm (1720 mg m⁻³)

UN No. 1146 HAZCHEM Code 3/E Conveyance classification flammable liquid

Supply classification highly flammable

Risk phrases Highly flammable – Harmful to aquatic organisms, may cause long-term adverse effects in the aquatic environment (R11, R52/53)

Safety phrases Keep out of reach of children (if sold to general public) – Keep container in a well ventilated place – Keep away from sources of ignition – No smoking – Do not empty into drains – Take precautionary measures against static discharges – Avoid release to the environment. Refer to special instructions/safety data sheet (S2, S9, S16, S29, S33, S61)

Mammalian & avian toxicity

Acute data

Lethal concentrations for mice in air 38,000 ppm (duration unspecified) (1).

Irritancy

Irritation of skin, burning sensation with blistering (species unspecified) (2).

Other effects

Other adverse effects (human)

Workers in an Italian shoe factory suffered polyneuropathy from exposure to solvents containing some cyclopentane (up to 18%) (3).

Any other adverse effects

Narcosis. A central nervous system depressant (3).

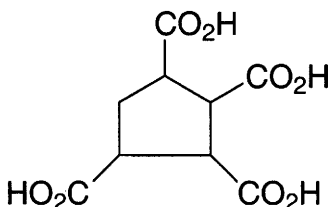
Other comments

Reviews on human health effects, experimental toxicology and physico-chemical properties listed (4).

References

1. Spector, W. S. *Handbook of Toxicology* 1956, Vol. 1, 330, Saunders, Philadelphia, PA, USA.
2. Oettel, H. *Arch. Exp. Pathol. Pharmacol.* 1936, 83, 641.
3. Abritti, et al *Brit. J. Ind. Med.* 1976, 35, 92.
4. *ECETOC Technical Report No. 71* 1996, European Centre for Ecotoxicology and Toxicology of Chemicals, 4 Avenue E. Van Nieuwenhuyse (Bte 6), B-1160 Brussels, Belgium

c523 cyclopentane-1,2,3,4-tetracarboxylic acid



$C_9H_{10}O_8$

Mol. Wt. 246.17

CAS Registry No. 51365-15-2

Synonyms

Uses Chemical intermediate. Detergent builder. Cross-linking agent. Textiles. Used in the manufacture of textiles.

Physical properties

M. Pt. 195°C

Ecotoxicity

Invertebrate toxicity

Reproductive effects on *Daphnia magna* but not toxic up to concentrations of 100 mg l⁻¹ (1).

Environmental fate

Degradation studies

Biodegradability equivocal (2).

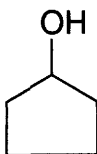
Other comments

Dianhydride m. pt. 222°C.

References

1. Nusch, E. A. Z. *Wasser/Abwasser Forsch.* 1974, 7, 85-91 (*Chem. Abstr.* 82, 26650e).
2. Gilbert, P. A. et al *Biotransform Fate Chem. Aquat. Environ., Proc. Workshop* 1979, 34-45 (*Chem. Abstr.* 94, 20131m)

c524 cyclopentanol



$C_5H_{10}O$

Mol. Wt. 86.13

CAS Registry No. 96-41-3

Synonyms cyclopentylalcohol; hydroxycyclopentane

EINECS No. 202-504-8

Uses Perfume and pharmaceutical solvent. Intermediate for dyestuffs, pharmaceuticals and other organics.

Physical properties

M. Pt. $-19^{\circ}C$ B. Pt. $139^{\circ}C$ Flash point $51^{\circ}C$ (99% purity) Specific gravity 0.949

Solubility Organic solvents: acetone, diethyl ether, ethanol

Occupational exposure

UN No. 2244 HAZCHEM Code 3  Conveyance classification flammable liquid

Ecotoxicity

Fish toxicity

LC₅₀ (duration unspecified) golden orfe 1490-1850 mg l⁻¹ (1).

Invertebrate toxicity

EC₅₀ *Daphnia magna* Straus 1295 mg l⁻¹ (2).

Lowest observed effective concentration *Microcystis aeruginosa* 28 mg l⁻¹ (3).

Environmental fate

Degradation studies

Adapted activated sludge product as sole carbon source 97% COD removal at 55 mg COD g dry inoculum⁻¹ hr⁻¹ (4).

Genotoxicity

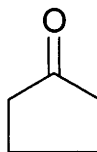
Salmonella typhimurium TA1535, TA100, TA1537, TA1538, TA98 with and without metabolic activation negative (5).

Escherichia coli WP2, WP2 *uvrA*⁻ with and without metabolic activation negative (5).

References

1. Juhnke, V. I. et al *Z. Wasser/Abwasser Forsch.* 1978, **11**(5), 161-164.
2. Bringmann, G. et al *Z. Wasser/Abwasser Forsch.* 1982, **15**(1), 1-6.
3. Bringmann, G. et al *Gwf. Wasser/Abwasser* 1976, 117(9).
4. Pitter, P. *Water Res.* 1976, **10**, 231.
5. McMahon, R. E. et al *Cancer Res.* 1979, **39**, 682-693

C525 cyclopentanone



C₅H₈O

Mol. Wt. 84.12

CAS Registry No. 120-92-3

Synonyms adipic ketone; ketocyclopentane; ketopentamethylene

EINECS No. 204-435-9

RTECS No. GY 4725000

Uses Intermediate for pharmaceuticals, insecticides and rubber chemicals.

Physical properties

M. Pt. -51°C B. Pt. 130-131°C Flash point 30°C (closed cup) Specific gravity 0.9509 at 18°C

Volatility v.den. 2.3

Solubility Organic solvents: acetone, diethyl ether, ethanol

Occupational exposure

UN No. 2245 HAZCHEM Code 3 $\frac{+}{-}$ Conveyance classification flammable liquid

Supply classification irritant

Risk phrases Flammable – Irritating to eyes and skin (R10, R36/38)

Safety phrases Keep out of reach of children (if sold to general public) – Do not breathe vapour (S2, S23)

Ecotoxicity

Invertebrate toxicity

EC₅₀ *Daphnia magna* 1440 mg l⁻¹ (1).

Toxicity threshold *Scenedesmus quadricauda* 370 mg l⁻¹; *Entosiphon sulcatum* 545 mg l⁻¹ (2).

Toxicity to other species

LD_{Lo} subcutaneous frog 3000 mg kg⁻¹ (3).

Environmental fate

Degradation studies

Adapted activated sludge – product as sole carbon source: 95.4% COD removal 57.0 mg COD g dry inoculum⁻¹ hr⁻¹ (4).

Lactone-forming mono-oxygenases metabolic biodegradation (5).

Mammalian & avian toxicity

Acute data

LD₅₀ intraperitoneal mouse 1950 mg kg⁻¹ (6).

Irritancy

A skin and severe eye irritant, 500 mg caused moderate effects to rabbit skin in (24 hr) and 100 mg severe effects to rabbit eye (7).

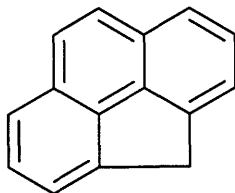
Other comments

Reviews on human health effects, experimental toxicology and physico-chemical properties listed (8).

References

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2. Bringmann, G. et al *Water Res.* 1980, **14**, 231-241.
3. *Arch. Exp. Pathol. Pharmacol.* 1903, **50**, 199.
4. Pitter, P. *Water Res.* 1976, **10**, 231.
5. Griffin, M. et al *Biochem. J.* 1972, **129**, 595.
6. *Comptes Rendus Hebdomadaires des Seances* 1982, **3**, 763.
7. *Food Cosmet. Toxicol.* 1982, **20**, 573.
8. *ECETOC Technical Report No. 71* 1996, European Centre for Ecotoxicology and Toxicology of Chemicals, 4 Avenue E. Van Nieuwenhuysse (Bte 6), B-1160 Brussels, Belgium

C526 4H-cyclopenta[def]phenanthrene



C₁₅H₁₀

Mol. Wt. 190.24

CAS Registry No. 203-64-5

Synonyms 4,5-methylenephenanthrene

EINECS No. 205-905-6

RTECS No. GY 5280000

Physical properties

M. Pt. 113-115°C B. Pt. 353°C

Mammalian & avian toxicity

Carcinogenicity and chronic effects

Single oral dose of 300 mg to ♀ rats caused increased incidence of breast and kidney carcinomas (1).

References

1. Griswold, D. P. Jr. et al *Cancer Res.* 1966, **26**, 619-625

C527 cyclopentene



C₅H₈

Mol. Wt. 68.12

CAS Registry No. 142-29-0

EINECS No. 205-532-9

RTECS No. GY 5950000

Physical properties

M. Pt. -93.3°C B. Pt. 44.24°C Flash point -34°C Specific gravity 0.77199 at 20°C

Occupational exposure

UN No. 2246 HAZCHEM Code 3ME Conveyance classification flammable liquid

Mammalian & avian toxicity

Acute data

LD₅₀ oral rat 1660 mg kg⁻¹ (1).

LD₅₀ dermal rabbit 2130 mg kg⁻¹ (1).

References

1. Smyth, H. F. et al *Am. Ind. Hyg. Assoc. J.* 1969, 30, 470-476

C528 1,3-cyclopentadiene



C₅H₆

Mol. Wt. 66.10

CAS Registry No. 542-92-7

Synonyms cyclopenta-1,3-diene; cyclopentadiene; *p*-pentine; pentole; pyropentylene

RTECS No. GY 1000000

Uses Manufacture of resins. Diels-Alder reagent in the production of sesquiterpenes, synthetic alkaloids, camphors.

Physical properties

M. Pt. -85°C B. Pt. 41.5°C Flash point -3°C (1) Specific gravity 0.8021 at 20°C with respect to water at 4°C
Solubility Organic solvents: miscible with acetic acid, aniline, benzene, carbon tetrachloride, ethanol, ether, liquid petrolatum

Occupational exposure

DE-MAK 75 ppm (210 mg m⁻³)

FR-VME 75 ppm (200 mg m⁻³)

US-TWA 75 ppm (203 mg m⁻³)

Ecotoxicity

Fish toxicity

5 ppm (24 hr) was not acutely toxic to fish (1).

Toxicity to other species

Cyclopentadiene vapour was narcotic in frogs within 10 minutes. Recovery was complete within 70 minutes (2).

Environmental fate

Degradation studies

No methanogenic degradation was observed in enrichment cultures using mineral media inoculated with anaerobic sewage sludge or anoxic aquatic sediments (3).

Mammalian & avian toxicity

Acute data

Subcutaneous rabbit 3.0 ml caused narcosis with fatal convulsions (2).

Other effects

Other adverse effects (human)

Probably moderately toxic by inhalation (4).

Other comments

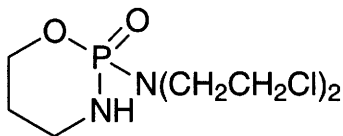
Decomposes violently at high temperatures and pressures. Reacts vigorously on contact with potassium hydroxide.

Health, safety and environmental effects reviewed (5,6).

References

1. Wood, E. M. *The Toxicity of 3,400 Chemicals to Fish* EPA 560/6-87-002, PB 87-200-225, August 1987, United States Environmental Protection Agency, Office of Toxic Substances, Washington, DC, USA.
2. Von Oettingen, W. F. *Toxicity and Potential Dangers of Aliphatic and Aromatic Hydrocarbons* Public Health Bulletin No. 255, 1940.
3. Schink, B. *FEMS Microbiol. Ecol.* 1985, **31**(2), 69-77.
4. *Sax's Dangerous Properties of Industrial Materials* 8th ed., Van Nostrand Reinhold, New York, USA, 1992.
5. *IPCS International Chemical Safety Cards* Office for Official Publications of the European Communities, 2 rue Mercier, L-2985 Luxembourg.
6. *EPA Health and Environmental Effects Documents (HEED)* National Technical Information Service (NTIS), 5285 Port Royal Road, Springfield, Virginia 22161, USA

c529 cyclophosphamide



$C_7H_{15}Cl_2N_2O_2P$

Mol. Wt. 261.09

CAS Registry No. 50-18-0

Synonyms 2-(bis(2-chloroethyl)amino)-1-oxa-3-aza-2-phosphacyclohexane 2-oxide; cyclic *N'*,*O*-propylene ester of *N,N*-bis(2-chloroethyl)phosphorodiamidic acid monohydrate; cyclophosphan; cyclophosphoramidate; 2-(di(2-chloromethyl)amino)-1-oxa-3-aza-2-phosphacyclohexane 2-oxide monobutylate; Cytosan; Endoxan; Genoxal; Neosar; Sendoxan

EINECS No. 200-015-4

RTECS No. RP 5950000

Uses Anti-neoplastic and immunosuppressive agent.

Physical properties

M. Pt. 49-51°C (monohydrate)

Solubility Water: 1 in 25 parts. Organic solvents: carbon tetrachloride, dioxane, ethanol, ethylene glycol

Environmental fate

Degradation studies

It is expected to be removed readily from water bodies by its reactivity with water, proteins and DNA, to form acrolein which is readily biodegradable (1).

Mammalian & avian toxicity

Acute data

LD₅₀ oral rat 94 mg kg⁻¹ (2).

LD₅₀ intravenous mouse 275 mg kg⁻¹ (2).

LD₅₀ intravenous rabbit 130 mg kg⁻¹ (3).

LD₅₀ intravenous guinea pig 400 mg kg⁻¹ (3).

Carcinogenicity and chronic effects

Sufficient evidence for carcinogenicity in humans and animals, IARC classification group 1 (4).

Considerable evidence for increased incidence of bladder and lymphoproliferative or myeloproliferative malignancies in patients using cyclophosphamide (5-7).

Metabolism and toxicokinetics

It is not cytotoxic, but it can be metabolised to aldophosphamide, which can break down to phosphoramidate mustard, which is cytotoxic. The liver mixed-function oxidase system is mainly responsible for its metabolism (8). Carboxycyclophosphamide is the major urinary metabolite and ≈10% is excreted in urine as 4-ketocyclophosphamide. The breakdown of aldophosphamide to phosphoramidate mustard and acrolein is spontaneous, but slow relative to its enzymic oxidation to carboxycyclophosphamide. Certain tumour cells may lack this enzyme explaining why cyclophosphamide appears to be selective. Phosphoramidate mustard is cytotoxic because of its alkylating activity: it causes breaks in guanine bases in DNA (9).

In rats acrolein is converted into 3-hydroxypropyl-mercaptopuric acid, after conjugation with glutathione (10).

Genotoxicity

It has been shown to be a leukaemogen (11-13); as it is metabolised to an alkylating intermediate, this intermediate is of greater significance (6,14).

It has been tested over a wide range of tests both *in vitro* and *in vivo* giving consistently positive reactions. It binds to DNA in kidney, lung and liver of mice and induces dominant lethal mutations, chromosomal aberrations,

micronuclei, sister chromatid exchanges, mutation and DNA changes in rodents treated *in vivo*. In human cells *in vitro* it induced chromosomal aberrations, sister chromatid exchanges and DNA damage. It was also active in bodyfluid assays of urine for humans and rodents exposed *in vivo*, and in a study using rat serum (14). *In vivo* mouse bone marrow micronucleus assay positive (15).

Other effects

Any other adverse effects

Crosses placental barrier and found in breast milk (1).

References

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2. *Toxic. Appl. Pharmacol.* 1962, **4**, 324.
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4. *IARC Monograph* 1987, **Suppl. 7**, 182-184.
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6. *IARC Monograph* 1981, **26**, 165-202.
7. Kinlen, L. J. *Am. J. Med.* 1985, **78**(Suppl. 1A), 44-49.
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9. *Martindale: The Extra Pharmacopoeia* 31st ed., 1996, The Royal Pharmaceutical Society, London, UK.
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12. Greene, M. H. et al *Ann. Int. Med.* 1986, **105**, 360-367.
13. Haas, J. F. et al *Br. J. Cancer* 1987, **55**, 213-218.
14. *IARC Monograph* 1987, **Suppl. 6**, 196-211.
15. Garriott, M. L. et al *J. Appl. Toxicol.* 1988, **8**(2), 141-144

C530 cyclopropane



C₃H₆

Mol. Wt. 42.08

CAS Registry No. 75-19-4

Synonyms trimethylene

EINECS No. 200-847-8

RTECS No. GZ 0690000

Uses Inhalation anaesthetic.

Physical properties

M. Pt. -127°C B. Pt. -33°C Specific gravity 1.879

Solubility Organic solvents: benzene, diethyl ether, ethanol

Occupational exposure

UN No. 1027 (liquified) HAZCHEM Code 2WE (liquified) Conveyance classification flammable gas (liquified)

Supply classification highly flammable

Risk phrases Extremely flammable (R12)

Safety phrases Keep out of reach of children (if sold to general public) – Keep container in a well ventilated place – Keep away from sources of ignition – No smoking – Take precautionary measures against static discharges (S2, S9, S16, S33)

Mammalian & avian toxicity

Acute data

LC_{Lo} (2 hr) inhalation mouse 282 g m⁻³ (1).

Carcinogenicity and chronic effects

Inadequate evidence for carcinogenicity to humans, no adequate data for carcinogenicity to animals, IARC classification group 3 (2).

Genotoxicity

Inadequate data available on genetic and related effects to humans (3).

Not mutagenic to bacteria (4).

Other effects

Any other adverse effects

Fertilised 24-72 hr old chicken eggs incubated in 20-50 vol % cyclopropane for 3-12 hr showed increased ratio of cells in metaphase to cells in prophase and decreased numbers of cells in mitosis (4).

Other comments

Reviews on human health effects, experimental toxicology and physico-chemical properties listed (5).

References

1. *J. Pharmacol. Exp. Ther.* 1936, **58**, 74.
2. *IARC Monograph* 1987, **Suppl. 7**, 93-95.
3. *IARC Monograph* 1987, **Suppl. 6**, 206-209.
4. Snegireff, S. et al *Anaesthesiology* 1971, **34**, 157-162.
5. *ECETOC Technical Report No. 71* 1996, European Centre for Ecotoxicology and Toxicology of Chemicals, 4 Avenue E. Van Nieuwenhuysse (Bte 6), B-1160 Brussels, Belgium

C531 cyclosporin A

C₆₂H₁₁₁N₁₁O₁₂

Mol. Wt. 1202.63

CAS Registry No. 59865-13-3

Synonyms

Uses Immunosuppressant, specifically of T-lymphocytes.

Occurrence Produced by *Tolypocladium inflatum* Gams, formerly designated *Trichoderma polysporum* [Link ex Pers.] Rifai and other fungi imperfecti.

Physical properties

M. Pt. 148-151°C

Solubility Water: slightly soluble in water. Organic solvents: acetone, chloroform, ethanol, ether, methanol

Ecotoxicity

Invertebrate toxicity

Culex pipiens larvae poisoned with cyclosporin A showed pathological changes to all tissues, characterised by the formation of minute vacuoles in the cytoplasm. Mitochondria were the main targets and underwent disintegration to vacuoles. Minor changes were seen in the endoplasmic reticulum and the Golgi apparatus (1).

Mammalian & avian toxicity

Acute data

LD₅₀ oral rat, mouse 1489, 2803 mg kg⁻¹, respectively (2).

LD₅₀ intraperitoneal rat 147 mg kg⁻¹ (2).

LD₅₀ subcutaneous rat 286 mg kg⁻¹ (2).

LD₅₀ intravenous rat, mouse, rabbit 24, 96, 10 mg kg⁻¹, respectively (2,3).

Sub-acute and sub-chronic data

Oral Wistar rats (14 days) 25 mg kg⁻¹ day⁻¹ induced acute nephrotoxicity (4).

Oral 2- and 4-month-old ♂ rats (7 days) 100 mg day⁻¹ resulted in a mortality rate of 85% within 10 days and a marked deterioration of kidney function accompanied by proximal tubular swelling and cytoplasmic vacuolation (5).

Carcinogenicity and chronic effects

National Toxicology Program classification: known to be a human carcinogen (6).

Cyclosporin treatment in humans is associated with an increased incidence of lymphoma, skin cancer and Kaposi sarcoma (7).

♂ Swiss Webster mice treated with a single dose of *N*-methyl-*N*-nitrosourea as a promoter followed by chronic feeding of 0.015% cyclosporin A developed an eight-fold higher incidence of thymic lymphomas than mice treated with a single dose of promoter followed by a basal diet. The authors suggest that cyclosporin A enhances the induction of thymic lymphomas by its promoting effect and that the underlying mechanism may be through a disturbance of the thymic microenvironment (8).

Teratogenicity and reproductive effects

Intragastric ♂ mice 507 mg kg⁻¹. No increase in unscheduled DNA synthesis in sperm cells (9).

Toxicological studies in a variety of different animal species showed that cyclosporin A does not have teratogenic effects (10).

Metabolism and toxicokinetics

In humans, absorption from the gastro-intestinal tract is variable and incomplete with a bioavailability of ≈30%. Blood and plasma concentrations peak at around 3.5 hr after an oral dose. Clearance from the blood is biphasic with a terminal elimination $t_{1/2}$ of 10-27 hr following an oral dose. Extensively metabolised in the liver and excreted in faeces via the bile. A small amount, ≈6%, is excreted in the urine with <0.1% unchanged (7).

First-pass metabolism in the gastro-intestinal tract rather than in the liver appears to account for the low oral bioavailability in humans (7).

Genotoxicity

Toxicological studies in a variety of different animal species showed that cyclosporin A does not have mutagenic effects (10).

Other effects

Other adverse effects (human)

Cyclosporin A causes nephrotoxicity in around one third of patients. This is characterised by fluid retention, increased serum creatinine and urea concentrations, a fall in glomerular filtration rate, and decreased sodium and potassium excretion (7).

Damage to kidney epithelial cell membranes in patients receiving cyclosporin A therapy results in the increased excretion of glutathione S-transferase isoenzymes in the urine (11).

Effects on blood and the cardiovascular system associated with cyclosporin treatment in some patients include erythraemia, thrombocytosis, hypertension and marked hyperlipidaemia (7).

Effects on the central nervous system and skeletal muscle and marked hyperuricaemia have been observed in a few patients undergoing cyclosporin therapy (7).

Non-toxic to cultured human foetal pancreas for 72 hr at the concentration range 10⁻⁸-10⁻⁴ M. Cryopreserved human foetal pancreas was transplanted under the kidney capsule of streptozotocin-induced diabetic nude mice

immunosuppressed with 30 mg kg⁻¹ cyclosporin A. No toxic effects of cyclosporin A to human foetal pancreas *in vivo* were demonstrated (12).

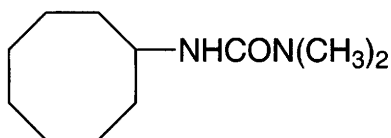
Other comments

Cyclosporin A is a cyclic oligopeptide of structure: cyclo-[4-(*E*)-but-2-enyl-*N*, 4-dimethyl-L-threonyl]-L-homoalanyl-(*N*-methylglycyl)-(N-methyl-L-leucyl)-L-valyl-(N-methyl-L-leucyl)-L-alanyl-D-alanyl-(N-methyl-L-leucyl)-(N-methyl-L-leucyl)-(N-methyl-L-valyl)-]. Cyclosporin A protected mice against cyclic peptide toxins of the cyanobacterium *Microcystis aeruginosa* and the toadstool *Amanita phalloides*. The authors consider that effects on hepatic macrophages are involved in the protection, although by a mechanism unknown (13). Cyclosporin A at concentration >10 nM protected isolated hepatocytes against the toxic effects of phalloidin (14).

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12. Leonard, D. K. et al *J. Surg. Res.* 1989, **46**(6), 625-632.
13. Adams, W. H. et al *J. Pharmacol. Exp. Ther.* 1989, **249**(2), 552-556.
14. Zeigler, K. et al *Biochim. Biophys. Acta* 1984, **805**(2), 174-180

C532 cycluron



C₁₁H₂₂N₂O

Mol. Wt. 198.31

CAS Registry No. 2163-69-1

Synonyms 3-cyclooctyl-1,1-dimethylurea; *O,N*-cyclooctyl-*N',N'*-dimethylurea

EINECS No. 218-493-8

RTECS No. YS 7875000

Uses Superseded pesticide.

Physical properties

M. Pt. 138°C

Solubility Water: 1.1 g l⁻¹. Organic solvents: acetone, benzene, methanol

Mammalian & avian toxicity

Acute data

LD₅₀ oral rat 1500 mg kg⁻¹ (1).

LD₅₀ oral mammal 2600 mg kg⁻¹ (species unspecified) (2).

Irritancy

No local irritation to backs or ears of rabbits treated for 20 hr with a 50% aqueous solution (3).

Legislation

WHO Toxicity Class Table 5 (4).

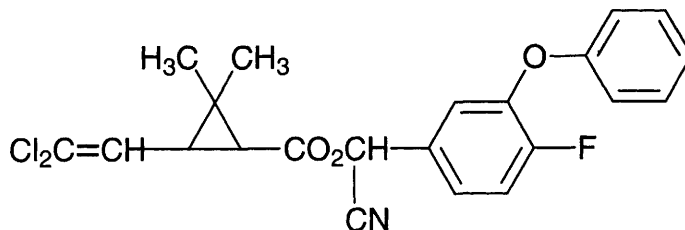
Other comments

Reviews on human health effects, experimental toxicology and physico-chemical properties listed (5).

References

1. *Pest. Chem. Off. Compend.* 1966, 294.
2. *Pflanzenschutz Schaedlingsbekaempfungsmittel* 1971, 81.
3. *The Pesticide Manual* 11th ed., 1997, The British Crop Protection Council, Farnham, UK.
4. *The WHO Recommended Classification of Pesticides by Hazard and Guidelines to Classification* 1998-1999 WHO/PCS/98.21.
5. *ECETOC Technical Report No. 71* 1996, European Centre for Ecotoxicology and Toxicology of Chemicals, 4 Avenue E. Van Nieuwenhuysse (Bte 6), B-1160 Brussels, Belgium

C533 cyfluthrin



$C_{22}H_{18}Cl_2FNO_3$

Mol. Wt. 434.29

CAS Registry No. 68359-37-5

Synonyms cyano(4-fluoro-3-phenoxyphenyl)methyl 3-(2,2-dichloroethenyl)-2,2-dimethylcyclopropanecarboxylate

EINECS No. 269-855-7

RTECS No. GZ 1253000

Uses Non-systemic contact insecticide.

Physical properties

M. Pt. diastereoisomer I (See Other Comments) 64°C, II 81°C, III 65°C, IV 106°C. Technical grade *c.* 60°C

Flash point 107°C (technical grade) **Specific gravity** 1.27-1.28 at 20°C (supercooled melt)

Partition coefficient log P_{ow} : diastereoisomer I 6.00, II 5.94, III 6.04, IV 5.91 **Volatility** v.p. diastereoisomer I 7.2×10^{-9} , II 7.5×10^{-11} , III 1.5×10^{-10} , IV 6.75×10^{-10} mmHg at 20°C

Solubility Water: diastereoisomer I 2.2, II 2.1, III 3.2, IV 4.3 $\mu\text{g l}^{-1}$ at pH 3. Organic solvents: dichloromethane, *n*-hexane, toluene

Ecotoxicity

Fish toxicity

LC₅₀ (96 hr) rainbow trout, golden orfe, bluegill sunfish, carp 0.0006-0.022 mg l⁻¹ (1).

Invertebrate toxicity

Toxic to honeybees (1).

Mammalian & avian toxicity

Acute data

LD₅₀ oral rat 400 mg kg⁻¹ (1).

LC₅₀ (4 hr) inhalation rat 0.5 mg l⁻¹ (1).

LD₅₀ dermal rats > 5000 mg kg⁻¹ (1).

Sub-acute and sub-chronic data

No-observed-effect level in dogs 160 mg kg⁻¹ in diet for 1 yr (2).

Metabolism and toxicokinetics

Inhalation ♂ human volunteers 10, 30, and 60 min at 160 µg m⁻³ or 60 min at 40 µg m⁻³. Urine collected during the first 2 hr after inhalation exposure to 40 µg m⁻³ for 1 hr contained < the limits of detection for metabolites, viz. 0.14 µg l⁻¹ for *cis*-3-(2,2-dichlorovinyl)-2,2-dimethylcyclopropane carboxylic acid (*cis*-DCCA), 0.15-0.28 µg l⁻¹ for 4-fluoro-3-phenoxybenzoic acid (FPBA). After inhalative exposure to 160 µg m⁻³ 93% of the metabolites were excreted within the first 24 hr with mean half-lives *cis*-DCCA 6.9 hr, *trans*-DCCA 6.2 hr, FBPA 5.3 hr. The mean *trans*:*cis*-DCCA ratio for each subject was 1.9. The amount of metabolites in urine depended on inhalation dose, exposure time, and showed interindividual differences (3).

Irritancy

Irritating to eyes but not skin of rabbits (1).

Sensitisation

Non-sensitiser in guinea pigs (1).

Other effects

Other adverse effects (human)

Exposure of volunteers (adult males, 18-25 yr), who had no previous exposure to pyrethroids, to cyfluthrin had no toxic effects on renal, hepatic, pulmonary function and nerve conduction. Mosquito nets impregnated with cyfluthrin at 50 mg m⁻² are therefore considered safe to use (4).

Legislation

Limited under EC Directive on Drinking Water Quality 80/778/EEC maximum admissible concentration 0.1 µg l⁻¹ (5).

WHO Toxicity Class II (6).

EPA Toxicity Class II (7).

ADI (FAO/WHO, 1987) 0.02 mg kg⁻¹ body weight (7).

Other comments

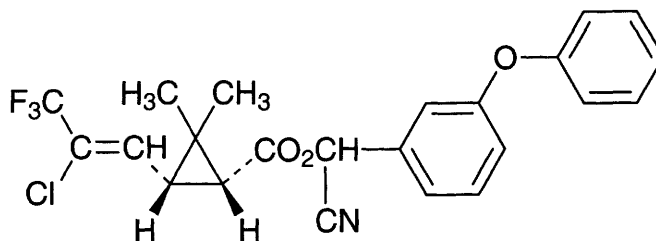
Cyfluthrin comprises a mixture of four diastereoisomeric pairs of enantiomers: I (*R*)-α-cyano-4-fluoro-3-phenoxybenzyl(1*R*)-*cis*- 3-(2,2-dichlorovinyl)-2,2-dimethylcyclopropanecarboxylate + (*S*)-α, (1*S*)-*cis*-; II *S*-α, (1*R*)-*cis*- + (*R*)-α, (1*S*)-*cis*-; III (*R*)-α, (1*R*)-*trans*- + (*S*)-α, (1*S*)-*trans*-; IV (*S*)-α, (1*R*)-*trans*- + (*R*)-α, (1*S*)-*trans*-. Technical grade cyfluthrin contains: 23-26% diastereoisomer I, 16-19% diastereoisomer II, 33-36% diastereoisomer III, and 22-25% diastereoisomer IV.

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7. *The Pesticide Manual* 11th ed., 1997, The British Crop Protection Council, Farnham, UK

c534 cyhalothrin



$C_{23}H_{19}ClF_3NO_3$

Mol. Wt. 449.86

CAS Registry No. 68085-85-8

Synonyms Charge; Commodore; Cypha; Demand; Excalibur; Grenade

EINECS No. 268-450-2

RTECS No. GZ 1227770

Uses Control of ectoparasites on sheep and cattle.

Physical properties

B. Pt. 187-190°C at 0.2 mmHg **Specific gravity** 1.25 at 25°C **Partition coefficient** 6.8 at 20°C **Volatility** v.p. -0.75×10^{-8} mmHg

Solubility Water: 0.004 ppb at 20°C. Organic solvents: acetone, dichloromethane, diethyl ether, ethyl acetate, hexane, methanol, toluene

Ecotoxicity

Fish toxicity

LC₅₀ (96 hr) rainbow trout 0.54 µg l⁻¹ (1).

Environmental fate

Degradation studies

t_{1/2} in river water in sunlight approximately 20 days (1).

Mammalian & avian toxicity

Acute data

LD₅₀ mallard duck >5000 mg kg⁻¹ (1).

LD₅₀ oral ♀, ♂ rats 144-166 mg kg⁻¹ (1).

LC₅₀ (4 hr) inhalation rat >0.086 mg l⁻¹ (1).

Carcinogenicity and chronic effects

No significant toxic effects in rats fed 2.5 mg kg⁻¹ day⁻¹ for 2 yr (1).

Irritancy

Moderate eye and mild skin irritant in rabbits (1).

Legislation

Limited under EC Directive on Drinking Water Quality 80/778/EEC maximum admissible concentration $0.1 \mu\text{g l}^{-1}$ (2).

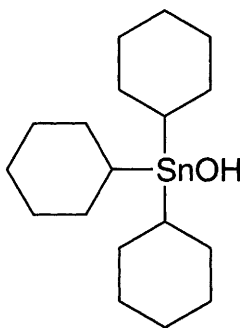
Acceptable daily intake for humans 0.02 mg kg^{-1} (1).

WHO Toxicity Class II (3).

References

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C535 cyhexatin



$\text{C}_{18}\text{H}_{34}\text{OSn}$

Mol. Wt. 385.18

CAS Registry No. 13121-70-5

Synonyms tricyclohexyltin hydroxide; stannane, tricyclohexylhydroxy-; Acarox; Acarpec; Acarstin; Etanyde; Mitacid; Pennstyl; Tetran

EINECS No. 236-049-1

RTECS No. WH 8750000

Uses Acaricide.

Physical properties

M. Pt. $195\text{--}198^\circ\text{C}$

Solubility Water: $<1 \text{ mg l}^{-1}$ at 25°C . Organic solvents: acetone, chloroform, methanol

Occupational exposure

FR-VME 5 mg m^{-3}

SE-LEVL 0.1 mg m^{-3} (as Sn)

UK-LTEL 5 mg m^{-3}

US-TWA 5 mg m^{-3}

SE-STEL 0.2 mg m^{-3} (as Sn)

UK-STEL 10 mg m^{-3}

Supply classification harmful

Risk phrases Harmful by inhalation, in contact with skin and if swallowed (R20/21/22)

Safety phrases Keep out of reach of children (if sold to general public) – Keep away from food, drink and animal feeding stuffs (S2, S13)

Ecotoxicity

Fish toxicity

LC₅₀ (24 hr) large-mouth bass 60 µg l⁻¹ (1).

LC₅₀ (24 hr) goldfish 550 µg l⁻¹ (1-3).

Invertebrate toxicity

Non-toxic to bees (2).

Environmental fate

Degradation studies

Experimental studies have provided evidence of the biotransformation of some triphenyl- and tricyclohexyltin compounds. There are also limited data suggesting methylation of tin by organisms present in the environment (4).

Mammalian & avian toxicity

Acute data

LC₅₀ oral mallard duck 31-89 mg kg⁻¹ diet (3).

LD₅₀ oral rat, 540 mg kg⁻¹ (2).

LD₅₀ guinea pig 780 mg kg⁻¹ (2).

LD₅₀ oral rabbit 500-1000 mg kg⁻¹ (2,5).

LC₅₀ (duration unspecified) inhalation weanling rat 244 mg kg⁻¹ (6).

LD₅₀ dermal rabbit 2420 mg kg⁻¹ (7).

LD₅₀ intraperitoneal weanling rat 13 mg kg⁻¹ (8).

Sub-acute and sub-chronic data

No toxic effects in rats fed 12.5 mg kg⁻¹ day⁻¹ for 19 days; 25 mg kg⁻¹ caused toxic effects (4).

Carcinogenicity and chronic effects

There is no conclusive evidence that organotin compounds are carcinogenic (4).

No-effect level 2-yr feeding trials dogs, 0.75 mg kg⁻¹ day⁻¹; mice 3 mg kg⁻¹ day⁻¹; rats 1 mg kg⁻¹ day⁻¹.

Admissible daily dose human 0.8 µg kg⁻¹ (3).

Level causing no toxicological effect mouse: 3 mg kg⁻¹ day⁻¹, dog 30 ppm in the diet, adjusted to give 0.75 mg kg⁻¹ day⁻¹ (9).

No increased incidence of tumours in rats fed up to 12 mg kg⁻¹ for 2 yr (4).

Teratogenicity and reproductive effects

No teratogenic or reproductive effects in a three-generation study in rats fed 4-6 mg kg⁻¹ day⁻¹ in the diet (4).

Not teratogenic in rabbits fed up to 3 mg kg⁻¹ day⁻¹ on days 8-16 of gestation (4).

Metabolism and toxicokinetics

Metabolism by rat liver microsomal monooxygenase system yields 2-, 3-, and 4-hydroxycyclohexyldicyclohexyltin derivatives. Further degradation of the 2-metabolite occurs to give cyclohexene and dicyclohexyltin compounds. Similar products were detected in the faeces of mice, guinea pigs and rabbits orally administered ¹⁴C-cyhexatin (10).

t_{1/2} in rats 5-40 days; via diet over a prolonged period; removed most slowly from the brain (4).

Trace amounts found in tissue of rats and dogs fed up to 12 mg kg⁻¹ day⁻¹ for 45 days to 2 yr (4).

Irritancy

1.2-60 mg kg⁻¹ day⁻¹ applied to skin of rabbits over 3 wk caused local irritation but no systemic effects (4).

Other effects

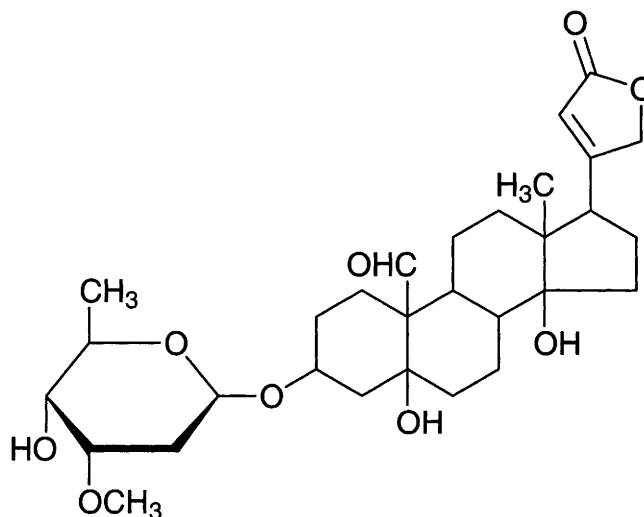
Any other adverse effects

Intra-ruminal injection in sheep of 15-500 mg kg⁻¹ resulted in transitory anorexia, no effect observed at a dose of 15 mg kg⁻¹, depression of the central nervous system (anorexia and hypodipsia) at a dose of 150 mg kg⁻¹ and higher (9).

References

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C536 cymarin



$C_{30}H_{44}O_9$

Mol. Wt. 548.67

CAS Registry No. 508-77-0

Synonyms K-strophanthin- α ; 3-[(2,6-dideoxy-3-O-methyl- β -D-ribo-hexopyranosyl)oxy]-5,14-dihydroxy-19-oxocard-20(22)-enol ide; WV 90043a

EINECS No. 208-087-9

RTECS No. GZ 5600000

Uses Cardiotonic.

Occurrence From certain plants including *Strophanthus kombé*; (Apocynaceae) and *Adonis vernalis* (Ranunculaceae).

Physical properties

M. Pt. 148°C

Solubility Organic solvents: chloroform, methanol

Mammalian & avian toxicity

Acute data

LD₅₀ intravenous rat 20-24.8 mg kg⁻¹ (1,2).

LD₅₀ intraperitoneal mouse 12 mg kg⁻¹ (1).

LD_{Lo} intravenous cat 95 µg kg⁻¹ (3).

Metabolism and toxicokinetics

Elimination t_{1/2} in rabbit 3.4 hr. Highest levels occurred in kidney, liver and adrenal gland; lowest levels in the brain (4).

Healthy ♂ humans absorbed single oral and intravenous doses at 47% of the given dose. Excretion by the kidneys, mainly as conjugated metabolites, accounted for 46 and 21% of the intravenous and oral doses, respectively. Elimination t_{1/2} 13 hr (intravenous) and 24 hr (oral) (5).

Other effects

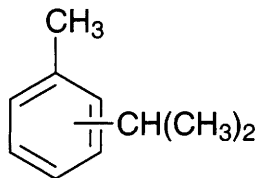
Other adverse effects (human)

Nausea, anorexia, vomiting, abdominal pain and diarrhoea may occur. Other effects include headache, dizziness, fatigue, weakness, mental confusion and disorientation. May have oestrogenic activity. May cause heart failure or aggravate an existing condition at toxic doses (6).

References

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C537 cymene



C₁₀H₁₄

Mol. Wt. 134.22

CAS Registry No. 25155-15-1

Synonyms cymol; isopropyltoluene; methylpropylbenzene; methyl(1-methylethyl)benzene

EINECS No. 246-674-1

Uses Solvent. Synthetic resin manufacture, metal polishes. Organic synthesis: oxidation to hydroperoxides used as catalysts for synthetic rubber manufacture.

Physical properties

Solubility Organic solvents: chloroform, diethyl ether, ethanol

Occupational exposure

UN No. 2046 **HAZCHEM Code** 3 **Conveyance classification** flammable liquid

Mammalian & avian toxicity

Acute data

LD₅₀ oral redwing blackbird 316 mg kg⁻¹ (1).

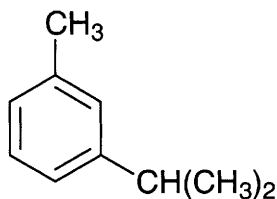
Other comments

Mixture of three isomers.

References

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C538 *m*-cymene



C₁₀H₁₄

Mol. Wt. 134.22

CAS Registry No. 535-77-3

Synonyms 3-isopropyltoluene

EINECS No. 208-617-9

Physical properties

M. Pt. -63.7°C B. Pt. 175.6°C Specific gravity 0.862 at 20°C with respect to water at 4°C

Solubility Organic solvents: acetone, benzene, diethyl ether, ethanol

Occupational exposure

UN No. 2046 HAZCHEM Code 3 $\frac{+}{-}$ Conveyance classification flammable liquid

Ecotoxicity

Bioaccumulation

No or low bioaccumulation (1).

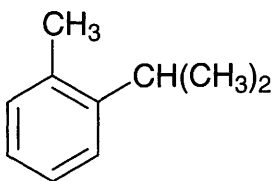
Other comments

MAC Ceiling Value 10.0 mg m⁻³ (2,3).

References

1. *JETOC Newsl.* No. 6 1988, 15-17, Japan Chemical Industry Ecology Toxicology and Information Center.
2. *Predelnd Dopustimye Kontsentratsii Vrednykh Veshchestv V Voidukhe Rabochei Zony (Maximum Allowable Concentrations of Harmful Substances in Occupational Air)* 1985.
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C539 o-cymene



$C_{10}H_{14}$

Mol. Wt. 134.22

CAS Registry No. 527-84-4

Synonyms 2-isopropyltoluene

EINECS No. 208-426-0

Physical properties

M. Pt. -71.5°C B. Pt. 177°C Specific gravity 0.8748 at 20°C with respect to water at 4°C

Solubility Organic solvents: acetone, benzene, diethyl ether, ethanol

Occupational exposure

UN No. 2046 HAZCHEM Code 3  Conveyance classification flammable liquid

Ecotoxicity

Bioaccumulation

No or low bioaccumulation (1).

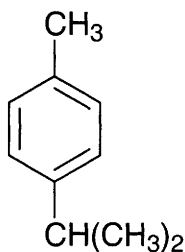
Other comments

MAC Ceiling Value 10.0 mg m^{-3} (vapour) (2,3).

References

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C540 *p*-cymene



C₁₀H₁₄

Mol. Wt. 134.22

CAS Registry No. 99-87-6

Synonyms 1-methyl-4-isopropylbenzene

EINECS No. 202-796-7

RTECS No. GZ 5950000

Uses Synthesis of pure *p*-cresol and carvacrol. Used as a diluent for lacquers, varnishes, dyes; in production of synthetic resin; component of fragrances for soap, cream and perfume.

Occurrence Occurs in essential oils distilled from plants including *Cuminum cyminum*, *Pinus palustris* and *Pinus caribaea*.

Physical properties

M. Pt. -67.9°C **B. Pt.** 176.5°C **Flash point** 47°C **Specific gravity** 0.8573 at 20°C with respect to water at 4°C

Partition coefficient Log *P*_{ow} 4.10 **Volatility** v.p. 1 mmHg at 17.3°C ; v.den. 4.62

Solubility Organic solvents: acetone, benzene, diethyl ether, ethanol

Occupational exposure

SE-LEVL 25 ppm (140 mg m⁻³)

SE-STEL 35 ppm (190 mg m⁻³)

UN No. 2046 **HAZCHEM Code** 3 **Conveyance classification** flammable liquid

Ecotoxicity

Bioaccumulation

Readily biodegradable (1).

Environmental fate

Abiotic removal

Evaporation rate relative to *n*-butyl-acetate which has been assigned a value of 1 at 25°C is 0.14 (2).

Mammalian & avian toxicity

Acute data

LD₅₀ oral rat (weanling) 4750 mg kg⁻¹ (3).

LC_{Lo} (45 min) inhalation rat 5000 ppm (4).

LD₅₀ dermal rabbit >5000 mg kg⁻¹ (5).

Sub-acute and sub-chronic data

Motor activity effects after administration to mice 6 × day⁻¹ at 2200 mg kg⁻¹ (duration and route unspecified) (6).

Metabolism and toxicokinetics

Urinary metabolites after administering 670 mg kg⁻¹ for three days by gavage to rabbit include *p*-cymene-9-ol, *p*-cymene-8-ol, α-*p*-tolylpropionic acid, α-*p*-tolyl-α-hydroxypropionic acid, α-*p*-tolyl acrylic acid,

p-isopropylbenzoic acid, and *p*-2-hydroxyisopropylbenzoic acid. Similar metabolites were found in rats and guinea pigs (7,8).

Irritancy

Dermal rabbit (24 hr) 500 mg/hr caused moderate irritation (5).

Genotoxicity

Saccharomyces cerevisiae 27 mg tube⁻¹ cytogenetic effects (9).

Other effects

Other adverse effects (human)

Headache and nausea reported in humans after ingesting 3-4 g day⁻¹ for 2-3 days (10).

Any other adverse effects

Neurotoxic effects in rats and mice at lethal inhalation and oral concentrations characterised by central nervous system excitation, tremors and convulsions followed by lethargy and near comatose condition (10).

Leukocytosis reported in rabbits after subcutaneous injection (6,10-12).

Other comments

Solubility parameter SP_o=8.1. SP_o is calculated by taking the square root of the sum of the squares of the Hansen solubility parameters SP_d, SP_p and SP_h (cal^{1/2}cm^{-3/2}) (2).

References

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2. *Texaco Chemical UK* 1992, 195 Knightsbridge, London, UK.
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C541 cymoxanil



C₇H₁₀N₄O₃

Mol. Wt. 198.18

CAS Registry No. 57966-95-7

Synonyms 2-cyano-*N*-[(ethylamino)carbonyl]-2-(methoxyimino)acetamide;

1-(2-cyano-2-methoxyiminoacetyl)-3-ethylurea; Curzate; Fusko

EINECS No. 261-043-0

RTECS No. AB 5957000

Uses Agricultural chemical and pesticide. Systemic fungicide.

Physical properties

M. Pt. 160-161°C **Specific gravity** 1.31 at 25°C **Partition coefficient** $\log P_{ow} = 3.9$ (pH 5), 4.7 (pH 7)
Volatility v.p. 6×10^7 mmHg
Solubility Water: 890 mg l⁻¹ at 20°C and pH 5. Organic solvents: acetone, benzene, chloroform, dimethylformamide, hexane, methanol

Ecotoxicity

Fish toxicity

LC₅₀ (96 hr) bluegill sunfish, rainbow trout 13.5-18.7 mg l⁻¹ (1,2).

Invertebrate toxicity

Non-toxic to bees (2).

Environmental fate

Degradation studies

Recoveries of cymoxanil added to untreated grapes range between 70% and 80% at 0.05 and 2.0 mg kg⁻¹ values, respectively (3).

t_{1/2} soil <2 wk (2).

Mammalian & avian toxicity

Acute data

LD₅₀ oral guinea pig, weanling rat 1096-1100 mg kg⁻¹ (1).

LD₅₀ dermal rabbit >3000 mg kg⁻¹ (1).

Sub-acute and sub-chronic data

LC₅₀ (8 day) oral bobwhite quail 2847 mg kg⁻¹ diet (1).

LC₅₀ (8 day) oral mallard duck >10,000 mg kg⁻¹ diet (1).

Carcinogenicity and chronic effects

No-effect level for oral rat (2 yr) 1000 mg kg⁻¹ in diet; body weight effects noted at 2500 mg kg⁻¹ (1).

Metabolism and toxicokinetics

Two ♂ rats maintained on diets containing 2.5 mg g⁻¹ cymoxanil for 24 days were given a single or four repeated daily doses of ¹⁴C-labelled cymoxanil. Urine samples were collected and assayed for cymoxanil metabolites. 90% of the ¹⁴C-activity was eliminated within 72 hr, 71% in the urine, 11% in the faeces, and 7% in the expired air. No ¹⁴C was found in the body tissues. More than 70% of the urinary metabolite-derived ¹⁴C-activity was identified. Major metabolites were free and conjugated glycine, hippuric acid, and phenylacetic acid (4).

Legislation

Limited under EC Directive on Drinking Water Quality 80/778/EEC. Maximum admissible concentration 0.1 µg l⁻¹ (5).

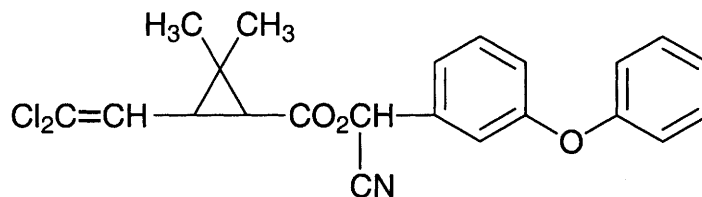
Other comments

Specific uses, limitations and safety precautions listed (6,7).

References

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7. *Seznam Provolených Přípravků Na Ochranu Rostlin (List of Permitted Chemicals for Plant Protection)* 1981

C542 cypermethrin



$C_{22}H_{19}Cl_2NO_3$

Mol. Wt. 416.30

CAS Registry No. 52315-07-8

Synonyms cyclopropanecarboxylic acid, 3-(2,2-dichloroethenyl)-2,2-dimethyl-, cyano(3-phenoxyphenyl)methyl ester; *RS*- α -cyano-3-phenoxybenzyl (1*RS*,3*RS*;1*RS*,3*SR*)-3-(2,2-dichloroethenyl)-2,2-dimethyl-cyclopropanecarboxylate; Afrisect; Supersect; Capture; Aimcocyper

EINECS No. 257-842-9

RTECS No. GZ 1250000

Uses Insecticide.

Physical properties

M. Pt. 80°C **B. Pt.** 220°C **Specific gravity** 1.23 at 20°C with respect to water at 4°C

Partition coefficient $\log P_{ow}$ 6.3 (1) **Volatility** v.p. 1.875×10^{-9} mmHg

Solubility Water: 0.045 mg l⁻¹ (pH 7, 25°C). Organic solvents: acetone, chloroform, cyclohexanone, ethanol, hexane, xylene

Ecotoxicity

Fish toxicity

LC₅₀ (96 hr) brown trout 2-2.8 µg l⁻¹ (2,3).

LC₅₀ (96 hr) Atlantic salmon 2-2.4 µg l⁻¹ (2,3).

Invertebrate toxicity

EC₅₀ (24 hr) *Daphnia magna* 2.0 µg l⁻¹ (2,3).

LC₅₀ (24 hr) mayfly 0.6 µg l⁻¹ (2,3).

LC₅₀ (24 hr) lobster 0.04 µg l⁻¹ (2,3).

LD_{Lo} (24 hr) worker honey bees, topical application 20 µg kg⁻¹ (total dose) oral administration 35 µg kg⁻¹ (4).

Environmental fate

Degradation studies

Under water-logged conditions the rate of hydrolysis of cypermethrin was slower than under aerobic conditions and 3-phenoxybenzoic acid accumulated in the anaerobic soil (5).

On crops, cypermethrin degradation occurs mainly by hydrolysis of the ester bond followed by hydrolytic and oxidative processes. Mainly unchanged chemical was found 21 days after application (4,5).

Abiotic removal

Comparatively immobile environment and transport between media. Strongly adsorbed from aqueous solutions by solid surfaces (5).

Mammalian & avian toxicity

Acute data

LD₅₀ oral hamster, rat 200-250 mg kg⁻¹ (6).

LD₅₀ oral mouse 82 mg kg⁻¹ (6).

LD₅₀ oral guinea pig 500 mg kg⁻¹ (6).

LD₅₀ dermal rabbit >2460 mg kg⁻¹ (6).
LD₅₀ intraperitoneal rat 198-315 mg kg⁻¹ (6).
LD₅₀ intraperitoneal CFI mice 485 mg kg⁻¹ (6).

Sub-acute and sub-chronic data

LD_{Lo} (21 day) French partridge >3000 mg kg⁻¹ (5).
LD_{Lo} (21 day) domestic fowl >2000 mg kg⁻¹ (total dose) (5).
Rats fed diets containing 1500 mg kg⁻¹ for 5 wk, incurred reduced body weight gain and food intake, piloerection, nervousness incoordinated movement, increased liver weight, and increases in blood urea and haemoglobin concentrations. Dog fed diets containing 1500 mg kg⁻¹ for 13 wk showed severe signs of toxic effects consisting of diminished food intake, weight loss, diarrhoea, anorexia, licking and chewing of the paws, whole body tremors, exaggerated gait, ataxia, incoordination, and hyperaesthesia. No effects were seen at 500 mg kg⁻¹ feed (6).
Pregnant ♀ rats fed 70 mg kg⁻¹ day⁻¹ (duration unspecified), slight to severe neurological disturbances including: slight splaying of the hind legs while walking ranging to severe splaying of all limbs, involuntary movements of the jaws, convulsive spasms, and hypersensitivity to noise (7).

Carcinogenicity and chronic effects

Two long-term studies on rats and one on mice were carried out. The dose levels in the rat studies ranged up to 1500 mg kg⁻¹ diet equivalent to 75 mg kg⁻¹ body weight. No effects were seen at 150 mg kg⁻¹ diet. At the highest dose level, reduced body weight gain, increased liver weights and some haematological and biochemical changes. No increase in tumour incidence. Similar effects were seen in the mouse study at 1600 mg cypermethrin kg⁻¹ diet. No effects were seen in the 400 mg kg⁻¹ diet group (8).
Did not produce any toxicological effects in dogs fed dietary concentrations of ≥300 mg kg⁻¹ feed over 2 yr (9).

Teratogenicity and reproductive effects

Gavage pregnant rats 50 mg kg⁻¹. A significant decrease in the absolute numbers of all thymocyte subsets was seen in pups during the first 30 days after birth (10).

Metabolism and toxicokinetics

Generally metabolised in mammals through ester hydrolysis, oxidation, and conjugation, no tendency to accumulate in tissues. Urinary excretion metabolites rapid average 78% of *trans* 49% of the *cis*-isomer within 24 hr; ester cleavage major route of metabolism of cypermethrin in humans (11).

Irritancy

Moderately irritant to occluded skin and eyes of New Zealand white rabbits; recovery in a few days. Severity of the irritation depended on the formulation and the solvent used (6,12).

Sensitisation

Mild skin sensitising potential in guinea pigs (6,13).

Genotoxicity

Salmonella typhimurium TA98, TA100, TA1535, TA1537, TA1538 with and without metabolic activation negative. Negative results in an *in vivo* chromosomal aberration test with Chinese hamsters and in dominant lethal studies on mice. In a host-mediated assay with mice, no increase in the rate of mitotic gene conversion in *Saccharomyces cerevisiae* (14).

Increased frequency of polychromatic erythrocytes with micronuclei in bone marrow of mice 7 and 14 days after oral treatment with 900 ppm, and after dermal application of 360 mg kg⁻¹ 2 × wk⁻¹ for 2 wk (15).

Increased frequency of bone marrow chromosome aberrations *in vivo* in mice after subcutaneous or intraperitoneal injection of 30-50 mg kg⁻¹. Marginal difference in incidence of sperm abnormalities in mice after intraperitoneal injection of 30-50 mg kg⁻¹ (16).

Statistically significant modest induction of sister chromatid exchanges in mouse bone marrow following oral exposure to 32 mg kg⁻¹ (17).

Other effects

Any other adverse effects

Cell viability of hepatocytes from ♂ and ♀ rats (2×10^6 cells, 37°C) exposed to 400 and 800 ng cypermethrin was reduced after 60 and 30 min, respectively. The viability of ♀ rat hepatocytes was reduced after exposure to 200 ng for 2 hr. The leakage of aspartate and alanine transaminases showed increases in a similar dose- and time-dependent manner. ♀ Hepatocytes were more sensitive to the toxic effects of cypermethrin than ♂ cells (18). High doses orally to rats caused an unusual gait in intoxicated animals; at lethal or near lethal dermal or oral doses histopathological changes (swelling and/or disintegration of axons of the sciatic nerve of rats) (16). Cypermethrin was given to pregnant rats by gavage during gestation. Pups showed a significant increase in peripheral blood natural killer and antibody-dependent cytotoxic activity parallel with a similar increase in the percentage of NK-RP1+ cells and decreased activity in the spleen. Pregnant cypermethrin-exposed dams showed no changes in peripheral blood or spleen cytotoxic function during the postnatal period (0-120 days) (19).

Legislation

Limited under EC Directive on Drinking Water 80/778/EEC. Maximum admissible concentration 0.1 µg l⁻¹ (20).
WHO Toxicity Class II (21).
EPA Toxicity Class (formulation) II (22).
ADI (JMPR) 0.05 mg kg⁻¹ body weight (22).

Other comments

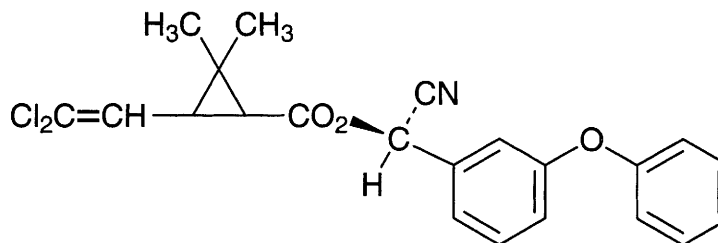
Toxicity reviewed (23-29).

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C543 α -cypermethrin



$C_{22}H_{19}Cl_2NO_3$

Mol. Wt. 416.30

CAS Registry No. 67375-30-8

Synonyms (1R,cisS) and (1S,cisR) enantiomeric isomer pair of α -cyano-3-phenoxybenzyl-3-(2,2-dichlorovinyl)-2,2-dimethylcyclopropane carboxylate; (1 α (S),3 α)-(+) -cyano(3-phenoxyphenyl)methyl 3-(2,2-dichloroethenyl)-2,2-dimethylcyclopropane carboxylate; Acquit; Alcance; Alphaguard; Bala; Concord; Dominex; Fastac; Renegade; **RTECS No.** GZ 1251400

Uses Non-systemic insecticide.

Physical properties

M. Pt. >80°C (closed cup) **B. Pt.** 200°C at 9.3 Pa **Specific gravity** 1.28 (22°C)

Partition coefficient $\log P_{ow}$ 6.94 at pH 7 **Volatility** v.p. 1.725×10^{-7} mmHg (20°C)

Solubility Water: ~0.01 mg l⁻¹ (25deg:C). Organic solvents: acetone, acetophenone, chlorobenzene, cyclohexanone, dichloromethane, ethylacetate, o-xylene

Ecotoxicity

Fish toxicity

LC₅₀ (96 hr) rainbow trout 2.8 µg l⁻¹ (1,2).

LC₅₀ (24 hr) rainbow trout 55 ppb (technical grade) (1-2).

Invertebrate toxicity

LD₅₀ (24 hr) bees 0.59 µg bee⁻¹ (not dangerous under field conditions) (1).

Environmental fate

Degradation studies

t_{1/2} sandy clay loam and clay loam 13 wk and 27 wk, respectively (1).

Likely to be degraded in water by photochemical and biological processes; surface and subsurface water in a

pond oversprayed with 15 g ha⁻¹ contained 5% and 19%, respectively, 1 day later; 0.1% and 2% 7 days later, and 5% was present in sediment after 16 days (4).

Not degraded in closed bottle and modified Sturm test or *Pseudomonas fluorescens* growth test (5).

Microbial transformation in aerobic batch enrichment cultures containing *Pseudomonas fluorescens*, *Achromobacter* spp. and *Bacillus cereus* studied; transformation occurred with t_{1/2} 7-14 days at 50 mg l⁻¹ in presence of 0.05% Tween 80 (v/v). 3-Phenoxybenzoic acid was the major transformation product, which was further transformed to 4-hydroxy-3-phenoxybenzoic acid (6).

Adsorption and retention

Strongly adsorbed onto soil particles; soil residues 1 yr after application of 0.5 kg ha⁻¹ were < 0.01 mg kg⁻¹ (7).

Mammalian & avian toxicity

Acute data

LD₅₀ oral rat 70-400 mg kg⁻¹ (1,3).

LD₅₀ oral mouse 35 mg kg⁻¹ (as 50 g l⁻¹ corn oil solution) (1,3).

LD₅₀ dermal rat > 500 mg kg⁻¹ (1,3).

Sub-acute and sub-chronic data

No-observed-effect level oral dogs in 13 wk study was 2.25 mg kg⁻¹ (8).

Carcinogenicity and chronic effects

In 90-day feeding trials, rats receiving 60 mg kg⁻¹ diet showed no ill-effects (1).

Metabolism and toxicokinetics

Eliminated in urine as sulfate conjugate of 3-(4-hydroxyphenoxy)benzoic acid and in faeces partly unchanged after oral administration to rats. 90% of single oral dose excreted after 4 days; 78% within 24 hr. Residues mainly in fat; concentration in fat 0.4 mg kg⁻¹ three days after oral dose of 2 mg kg⁻¹. Biphasic elimination from fat; first phase t_{1/2} 2.5 days; second phase t_{1/2} 17-26 days (9).

In humans 43% of 0.25-0.75 mg oral dose excreted within 24 hr in urine as free or conjugated *cis*-cyclopropane (10).

Irritancy

Technical grade minimally irritating when applied as single occlude dose for 24 hr to intact or abraded rabbit skin (11).

EC formulations (30 or 100 g l⁻¹) caused severe eye irritation in Draize test on rabbits, causing corneal opacity and iris damage (12).

Sensitisation

No sensitisation in guinea pig maximisation test (intradermal injection of 0.05% (v/v) in corn oil followed by topical challenge with 50% (m/m) in vaseline) (11).

Genotoxicity

Salmonella typhimurium TA98, TA100, TA1535, TA1537, TA1538 with and without metabolic activation negative.

Escherichia coli WP2, WP2 uvr A with and without metabolic activation negative (13).

Saccharomyces cerevisiae JD1 with and without metabolic activation negative (13).

In vitro rats liver cell cultures chromatid aberrations, breaks or gaps negative (13).

In vivo rats 2-8 mg kg⁻¹ no increase in chromosome aberrations or polyploidy in bone marrow cells (13).

Other effects

Any other adverse effects

Produces a distinct toxic syndrome in mammals, the CS-syndrome, characterised by choreo-athetosis and salivation. Produces minor lesions in sciatic nerves of rats (8).

Legislation

Limited under EC Directive on Drinking Water Quality 80/778/EEC. Maximum admissible concentration 0.1 µg l⁻¹ (14).
WHO Toxicity Class II (15).
EPA Toxicity Class II (3).
Partition coefficient exceeds EU limit of 3.0.

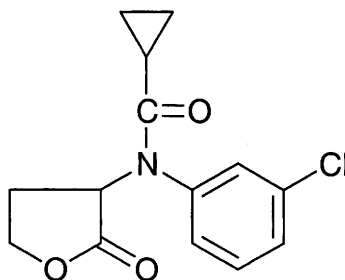
Other comments

Not dangerous to birds under field conditions (1,3).
Toxicity reviewed (16).

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c544 cyprofuram



C₁₄H₁₄ClNO₃

Mol. Wt. 279.72

CAS Registry No. 69581-33-5

Synonyms N-(3-chlorophenyl)-N-(tetrahydro-2-oxo-3-furanyl)cyclopropanecarboxamide;

(±)-α-[N-(3-chlorophenyl)cyclopropanecarboxamido]-γ-butyrolactone; Vinicur

EINECS No. 274-050-9

RTECS No. GZ 1016000

Uses Superseded fungicide.

Physical properties

M. Pt. 95-96°C **Volatility** v.p. 5×10^{-8} mmHg at 25°C

Solubility Water: 574 mg l⁻¹. Organic solvents: acetone, cyclohexanone, dichloromethane, xylene

Ecotoxicity

Fish toxicity

LC₅₀ (96 hr) carp, rainbow trout 35-75 mg l⁻¹ (1).

Invertebrate toxicity

Non-toxic to bees (1).

Mammalian & avian toxicity

Acute data

LD₅₀ oral rat, mouse 174-314 mg kg⁻¹ (1).

LD₅₀ dermal rabbit >1000 mg kg⁻¹ (1).

LD₅₀ oral mallard ducks, quail >2000 mg kg⁻¹ (1).

Legislation

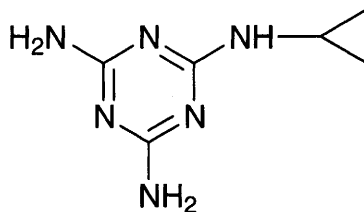
Limits under EC Directive on Drinking Water Quality 80/778/EEC. Maximum admissible concentration 0.1 µg l⁻¹ (2).

WHO Toxicity Class II (3).

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C545 cyromazine



C₆H₁₀N₆

Mol. Wt. 166.19

CAS Registry No. 66215-27-8

Synonyms N-cyclopropyl-1,3,5-triazine-2,4,6-triamine, Armor; Citation; Larvadex; Neporex; Trigard; Vetrazin

EINECS No. 266-257-8

RTECS No. XZ 1056500

Uses Pesticide. Insect growth regulator (1).

Physical properties

M. Pt. 224.9°C **Specific gravity** 1.35 at 20°C **Partition coefficient** log P_{ow} -0.061 at pH 7

Volatility v.p. 3.36×10^{-9} mmHg at 25°C

Solubility Water: 13 g l⁻¹ at pH 7.1 and 25°C. Organic solvents: acetone, hexane, isopropanol, methylene chloride, *n*-octanol, toluene

Ecotoxicity

Fish toxicity

LC₅₀ (96 hr) bluegill sunfish, carp, catfish and rainbow trout >100 mg l⁻¹ (2).

Invertebrate toxicity

A bioassay procedure was developed to evaluate the dosage/response mortality relationship of cyromazine to *Liriomyza trifolii* (Burgess) using infested cowpea, *Vigna sinensis*, plants. Twenty-five out of 42 generations of *Liriomyza trifolii* larvae were exposed to 6 ppm of cyromazine. LC₅₀ and LC₉₀ values indicated that no resistance had developed (2).

Practically no effect to adult honey bees (3,4).

No contact action upto 5 µg bee⁻¹ (4).

Mammalian & avian toxicity

Acute data

LD₅₀ oral bobwhite quail, Japanese quail 1785, 2338 mg kg⁻¹, respectively (3,4).

LD₅₀ oral rat 3390 mg kg⁻¹ (3).

LC₅₀ (4 hr) inhalation rat >2720 mg l⁻¹ (3,4).

LD₅₀ dermal rat >3100 mg kg⁻¹ (3,4).

Carcinogenicity and chronic effects

No-effect level in 2-yr feeding studies: oral rat 300 mg kg⁻¹ diet; oral mouse 1000 mg kg⁻¹ diet (3,4).

Legislation

Limited under EC Directive on Drinking Water Quality 80/778/EEC. Maximum admissible concentration 0.1 µg l⁻¹ (5).

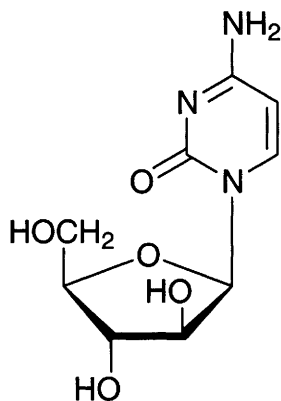
WHO Toxicity Class Table 5 (6).

EPA Toxicity Class (formulation) III (3).

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C546 cytarabine



C₉H₁₃N₃O₅

Mol. Wt. 243.22

CAS Registry No. 147-94-4

Synonyms NSC-63878; NCL-C04728; 1-(β-D-arabinofuranosyl)cytosine; 4-amino-1-arabinofuranosyl-2-oxo-1,2-dihydropyrimidine; arabinosylcytosine; 4-amino-1-β-D-arabinofuranosylpyrimidin-2-(1H)-one; Alexan; Cytosar-U

EINECS No. 205-705-9

RTECS No. HA 5425000

Uses Anti-neoplastic agent inhibiting synthesis of deoxyribonucleic acid. Antiviral agent.

Physical properties

M. Pt. 212-213°C

Solubility Water: 1 in 10. Organic solvents: chloroform

Mammalian & avian toxicity

Acute data

LD₅₀ oral mouse 3150 mg kg⁻¹ (1).

LD₅₀ intraperitoneal intravenous mouse 6400-7000 mg kg⁻¹ (2,3).

TD_{Lo} intraperitoneal pregnant rat 20 mg kg⁻¹ (4).

LD_{Lo} intraperitoneal mouse 360 mg kg⁻¹ (5).

TD_{Lo} (12 day) intermittent dose subcutaneous woman 6480 μg kg⁻¹ (6).

TD_{Lo} (36 hr) intermittent drug intravenous human 444 mg kg⁻¹ (7).

Irritancy

Primary irritant to human eye dosed at 105 mg for 7 days intermittently (8).

Other effects

Other adverse effects (human)

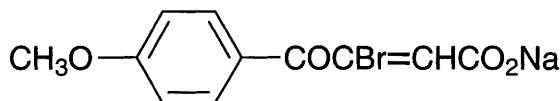
High doses of cytarabine (1 hr infusions of 3 g m⁻² 12 hr for 6 days) administered to patients with relapsed and refractory leukaemia caused nausea, vomiting, diarrhoea, alopecia, bone marrow depression, acute ceratitis, conjunctivitis and erythroderma (9).

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C547 cytembena



$C_{11}H_8BrO_4Na$

Mol. Wt. 307.08

CAS Registry No. 21739-91-3

Synonyms NCI-C50737; NSC-104801; 3-*p*-anisoyl-3-bromoacrylic acid, sodium salt; 3-bromo-3-(4-methoxybenzoyl)acrylic acid, sodium salt; sodium bromebrate

RTECS No. AS 4750000

Uses Pharmaceutical for malignant diseases. Folate inhibitor.

Mammalian & avian toxicity

Acute data

LD₅₀ intraperitoneal mouse 50 mg kg⁻¹ (1).

LD_{Lo} intravenous adult dog 1200 mg kg⁻¹ (2).

LD_{Lo} intravenous dog 200 mg kg⁻¹ (3).

TD_{Lo} 5 days intravenous human 60 mg kg⁻¹ (4).

Carcinogenicity and chronic effects

National Toxicology Program investigated cytembena in rat, mouse via intraperitoneal injection. Designated carcinogen in ♀ and ♂ rat, non-carcinogen in ♀ and ♂ mouse (5).

Genotoxicity

Mouse lymphocytes 48 mg l⁻¹ DNA inhibitor (6).

Micronucleus test intraperitoneal mouse 3200 mg kg⁻¹ positive (6).

Other effects

Other adverse effects (human)

200 mg m⁻² administered intravenously twice daily for 5 days every 5 wk to patients with stage III and IV alkylating agent-resistant ovarian carcinoma caused nausea, vomiting, mild diarrhoea, alopecia but no tumour regression (4).

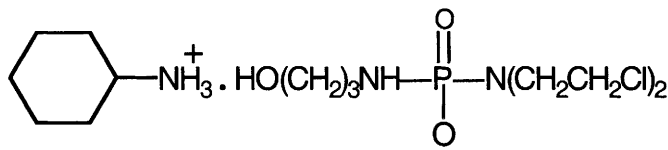
Other comments

Alkylating action has been used to potentiate the action of methotrexate (7).

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C548 cytocal alcohol cyclohexylammonium salt



$C_{13}H_{30}N_3O_3P$

Mol. Wt. 307.37

CAS Registry No. 4465-94-5

Synonyms phosphorodiamidic acid, *N,N*-bis(2-chloroethyl)-*N'*-(3-hydroxypropyl), cyclohexylamine salt; NCI-C04922

RTECS No. TD 2540000

Mammalian & avian toxicity

Acute data

LD₅₀ oral mouse 1618 mg kg⁻¹ (1).

LD₅₀ subcutaneous mouse 966 mg kg⁻¹ (2).

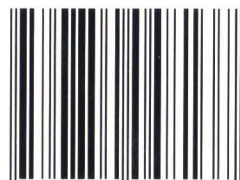
LD₅₀ intravenous mouse 400 mg kg⁻¹ (3).

TD_{Lo} intraperitoneal mouse 29 mg kg⁻¹ (4).

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ISBN 0-85404-813-8



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