Introduction to Military Toxicology: a crush course.

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Disclaimer:

It is not possible to learn the whole military toxicology in a short course. All the data given are compressed to the maximum extent. Many compounds that aren’t designed as chemical or biological warfare agents, but are included in classical military toxicology textbooks (military smokes, perfluoroisobutylene, fuels, oxidants etc.,) are not covered here. Unless specified, all concentrations / doses mentioned here are given for humans. Use this information with wisdom!

The Foundation.

Military Toxicology is a complex discipline underlined by a broad knowledge base ranging from clinical medicine and experimental pharmacology to physical chemistry, meteorology, mathematical modelling and military organisation. It deals with chemical, biological and radiological threats in modern warfare, hazardous compounds encountered on the battlefield (rocket fuels, antifreeze substances, explosives, exhaust fumes etc.,), various protection & decontamination means and so forth. This course covers synthetic and natural substances with potential of deliberate (mis)use by aggressive states / terrorist groups. Live organisms and radiation sickness are excluded due to limitations of the course.

There are more than 15 000000 compounds currently known to mankind, with approximately third part of this amount being sufficiently toxic to cause severe illness or death in humans. However, only a very limited amount is weaponised. The reasons for that lay beyond substances toxicity and are underlined by their physicochemical properties including stability, phases in which those compounds can exist in given conditions, olfactory and gustatory qualities, ease and cost of production / mass production.

NB!: In the case of terrorist use some of those reasons may lose or gain significance. Mass production of the agent chosen is rarely needed, it is not required to store it for a significant amount of time, and inflicting psychological shock rather than causing lethal casualties to occur may be the primary reason of use (e.g. current anthrax attacks in the US or Tokyo tube attacks). Besides, conventional chemical warfare agents are designed with

protected / trained enemy personnel in mind, while terrorists tend to target civilians. Even in military conflict, when chemical warfare is used on a large scale, proportion of civilians: military personnel affected is 20:1 (8:1 with nuclear weapons).

■ Physical properties of the agent include density, solubility, volatility / saturated vapour pressure, boiling/melting and freezing temperatures, viscosity and surface tension.

Density is expressed in kg/m^3 and is dependent on temperature. For example, density of sulphur mustard gas is 1.2741 kg/m^3 (20 C°). Compare it with density of water at room temperature and you'll see that mustard gas, which is liquid at 20 C°, will sink to the bottom of contaminated water sources, making its detection more difficult. In military toxicology the most useful density value is a relative density of agent compared to density of dry air at 0 C° (760 mm atmospheric pressure): 5 = 6 agent / 5 air = M agent / 28.9. To illustrate, 5 (phosgene) = 3.48, 5 (HCN) = 0.947 and 5 (Sarin) = 4.86. Thus, HCN would be quickly dispersed to upper atmospheric layers, while phosgene and Sarin are likely to contaminate low layers, especially air in various underground facilities, with Sarin being more persistent and requiring decontamination procedures.

Solubility of agents determines bioavailability (e.g. lipid solubility directly correlates with transcutaneous toxicity), efficiency of contaminating water sources and soil (water-soluble compounds have advantage), and possibility of combined use with chemical warfare agents (more on it later).

Saturated vapour pressure (P) of chemical warfare (CWA) agent can

be determined using following formula:

$\log P = 2.763 - 0.019\ T_b + 0.024\ T_{env}$

where T_b - agent's boiling temperature and T_{env} - environment temperature at given air pressure. Compounds with low P can contaminate air by evaporation (e.g. Sarin in Tokyo tube), while compounds with high P (e.g. VX) have to be aerosolised employing various techniques, such as explosive release or spray delivery.

Volatility of compounds is evaluated using maximum concentration (C_{max}), which is the amount of compound taken in the unit of saturated vapours volume at given temperature: $C_{max} = 16MP / T$, where M - molecular mass of the agent, P - saturated vapour pressure and T - temperature. In reality, C_{max} can not be achieved due to wind, rain and changes of air pressure - the compound would evaporate before reaching the balanced state with its vapour. Thus, real life concentrations of agents are likely to be 10 - 100 times lower than C_{max}. Although, they still may sufficient: Sarin C_{max} (20 C°) = 11.3 mg/L, divided by 100 = 0.113 mg/L, which is 1.5 times higher than it's LCt_{50} in unprotected humans, exposed to vapour for a minute (0.075 mg x min / L)!

Since P is dependent on boiling temperature, sometimes CWA's are divided on *volatile* (T_b < 130 C°) and *persistent* (T_b =130 - 300 C°), but as P also depends on the T_{env}, this classification is very relative. On the open terrain diphosgene is efficient for 30 min in summer time, in winter it would be efficient for <12 hrs. In case of Sarin those values are 4 hrs and 48 hrs. The dependence of C_{max} on T boiling was evaluated empirically: for compounds with T_b < 230 C° lowering of T_b on 10 C° increases volatility by 1.6 - 1.5 times, for compounds with T_b between 230 - 300 C° it would double the volatility. Chloropicrin (T_b = 113 C°) is 1.5 times more volatile than diphosgene (T_b = 128 C°). For changes of T_{env}, it is

estimated, that in between 10 - 30 C° volatility of CWA's increases by 10 % with 1° temperature rise (e.g. C_{max} of sulphur mustard is 0.625 mg/L at 20 C° and 0.958 mg / L at 25 C°). This correlation is called Herbst rule after a German chemist who established it in 1926.

From military standpoint highly volatile compounds are offensive since they can clear up the terrain from opposition forces without a need of specific decontamination when the terrain is captured. Persistent low - volatile compounds are defensive in tactical terms, since they can be used to deny contaminated areas to enemy troops (first use of mustard gas in 1917 by German army postponed planned UK/French offensive operation by 3 weeks). Sulphur mustard (H) -scorched earth was labelled "yellow zone", since German H - shells were marked by yellow cross. The term survived to modem times and is expanded to zones, contaminated by any CWA. In strategic terms, non-volatile CWA's can be used against populated areas and industrial centres as a mass destruction weapon ("poor man's nuclear bomb"). *UN Commission on Disarmament has estimated that complete decimation of 1 km^2 terrain would cost 2000 $ with conventional weapons, 800 $ with nuclear, 600 $ with VX and 1 $ with XR (!!).*

Terrorists would find that volatile agents are easier to deploy (since they may not require specific delivery equipment), but if appropriate delivery means are available, non-volatile CWA's would cause more fatalities by making rescue efforts more complicated and creating a yellow zone.

Finally, <u>viscosity and surface tension</u> of CWA's determine aerosol - forming ability of the agent, persistence of aerosol and agent's penetration into porous materials, including clothing and soil.

CWA's with low viscosity are easily dispersed on drops, evaporate fast and impregnate soil, wood and cloth quickly. They can not be used by dispersing from high attitudes due to significant loss of the agent via evaporation on its way to the ground. *Highly viscous compounds can be used from "carpet bombing height" and tend to stick to contaminated surfaces, which increases the dose delivered and makes decontamination more difficult. Substances with high surface tension are very well dispersed forming fine small droplets with minimal surface area, thus evaporating slowly and being capable of creating a persistent aerosol cloud which can cross significant distances downwind.*

Sophisticated mathematical models predicting behaviour of aerosols, including their deposition in the respiratory tract exist and are beyond the scope of this course. I*t deserves to be mentioned, that particles larger than 5 uM remain in upper airways, while those under 1 uM tend to get exhaled without significant absorption. Thus, optimal effective aerosol particle size is considered to be between 1 and 5 uM.*

■ **Important chemical properties of CWA's are their thermal stability, hydrolysis stability, interaction with oxidants, acids and bases, long - term storage stability.**

The majority of modem CWA's resist short periods of extreme heat. For example, loss of Sarin and sulphur mustard dispersed by explosive charges does not exceed 1-5 %. Solid phase heat and detonation - resistant CWA's, such as BZ, chloroacetophenone and Adamsite are deployed in thermogenerators, "smoking bombs", and can be melted with explosives to be delivered. Pyrolysis of some CWA's lead to other toxic compounds, for example diphosgene is decomposed to 2 phosgene molecules and chloropicrin forms mixture

of phosgene with NOCL at 400 - 500 C°. Obviously, proteins and peptides are not resistant to high temperatures / detonation and have to be delivered via spray delivery or special aerosol generators.

CWA's are resistant to hydrolysis by water and atmospheric oxygen. Their resistance to bases, acids, strong oxidants and halogenation determines decontamination means. Military grade CWA's are stabilised to avoid autooxidation, hydrolysis, polymerisation and corrosion. CWA munitions are usually discarded and replaced every 15-20 years. Some CWA's are incredibly reactive and can destroy protective equipment, including gas mask filters.

■ **Military properties of CWA's, such as battle concentration, contamination density, persistence and depth of toxic cloud spread are derived from their physicochemical properties, tactics of use, toxicity and environmental conditions.**

Battle concentration (mg/L, mg/m^3 or g/m^s) is a concentration of CWA, necessary for it to exert its toxic effect. For Sarin, battle concentrations are lying between 0.0001 mg/L (miosis, chest tightness) and 0.1 mg/L (instant death).

Contamination density is a mass of CWA per unit of surface area: A = M/S (g/m^2, ton/km^2). As an example, contamination density necessary to eliminate opposition protected by gas masks is 0.02 - 0.1 ton/km^2 for VX and 2-5 ton/km^2 for HD (distilled sulphur mustard with additives).

Contamination persistence is determined using Leitner formula: $\mathbf{S = p_1/p_2 \backslash M_1 \ x \ t_1 \ / \ M_2 \ x \ t_2}$, where p_1 = vapour pressure of water at 15

C°, p_2 = vapour pressure of agent at temperature t_1, M_1 = molecular weight of water (18), M_2 = molecular weight of agent, t_1 = absolute temperature, t_2 = absolute temperature corresponding to 15 C° (288 K). Basically, this formula compares persistence of agent in question with persistence of water. To illustrate, at 20 C° S values are 5707 for VX, 67 for HD, 9.9 for Soman, 3.13 for Sarin and 9.6 for Lewisite.

Real persistence of CWA's on terrain depends on meteorological factors, landscape and soil type. For example, on a sunny day, light wind, 15 C° VX persists for 21 day, HD for a week, Sarin for 4 hrs. Rain, medium strength wind and 10 C° change those values to 12 hrs VX, 2 days HD and 1 hr Sarin. In calm, sunny winter (-10 C°) conditions VX may persist for 4 month, HD - 2 month and Sarin - 2 days. On desert - type terrain persistence of CWA's is expected to be low, while clay - type soil with dense vegetations (e.g. forests) may increase agents persistence by the factor of 7.

The depth of toxic cloud spread depends on the initial concentration of CWA, speed of wind, vertical stability of atmosphere and the landscape. There are three types of vertical atmospheric stability:

Inversion (when low air layers are colder and heavier, air currents are descending) - night, early morning, clear winter days. Toxic cloud is stable, spreads efficiently as far as 20-40 km from a single release source.

Isothermia (when air temperature is balanced at 20-30 m above the surface) - morning / evening, cloudy weather. Toxic

cloud is spread to 10 -12 km from a single releasesource.

Convection (when warm and light low air layers ascend) - bright hot summer days. Toxic cloud is spread to 3 - 4 km from a single release source.

In isothermic conditions, plain terrain, single B-52 loaded with 7 tons of Sarin bombs can create toxic cloud covering approximately 250 km^2 area (since there are multiple release sources !) , leading to ~ 30 % mortality among those caught in the cloud.

■ **Toxicity of CWA's is estimated differently from toxicity estimation / evaluation in general, industrial, medical etc., toxicology.**

The fundamental difference is due to primarily inhalational and transcutaneous administration ways, usually short exposure period and the fact that many CWA's are designed to incapacitate rather than kill the victims. While LD_{50} and LD_{100} values are still used in military toxicology, the major value employed is LCt_{50}, or half-lethal concentration. LD_{50} relates to dose of compound received, while LCt_{50} relates to exposure. EXPOSURE DOES NOT EQUAL DOSE! In fact, the dose of CWA for a human with mass G (kg), inhaling air with CWA concentration C (mg/L) for time t (min) with breathing intensity V (L/min) would be **D (dose) = CtV/G.**

In sake of creating a formula allowing comparison between CWA's, Fritz Haber considered V/G ratio to be the same for same species placed in same conditions. By dividing D = CtV/G equation on V/G he derived equation ***W = Ct***, where W = "todlichkeitsprodukt" or "lethal index" = constant for a taken compound. ***W = Ct***

relationship is represented by a hyperbola and is cornerstone of military toxicology. The lower is W, the more toxic is compound evaluated. For example, W value is 80 for Soman, 150 for Sarin, 450 for Tabun, 4 000 for CLCN, 5 000 for phosgene, 15 000 for diphenylchlorarsine and 20 000 for chloropicrin. Thus, you can see that WW II - designed organophosphates exceed WW I agents by more than an order of toxicity, while diphenylchlorarsine and chloropicrin are not very toxic and are primarily used as irritants.

In reality, many of CWA's follow the Habers law, but some don't. A classical example is HCN: at low concentration CN - anions are efficiently metabolised, thus, as long as C is low, substantial total exposure may be tolerated. To refine this, Habers equation was written as ***W = C (A - E) t***, where A and E are speed of agent administration / adsorption and agent elimination in the body. Further on, the equation was adjusted to reflect crucial characteristics of targeted population. Final form of Haber's law is written as ***W = j C (A - E) t***, where j = empirically derived Jacquot coefficient, which takes following values:

J = 1 => unprotected, untrained, not warned;

J = 2 => any of 3 above positive;

J = 4 => any 2 of 3 above positive;

J = 20 => all 3 are positive;

Thus, training and education (hopefully, this course) alone can double the rate of survival ! It should be said that j = 20 is practically non - realistic value, and civilian population in Western world can be assumed to have j = 1 - the worst scenario, in which survival depends only on terrorists and the weather (or on terrorists alone, if in enclosed space)!

Since in military terms (or to inflict terror), incapacitation

could be more important than elimination, *incapacitation parameters, such as ICt50, ICt10 and ICt5 are very useful*. They are the only realistic means of toxicity/efficiency evaluation of non-lethal compounds such as irritants and psychotomimetics.

Transcutaneous toxicity can be assessed in mg (agent) per cm^2 skin surface. Transcutaneous bioavailability may be estimated using skin-venous or skin-arterial coefficients, which are ratios of transcutaneous and i.v. or i.a. LD50'es. In research facilities and manufacture of CWA's TLV (threshold limit values) are employed to protect involved personnel.

• **Classification of CWA's.**

Available classifications of CWA's include:

Classification by phase at given temperature: *solid, liquid and gaseous.* Mention, that at room temperature only few "poison gases" are actually gases !

Classification by chemical structure: organophosphates, halogenated thioethers, oximes, arsines and so on.

Toxicological classification is probably the most important to grasp for this course. It is based on ***predominant*** action mechanisms of compounds studied and is summarised in the table below:

Group and common or chemical name	**NATO designations (if any)**
Organophosphate nerve agents:	
Tabun	GA
Sarin	GB
Soman	GD
Cyclosarin	GF

Isopropylethylphosphonofluoridate	GE
Diisopropylphosphofluoridate	DFP
O-Ethyl-S-[2-(diethylamino)ethyl] methylphosphonothiolate	VM
O-Ethyl-S-[2-(diethylamino)ethyl] ethylphosphonothiolate	VE
O,O-Diethyl-S-[(diethylamino)ethyl]ethylphosphonothiolate	VG
O-ethyl-S-[2(diisopropylamino)ethyl] methylphosphonothiolate	VX
Cyclopenthyl-S-[2-(diethylamino)ethyl]methylphosphonothiolate	EA3148

Vesicants:

Sulphur mustard gases, including sesqui, double and oxygenated mustard	H, Q, HD, HQ, HT
Nitrogen mustard gases	HN-1, HN-2, HN-3
Lewisite	L
Ethyldichlorarsine, methylchlorarsine, phenylchlorarsine	MD, the "Dicks"
Dichlorformoxime (phosgenoxime)	CX
N-(2-chlorethyl)-N-nitroso-O-methylcarbamate	KB-16
N-(2-chlorethyl)-N-nitroso-O-ethylcarbamate	KB-10

Generally toxic agents:

HCN	AC
CLCN	CK
BrCN	BK
AsH3	SA
PH3	
Fe (C0)5	
Pb (C2H5)2	TEL
TCDD ("dioxin")	As a contaminant of "Agent Orange"

Suffocants:

Phosgene	CG
Diphosgene	DP
Triphosgene and other derivations of COCL2	
Chloropicrin	PS

Other halogenated nitromethanes and nitroethanes	
S2F10	Z
CLF3	

Psychotomimetics:

3-quinuclidylbenzylate	BZ
Phencyclidine	SN
LSD-25 hydrazide	LSD
Ditran (jb-329) and other "jb" compounds jb-318, jb-336)	

Irritants:

2-chlorobenzilidene malonodinitrile	CS
2-chloroacetophenone	CN
Dibenz9b.f.)-1:4-oxasepine	CR
Adamsite	DM
Diphenylchlorarsine	DA
Diphenylcyanarsine	DC
Capsaicin	CA
1-methoxy-1,3,5-cycloheptatrien	CH
Phenylbromacetonitrile	BBC
Ethyliodoacetate	SK
Pelargonic acid morpholide	

Toxins are usually reviewed separately, since they margin both chemical and biological warfare. Those, which are weaponised, include :

Clostridial neurotoxin A	XR
Staphylococcal enterotoxin B (SEB)	PG
Ricin	W
Trichothecenes and similar mycotoxins	"Yellow Rain"
Anthrax toxin	

Bacterial toxins known to be suggested for military use include

pertussis, cholera, diphtheria and tetanus exotoxins.

More general classifications, which follow from toxicological classification above include:

Lethal (organophosphate nerve agents, vesicants, generally toxic agents, suffocants, XR, W, Yellow Rain, anthrax toxin) and non - lethal (psychotomimetics, irritants, PG and other incapacitating substances) CWA's.

Slow (sulphur mustards, phosgene derivations, ricin, TCDD) and fast (the rest of CWA's) acting agents.

It is obvious, that those classifications are highly relative depending on battle concentrations of CWA's achieved, environmental conditions and j values. During WW I mortality from sulphur mustard did not exceed 2.6 %, while 2 % mortality from use of CN and CS occurred in Viet Nam ! Nevertheless, sulphur mustards are considered to be lethal, while CS and CN aren't (on the basis of their LCt50 and W values). Phosgene is a slow - acting agent, but a gasp of air with 5 mg/L phosgene kills in 2 - 3 seconds.

Military classifications of CWA's include:

Persistent and not persistent agents - reviewed in "physical properties" chapter.

Defensive (persistent), offensive (volatile, non-persistent), riot control (irritants) and sabotage agents.

Sabotage agents are compounds of particular interest for terrorists aiming to contaminate food or water supplies. Many of classical CWA's can be used to accomplish it, as well as a great deal of compounds not traditionally viewed as efficient on a battlefield. To deal with acts sabotage, very broad knowledge of toxicology / toxinology is needed. An example of CWA's specifically designed to contaminate food and water stocks include HCL salts of nitrogen mustards or a vast variety of monofluoracetate derivations, including fluorocarbon acids, their aliphatic and aromatic ethers and fluorinated alcohols. Vast variety of extremely potent natural toxins (saxitoxin, palytoxin, aconitine, anatoxin A, verrucullogen, citreoviridine, amanitine, abrin, aflatoxins etc.,) as well as tested and tried inorganic compounds (cyanides, fluorides, As2O3, arsenites, Sb, Tl, Be, Cd, Ba, Hg salts) can be used. Dealing with those compounds goes beyond the scope of this course.

Finally, on the basics of their military usefulness US army divides CWA's on group A (armed : V-gases, XR, PG, GB, HD, HT, HQ, CN, CS, CR etc.,), group B (reserve: GA, L, H, DM, DA, DC, W) and group C (obsolete, but still can be used as mass production of them takes place : CG, CK, DP, BBC, SK and so on). While group C compounds may not be efficient against protected troops anymore, they are still devastating for civilian population. Since they are produced in massive amounts for non-military use, there is a danger of terrorists sabotaging storage / manufacturing facilities of those compounds to cause their leakage and spread to populated areas. The same applies to any industrial installation employing isothiocyanates (Bhopal disaster), dioxins (Seveso disaster), some highly toxic organophosphate insecticides (TEPPh, Phosdrin, Parathion, Malathion, Tetram, Timet, Disystox, Mercaptophos etc.,), fluorine-containing oxidants, tetraethyl lead, or even common in industry gases like chlorine and ammonia.

• **Tactical mixtures of CWA's.**

To achieve maximum efficiency, agents listed above can be used in mixture with various additives and each other. There are several reasons to employ mixed CWA's:

a)Altering physical properties of agents.

Some CWA's have high freezing temperatures which make them inefficient in winter times. For example, sulphur mustard is solid below 14.5 C°. To decrease its freezing temperature, various mixtures were tested with sulphur mustard : Lewisite (66 : 34) being probably the most efficient, since both are vesicants / radiomimetics and amplify each other's action, while the mixture freezes at - 30 C°. Another frequently altered property of CWA's is their viscosity. Increasing viscosity to make agents stickier and allow their dispersion from high attitudes is achieved by adding polymers, especially polyacrylates. Examples include HD with 4-8 % polymethylacrylate or VR-55.

b)Stabilising stored CWA's.

For example, HCN tends to be very unstable when stored as it is prone to exothermic polymerisation, which may even lead to an explosion. Addition of H3PO4 in small amounts makes storing HCN possible.

c)Increasing agents skin penetration.

Some solvents significantly enhance skin absorption of CWA's. DMSO, octylamine and N,N-dimethylamide palmitate were found to be the most efficient. Experiments in Edgewood Arsenal (US) demonstrated that mixture of VX with DMSO applied cutaneously kills rabbits twice faster than pure VX. Damaged skin is penetrated very easily, thus, agents which cause fast skin necrotisation also cause

tremendous enhancement in absorption of other CWA's in mixture. CX is perfectly suited for this role and CX solution in VX is considered to be a devastating weapon.

d)Increasing toxicity of CWA's.

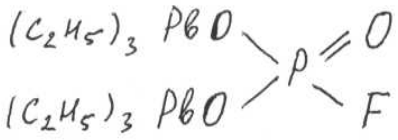
In some cases mixing CWA's increases toxicity of the mixture beyond toxicity of individual components. Mixture of CS and CN possesses stronger irritant properties than the individual compounds - sprays containing 2 % CS + 2 % CN are manufactured in Germany as efficient self-defence weapons, while modern US "Mace" is a mixture of 2 % CN with 15 % Capsaicine in oily solvent. In large concentrations, mustard gases, nitrogen mustards in particular, have anticholinestherase activity which adds on to toxicity of organophosphates. Tris-o-cresylphosphate (TOCP) has practically negligible anticholinestherase activity, but is known to increase toxicity of anticholinestherase organophosphates by orders of potency (plus elevate risk of delayed peripheral neuropathy - see data on "Ginger Jake paralysis" in toxicology textbooks). An interesting example of toxicity enhancement is particle vectoring. Adsorption of CWA's on small particles could lead to bypassing the upper respiratory tract and slow release of agents high local concentrations in the gas-exchanging low parts of pulmonary acinus. While sulphur mustard is debilitating, but rarely lethal, sulphur mustard vapour in presence of submicronic inert carbon-black particals is absolutely lethal causing lung oedema and death in less than 6 hours.

e) Various tactical reasons.

In general, mixtures of CWA's are more difficult to identify and decontaminate, and casualties are more difficult to treat. Sometimes irritants were used together with slow-acting agents to mask their use. DA, DC and DM have a short (1-5 min) latent period

and were used in mixture with lethal agents (DA+DP+CG) at the end of WW I. The logic behind such use is that if the targets were exposed to "blue cross" irritants before masking, strong irritant and emetic action of these compounds after the latent period would force enemy soldiers to unmask and become vulnerable to suffocating agents.

■ **Design of CWA's with mixed properties** opens the way to combine different toxic mechanisms in a single molecule. The earliest examples include CLCN (CK) and Palinite (COCLCN) combining toxicity of chlorine and phosgene with toxicity of HCN. On the peak of Cold War some interesting compounds combining different CWA class properties were designed, for instance bis-(3-ethyllead)-fluorphosphonate - an incredibly potent DM-like irritant at low concentrations and GB - comparable anticholinestherase agent as the concentration increases:



Modern research in this direction is rotating around chimeric proteinaceous toxins.

• **Combined injury inflicted by CWA's, conventional, nuclear and biological armaments may take place and is difficult to deal with.** Wounds or skin burns "open the gates" for chemical or biological agents to enter, with bleeding wounds being less dangerous since the agent is washed away. Vesicants are radiomimetic / immunosuppressant and add on to action of ionising radiation while decreasing resistance of affected to infection. Wounds, contaminated with vesicants, are very difficult to heal. Suffocants, inhaled ricin and anthrax spores drastically decrease already very low chances of survival if combined. Psychotomimetics

can be used to spread chaos and panic in areas, affected by biological or nuclear weapons, thus making rescue, disinfection and decontamination tasks incredibly difficult.

■ **Bypassing protective equipment** can be done by various means.

Compounds which are only weakly absorbed by charcoal of filtering gas mask include HCN and CLCN. The capacity of mask filter is worn out in 5 - 10 minutes when high concentrations of those compounds are applied.

Carbon monoxide is not absorbed by charcoal and needs a filter containing 60 % MnO2 + 40 % CuO (Hopkalite). Efficient concentrations of CO can be created in enclosed spaces by using explosive mixture of TEL and tetranitromethane (all carbon of the mixture is released as CO!). Alternatively, metal carbonyls can be used. Solutions of HCN or phosgene in metal carbonyls demand both hopkalite and traditional filters applied simultaneously and lays hopkalite filters to waste very fast.

Boron hydrides are incredibly toxic and are not absorbed by charcoal at all.

PH3 and AsH3 undergo highly exothermic oxidation on porous surfaces, leading to filter overheating and unmasking. Sulphur pentafluoride (S2F10, Z) is even more destructive for the filter contents. Chlorine trifluoride (CLF3) is an ultimate non-nuclear offensive weapon capable of setting gas mask filters and protective clothing ablaze while possessing lethal toxicity.

Liquid Lewisite easily penetrates / corrodes rubber and many

organic polymers. It can be used to get through protective gear alone or as a solvent for other, more toxic CWA's.

In general, the capacity of gas mask filter is limited and even more conventional CWA's, such as organophosphates, will eventually leak through the filter in case of continuous exposure. Thus, leaving contaminated zone as soon as possible is highly recommended, escaping should be done in a direction, perpendicular to the direction of blowing wind.

- **Delivery means**

Dispersion:

Spray delivery: the most efficient and optimal for toxins, but requires planes flying at slow speed and low attitude.
Point source explosive
release Line source
explosive release

- Bulk release - "skin" of a warhead is blown off, exposing the agent to aerodynamic release
Base ejection

Condensation:

thermogenerators, evaporating liquid CWA's quickly
pyrotechnic mixtures (for solid heat-resistant compounds - CN, DM, BZ)

Reaction:

Some compounds, so-called "gas generators", can rapidly decompose releasing massive volumes of hot gas, which heats up, disperses and spreads CWAs. An example of efficient gas generator is 3,7-dinitroso-1,3,5,7-tetraazabicyclo[3.3.1]nonane, 1 g of which releases 240 ml of nitrogen when heated.

• **A note on binary weapons.**

The first binary weapon was SA bomb, split on two compartments, one filled with Mg arsenide and second - with sulphuric acid (US, WW II). Later vesicant binary weapons employed otherwise too unstable to be stored KB-16 and KB-10 compounds. With emergence of organophosphates binary GB-2 and VX-2 ("Big I" bomb) systems became available (usual designation for binary agents is adding "2" to the unitary name). The advantages of binary weapons include safer storage, manufacturing and lower price. In addition, modular deployment is possible - replace GB-2 isopropanol container with pinacolyl alcohol container, and you get GD-2 instead ! However, there are definite disadvantages too. No chemical reaction would give 100 % outcome, thus the payload of binary munitions is 30-35 % lower, if compared to unitary ones. Besides, the reaction would not happen instantly, giving the attacked 10-20 seconds to use their protective means. In addition, components of binary munitions or reaction by-products may have specific smell or be irritating for eyes and upper airways, making detection of the attack easier. Thus, lower efficiency of binary weapons is a trade-off for their safety of manufacturing / deployment and lower production cost.

The Agents.

Organophosphate (OP) Nerve Agents.

- ***Mainstream CWA's in the majority of modern military forces due to their high toxicity, transcutaneous action and appropriate physicochemical properties.***

- Inhibit a variety of esterases, including *neuronal acetylcholinesterase (AChE), glycoprotein butyrylcholinestherase (blood plasma), erythrocytic AChE, neuropathy target esterase (NTE).* Inhibition of neuronal AChE is the most important for OPs lethal action; interaction with blood cholinesterases plays role in establishing diagnosis of OP poisoning, but does not correlate with severity of symptoms and outcome of intoxication. Peripheral AChE's may temporally sequester organophosphates, limiting their access to nervous system. In neurones, low (polyacrylamide gel) mobility AChE isoform is more sensitive to the effects of organophosphates than high mobility isoform.

- ***Inhibition of AChE's caused by organophosphates is irreversible and requires re-synthesis of an enzyme.*** Carbamates (physostigmine, pyridostigmine, neostigmine, edorphonium, tacrine) are reversible AChE's inhibitors – affected enzymes recover by 50 % in ≈ 30 min (42 μsec for bound acetylcholine). General classification of AChE's inhibitors distinguishes inhibitors binding to the anionic centre of cholinesterases (quaternary ammonium salts, methylene blue, choline itself), inhibitors that react with esteratic centre of enzymes (organophosphate insecticides, G-gases) and inhibitors acting on both catalytic centres (neostigmine, physostigmine, V-gases). Incredible toxicity of V-gases can be explained by binding to both active centres (which was the rationale behind their

design): the molecule is bound to AChE more tightly and is far more difficult to displace if compared to single–centre bound inhibitors.

- Important *non-cholinesterase effects of OP* CWA's were reported, including open-channel block of nicotinic receptors and decreasing of sodium channels inactivation by V-gases. Only 100 pmol of VX (≈ 200-fold lower than IC50 for AChE) increases neuronal excitability and facilitates neurotransmitters release, apparently – via increasing Na+ conductance. While blockade of nicotinic receptors is crucial in extreme (paralytic) OP poisoning, action of V-gases on voltage-gated Na channels may further contribute to their higher toxicity if compared to the rest of anticholinesterase compounds.

- In humans, OPs detoxification involves a high-density lipoprotein-associated polymorphic enzyme paraoxonase. Arg192 paraoxonase is more common among Japanese and hydrolyses GB & GD less rapidly than Gln192 isoform.

- ***First symptoms of OP poisoning*** strongly depend on the route of administration. If the route is inhalational, chest tightness followed by miosis in 5-7 min are first alarming signs. If skin is exposed, cold sweating of contaminated area and muscle twitching beneath it appear. Interestingly, if those affected through skin are masked, midriasis, rather than miosis, occurs as the intoxication develops. Digestion of contaminated food leads to fast development of intestinal pain, profuse diarrhoea, nausea and vomiting.

- Main effects of organophosphate nerve agents can be divided on ***muscarinic, nicotinic and central:***

Muscarinic:	*Glands*	
	Nasal mucosa	Rhinorrhea
	Bronchial mucosa	Bronchorrhea
	Sweat glands	Cold sweating
	Lacrimal glands	Lacrimation
	Salivary glands	Profuse salivation
	Smooth muscle	
	Iris	Miosis
	Ciliary muscle	Loss of accommodation
	Gut	Abdominal cramps, diarrhoea
	Bladder	Frequency, involuntary micturition
	Heart	Bradycardia
Nicotinic:	Autonomic ganglia	Sympathetic effects, pallor, tachycardia hypertension
	Skeletal muscle	Weakness, fasciculation
Central:		hypoxia, seizures giddiness, anxiety, restlessness, headache, tremor, confusion, failure to concentrate, convulsions, respiratory depression.

- ***Clinically, OP poisoning can be split on following categories:***

1. Light – initial symptoms outlined above. Recovery in 2 to 5 days.

2. Medium – predominance of muscarinic effects, so called bronchospastic or asthmatic stage. Can be fatal due to combination of bronchorrhea / bronchoconstriction. Recovery lasts for 1-2 weeks.

3. Severe or generalised – split on 3 sub-stages:

    - initial – severe muscarinic effects, suffocation & cyanosis, central effects start strongly manifest themselves: fear, dizziness, headache, speech difficulties, tremor, blurry consciousness.
    - seizure stage – tonic – clonic seizures, unconsciousness, foaming froth / salivation, no light reflex, may last for several minutes or even hours. If antidotes are not administered earlier than 10 min after seizures begin, the prognosis is very poor.
    - paralytic or comatose stage – predominance of depolarising block / nicotinic effects. Loss of pulse, body temperature falls, spontaneous defecation / urination, respiratory depression, death.
      Recovery from severe intoxication occurs in 3-8 weeks, usually with long-lasting after-effects.

4. Lightning form – strikes in 30 seconds, immediate loss of consciousness, comatose stage in 1-3 min, death in 5-15 min.

- ***Transdermal toxicity*** is accompanied by a latent period of 10-30

min and is difficult to treat as depots of OP in subcutaneous fatty tissues can be formed and sudden release of OP from them occur. If the wound is contaminated, muscle fasciculations in it can be seen.

- ***Delayed effects of OP's include:***

  - muscle necrosis. Lesions may appear in 12 to 24 hrs, recovery begins in 2 days and is complete in 2 weeks. Prevented by proper use of standard OP antidotes. More severe in high activity musculature, e.g. diaphragm.

  - intermediate syndrome. Proximal skeletal musculature weakness and cranial nerve palsies; 12–84 hrs post-exposure, may require artificial ventilation.

  - delayed neuropathy. Symmetrical sensorimotor axonopathy which tends to be more severe in long axons and occurs 7-14 days post-exposure. It is caused by inhibition of neuropathy target esterase (NTE) by OP's, leading to axonal demyelnisation. Organophosphate agents are unlikely to cause delayed neuropathy since NTE – inhibiting concentrations of those compounds exceed their lethal concentrations by 1-2 orders of magnitude.

  - chronic neuropsychiatric abnormalities, which are likely to be due to excitotoxic events accompanying OP poisoning. Subseizure epileptic discharges: increased frequency, increased β-rhythm, abnormal high voltage slow waves. Excessive dreaming, sleep-talking, nightmares, insomnia, jitteriness, restlessness, tension, emotional liability, depression. Morphological changes resembling those following

status epilepticus are present.

- Individual agents (Figure 1) were selected on the basis of their toxicity, required physicochemical properties and ease of production. G-gases (supposedly, “G” comes from “German”) were discovered in search for insecticides, V-gases (supposedly, “V” stands for “Venomous”) are designer substances, exploiting our knowledge of cholinergic transmission. A variety of OP CWA’s presented on the table enclosed was developed to suit different tactical aims. For example, VX (Tb ≈ 298 C°) is ideal for creating yellow zones; Sarin (Tb ≈ 151.5 C°) is suitable for fast offensive action without a need to decontaminate terrain afterwards, while Soman (Tb ≈ 198C°) is somewhat in between VX and Sarin in terms of both toxicity and tactical properties. GB, GD and VX are probably the most common organophosphate nerve agents expected to be used on the battlefield; however terrorists may opt for any OP CWA available. Tabun, even though it is obsolete, was used by Iraq in Iraq-Iran war since it does not contain fluorine, thus manufacturing of GA is easier & cheaper if compared to other OP’s (silver-lined reactors not required).

Tabun (GA) is a colourless transparent liquid with pleasant fruity smell. Impure product is yellow-green to brown and smells bitter almonds (HCN) or, in large concentrations, fish (dimathylamine). Tb ≈ 237-240 C°, T freezing ≈ - 48 C°, C max = 0.6 mg/L(20C°), which does not allow to create lethal concentrations by evaporation at room temperature and below. Detonation-unstable, thus spray dispersion is the only efficient mean of Tabun delivery. Density ρ = 1.0778 g/cm² (20 C°), δ = 5.6. Water solubility is 12 % at 20 C°. Half – life in water - 9 hrs (20C°), soil – 1-1.5 days. Viscosity 2.6 P (20C°). LCt50 = 0.4 mg x min / L; LD50 cut = 15 mg/kg; LD50 per os = 5 mg / kg.

Sarin (GB) is a colourless transparent liquid with very weak fruity smell. Tb ≈ 151.5 C°, T freezing ≈ - 57 C°, C max = 11.3 mg/L (20C°), which allows creating lethal concentrations by evaporation under 1 min exposition. Detonation-resistant. Density ρ = 1.0943 g/ cm² (20 C°), δ = 4.86. Completely miscible with water, half – life in water – 46 hrs (20C°, neutral pH). In soil, 90 % are eliminated in 5 days. Viscosity 1.82 P (20C°). LCt50 = 0.075 mg x min / L; LD50 cut = 24 mg/kg; LD50 per os = 0.14 mg / kg. NATO ammunition marking: 3 green rings and label “GB GAS”.

Soman (GD) is a colourless transparent liquid with a smell of camphor. Impure product is yellow – brown. Tb ≈ 198 C°, T freezing = -80 C°, C max = 3 mg/L (20C°), which allows creating lethal concentrations by evaporation under 1 min exposition. Detonation-resistant. Density ρ = 1.0131 g/ cm² (20 C°), δ = 6.33. Limited water solubility (1 % at 0 C°, 1.5 % at C°), but due to its high toxicity even this amount of GD dissolved can be fatal. Half – life in water 10 hrs at 30C°, neutral pH. Rapidly hydrolyzes in soil. Viscosity is high and was not disclosed to public. LCt50 = 0.03 mg x min / L; LD50 cut = 10 - 20 mg/kg; LD50 per os = 0.02 – 0.04 mg / kg. Strongly cumulative. NATO ammunition marking: 3 green rings and label “GD GAS”.

VX is a colourless transparent liquid resembling glycerol. Impure products are oily (resembling motor oil), yellow to dark brown and smell rotten fish. Tb ≈ 298 C°, T freezing = -39 C°, C max = 0.0105 mg/L (25C°), which does not allow creating lethal concentrations by evaporation in moderate climes; however in tropics it is possible. Detonation-resistant. Density ρ = 1.0083 g/ cm² (25 C°), δ = 9.2. Water solubility 3 % at 25 C°, half – life in water 428 hrs (20 C°, neutral pH). In soil 90 % are degraded in 15 days. . Viscosity is high and was not disclosed to public. LCt50 = 0.01 mg x min / L; LD50 cut = 0.1 mg/kg; LD50 per os = 0.07 mg / kg. Strongly

cumulative. Very lipid soluble, absorbed through skin in 5 minutes. 95 mg liquid VX on the surface of contaminated summer garments worn for 8 hrs constitute LD50 for a 70 kg human, symptoms will appear in 3-24 hrs. For undamaged, unprotected skin this dose is 10 mg, symptoms emerge in 1-24 hrs. NATO ammunition marking: 3 green rings and label “VX GAS”.

- **Antidotes for OP poisoning include M-blockers, cholinesterase reactivators and diazepam.**

Atropine citrate is administered i.v. or i.m. in aliquots of 2 mg as often as every 5 min, until secretions dry out and heart rate is above 90 beats / min. Up to 50 mg of atropine may be needed in 24 hrs period. *Diazepam* (10mg) is administered (i.m.) with the third dose of atropine to combat convulsions, fasciculations and tremor. Lipid soluble M-blockers, which can reach CNS (ironically, they include BZ!), have advantage over atropine, but were withdrawn in 70-es due to their psychotomimetic side effects. Soviet military medics developed *Afin and Budaxim*, that combine M- and N-anticholinergic activity and are efficient at reversing nicotinic effects of OP’s, including depolarising neuromuscular block occurring at the comatose stage. Anticholinergic therapy MUST be supplemented with cholinesterase reactivators, since atropine & Co are competitive antagonists that form ionic bond with active site of M-cholinoreceptors, while OP’s covalently bind to cholinesterase deactivating affected enzyme molecules forever. Thus, with the time action of OP’s is likely to overcome blockade of cholinoreceptors unless active cholinesterase level is restored.

Cholinesterase reactivators are oximes (see Figure 2), capable of nucleophilic attack on the phosphorus in enzyme-bound OP, which is followed by splitting of oxime-phosphonate, as shown on the scheme. The efficiency of oximes as antidotes depends on the agent they are used to antagonize. Pralidoxime is effective against Sarin and VX

but not Tabun, Obidoxime is efficient against both Tabun and Sarin, HLo-7 works for Tabun and GF (Cyclosarin) poisoning. Standard military manuals prescribe 15 % dipiroxime bromide 1-2 ml i.m., 30 % pralidoxime chloride or iodide 1 ml i.m., or 25 % obidoxime dibromide 1-2 ml i.m. Due to the phenomenon called “cholinesterase ageing” (see Figure 3), cholinesterase ageing time for Soman is 2 min, Sarin – 5 hrs, Tabun – 14 hrs and is very long-lasting for VX), oximes are not efficient against Soman intoxication, with possible exemption of novel Hagedorn oximes HI-6 and HLo-7. However, use HI-6 and HLo-7 presents practical difficulties, since these oximes are not stable in aqueous solutions and expensive “wet-dry” auto injection devices are needed. Thus, pre-treatment by a carbamate anticholinesterase is recommended if Soman use is expected.

- *Prophylaxis of OP poisoning* is based on the idea that carbamate-bound AChE would not bind OP’s, but would reactivate spontaneously in ≈ 30 min. Administration of 30 mg pyridostigmine bromide (PB) every 8 hours orally maintains AChE activity at 60-80 % of physiological norm without significant performance degradation and was employed during the Desert Storm operation. Pyridostigmine pre-treatment provides strongest benefits with Soman and Tabun, but no benefit with Sarin or VX. Besides, while being life-saving, pre-treatment does not protect from performance impairment inflicted by GA and GD.

- *Gulf War syndrome* is an issue directly related to pyridostigmine pre-treatment. A study of 41 650 US soldiers, 34 000 of whom took PB pills for 6-7 weeks reported mild muscarinic effects (increased flatus, abdominal cramps, soft stools, urinary urgency, headaches, rhinorrhea, diaphoresis and extremity tingling) in approximately half of that population. Many Gulf War veterans experienced bad dreams, vertigo, slurred speech, rashes, oedema and urticaria,

spiking hypertension with epistaxis which correspond very well to psycho-neurological consequences of anticholinesterase agents exposure combined with … early and well-forgotten symptoms of bromism ! Indeed, Gulf War participants were subjected to long periods of heat stress & dehydration with water but no salt supplementation pills available. Low-salt diet greatly increases the half-life of bromine elevating possibility for intoxication by bromide of PB. In additional, forced swimming tests in mice demonstrated that stress increases pyridostigmine access through blood-brain barrier by 2 orders of magnitude (!), suggesting that war stress makes affected far more succeptible to central effects of pyridostigmine. Another study demonstrated, that various sympathomimetics and caffeine greatly exaggerate pyridostigmine toxicity.

Vesicant Agents.

● Even though the majority of vesicants was designed during WW I and in a period between both world wars, *they still remain to be mainstream CWA's in the majority of armies, due to their transcutaneous action, high incapacitating potential, delayed action / high persistence of some vesicants and, perhaps most essentially, easy accessibility, mass production and very low cost of manufacturing.*

● Chemically, vesicants are united by one common property: they all are actively *alkylating or acylating compounds* attacking atoms with free electron pairs (Figure 4). However, this property is shared by many classes of organic compounds, including halogenated thioethers and tertiary amines, primary arsines, oximes, ketones and complex ethers of strong acids. Acylating compounds tend to be less persistent than alkylators and their toxic effects develop more

rapidly.

● Even though vesicant effects of crude mustard gas were spotted as early as 1859, mechanisms underlining blister formation are still unclear. Recently, it was suggested, *that inhibition of protein phosphatases, in particular protein phosphatase IIa by vesicants disrupts desmosomal integrity and leads to blistering.*

● On the contrary, *mechanisms explaining general toxicity possessed by vesicant CWA's are well-established*. *They involve alkylating or acylating key cellular macromolecules, especially DNA,* as the enclosed Figure 5 shows using "classical" mustard gas as an example. Its sulphonium ion produces adducts at the N7 position of guanine and N3 position of adenine; immonium ions formed by nitrogen mustards only form N7 alkylguanine. *Cells in early S phase (DNA synthesis) and in late G1 phase (interphase) are particulary sensitive to the effects of vesicant attack on DNA and RNA.* Cross-linkage, coding errors (alkylated guanine – thymine pairs) and breaks of DNA strands stop normal DNA replication and lead to activation of PARP. Since for a single act of adenine polymerisation PARP requires 4 molecules of NAD, PARP activation may lead to a fast ATP depletion. Besides, alkylators are renowned for their glutathione-depleting properties. Altogether, systemic toxic effects of vesicants resemble consequences of free radical overload observed in radiological damage, thus these CWA's are commonly called ***"radiomimetics".*** This resemblance spans into an actual clinical intoxication picture, which includes severe immunosuppression, damage to rapidly reproducing tissues, nausea and vomiting, hair loss, depression, post-mortem changes resembling changes in radiation sickness, mutagenesis and carcinogenesis.

● *Most-known vesicant CWAs include sulphur and nitrogen mustard gas variations, Lewisite and dichlorformoxime (phosgeneoxime),* as supplemented Figure 4 shows. Very frequently mixtures of vesicants

are used due to easier bulk synthesis of their mixtures compared to pure agents and advantages, provided by mixtures in terms of their physical properties.

Sulphur mustard (β,β-dichlorodiethylsulphide, H – impure, HD - distilled) is a colourless oily liquid with a weak smell of castor oil. Impure product is yellow to dark brown oil with a specific smell of mustard / garlic. Tb ≈ 217 C°, T freezing ≈ 14.4 C°, C max = 0.625 mg/L(20C°), which is 10 times of lethal concentration at 30-60 min exposition and will definitely lead to formation of skin lesions. Detonation-stable, great deal of delivery means is available. Density ρ = 1.2741 g/cm² (20 C°), δ = 5.5. Water solubility is 0.08 % at 20 C°, forms thin oily film on water surface due to its high surface activity. Half – life in water – 10 min (20C°); hydrolysed and bound in soil. Viscosity 5.91 P (10C°) and is often adjusted to higher values by polymeric additives, for example US military employs UCON 75-M-50000, which increases HD viscosity by 2 orders of magnitude. LCt50 = 1.5 mg x min / L; LD50 cut = 70 mg/kg; LD50 per os = 1-2 mg / kg. Transdermal LD50 (1-1.5 teaspoons) covers 25 % of body surface. A droplet as small as 10 μg induces vesication. Skin penetration by HD vapour is 1.4 μg / cm² x min (70 F°), 2.7 μg / cm² x min (88 F°); liquid – 2.2 μg / cm² x min (60 F°), 5.5 μg / cm² x min (102 F°). Thus, hot weather significantly amplifies mustard gas toxicity. If a droplet of HD is placed on skin, 80 % of it will evaporate, 2 % remain bound in the skin and 18 % reach circulation. Out of these 18 %, 22 % will be excreted in 24 hrs, but the bulk would remain tightly bound to affected tissues due to mustard gas alkylating properties. Genitals and eyes are particularly sensitive to vesicant action of HD; concentrations causing skin erythema of genitals are half of the concentrations causing it in skin elsewhere; 1.2 μg/L after 45 min exposure cause photophobia, blepharospasm and conjunctivitis lasting for 4 weeks, with a complete recovery in 3 month.

HD-induced skin lesions appear after *asymptomatic latent period* lasting for 2-24 hrs and start from erythema, resembling one in sunburn or scarlet fewer. Erythema of more than 20 % body surface indicates fatal poisoning. Blistering appears 12-24 hrs post-exposure, on the margin of erythematic skin small vesicles are formed (so-called “mustard bracelets”) and expand, eventually merging into large blisters, or bullas. The blisters are 0.5 to 5 cm^2 in diameter, dome-shaped, thin-walled, painless, easy to rub off, surrounded by erythema, blister fluid is initially thin and clear, later it turns yellowish and coagulates. It does not contain sulphur mustard and is not a vesicant. After the blisters burst / open up, deep necrotic ulcers appear with a possible full-sickness skin loss, in particular in genital area. Skin inflammation reaches maximum in 10-14 days, regeneration stage starts in 2-4 weeks. Recovery is very slow and may last for 1-4 month. Affected skin is blackened and scarred. Skin contact with HD vapour usually results in I-II degree and liquid HD – III-rd degree burn. Dark-skinned individuals are more resistant to vesicant action of HD than whites.

Inhalational effects of HD also starts following a latent period lasting from 12 hrs (light degree) to 30 minutes (probably fatal case). Symptoms incorporate hoarseness or even aphonia, dry barking cough, loss of taste/smell, tachypnea, chest pain, necrosis of larynx, trachea and bronchi epithelium, formation of obstructing “diphtheric” membranes in severe cases. Laryngospasm is a cause of acute death in HD poisoning, among patients who need artificial ventilation 87 % die. Delayed death usually occurs in 4-7 days from massive pulmonary damage complicated by infection, including (immunosuppression-propelled) sepsis.

Neurological effects of HD in excessive amounts include hyperexcitability, convulsions, coma and death with few pathologic

abnormalities. Anticholinesterase action is suspected.

Radiomimetic action of HD is manifested by nausea/vomiting, diarrhoea, apathy, depression, high fever, weight loss, depletion of all elements of bone marrow and a replacement with fat. Granulocytes and megacaryocytes are more susceptible to HD damage than erythropoietic cells. From day 1 to day 3 white blood cells count in peripheral blood increases (inflammation). Severe leukopenia begins on day 3 and reaches nadir in 6-9 days. If white blood cells count falls below 200 cells/m^3, the prognosis is very poor.

Long term effects of HD include chronic respiratory diseases including cancers, skin pigmentation abnormalities, scars, skin cancer, ophthalmologic problems, bone marrow depression, sexual dysfunctions, teratogenesis, sensitivity to HD & Co and psychological effects.

HD derivations include “oxygen mustard”, “double mustard”, “sesqui mustard” and nitrogen mustards.

Oxygen mustard (T) is usually deployed as a component of HT mixture of 60 % HD with 40 % T. Oxygen mustard is a colourless oil, ρ = 1.2311 g/cm^2, C max = 0.0024 mg/L (25C°) (won’t be efficient by evaporation), Tb > 320 C°, T freezing = 10 C°, but HT freezes at -25 C°. Oxygen mustard is 3.5 times more toxic, than HD.

Sesquimustard (Q) is crystals with low water solubility, Tb > 300 C°, T melting = 56.5 C°, C max = 0.0004 mg/L (25C°). Sesquimustard is 5 times more toxic, than HD, and is usually deployed in a mixture with HD, designated HQ.

NATO sulphur mustards ammunition is marked by two green rings and

“HD GAS” label (“HT GAS” or “HQ GAS” when appropriate).

Nitrogen mustards were developed to contaminate soil and water sources during the WW II. They appear to be less potent vesicants but more efficient radiomimetics than HD, with a higher incidence of neurological symptoms as well. Transcutaneous LD50 of nitrogen mustards lies between 10 and 20 mg/kg, which is 3.5 – 7 times lower than its value for HD, they are also 10 times more potent than HD when affecting the eyes. Nitrogen mustards are oily liquids without colour and smell; impure products are yellow-brown and smell fresh fish. Properties of nitrogen mustards are summarised on the table below:

NATO code	LCt50 Mg x min /L	T b C°	T freez C°	C max mg/L	ρ g/cm³
HN-3	1.5	230-235	-4	0.12	1.23
HN-2	3	180	-60	3.58	1.12
HN-1	1.5	195-200	-34	2.29	1.09

Due to the potent radiomimetic action of these compounds, leukaemia is a frequent long-term of nitrogen mustards exposure, not usually seen with HD.

Lewisite (L) is oily colourless liquid which consists of trans- and cis-isomers with trans-lewisite being more toxic. Impure product is amber to black with odour of geraniums. Tb = 190C°, T freezing = -10-15 C°, C max = 4.41 mg/L(20C°), ρ = 1.88 g/cm³, δ = 7.2. Water solubility is $\approx$ 0.05 %, hydrolyzed by water, thus is not very suitable for use in rainy conditions. LCt50 = 1.3 mg x min/L, LD50 cut = 20 mg/kg (30 drops for a 70 kg man), LD50 per os = 5-10 mg/kg.

Main differences between L and mustard (H) “gases” are:

- there is no latent period with L
- L is a strong irritant that causes pain and adsorbs through skin 2-4 times faster
- erythema is painful and oedematic
- instead of merging vesicle “bracelets” large vesicles are formed straightaway
- inflammation peak is 2-3 days
- recovery (1 week) and healing (3-4) weeks is faster
- can cause pulmonary oedema in large concentrations
- can cause “lewisite shock” by increasing capillary permeability
- secondary infections are less common
- less eye damage
- subsequent skin pigmentation less common
- efficient antidotes exist

Many of L effects are determined by the presence of As, and linked to binding to dihydrolipoic acid of the piruvate dehydrogenase complex => preventing formation of Acetyl-CoA from piruvate. Lewisite ingested with food would cause typical signs of arsenical poisoning: severe stomach pain, vomiting, watery diarrhoea, numbness and tingling, especially in the feet, thirst and muscular cramps. Neuropathy, encephalopathy or nephritis may follow, intravascular haemolysis and haemolytic anaemia can lead to renal failure.

Other organic arsines similar to L, but less potent, include methyl-, ethyl- and phenyl dichlorarsines. While they have lost their military significance now, terrorists may opt for whatever they’ve got at hands.

Dichlorformoxime (phosgeneoxime, CX) is colourless prismatic crystals; impure product is a yellow-brown liquid with an irritating smell. Crystals melt at 39-43 C° and boil at 129 C°. C max is very high: 20-25 mg/L. CX is unstable in water but can be stored indefinitely in ethyl acetate. Dichlorformoxime is a potent radiomimetic, but is not strictly a vesicant like H-gases and L. It causes very fast and painful lesion onset (thus, called “nettle gas”) followed by rapid tissue necrosis. Pain spreads around the whole body, including uncontaminated areas. Affected site becomes greyish with a boarder of erythema, healing of necrotic ulcers is very slow. Inhalation of CX leads to phosgene-like lung oedema and thrombosis of pulmonary arteries. CX is very well-absorbed and, independently of the administration route its LD50 is in range of 10-30 mg/kg. Concentrations above 1 mg/L induce strong nettle effects. Solutions of CX are efficient when its concentration is above 8 %.

Both L and CX penetrate garments, even rubber very quickly.

- ***Treatment*** of H-gases and CX poisoning is largely symptomatic. It has been suggested that early 30 % i.v. infusion of 30 % $Na_2S_2O_3$ can decrease radiomimetic effects of “mustards”, besides, compounds given in radiation sickness (cystamine sulphate, WR-2721) or immuno stimulants can be used. Antibiotics are crucial, since in many cases secondary infection rather than immediate toxicity of radiomimetic agents is a cause of death. For organic arsines poisoning, specific and efficient antidotes are available (Figure 4), and include Dimercaprol (BAL), which is water-insoluble and applied on skin, while more modern DMSA and DMPS can be administered orally or i.m. All those compounds are –SH group-possessing arsenic chelators, which bind L as shown on a Figure 4.

“Generally Toxic” chemical warfare agents

are a group of miscellaneous compounds, united by the fact of being able to affect multiple organs without predominance of a single physiological mode of action, such as neuromuscular block & muscarinic effects of organophosphates. In the majority of Western sources this group is not defined, while separate members of the group (usually cyanides) are described. This leads to some potentially lethal agents being overlooked and ignored, as in the case of phosphine, arsine and various organometallic substances.

Many, but not all compounds belonging to this group are metabolic poisons, which interfere with tissues oxygenation.

Practically all compounds described here are very widely used in industry, thus excessive amounts of information considering their (especially chronic) toxicity are available in industrial toxicology/ hygiene literature, thus, this chapter is centred around acute toxicity and peculiarities of those substances if employed for military/terrorist use.

Practically all compounds described here are Class C (reserve) or potential chemical warfare agents. Only HCN and CLCN have seen / are likely to see significant military use, while AsH3/PH3/metal carbonyls could be reserved for special occasions, likely as components of multi-agent mixtures or binary munitions. Since to employ these agents efficiently significant battle concentrations must be achieved, sophisticated delivery means and large agent quantities are demanded, putting specifically synthesised and deployed generally toxic CWA’s out of terrorists reach. However, ***it is mass production of those substances which makes them dangerous in terms of terrorist use,*** as it was outlined in The Foundation.

Insecure HCN – storing/producing facility upwind from a populated area is an obvious target for conventional attack with explosives. Besides, those agents play well-known role in assassinations and contamination of food stocks, such as recent KCN contamination of tomato juice batch, in which Al Quaeda are primary suspects.

Cyanides are probably the most important generally toxic CWA's. HCN seen some action in WW I mixtures, when the French used Vinsennite (50 % HCN, 30 % AsCL3, 15 % SnCL3, 5 % chloroform) and Mangannite (46 % HCN + 54 % AsCL3), while the British released mixture of 50:50 HCN/AsCL3 (apparently, without any colourful name attached). However, delivery means of the time were not sufficient to create necessary battle concentrations and expectations about military efficiency of HCN have failed. Zyklon B, used in Nazi concentration camps, consisted of Ca sulphate (in accordance to some sources - Ca oxalate) impregnated by HCN (40 % of Zyklon B powder by mass). Since WW II, improved delivery methods allow creating concentrations of HCN reaching 10 mg/L in low atmospheric lair for a short period of time. Concentrations that high would be absolutely lethal for masked personnel, due to both skin resorbtion and exhaustion of mask filter capacitance for HCN.

HCN (AC) is a colourless transparent liquid with the infamous smell of bitter almonds (different sources I came across tell that 20, 40 or 60 % of humans do not detect this smell). HCN vapour is known to alter the taste of tobacco smoke and make it intolerable, thus providing additional empiric mean of detection. Tb = 25.7 C°, T freezing = - 13.3 C°, C max = 873 mg/L(20C°), which allows creating lethal concentrations by evaporation under 1 min exposition. Detonation-sensitive, in fact liquid NCN is an explosive nearly as potent as trinitroglycerol, providing the detonator was applied. Mixtures of HCN with air are also explosive, generating volume (vacuum) explosions. Density ρ = 0.6894 g/ cm² (20 C°), δ = 0.947.

Completely miscible with water, but water solutions are easily hydrolyzed. Viscosity is very low, this HCN is famous for being easily diffused through porous materials (e.g. garments) and highly absorbed by various objects (even rubber would absorb HCN, 2 g HCN per 100 g rubber; food, red bricks, wood and even concrete can absorb HCN). LCt50 = 2 mg x min / L; LD50 cut = 100 mg/kg; LD50 per os = 1.0 mg / kg (1.8 mg/kg for KCN and 2.4 mg/kg for NaCN). NATO ammunition marking: 1 green ring and label “AC GAS”.

Cyanides mainly act by binding to the Fe^{3+} in the cytochrome oxidase complex (cyt a-a3), thereby preventing reduction of iron and inhibiting the final step of oxidative phosphorylation in the respiratory chain. Apart from cytochrome oxidase, CN anions inhibit other metalloenzymes (catalase and peroxidase – Fe3+; succinate dehydrogenase (Fe-S); SOD (Cu, Zn); carbonic anhydrase, alkaline phosphatase and alcohol dehydrogenase (Zn); xanthine oxidase, xanthine dehydrogenase, aldehyde and sulphite oxidases (Mo) and glutathione peroxidase (Se). Besides, cyanides form cyanohydrins with enzymes containing carbonyl group in the active centre (pyridoxal phosphate-dependent enzymes, for example glutamate decarboxylase – contribution to cyanide-induced seizures ?).

Interestingly, HCN exists as two tautomers: nitrile and isonitrile ($HCN <-> HNC^{--}$) and isonitrile is far more toxic than the nitrile. At room temperature HCN contains 99-99.5 % of nitrile and 0.5-1 % isonitrile, which is mainly responsible for its toxicity.

Since cyanides are frequently encountered in nature, multiple mechanisms of their elimination exist. It was calculated that in humans 0.017 mg of CN- are eliminated per kg weight / min, thus HCN does not follow the classical Haber’s Law. Main elimination path for HCN is via mitochondrial rhodanese (thiosulphate reductase) – catalysed transformation of CN- into SCN- in the presence of

sulfane sulphur (from Cys or Met). Other enzymes that metabolise CN- include mercaptopiruvate sulphurtransferase and cystathionase. Methaemoglobin, NO, heavy metals and carbohydrates all scavenge cyanide anions.

Light HCN poisoning is manifested by feeling the smell of bitter almonds (but see the comment above), metallic taste and bitterness in the mouth, “scratching” in the throat and nose, dizziness, fatigue, weakness. *Medium stage HCN poisoning adds* noise in the ears, pulsation of temporal arteries, nausea & vomiting, gasping for air, speech difficulties, bradicardia, pain in the chest, muscle weakness. Mucose membranes and face often turn pink. *As severe poisoning develops,* hyperpnea follows, skin is pink, pulse is slow and tense, consciousness is dimmed, affected are excited, anxious, afraid of dying, experience angina-like chest pain, stagger, pupils are dilated. Then the consciousness is lost and intense tonic-clonic seizures develop. During the seizures skin is bright pink, pupils dilated, exophthalmia, corneal reflex is absent, pulse is slow, blood pressure is normal or slightly elevated, breathing is arrhythmic and infrequent, urination and defecation often take place. Seizures may last from several minutes to several hours and are followed by paralysis, coma and cardiac arrest.

Lightning form of cyanide poisoning leads to hyperpnea in 15 seconds, loss of consciousness and fall in 30 seconds, apnea and seizures in 3-5 min, coma and cardiac arrest in 5-8 min. Oral cyanide poisoning is similar to the inhalational, but develops slower, in 15 – 30 min.

A common misconception is to think that cyanide-caused death is immediate or followed by a complete recovery. Recent studies suggest that death could be delayed for up to 8 days. Neurological

sequelae of HCN poisoning can be delayed for as long as year and are excitotoxicity – related (similar to changes observed after severe CO poisoning; include peripheral neuropathies, difficulties to concentrate & memory disturbances and, in some patients, Parkinsons-like syndrome).

Treatment of cyanide poisoning is based upon combination of enhancing natural metabolic elimination of cyanides and chemical scavenging of CN-anions. Enhanced enzymatic detoxification is done via providing additional sulfane sulphur, since its availability is a rate-limiting factor for mitochondrial rhodanese. Usually sodium thiosulfate (30 % solution, 20-50 ml i.v.) is employed: $Na2S2O3 + CN- = SCN- + Na2SO3$.

Since in high loads of CN- natural detoxification of cyanides causes only a slow fall in blood plasma CN-, immediate CN-binding is required. This is performed by several means, such as methaemoglobin-forming compounds (amylnitrite to sniff (1ml ampulae, every 10-12 min) sodium nitrite (1 % solution, 10-20 ml i.v.), 4-dimethylaminophenol (15 % solution, 3-4 mg/kg i.v.), cobalt-containing CN-complex-forming antidotes (dicobalt edetate (15 % solution, 10-20 ml i.v, hydroxycobalamine), or cyanhydrin-forming substances (glucose (10-20 ml 20-40 % solution i.v.), dioxyacetone). Consider the following reactions:

MetHb (Fe+++) + CN- = CN(Fe+++)MetHb (therapeutic level is ≈ 30 % MetHb)
Co2 EDTA + 2 CN- = (CN)2 Co2 EDTA
O=CH-(CHOH)4-CH2OH + HCN = NC-CHOH-(CHOH)4-CH2OH (the forming of cyanhydrine with glucose).

NB!: *in fire victims fatalities have ≈ 5 times HCN concentration in blood plasma then survivors. CO and HCN show synergism, as they block tissue oxygenation on two different levels.* Thus, in cases of

cyanide poisoning combined with fire/gunpowder/etc., smoke lowering levels of functional haemoglobin with MetHb–formers is undesirable. Use cyanhydrin–producing antidotes. In oral cyanide poisoning give potassium permanganate solution (1:1000), induce vomiting and follow with antidotes listed above. Symptomatic treatment of cyanide poisoning may include administration of diazepam and chlorpromazine.

Cyanogen Chloride (CK) is an colourless gas which smells HCL. Tb = 12.6 C°, T freezing = - 6.5 C°, C max = 3300 mg/L (20C°), which allows creating lethal concentrations by evaporation under 1 min exposition. Detonation-resistant. Density ρ = 1.218 g/ cm^2 (4 C°), δ = 2.1. Water solubility is low, hydrolysed on HCL and HOCN at room temperature, however air humidity does not lead to fast CLCN hydrolysis. LCt50 = 11 mg x min / L, death would occur in 1-15 min; not toxic transcutaneously. *CK is a strong irritant at low concentrations*, irritation threshold ≈ 0.0025 mg/L. In WW I CK was used in mixture with AsCL3.

Arsine (SA) is a colourless gas which smells garlic. Tb = - 55 C°, T freezing = – 116.3 C°, C max is not applicable as it can only be deployed via arsenides hydrolysis (2AsAL + 3 H2O = 2AsH3 + AL2O, also see the Note on Binary Weapons in The Foundation). Mixtures of AsH3 with air in range between 4.5 – 68 % are explosive. δ = 2.69. Chemical properties are outlined in inorganic chemistry literature. LCt50 = 1.8 mg x min / L; concentrations below 0.01 mg/L are safe. Not toxic transcutaneously.

AsH3 blocks erythrocyte catalase, resulting in H2O2 accumulation and haemolysis. Haemolysis leads to liver and spleen necrosis; nephrons are clogged by decomposing red blood cells (possibility of kidney failure); anaemia causes CNS hypoxia (primary cause of death in acute AsH3 poisoning). Depending on the concentration of AsH3, symptoms of poisoning occur after 2-15 hrs latent period; if the

concentration is very high – after 20-30 min. If the latent period is below 3 hrs, the poisoning is severe; 6 hrs or more – medium or light. Poisoning starts with dizziness, headache, weakness, nausea and vomiting. Urine turns red (haemoglobin) and then dark brown (haematin), liver and spleen are enlarged, fever and jaundice are observed. In severe cases anoxia and seizures follow, death occurs in 2-8 days. Dispersed metal arsenides are highly toxic and can cause skin necrotisation. *Traditional chelating antidotes for arsenic (see data on Lewsite) are inefficient against AsH3, cystamine sulphate must be used in conjunction to symptomatic treatement.*

Phosphine is a colourless gas which smells calcium carbide. Tb = – 87.8 C°, T freezing = – 133.8 C°, C max is not applicable as it can only be deployed via phosphides hydrolysis ($Ca_3P_2 + 6H_2O = 2PH_3 + 3Ca(OH)_2$). δ = 1.17. Chemical properties are outlined in inorganic chemistry literature. 1.5 mg/L kill after 10 min exposure, 0.3 mg/L are absolutely lethal; concentrations below 0.01 mg/L are safe. Not toxic transcutaneously.

PH3 does not cause haemolysis like AsH3, but induces lung oedema. Poisoning symptoms include headache, dizziness, shortness of breath, weakness and nausea. Midriasis and loss of consciousness follow. Death occurs in several days from lung oedema or cardiac arrest. Survivors of acute phase suffer from liver necrosis and pneumonia.

As outlined in The Foundation, main military value of arsine and phosphine lies in their ability to oxidise on porous surfaces releasing significant amounts of heat, thus leading to unmasking.

Tetraethyl lead (TEL) is a colourless volatile liquid with pleasant aromatic smell. Tb = 200 C°, T freezing = – 130.2 C°, C max = 4.6 mg/L, δ = 1.65. Highly lipid soluble, solubility in water

0.2-0.3 mg/L (0-30 C°). In large concentrations can penetrate skin. Toxicity of TEL is well-described in industrial toxicology sources. TEL tends to cause widespread cerebral and cerebellar neurodegeneration, presumably secondary to microvasculutare damage in the CNS. Light intoxication is manifested by headache, insomnia, nightmares, loss of appetite, coordination disturbances, gastric pain, vomiting, diplopia, pallor and shaking hands. Severe TEL poisoning induces delirium, dimmed consciousness, sweating, weight loss, ataxia, coma and death. Depending on the concentration/dose symptoms appear in 1-12 hrs, poisoning is prolonged and lasts for weeks. Survivors suffer from irreversible dementias and cerebellar ataxia.

Dioxins are mentioned here because of the role 2,3,7,8 – TCDD played in Vietnam war (only about 3 tons of pure 2,3,7,8 – TCDD dropped, millions affected) and industrial accidents (BASF in 50'es, Seveso (Italy) in 1976 etc.,). Vast amounts of data on dioxins toxicity is available in industrial and environmental toxicology literature, thus interested readers are referred elsewhere: toxicity of AhRp ligands goes beyond the scope of this course. It deserves to be mentioned that *many of TCDD's toxic effects can be explained by TNF-alpha overproduction, growth factors (e.g., EGF) pathways over-activation & cytochrome P450 1A1 / 1A2 induction.* In humans, *chloracne, psychological changes (e.g. depression), severe weight loss and immunodeficiency are the main symptoms of dioxins poisoning*, liver enlargement is rare. *Even if the delivered dose exceeds lethal by orders of magnitude, first symptoms of poisoning will develop in 7-8 days, death would not occur earlier than 2 weeks.*

Metal carbonyls, such as Fe(CO)5 and Ni(CO)4, were weaponized by Germans during WW II, since they were (and are) considered to be efficient at defeating gas mask filters, especially when used as solvents for other chemical warfare agents. Surprisingly, *metal*

carbonyls toxicity differs from toxicity of CO. Vapours of metal carbonyls cause cough, suffocation, headache, dizziness, vertigo, fever, delirium, seizures and death from pulmonary oedema, which develops in 10-15 hrs post-exposure. Fe(CO)5 is a yellow liquid, Tb = 102.7 C°, T freezing -20 C°, C max = 310 mg/L (18 C°), δ = 1.46. Ni(CO)4 is a colourless, highly volatile liquid, Tb = 42.8 C°, T freezing -25 C°, δ ≈ 6. Metal carbonyls are highly lipid soluble and can penetrate skin. *When in contact with gas mask filter charcoal, they decompose to CO, corresponding metal and carbonyls with different metal coordination numbers, such as Fe2(CO)9 and Fe(CO)4.*

Suffocating Agents.

This group of chemical warfare agents consists of compounds which selectively target lung tissue and cause lethal lung oedema. *Major/classical representatives of this group, such as phosgene, diphosgene and chloropicrin are obsolete military class C compounds.* However, since *phosgene is mass-produced and widely used in chemical industry*, incidental (or intentional, in case of terrorism) release of it may present a serious threat. Also, more advanced suffocating agents were/are in development, which makes frequent statements about “suffocating agents being obsolete and irrelevant” rather questionable.

Phosgene (CG), COCL2, is an colourless gas which smells hay or rotten apples. *Since olfactory receptors are rapidly desensitised by phosgene, its smell is quickly lost, making olfactory detection of phosgene very unreliable. In presence of phosgene, tobacco smoke has flat metallic taste.* CG Tb = 8.2 C°, T freezing = - 118 C°, C

max = 6370 mg/L (20C°), which allows creating lethal concentrations by evaporation under 1 min exposition. Detonation-resistant. Density ρ = 1.4203 g/ cm² (0 C°), δ = 3.48. Water solubility is 0.9 % at 20C°, dissolution is accompanied by hydrolysis. Highly lipid/oil/organic solvent soluble. LCt50 = 3.2 mg x min / L; not toxic transcutaneously. Phosgene accounted for up to 85 % of chemical warfare death cases in WW I. It was usually deployed in mixtures with diphosgene, chloropicrin, chlorine, SnCL4, AsCL3, carbon disulphide and so on.

The mechanism by which phosgene causes lung oedema is unclear. Inhibition of carbonic anhydrase, alkaline phosphatase, cytochrome C oxidase, ATPase and lactate dehydrogenase in lung epithelium/capillary lining were all suggested. Old theory about HCL, produced by phosgene hydrolysis in the lung, causing lung oedema is erroneous. Phosgene would have to release 800 times more HCL by hydrolysis for this theory to work!

In winter phosgene cloud persists for 3 hrs, in summer – 30 min or less. Initial or reflectory stage of CG poisoning is manifested by sensing the smell of phosgene, unpleasant taste in the mouth, eye irritation, cough, nausea and may not be present at all. Latent period lasts from 30 min to 24 hrs, the shorter is the period – the lower is the chance of survival. *During the latent period the affected do not show any signs of poisoning, even if several lethal doses of phosgene were inhaled. Any exercise during the latent period significantly deteriorates the prognosis and may precipitate the end of the period and sudden collapse.* As the intoxication develops, burning in the larynx and cough appear. Poisoned gasp for air, cough worsens and becomes painful, skin turns blue, increasing quantities of frothy while or yellowish fluid (1-1.5 L per day) are expectorated. Later the fluid becomes pink – tingled, and a mushroom-like efflux of pink foam may appear at the mouth of dying. Before death skin often turns grey, breathing becomes sporadic and

arrhythmic, pulse is fast and weak, maximal blood pressure falls below 70 mm hg. Death occurs in 2 days. Survivors are at risk of developing secondary lung infections and pulmonary arteries thrombosis. Chronic bronchitis and lung emphysema may follow.

When the concentration of phosgene is above 5 mg/L, after a few gasps for air the poisoned falls, skin turns purple – blue, seizure takes place and death occurs in 2-3 seconds.

Post-mortem, the mass of affected lungs is increased from 500 – 600 g (physiological norm) to 2.5 kg, since more than 30 % of blood plasma crosses into lungs. This is why phosgene and related poisonings are often referred to as *“dry drowning”.*

Treatment of phosgene poisoning is limited to standard treatment of pulmonary oedema (oxygenation, steroids, diuretics, etc.,). Claims that hexamethylenetetramine injections (20 ml 20 % solution i.v.) during the latent period are efficient need to be verified.

Diphosgene (DP), CCL3OCOCL, is an colourless liquid that also smells hay or rotten apples. Tb = 128 C°, T freezing = 57 C°, C max = 120 mg/L (20C°), which may allow creating lethal concentrations by evaporation under 1 min exposition. Reasonably detonation-resistant, may decompose to two molecules of phosgene. Density ρ = 1.6403 g/ cm² (20 C°), δ = 6.9. Highly lipid/oil/organic solvent soluble. LCt50 = 3.4 mg x min / L; not toxic transcutaneously. Toxicity of DP is identical to toxicity of CG, *the main difference being higher persistence of DP vapour cloud* (0.5 – 3 hrs in summer; 10-12 hrs in winter).

Chloropicrin (PS), CCL3NO2, is a colourless oily liquid with strong irritating smell. Impure PS is yellow – green (chlorine and nitrogen oxides presence).Tb = 113 C°, T freezing = -69.2 C°, C max

= 184 mg/L (20C°), which may allow creating lethal concentrations by evaporation under 1 min exposition. Detonation-unstable decomposes to phosgene and nitrosyl chloride. Density ρ = 1.6579 g/ cm² (20 C°), δ = 5.7. Highly lipid/oil/organic solvent soluble. Solubility in water 0.16 % (25 C°). LCt50 = 20 mg x min / L; liquid chloropicrin causes skin burns*. Unlike phosgene, PS is a strong irritant/ lachrymator (ICt50 = 0.2 mg x min / L), thus it is frequently classified as a riot control, rather than a suffocating agent.*

Symptoms of PS poisoning include nausea and *vomiting* (thus "vomiting gas"), severe lachrymation, gastric pain, loss of consciousness (due to the chloroform-like narcotic effect). Pulmonary oedema develops when PS concentration exceeds 0.1 mg/L and is accompanied by internal haemorrhages, often in myocardium. The mechanism of oedema development is unclear, but seems to be *different from phosgene intoxication*, since CG and DP injected i.v. had no effect, while i.v. PS still causes lung oedema. Exposure to 2 mg/L PS for 10 min quickly causes death. Treatment of chloropicrin poisoning is symptomatic.

Other halogenated nitroalkanes which supersede PS toxicity by a large margin were proposed as novel suffocating agents. Tetrachlordinitroethane is crystals which melt at 130 – 140 C°. It is 6 times more toxic than PS, and 8 times more potent than PS as an irritant. Fluoropicrin, CF3NO2, was reported to be remarkably lethal and is rumoured to be weaponised by Israel despite unfavourable physical properties (Tb = -31.1 C°). It causes severe bouts of cough followed by sudden death. Simm-tetrafluordinitroethane O2NCF2 - CF2NO2 is even more toxic with more appropriate (for an offensive agent) physical properties (Tb = 57-58 C°, T freezing = -41.8 C°, δ = 1.595). It was reported to be mass-produced in the US.

Chlorine trifluoride (CLF3) is a colourless gas with slightly sweet smell, liquid CLF3 is yellow-green. Tb = 11.76 C°, T freezing = -76.3 C°, C max = 5369 mg/L (20C°), which allows creating lethal concentrations by evaporation under 1 min exposition. Density ρ = 1.8662 g/ cm² (10 C°), δ = 3.2. Violently reacts with water, organic materials and many metals. Concentrations above 0.3 mg/L are absolutely lethal even with a short exposure. CLF3 produces severe skin and mucosal tissues irritation, mucosal tissues ulceration, laryngospasm, suffocation, rapidly developing lung oedema or lung gangrene at higher concentrations. Liquid CLF3 (or high concentrations of CLF3 vapour) causes deep necrotic skin and subcutaneous damage. It is also capable of setting wood, paper and textile aflame. The exceptional offensive value of CLF3 lies in its ability to destroy gas mask filters (porous charcoal!) and protective NBC garments, as it was mentioned in The Foundation. *It is truly positioned on the boundary between chemical and incendiary warfare agents.*

Sulphur pentafluoride, (Z), S2F10 is a colourless highly volatile liquid. Tb = 29 C°, T freezing = -92 C°, Density ρ = 2.08 g/ cm² (0 C°). *Z was proposed as a cheaper and easier-to-store-and-deploy alternative to CLF3. It is not hydrolysed by water at room temperature* and is *less reactive then CLF3, while still being able to cause severe damage / overheating of gas mask filters. By its toxic action Z resembles phosgene, but was reported to be several times more potent.*

Irritants (Riot Control agents).

Riot control agents are designed to incapacitate, rather than injure or kill. The difference between their ICt50 and LCt50 is by orders of magnitude, thus ICt50 is the most useful value when describing toxicity of irritants. Nevertheless, *in certain conditions irritants can be lethal*: enclosed space, susceptible individuals (children, elderly, asthma sufferers) and so on. Some of the irritating agents possess significant toxicity and are described in other chapters of this course (cyanogens chloride, phosgeneoxime, chloropicrin). The first riot control agent to be used was ethyl bromoacetate, employed by police in Paris (1912). The majority of irritants used in WW I (e.g., bromobenzylcyanide, bromoacetone, ethyliodoacetate, xylilbromide) are now obsolete and replaced by more efficient agents. They are not covered in this course.

Irritants are compounds belonging to various chemical groups (see the list of Riot Control agents formulas on Figure 6), many of them are SN2 (substitution nucleophilic second order) – type alkylating agents. No definite mechanism explaining irritation produced by those compounds is known, with an exemption of capsaicin action. Classification of irritating chemical warfare agents on sternites and lacrimators, which existed before the end of WW II is somewhat obsolete, since modern irritants tend to combine both modes of action. Although, it could be useful to outline those modes, as various agents may “emphasize” one “type of irritation” over the other.

Lacrimator action is defined as burning and stinging pain in the eyes, conjunctivitis, running tears, blepharospasm and temporary vision impairment. CN (chloroacetophenone) is a classical example

of a lacrimator that does not have significant sternite activity.

Sternite action is defined as severe irritation of upper airways, manifested by violent sneezing, burning in the nose and pharynx, tightness in the chest, restrosternal pain radiating to back and arms, pain in the teeth, jaws and ears, severe headache caused by mucous membrane congestion in paranasal cavities, nausea and, sometimes, vomiting. Classical examples of sternites are arsenic-containing irritants, such as DA, DC and DM. Modern irritants like CS, CR and pelargonic acid morpholide also possess sternite activity.

Algogenic action refers to compounds ability to cause pain, "nettle effect" is a specific case of algogenic action when a substance is applied on the skin surface. Capsaicin is the most frequently mentioned algogenic compound, CH agent is a "pure algogene". Practically all riot control agents possess certain degree of algogenic activity.

CS, o-chlorobezlylidenmalonodinitrile is white crystals with taste and smell of pepper (though, it does not appear to act on capsaicin receptors!). Tb = 315 C°, T melting = 95 C°, C max = 0.00012 mg/L (20C°), which does not allow creating incapacitating concentrations by evaporation under 1 min exposition. Detonation-resistant. Density ρ = 1.04 g/cm² (20 C°), δ = 6.5. Solubility in water (20C°) 0.01% , easily dissolved in benzene, chloroform, acetone, dioxane. LCt50 = 61 mg x min / L; ICt50 = 0.02 mg x min / L; lung damage may occur above 2.7 mg x min / L. NATO ammunition marking: 1 red ring and label "CS TAC" for shells/bombs, "CS RIOT" for grenades and gun cartridges.

CS is used in solutions and pyrotechnic mixtures containing 40-50 % CS. Tactical preparations CS-1 (fine powder containing 5 % silica gel mixed with CS, persists on terrain for up to 5 days) and CS-2

(another siliconized CS-1 - based mixture, persists for up to 1.5 month) are deployed by military, but not police. Typical commercial self-defence CS sprays contain 2 % CS, police sprays go up to 20 % CS (though I've encountered 60 % specimen once), gas gun cartridges usually contain 80 mg CS and are labelled with yellow plastic caps. CS combines sternite and lacrimatory action, causes irritation of wet skin. The effect lasts for ≈ 30 min. *Tolerance to CS can build up*. In high doses, *liberation of CN-anions contributes to oral, but not inhalational toxicity of CS.* Reports that CS is a teratogen exist but need verification.

CN, α-chloroacetophenone is white crystals with pleasant flowery smell. Impure CS can be yellow or grey. Tb = 245 C°, T melting = 59 C°, C max = 0.11 mg/L (20C°), which may allow creating incapacitating concentrations by evaporation under 1 min exposition. Detonation-resistant. Density ρ = 1.321 g/cm² (20 C°), δ = 5.3. Solubility in water (20C°) 0.1%, easily dissolved in majority of organic solvents. LCt50 = 10-11 mg x min / L; ICt50 = 0.08 mg x min / L; NATO ammunition marking: 1 red ring and label "CN TAC" for gas generators, "CN RIOT" for grenades. Dispersion preparations such as CNB (10 % CN, 45 % CCL4, 45 % benzene), CNC (30 % CN & 70 % CHCL3) and CNS (24 % CN, 38 % PS and 38 % CHCL3) were developed in the US for military use. Typical self-defence CN sprays contain 2 % CN, often in mixture with 2 % CS or 15 % capsaicin; gas gun cartridges usually contain 80 mg CN and are labelled with purple/dark blue plastic caps, CS / CN – mixture cartridges have white plastic caps.

CR, dibenz[b,f][1,4]oxazepine is a yellow powder. Tb = 339 C°, T melting = 72 C°, C max = 0.0012 mg/L (20C°), which does not allow creating incapacitating concentrations by evaporation under 1 min exposition. Detonation-resistant. Density ρ ≈ 1.0 g/cm² (20 C°), δ = 6.7. Solubility in water (20C°) 0.008 %, easily dissolved in

majority of organic solvents. LCt50 = 350 mg x min / L; ICt50 = 0.005 mg x min / L. CR is a very potent irritant which combines sternite, lacrimatory and algogenic action while being free from adverse effects on low airways.

Capsaicin is white crystals with taste and smell of pepper. Capsaicin is not soluble in water, but is easily dissolved in alcohols, ethyl ether and chloroform. Tb = 65 C°. Detonation-unstable; usually used in self-defence and police sprays with concentrations ranging from 2 to 20 %, often in mixture with CS and CN. Classical algogene acting on capsaicin receptors. Its painful burning effect may last for up to 1 hour.

CH, 1-metoxy-1,3,5-cycloheptatriene is a colourless liquid. Tb = 184 C°, C max = 0.008 mg/L (20C°), which does not allow creating incapacitating concentrations by evaporation under 1 min exposition. Detonation-unstable. CH is easily dissolved in majority of organic solvents. LCt50 ≈ 120 mg x min / L. CH is a pure algogene, its vapour causes strong pain while in contact with skin surface, as long as CH concentration exceeds 0.025 mg/L.

Pelargonic acid morpholide is colourless crystals. Tb = 120-130 C° (0.5 mm hg). Detonation-unstable. Density ρ = 0.95 g/cm² (20 C°). Not soluble in water, but easily dissolved in polar organic solvents. LCt50 = 58 mg x min / L. Combines sternite, lacrimatory and algogenic action. As a lacrimator it is 5 times more potent than CN, while as a sternite it is comparable to DM (described below). Effects of this compound tend to wear of faster than effects of CN and DM.

Irritating Arsines are first efficient sternite agents to be discovered and deployed. While having little or no effect on the eyes, those compounds produce extreme irritation of upper airways, which occurs after a *short latent period of 5 to 10 minutes.* This

period and the fact that early gas masks did not have an “anti-smoke” filter (while irritating arsines are used as toxic smokes) lead to the efficient use of those compounds to force unmasking at the end of WW I (see The Foundation). *Being arsenic-containing compounds, in large doses irritating arsines can cause systemic poisoning, characterised by pulmonary oedema, general weakness, weight loss, malaise, hypotension, severe limb pain, ataxia, paresthesias, paralysis, unconsciousness and kidney damage. DA and DC, but not DM, cause severe skin irritation and even blistering* (in large concentrations): compare with “Dicks” and Lewisite. However, vesicant effects of DA and DC are transient and far from being as serious as dermal effects of true vesicants. Properties of sternite arsines are summarised in the table below:

	DA	DC	DM
ICt50 mg x min / L	0.015	0.025	0.02
LCt50 mg x min / L	15	10	15-30
T boiling, C°	333	346	410
T melting, C°	44	31.5	195
Density, 20 C°, g/cm^3	1.422	1.45	1.648
C max, mg / L	0.00068	0.00015	0.00002
Δ	9.1	8.38	9.57
Water solubility, 20 C°, %	0.2	0.2	≈ none

Pure DA and DC are colourless crystals; impure products are grey to dark brown solid substances or viscous, semi crystal liquids. DA smells garlic, DC – garlic and bitter almonds. DM is bright – yellow needle – shaped crystals without smell. Impure DM is green. Besides water, DM is not easily dissolved in many organic solvents, apart from acetone*. Since DA and DC are detonation – unstable and difficult to store, they are mainly replaced by more stable DM.*

Treatment of irritant poisoning is limited to decontamination with water & soap or 6 % Na2CO3 (3 % in case of NaHCO3) solution. Local anaesthetics may be required. "Antismoke mixture", containing 40 ml ethyl ether, 40 ml chloroform, 20 ml ethanol and 10 drops of 10 % ammonia solution per ampoule is produced for military use in some countries. In case of general intoxication by organic arsines appropriate antidotes should be administered (see the chapter on Lewisite).

A note on irritants as means of self – defence: *while 2 % CS or CN are efficient to repel casual attacker, violent persons in the state of affect (stimulant overdose, psychosis) may not be readily susceptible to the effects of these riot control agents, even if high concentrations are applied.* However, *capsaicin and capsaicin – containing mixtures tend to do a good job. Dogs are also not very susceptible to CS & CN, while 2 % and more capsaicin would incapacitate a raging canine;* "AntiDog" sprays sometimes given to postmen contain 2 % capsaicin in sticky oil.

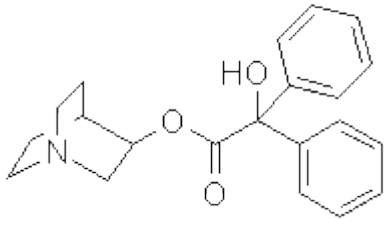
A note on irritants and terrorism: while those compounds are not lethal, they are relatively *easily available and may be used if one's aim is to cause panic. In enclosed space (underground, plane etc.,) irritants (especially mixtures of irritant arsines with CN) can inflict severe injuries.* Whereas usually an attacker does not want to see his attack detected until the casualties start dropping injured or dead, history knows cases when irritants were used *to*

mask use of more lethal agents, for example vesicants. It might take place when irritant attacks are an expected routine or when the attacking side is not proven to have lethal agents in possession.

Psychotropic Incapacitants

are chemical warfare agents designed to cause prolonged incapacitation of the affected by producing acute psychotic condition, leading to panic, chaos, demoralisation and inability of victims to defend themselves. A vast selection of psychotomimetic compounds was tested to fit this role, including *indolylamines, phenylalkylamines and piperidines.* Even though LSD-25 hydrazide and PCP hydrochloride (military code “SN”) came close to fulfil the criteria for military grade psychotomimetics because of their exceptionally high physiological activity, difficulties in their mass manufacturing and efficient delivery hampered the efforts to deploy them as chemical warfare agents. For example, only 0.0025 mg/kg LSD-25 orally are incapacitating, while for 5 μm–sized particles ID50 is 0.0056 mg/kg. However, LSD-25 is degraded at its melting temperature (83 C°) and cheap LSD-25 mass production method is not currently known. Thus, only a single compound, BZ, was selected out of hundreds of thousands substances tested to be deployed by military. BZ was synthesised by John Bill in 1955, ironically, as a potential antidote for organophosphate poisoning. After determining its high psychotomimetics activity in 1961, BZ manufacturing facility became operational in Pine Bluff Arsenal (1962); field testing of BZ was finished by 1966. Destruction of BZ stores by the US is claimed to be complete by 1987. However, Iraq has manufactured significant amounts of BZ (designated “Agent 15” by Iraqi forces) by 1991 and there were claims of military BZ use in Bosnia in 1996.

BZ, 3-quinuclidinyl benzilate is white crystals without taste and smell. Tb = 412 C°, T melting = 190 C° (168 C° for racemate), C max = 0.0005 mg/L (20C°), which would not allow creating incapacitating concentrations by evaporation under 1 min exposition. Detonation-resistant. Density ρ = 1.33 g/cm² (20 C°), δ = 11.6. Solubility in water is negligible, easily dissolved in chloroform and other halogenated hydrocarbons. LCt50 = 110 mg x min / L; ICt50 = 0.11 mg x min / L (particle size 1.0 μm); ID50 per os 6.2 μg/kg ≈ 0.5 mg per person. NATO ammunition marking: two red rings and label "BZ GAS". In 1970 the price of manufacturing 1 kg BZ was 44 $ (compare with 4 $ per kg Sarin).



BZ

BZ is usually deployed in pyrotechnic mixtures (50 % BZ, 23 % KCLO3, 9 % S and 18 % NaHCO3 in US military) due to its *high thermal and detonation stability*. *BZ solution can penetrate skin:* 5-10 % absorption was reported for propylene glycol solution, in DMSO percutaneous transfer of BZ increases 25-fold; if BZ is delivered transcutaneously, its effects are delayed by 24 hrs.

BZ is a very potent antagonist of central muscarinic receptors, described as being 3 times more potent than scopolamine. Since central antimuscarinic effects of BZ tend to dominate peripheral manifestations, BZ has a large safety margin and usually does not cause death exempt cases of individual sensitivity. In sensitive individuals / high doses ventricular fibrillations and thermoregulation disturbances may occur. BZ poisoning is manifested by midriasis, dry mouth, dry flashed skin, tachycardia, dizziness, muscular weakness and ataxia. In 30-60 minutes orientation is lost;

patient is restless, delirious, hallucinating, out of contact with reality and may not respond to external stimuli. Pulse reaches 150 – 180 beats / min, hypertension and urinary retention are observed. At this stage *unmotivated aggressive behaviour frequently takes place; negativism (doing opposite to asked/proposed, negative perception of the surroundings) might render the affected dangerous for others (especially if s/he is armed). This negativism is a great advantage of BZ over LSD-25 and Co, from the attacker's viewpoint. Another advantage is rather predictable effects of BZ if compared to LSD-25, response to which is strongly dependent on affected individuals mindset / emotional state. BZ psychosis lasts for from 2 to 4-5 days; recovery often accomplished by paranoid delusions and is followed by a deep sleep*. As expected, *amnesia for the period of BZ psychosis is frequent and the affected may not be aware of his/her actions in the psychotic state.*

BZ intoxication treatment consists of administering anticholinestherase drugs, such as physostigmine, aminostigmine or galantamine (e.g. aminostigmine 1-2 ml 0.1 % subcutaneously every 1-4 hrs) *and propranolol* injections (0.1 % 1-3 ml i.v. slowly) or tablets (0.02 mg 3-4 times a day). Trifluoroperazine (2-3 ml 0.2 % subcutaneously) was recommended to block hyper excitability and aggression; symptomatic treatment against hyperthermia may be needed, especially in hot climate. Interestingly, *anticholinestherases do not appear to be efficient first 4 to 6 hrs of BZ intoxication, but they do speed up recovery to a significant extent.*

A note on other means of incapacitation :

Quite a selection of "non – psychotropic" compounds was tested as possible incapacitants due to coordination disturbances or malaise they are capable to induce without being lethal. Examples include oxotremorine, IDPN (3,3-iminodipropionitrile), IX and apomorphine.

Olfactory assault employing scatol & mercaptanes was considered, but found to be inferior to the use of traditional riot control agents (see the chapter devoted to those compounds). Besides, a casual gas mask would protect against it. *Physical means of incapacitation* include utilizing noise (for example, 9 Hz infrasound induces panic in humans, so does β-carbolines administration!), microwave bombardment and high intensity photostimulation (flash bombs). At the moment, especially on the mass scale, those means are somewhat substandard if compared to modern irritants or BZ.

Natural Toxins As Chemical Warfare Agents.

Akin to the psychotomimetics case, a great deal of natural toxins was tested and tried, but only few fulfil the requirements laid in The Foundation to the extent of being actively produced and deployed. This chapter deals with military/terrorist attack aspects of *clostridial neurotoxins, staphylococcal enterotoxin B, ricin, anthrax toxin and fusarium/trichothecene fungal toxins (so-called "Yellow Rain"). Due to the nature of the course it does not cover utilisation of live organisms. However, a brief reference table covering properties of major biological agents is provided for the interested (Figure 7).*

Four of the agents covered here are proteins. *The advantages of using proteinaceous toxins as warfare agents include their incredibly high toxicity, ease of mass production using modern technological means and their natural "modular design" which could be altered to meet specific requirements. Although, a lot of problems encountered when using proteins as drugs are stumbled upon when proteins are employed for nefarious aims. All protein toxins*

are detonation-unstable, require specific means of long-term storage and delivery (aerosols, 1-5 μm particles only), are easy to detect at spot (abnormal concentration of protein in the air) and be identified more specifically later (express-detection ELISA kits etc.,). Once the threat is identified, casual gas masks or even respirators provide decent protection (protein toxins do not penetrate skin, although they (e.g. ricin) can damage it) and antiserums can be employed as specific antidote therapy means. Vaccination can be / is used to immunize population against those substances. From the terrorists standpoint, delivery of proteinaceous aerosols is a very complicated task, however, using natural toxins to contaminate food stocks is a great threat, amplified by difficulties of distinguishing such attack from a naturally occurring outbreak (consider naturally occurring botulism and intended clostridial neurotoxins contamination of food known to be a potential source of clostridial infection).

Many non-proteinaceous substances, such as palytoxin, fungal tremorgenes or saxitoxin are sufficiently toxic and stable to be employed as warfare agents; however their manufacturing is too expensive to deploy those substances on a mass scale. Though, they can still be used for contamination of foodstuff on a limited scale or assassinations. We deal with vesicant/ immunosuppressive fusarium/trichothecene toxins here, aflatoxins are worth considering since Iraq was found to possess a stock of munitions filled up with some 2200 L of aflatoxins mixture by the end of the Gulf War.

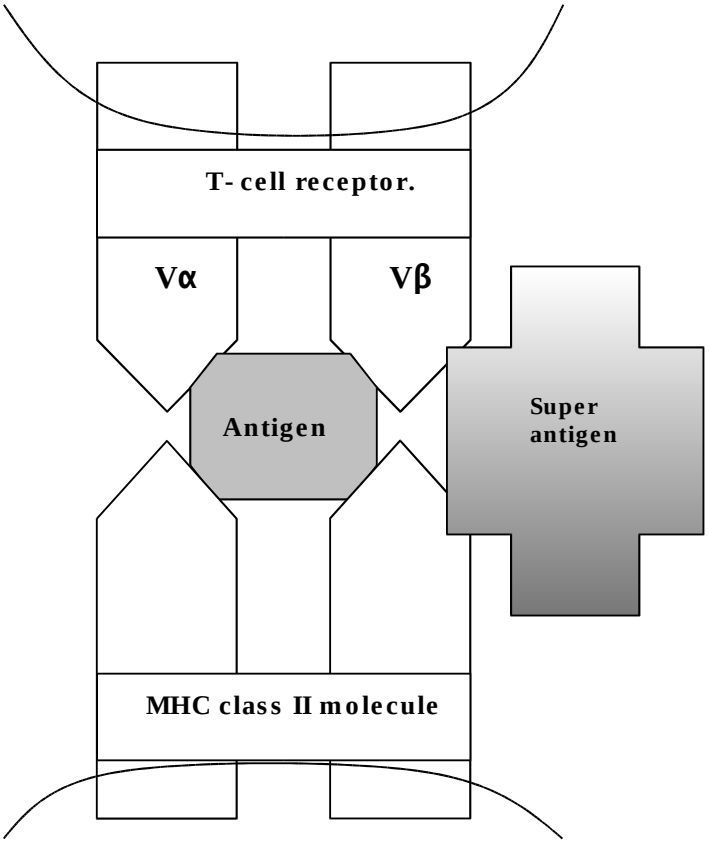
Agent XR is amorphous clostridial neurotoxin A, weaponized by the US in 1975 (Pine Bluff Arsenal). It is a very fine grey powder without taste or smell. XR is hygroscopic and forms stable lyophilised gels in watery solutions (pH = 2-7). At 100 C° XR solutions in water are hydrolysed in 10-15 min. In cold stagnant water (wells etc.,) XR persists for a week. Dry XR is resistant to

sunlight, bacterial decay and temperatures between -30 and + 50 C°. XR gels with preservatives can be stored for as long as 13 years (0-4 C°, darkness). XR can be delivered using aerosol generators or aircraft dispersion tanks. Toxic cloud persists for up to 12 hrs.
Dry XR LCt50 = 0.00002 mg x min / L, XR gels LCt50 = 0.0001 mg x min / L; percutaneous XR LD50 = 0.000002 – 0.00004 mg / kg; oral XR LD50 = 0.000057 mg / kg, making it the most toxic substance currently known (estimated 15 000 times more toxic than VX). *Clostridial neurotoxin A works by cleaving core synaptic vesicle docking/fusion protein SNAP-25 at Gln197-Arg198, which leads to complete inhibition of neurotransmitter release. The cleavage is done by (zinc-dependent endopeptidase) L (light, 50 kDa) chain, while H (heavy, 100 kDa) chain selectively targets the toxin to motoneurons. Symptoms of XR poisoning correspond to symptoms of naturally occurring botulism* (latent period from several hrs to 2-3 days, muscle weakness, dry mouth, nausea & vomiting, midriasis & diplopia, swallowing difficulties, aphonia, muscle paralysis). *When several lethal doses are administered by inhalation, death occurs in 2-3 days; when the lethal dose is exceeded by 100-1000 times – in several hrs.* If XR is injected / absorbed from a contaminated wound, latent period lasts from several dozens of minutes to a few hrs. Survivors of XR intoxication suffer from facial muscles paralysis and diplopia for quite a few months.

Treatment of XR poisoning is based upon a combination of trivalent equine antitoxin (give it i.v. as early as possible, since it can only neutralise circulating toxin) and supportive therapy (artifical ventilation etc.,). Vaccination against XR can be employed as a preventive measure. However, *anti – clostridial neurotoxins vaccine is not efficient in 10 – 30 % of the population and immunity to XR appears only after 4 weeks or more. Besides, doses of XR exceeding LD50 by 1000-10000 times (not that difficult to achieve, see lethal doses / concentrations values above) overwhelm the immune response.*

Agent PG is pure amorphous staphylococcal enterotoxin B (SEB, weaponised by the US in 1975). It is a snow-like white powder without taste or smell. PG is hygroscopic and forms gels in water. It is more stable than XR; dry agent resists heating up to 80 C° and does not lose toxicity after 30 minutes in boiling water. PG can be delivered using aerosol generators or aircraft dispersion tanks.

The toxin is a bivalent molecule with two distinct interaction sites. One binds to MHC class II molecules; the other one interacts with variable parts of the T cell antigen receptor. Thus, SEB belongs to a group of superantigen bacterial toxins, together with pyrogenic exotoxins of Streptococcus pyogenes and toxic shock syndrome toxin-1 (TSST-1) produced by Staphylococcus aureus (see the scheme below).



How superantigen toxins, such as SEB (“Agent PG") work.

PG is a very efficient incapacitating agent. When inhaled or swallowed, PG causes salivation, nausea, vomiting, pain in the gut, bloody diarrhoea, weakness, sedation and body temperature fall. Symptoms of PG poisoning appear after several minutes – several dozens of minutes (inhalational route) or 30 min – 6 hrs (ingestion) and last for approximately 24 hrs. During this period the affected are completely out of action. PG ICt50 = 0.02 mg x min / L, ICt10 = 0.0005 mg x min / L; oral ID50 = 0.0004 mg / kg, ID10 = 0.000015 mg / kg. *LCt50 and LD50 exceed ICt50/ID50 by 250 times; death rate in poisoned by PG does not surpass 5 %.* In very high concentrations of inhaled PG death may occur from lung oedema.

Anthrax Toxin is suspected to be weaponised as well as anthrax spores; spores and toxin can be used in mixture, since an interesting inverse correlation between sensitivity to pure anthrax toxin and B. anthracis spores was observed in various species. Since no information on defined military anthrax toxin formulations is available, it is not possible to outline physical properties and toxicity range of anthrax toxin, since it would depend on a preparation. Anthrax toxin is a mixture of three proteins, namely anthrax lethal factor (LF, 90 kDa), anthrax oedema factor (EF, 89 kDa) and anthrax protective antigen (PA, 83 kDa), responsible for delivery of LF and EF across the membranes of target cells. Anthrax oedema factor is a calmodulin-dependent adenylyl cyclase that participates in Bacillis anthracis – induced immunosuppression of a target host (think about the role of β-adrenoreceptors in leukocytes!). We are mainly concerned with action of LF/PA complex here.

Macrophages are the main target affected by LF/PA complex. PA forms seven-fold symmetry pores in the lipid bilayer, letting LF through biological membranes. LF is a zinc-dependent metalloprotease (similarly to clostridial neurotoxins!) with

undefined intracellular targets. Action of LF on macrophages involves massive release of pro-inflammatory cytokines (such as IL-1β and TNF-α) and nitric oxide, at higher concentrations hyperstimulation of macrophage oxidative burst by LF results in free radicals-mediated cell lysis within 60-90 minutes in vitro.

While inhalational anthrax is a grave disease that usually lasts for 1 to 6 days, anthrax toxin poisoning via various routes is manifested by immediate shock, fall of blood pressure, collapse and sudden death, explained by the mechanism outlined above. Death occurs in minutes or even seconds. Corpses darken and decay rapidly, probably due to the oxidative stress-mediated tissue lysis.

Ricin (W) is more famous for its role in assassinations, however it was studied as a chemical warfare agent since WW I and weaponised in the US during WW II (“W-bomb). It is a heat-stable white powder without taste and smell, LD50 in mice = 2.6 μg / kg, LD50 in humans is approximately 1 mg per 70 kg person. Ricin is very easy to mass-produce (1.2 g from a kg of castor seeds), since it is a by-product of castor oil manufacturing: ricin remains in the “castor meal” after oil extraction and is salted out readily. Ricin consists of B-chain (31-36 kDa), which binds to cell membrane surface carbohydrates with configuration of D-galactose and initiates translocation of the smaller (28-31 kDa) A-chain into the target cell. A-chain is N-glycosidase that inhibits protein synthesis by removing adenine (position 4324) from the 28 S RNA of the 60 S ribosomal subunit, efficiently preventing binding of the elongation factor 2.

Symptoms of ricin poisoning are delayed by 8-24 hrs even if multiple lethal doses are received and are strongly depended on the route of administration. Ricin inhalation leads to the development

of acute pneumonia and death in 36-48 hrs from pulmonary oedema. In oral poisoning nausea, vomiting, fever, thirst, sore throat, abdominal pain, diarrhoea and anal haemorrhage are prevalent. Ulceration of stomach & small intestines and necrosis of mesenteric lymph nodes are observed post-mortem. Injected ricin & systemic ricin poisoning cause fever, midriasis, headache, liver and spleen enlargement, anuria, cramps, vascular collapse and shock. On autopsy, liver (Kupffer cells = macrophages are the primary target), spleen, lymph nodes necrosis and, occasionally, diffuse nephritis are seen.

Treatment of ricin poisoning is mainly symptomatic. D-galactose (ricin binding!), AZT and Brefeldin A (inhibition of Golgi ricin transport) were all suggested as possible antidotes.

"Yellow Rain" is a *mixture of mycotoxins* originating from fungal Fusarium, Trichoderma, Cephalosporum, Verticimousporum or Stachybotrys species. *Trichothecenes are assumed to be the main acting components of the mixture, although toxins from other groups may contribute to the mixture toxicity.* It is a fine yellowish powder; preparations of it in viscous oily solvents are known to exist for dispersion from high attitudes. The mixture has high physicochemical stability; it can be stored for an indefinitely long time and has high persistence on the contaminated terrain. Dry Yellow Rain powder is non-volatile; it is highly lipid soluble and rapidly absorbed if digested or inhaled, blood concentration peaking in 1 hr. Yellow Rain is easy to mass-produce by solid substrate fermentation – taking T-2 toxin as an example, 9 g of T-2 are present in kg of Fusarium substrate while 2-3 g of crystalline product can be obtained from it in pure form.

Trichothecene toxins are family of more than 60 structurally-related compounds divided into four (A,B,C and D) subclasses. All trichothecene toxins possess an epoxy group at C-12, 13 and a

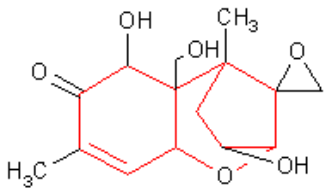
double bond between C-8,9 (see the formulas of well-known trichothecenes for reference). Trichothecenes provide a rare example of chemically stable epoxide molecules. The toxic action appears to be determined by the structure of a side chain. *Macrocyclic trichothecenes (subclass D), represented by Roridines and Verrucarines possess the longest R2-R4 side chain and are the most toxic trichothecene toxins known,* Roridine's A LD50 (i.v., mice) being in range of 1 mg/kg. *Among the simpler trichothecenes only T-2 toxin exhibits toxicity comparable to toxicity of the macrocyclic toxins. Military sources consider T-2 to be the major acting component of the Yellow Rain.* In nanogram quantities T-2 causes significant skin irritation, erythema, oedema, vesication and necrosis. *T-2 is 400 times more potent than sulphur mustard in producing skin lesions.* LCt50 of T-2 is 1-2 mg x min / L; transdermal T-2 LD50 = 2-12 mg / kg (10 times less than for sulphur mustard); oral LD50 = 5.2 mg/kg (rats).

The mechanism underlining toxicity of the entire thrichothecene group is protein synthesis inhibition caused by irreversible binding of trichothecene toxins to 60 S subunits of eukaryotic ribosomes. Other toxins which contribute to toxicity of Yellow Rain include potent *inhibitor of PI-3 kinase Wortmannin*, implicated in Yellow Rain – induced bleeding and immunodeficiency and (sphingomyelin pathway activating) *apoptosis-inducers Fumonisines*, known to cause equine leucoencephalomalacia and immunosuppression.

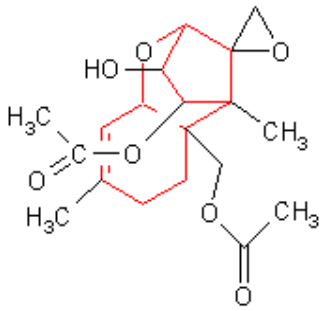
All over, Yellow Rain can be characterised as a naturally derived next generation radiomimetic and vesicant agent superior to synthetic vesicants, such as sulphur mustard, in terms of toxicity, detection and decontamination difficulties. Generalised acute effects of Yellow Rain intoxication include anorexia, lassitude, nausea, vomiting, lethargy, weakness, dizziness, loss of coordination and shock. In 3-12 hrs dyspnoea, coughing, sore mouth, bleeding from the gums & bloody diarrhoea & multiple haemorrhages,

abdominal and chest pain, hypotension, hypothermia and tachycardia appear. Death is often preceded by coma, seizures and tremor. Survivors suffer from immunodeficiency-related and other disorders, similar to an aftermath of “classical” vesicant agents poisoning. Chronic toxicity of Yellow Rain mycotoxins goes beyond the scope of this course and is well-described in toxicological literature: interested are suggested to search for data on alimentary toxic aleukia (ATA), equine stachyobotrotoxicosis, “cotton lung” and “red mould disease” syndromes.

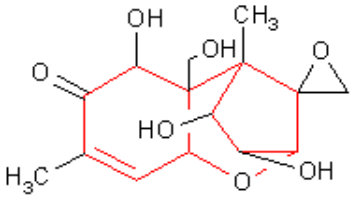
Structures of some toxins involved in Yellow Rain action:



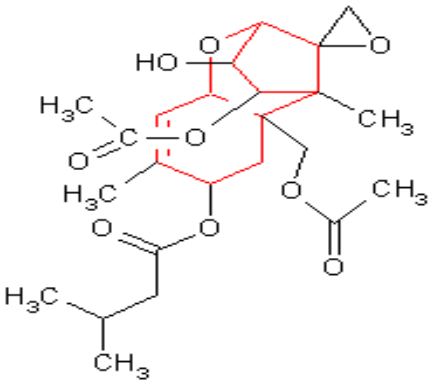
Deoxynivalenol



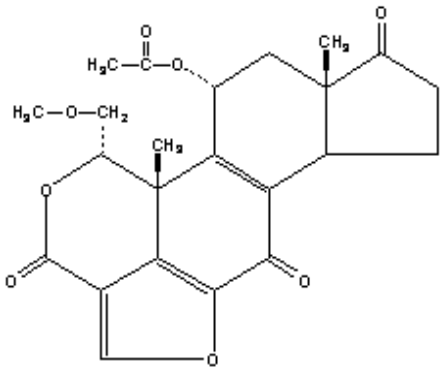
Diacetoxyscirpenol



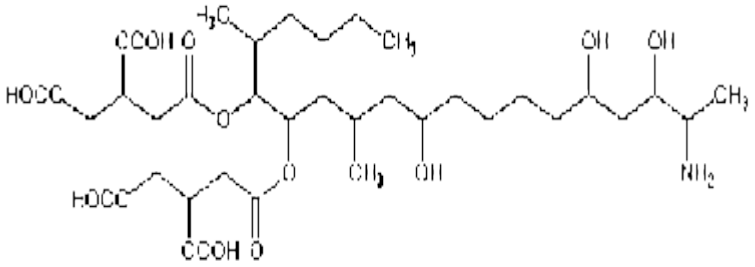
Nivalenol



T-2 Toxin



Wortmannin



Fumonisin B

Appendix.

a) How to put on a gas mask properly:

1. Close your eyes and hold your breath.
2. Take off your hat.
3. Take out the mask and put it on quickly.
4. Adjust the mask to fit you properly.
5. Breathe out with force.
6. Open your eyes.

All 6 stages have to be done in less than 7 seconds.

b) Solutions that could be used to decontaminate skin and eyes:

Organophosphates:	5-10 % $NaHCO_3$ or 10 % ammonia – skin; 2-3 % $NaHCO_3$ – eyes;
Cyanides:	5-10 % $NaHCO_3$ – skin;
Tetraethyl lead:	kerosene, petrol – skin;
Vesicants:	1 % potassium permanganate or 2 % H_2O_2 – skin; 2 % $NaHCO_3$ – eyes;
Irritants:	3-5 % $NaHCO_3$ – skin;
Proteins:	2 % formaldehyde, strong alcohol solutions – skin;

c) Solutions that could be used to decontaminate area surfaces:

Organophosphates:	10 % NaOH in 30 % methanol, 10 % water or water/alcohol ammonia solution.
Mustards:	10 % water or water/alcohol monochloramine solution, 10 % dichloramine in dichlorethane.
Vesicant arsines:	20 % water or water/alcohol NaOH solution.
Irritant arsines:	5 % potassium permanganate solution, 10 % H_2O_2, concentrated nitric acid.
Cyanides:	10 % NaOH solution with addition of soap and $FeSO_4$.

Halogenated ketones and nitroalkanes:	20 % Na2S in water / alcohol mixture.
Proteins:	10 % formaldehyde solution. Strong or pure alcohol.

CONTROL QUESTIONS.

Basics: The Foundation:

1. Define strategic and tactical significance of nuclear, chemical and biological weapons. Why chemical and biological warfare is called “poor man’s nuclear bomb”?
2. How many of the “poison gases” are actually gases at 20 C°?
3. In accordance to military manuals, Sarin used against unprotected and untrained civilians causes 70 % death rate among the affected. In Tokyo tube terrorist attack out of ≈ 6000 affected 15 died, which constitutes 0.25 %. Explain the reasons for this discrepancy.
4. What are the advantages and disadvantages of using protein toxins as warfare agents?
5. In the media you can often hear about “military grade anthrax”. What does it imply?
6. What is extended Haber’s Law and which value of “j” coefficient applies to you personally?
7. If you are masked and wear protective gear, are you 100 % safe?
8. What data do you need to estimate the efficiency and outcome of a chemical attack?

Organophosphate Agents:

1. What causes death in anticholinesterase organophosphates (OP) poisoning?
2. Why excitotoxic events take place in OP intoxication and what is their importance?
3. Outline treatment / antidotes for organophosphates. Is there

a universal antidote against them?

4. How organophosphate agents can be related to the Gulf War syndrome?

Vesicants / radiomimetics:

1. What causes death in vesicant poisoning?
2. Describe differences between “mustards” and “arsines”? Do all arsenic-containing chemical warfare agents cause blisters?
3. Is there an antidote for vesicants? Outline treatment for vesicant poisoning.

Generally toxic chemical warfare agents:

1. 0.1 μg/dl of cyanide are detected in the blood plasma. What is your course of action?
2. Classical crime stories & films always show victims of cyanide poisoning dying instantly after swallowing poisoned drink / food. The detective suspects cyanide poisoning after sensing a smell of bitter almonds. How much of the described is actually true?
3. Why complex therapy of cyanide poisoning is always needed?
4. What are advantages and disadvantages of arsine, phosphine and carbon monoxide as chemical warfare agents?

Suffocating agents:

1. Do phosgenes and halogenated nitroalkanes act via the same mechanism? What are the main differences between those groups of suffocants?
2. Are suffocating agents obsolete and inefficient?

Irritants:

1. Which value is the most useful in assessing irritants efficiency / toxicity?
2. Which riot control agents are used for police action / self defence? Should self defence sprays become legalised in the UK?

Psychotomimetics:

1. There are thousands of hallucinogens out there, including many well-known drugs of abuse. However, only a single substance was weaponised on a large scale. Why?

Natural toxins as chemical warfare agents:

1. Which compound is the most toxic substance known to the mankind and how does it work?
2. Can natural toxins be used as incapacitants? What would be the difference between using such use and employing “classical” riot control agents?
3. Why the symptoms of ricin poisoning are so dependent on the administration route?
4. Which fungal toxins can be / are used as warfare agents?

ANSWERS TO CONTROL QUESTIONS.

Basics: The Foundation:

1. Define strategic and tactical significance of nuclear, chemical and biological weapons. Why chemical and biological warfare is called "poor man's nuclear bomb"?

Biological warfare is purely strategic: use of biological agents against highly mobile and trained troops is unproductive. Chemical warfare is versatile and is well-suited for accomplishment of various tactical tasks, including dislodging well-trained, protected and dug-in troops and making terrain unusable. However, chemical weapons have strategic significance only if used on a massive scale (e.g. by superpowers). In case of nuclear weapons everything depends on the warhead size and type of explosion. Considering recent advances in the field of biological/chemical warfare, these weapons can rival the nukes (if used properly), while having significantly lower price of manufacturing & deployment and being easy to obtain.

2. How many of the "poison gases" are actually gases at 20 C°?

Cyanogen chloride, arsine, phosphine, phosgene, fluorpicrin, chlorine trifluoride.

3. In accordance to military manuals, Sarin used against unprotected and untrained civilians causes 70 % death rate among the affected. In Tokyo tube terrorist attack out of ≈6000 affected 15 died, which constitutes 0.25 %. Explain the reasons for this discrepancy.

Even though concentrations exceeding C max of Sarin by two orders of magnitude can be reached via evaporation, its boiling temperature (151.5 C°) still places GB among non-volatile agents. Thus, dispersion or explosive source release are necessary for the efficient use of GB. Also, high concentrations created by evaporation would apply only to the area localised around the contamination site. Since limited amounts of GB were used by Aum terrorists, that area is expected to be restricted. Besides, they used water solution of GB rather than the pure agent.

4. What are the advantages and disadvantages of using protein toxins as warfare agents?

Very high toxicity, modular design and low production price are the advantages. Detonation & thermal instability, inability to penetrate undamaged skin or protective equipment and strong antigenic properties (in terms of both immunochemical detection and antitoxin treatment / vaccination) are the disadvantages.

5. In the media you can often hear about "military grade anthrax". What does it imply?

Stable preparation consisting of 1 – 5 μum particles containing highly virulent spores of bacillis anthracis.

6. What is extended Haber's Law and which value of the "j" coefficient applies to you personally?

W = j C (A – E) t; unless you've served in the military etc., unfortunately your j = 1.

7. If you are masked and wear protective gear, are you 100 % safe?

No. Gas mask filters have limited filtering capacity which would be eventually exhausted. They are also characterised by leakage, which can become an issue with high concentration of highly toxic and strongly cumulative agents. Certain agents are deployed with bypassing gas mask filters (CLF3, S2F10, PH3, AsH3, metal carbonyls, high concentrations of HCN / CLCN) or skin protection means (liquid Lewisite, thick phosgene oxime preparations, CLF3) in mind.

8. What data do you need to estimate the efficiency and outcome of a chemical attack?

Knowing the temperature at the site of attack and the agents boiling temperature you can calculate its saturated vapour pressure. Knowing the molecular weight of the agent and its saturated vapour pressure you can get C max. Divide C max by 100 to get more realistic maximum concentration. Consider the means of delivery (see the question on Tokyo tube attack above). Compare your C max / 100 value with LCt/ICt50 of the agent. If j > 1, increase LCt/ICt values used for comparison by the factor of j. If the exposure time is one minute or more, this would give you a very crude estimate of immediate attack efficiency / outcome. Tables of contamination densities and nomograms, showing persistence of CWA's in different meteorological conditions on various landscapes are available to the militaries. Knowing whenever this particular agent follows the Haber's Law is essential if cloud is persistent.

Organophosphate Agents:

1. What causes death in anticholinesterase organophosphates (OP) poisoning ?

Bronchoconstriction & excessive bronchial secretion – caused

hypoxia at lower concentrations. Rapidly developing neuromuscular block at higher concentrations.

2. Why excitotoxic events take place in OP intoxication and what is their importance?

Hypoxia and excessive Ach stimulating the release of glutamate contribute to excitotoxic events in OP poisoning (activating Na channels may play role in the case of VX). Excitotoxicity contributes to seizures development and late psychoneurological consequences of OP intoxication.

3. Outline treatment / antidotes for organophosphates. Is there a universal antidote against them?

Antagonists of cholinoreceptors combined with cholinesterase – reactivating oximes are used. In the case of Soman, pyridostigmine prophylaxis is necessary due to the phenomenon of cholinestherase-OP complex aging. Reactivating oximes tend to have various efficiency, depending on the OP agent they are employed to counter. Antimuscarinic drugs are used in poisoning by all OP’s, but have limited value on their own. Diazepam i.v. is used if seizures develop.

4. How organophosphate agents can be related to the Gulf War syndrome?

Many of the symptoms listed as signs of Gulf War syndrome correspond well to side effects of pyridostigmine bromide, given to NATO troops in the Gulf in significant amounts for weeks.

Vesicants / radiomimetics:

1. What causes death in vesicant poisoning?

Laryngospasm / upper airways obstruction in acute cases. Severe bronchopneumonia in 4 – 7 days, often accompanied by bronchopulmonary infection and sepsis. Pulmonary oedema and "Lewisite shock" may occur in case of L exposure, CX inhalation can cause pulmonary oedema and pulmonary arteries thrombosis.

2. Describe differences between "mustards" and "arsines"? Do all arsenic-containing chemical warfare agents cause blisters?

Arsines are strong irritants without a latent period. They can cause pulmonary oedema and generalised arsenic poisoning syndromes. Arsines – induced skin lesions heal faster than mustard lesions; immunosupression caused by arsines is weaker. Efficient antidotes for arsines poisoning treatment are well-known. DM, an aromatic arsine irritant, is not known to cause skin damage.

3. Is there an antidote for vesicants? Outline treatment for vesicant poisoning.

Arsenic-containing vesicants can be countered with As-chelating agents. Na2S3O3 can neutralise sulphur mustard in the bloodstream, but its efficiency is questionable. Symptomatic treatment directed at prevention of secondary infection and wound-healing is essential.

Generally toxic chemical warfare agents:

1. 0.1 μg/dl of cyanide are detected in the blood plasma. What is your course of action?

None. Cyanides are normal metabolites present in various tissues. Concentrations below 0.14 µg/dl cyanide in the blood plasma are completely normal. Besides, many of the common food products contain measurable cyanide quantities, for example 5-25 mg/l cyanide in cherry juice.

2. Classical crime stories & films always show victims of cyanide poisoning dying instantly after swallowing poisoned drink / food. The detective suspects cyanide poisoning after sensing a smell of bitter almonds. How much of the described is actually true?

Unless there is more cyanide than food on that plate or wine in that goblet, death would occur in some 15-30 minutes. Instant death from cyanide occurs when large concentrations of HCN are inhaled. The detective has 20 to 60 % chance of not being able to smell cyanide, however many reliable chemical methods of cyanide detection exist.

3. Why complex therapy of cyanide poisoning is always needed?

Because you need to deal with the cyanide in the bloodstream immediately, before (mitochondrial) rhodanese, boosted by your sulfane sulphur donors, is able to metabolise it in the liver and other tissues.

4. What are advantages and disadvantages of arsine, phosphine and carbon monoxide as chemical warfare agents?

Low boiling temperatures allow deployment of arsine and phosphine only as products of a binary mixture reaction and CO in form of metal carbonyls. Arsine, phosphine and, especially, CO are not as toxic as modern chemical warfare agents are. None of those gases can penetrate skin. However, conventional gas mask filters are

inefficient at stopping these agents and treatment of AsH3 / PH3 poisoning is rather difficult.

Suffocating agents:

1. Do phosgenes and halogenated nitroalkanes act via the same mechanism? What are the main differences between those groups of suffocants?

Unlikely, since i.v. phosgenes do not cause pulmonary oedema, while i.v. chloropicrin does. Halogenated nitroalkanes lack latent period and are strong irritants.

2. Are suffocating agents obsolete and inefficient?

None of the chemical warfare agents is obsolete, if used against unprotected civilians by terrorists. CLF3 and S2F10 are very chemically aggressive and can bypass traditional protective means. Also, there is no adequate antidote treatment for both traditional and novel suffocating agents.

Irritants:

1. Which value is the most useful in assessing irritants efficiency / toxicity?

ICt50, since irritants incapacitate, rather than kill.

2. Which riot control agents are used for police action / self defence? Should self defence sprays become legalised in the UK?

CS, CN, capsaicin and, possibly, CR. Mixtures is frequently employed. Persistent CS/CN preparations are not used by the

police. Question about the UK legislation is left for you to ponder. In my opinion, they are efficient means of self-defence and aren't the favourite attacking weapon of thugs – they find mugging or raping someone in a dense cloud of capsaicin/CN mixture aerosol to be somewhat unattractive and tend to stick to more traditional ways of causing trouble.

Psychotomimetics:

1. There are thousands of hallucinogens out there, including many well-known drugs of abuse. However, only a single substance was weaponised on a large scale. Why?

BZ has suitable physicochemical properties to be efficiently deployed in pyrotechnic mixtures. It has a reasonable production price if compared to other psychotomimetics. It guarantees complete incapacitation of the affected for a given time. Negativism and aggression are a possible bonus: opposite forces fighting each others must be a remarkable show to observe.

Natural toxins as chemical warfare agents:

1. Which compound is the most toxic substance known to the mankind and how does it work?

Clostridial neurotoxin A. It blocks Ach release in motoneurones by cleaving core neurotransmitter vesicle docking/fusion protein SNAP-25.

2. Can natural toxins be used as incapacitants? What would be the difference between using such use and employing "classical" riot control agents?

PG is a very efficient incapacitant. "Classical" vesicants in non-

lethal concentrations are very efficient long-term incapacitants, the same could be said about Yellow Rain. The safety margin of PG is lower than the one for modern irritants and there is a latent period. Besides, its action lasts for the whole day. Thus, PG is unsuitable for police or self-defence use.

3. Why the symptoms of ricin poisoning are so dependent on the administration route?

Because it does not bind to very specific binding sites on cell membrane surface – D-galactose-like carbohydrates are abundant in various tissues. Macrophages, including very sensitive to ricin toxicity Kupffer cells in the liver, can also bind ricin A-chains via mannose residues present in the chain.

4. Which fungal toxins can be / are used as warfare agents?

Trichothecenes / fumonisines / wortmannin of the Yellow Rain. Aphlatoxin, weaponised by Saddam’s army. A variety of highly toxic mycotoxins to choose from is enormous. Both Yellow Rain toxins and aphlatoxins are simply one of the most studied mycotoxins due to their role in causing well-documented human and animal food poisoning outbreaks (ATA, Turkey X disease and so on).

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ARYTHMETICS OF MILITARY TOXICOLOGY.

1. Physicochemical properties of agents.

Relative density: δ = δ [agent] / δ [air] = δ [agent] / 28.9 (0°C, 760 mm Hg).

Solubility: C = C [agent in water] / C [agent in octane]

Saturated vapour pressure: log [P] = 2.763 – 0.019*Tb + 0.024*Tenv (Tb- boiling temperature; T env- environment temperature at given pressure).

Volatility: Cmax = 16 M*P / T (M-molecular mass, P-saturated vapour pressure). Real life concentrations are 10-20 %of Cmax !

2. Tactical properties of agents.

Contamination density: Δ = M/S (g/m^2 or ton/km^2)

Contamination persistence: S = p1/p2 $\sqrt{}$ M1*t1 / M2*t2
(p1- vapour pressure of water at 15 °C, p2- vapour pressure of agent at t1, M1- molecular weight of water (18), t1- absolute temperature, t2- absolute temperature corresponding to 15 °C (288 K).

3. Toxicological properties of agents.

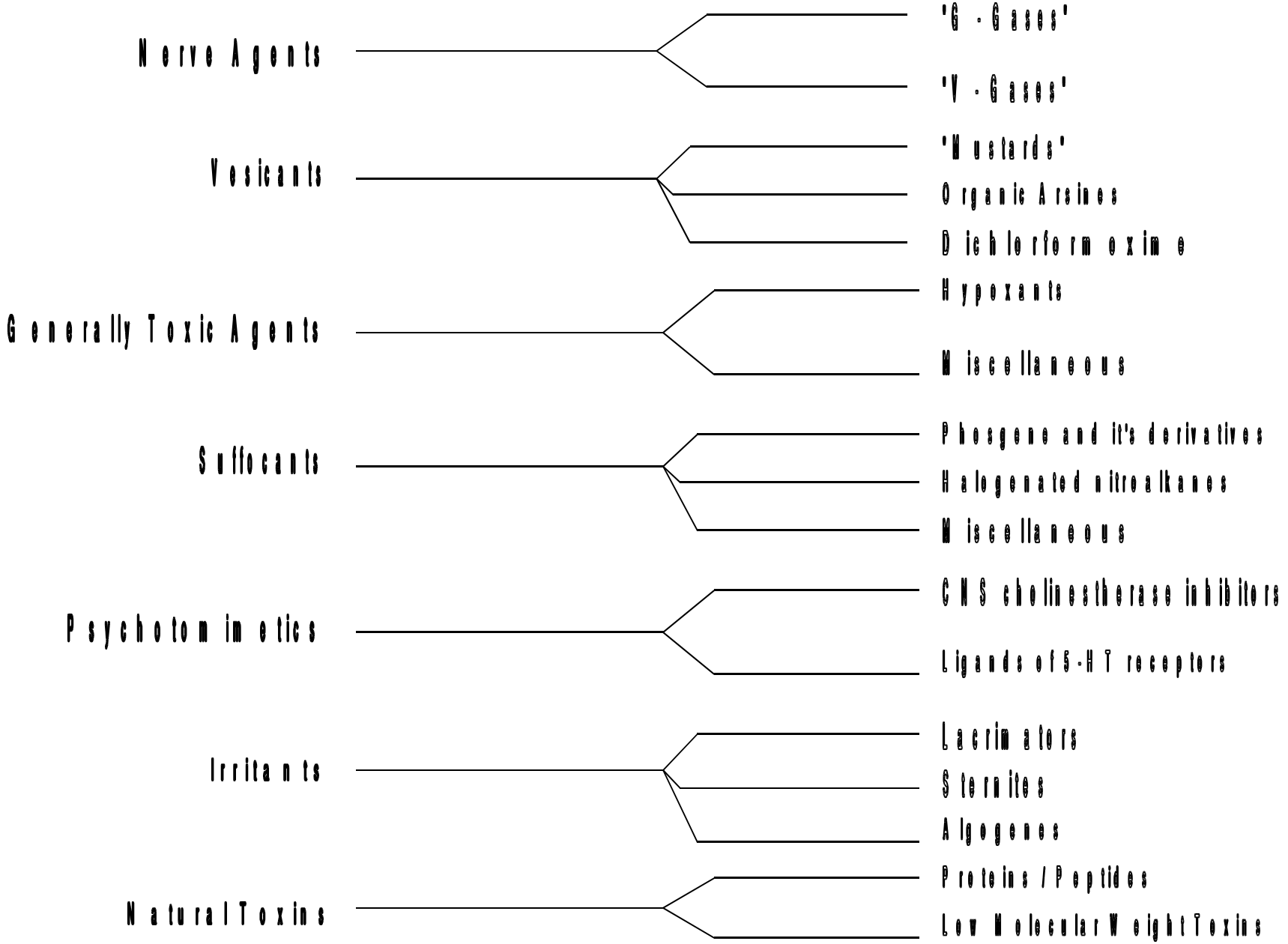
Dose via inhalation: D = CtV/G (C- concentration (mg/L), t- time (min), V- breathing intensity (L/min).

Habers Law: W = Ct (W- "lethal index", value constant for an agent).

Extended Habers Law: W = jC (A - E) t (j- Jacquot coefficient, A- speed of agent administration / adsorbtion, E- speed of agent elimination)

Transcutaneous bioavailability: SVC = LD50 transdermal / LD50 i.v. (skin- venous coefficient); SAC = LD50 transdermal / LD50 i.a. (skin- arterial coefficient).

Classification of Chemical Warfare Agents.



Chemical / Biological Agents Delivery Means.

Dispersion:

- **Spray Delivery**
- **Point Source Explosive Release**
- **Line Source Explosive Release**
- **Bulk Release**
- **Base Ejection**

Condensation:

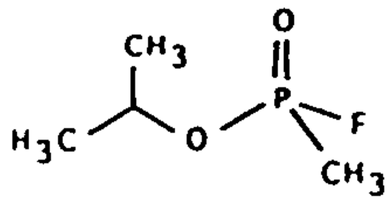
- **Thermogenerators for Liquid Evaporation**
- **Pyrotechnic Mixtures for Solid Agents**

Reaction:

- **Use of “Gas Generating” compounds**

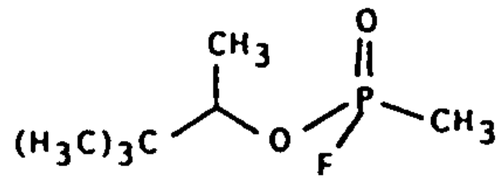
Contamination of water and food supplies.

Soil contamination.



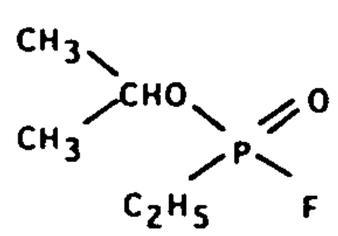
SARIN
$C_4H_{10}FO_2P$

Isopropyl methylphosphonofluoridate; GB; Sarin; Zarin



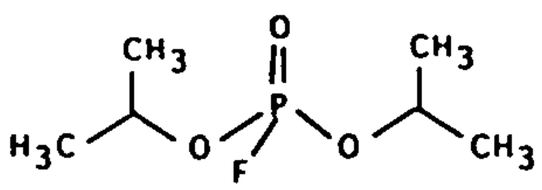
SOMAN
$C_7H_{16}FO_2P$

Methylphosphonofluoridic acid 1,2,2-trimethylpropyl ester; Pinacolyl methylphosphonofluoridate; GD; Soman; Zoman



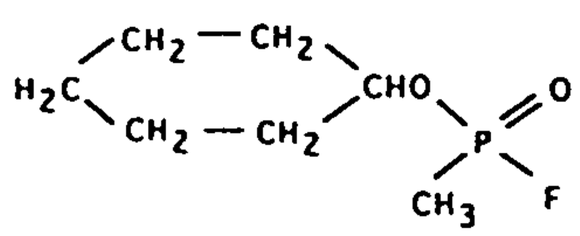
GE
$C_5H_{12}FO_2P$

Isopropyl ethylphosphonofluoridate; GE



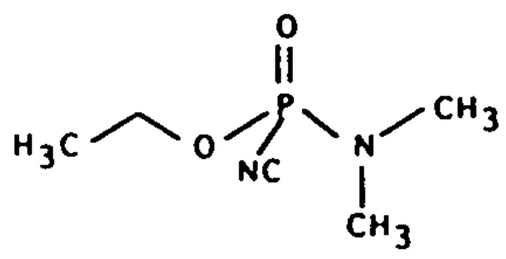
DFP
$C_6H_{14}FO_3P$

Diisopropylphosphorofluoridate; DFP



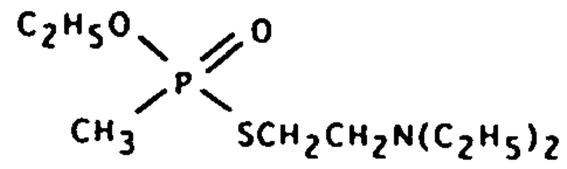
GF
$C_7H_{14}FO_2P$

Cyclohexyl methylphosphonofluoridate; GF



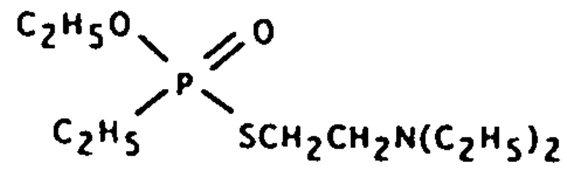
TABUN
$C_5H_{11}N_2O_2P$

Ethyl *N*-dimethylphosphoramidocyanidate; GA; Tabun; Taboon A; Trilon 83; Gelan 1



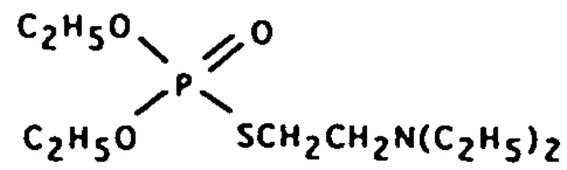
VM
$C_9H_{22}NO_2PS$

O-Ethyl *S*-[2-(diethylamino)ethyl] methylphosphonothiolate; VM



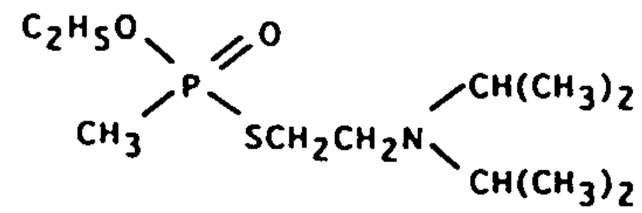
VE
$C_{10}H_{14}NO_2PS$

O-Ethyl-*S*-[2-(diethylamino)ethyl] ethylphosphonothiolate; VE



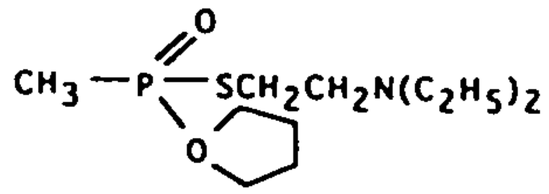
VG
$C_{10}H_{24}NO_3PS$

O,O-Diethyl *S*-[2-(diethylamino)ethyl] phosphorothiolate; VG



VX
$C_{11}H_{25}NO_2PS$

O-Ethyl *S*-[2-(diisopropylamino)ethyl] methylphosphonothiolate; VX



EA3148
$C_{12}H_{26}NO_2PS$

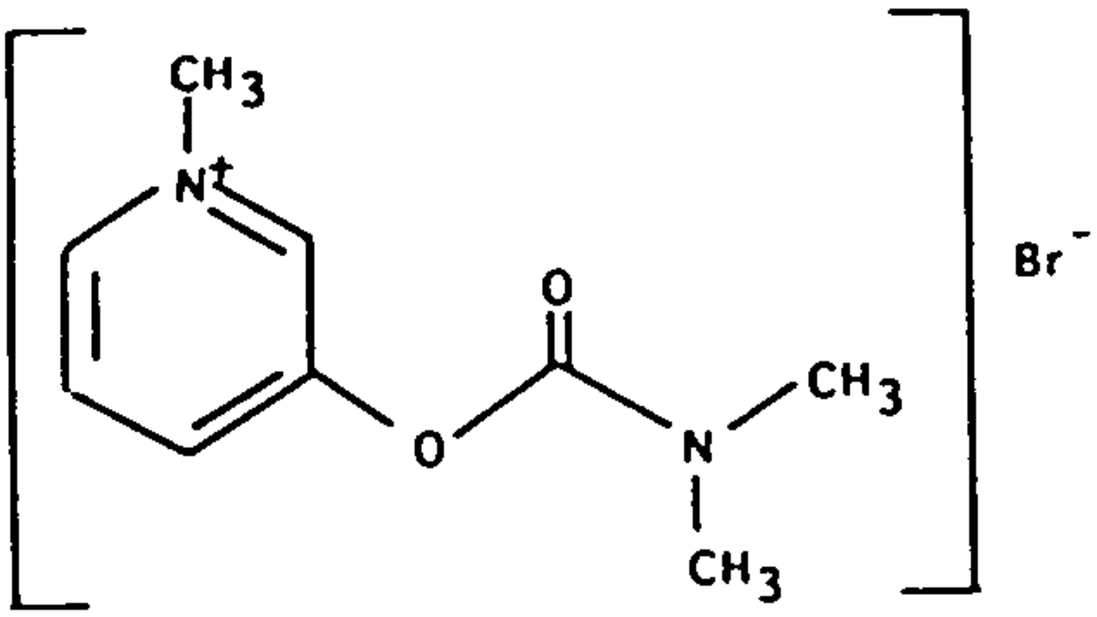
Cyclopentyl *S*-[2-(diethylamino)ethyl] methylphosphonothiolate; EA3148

NEUROTOXICITY RATING

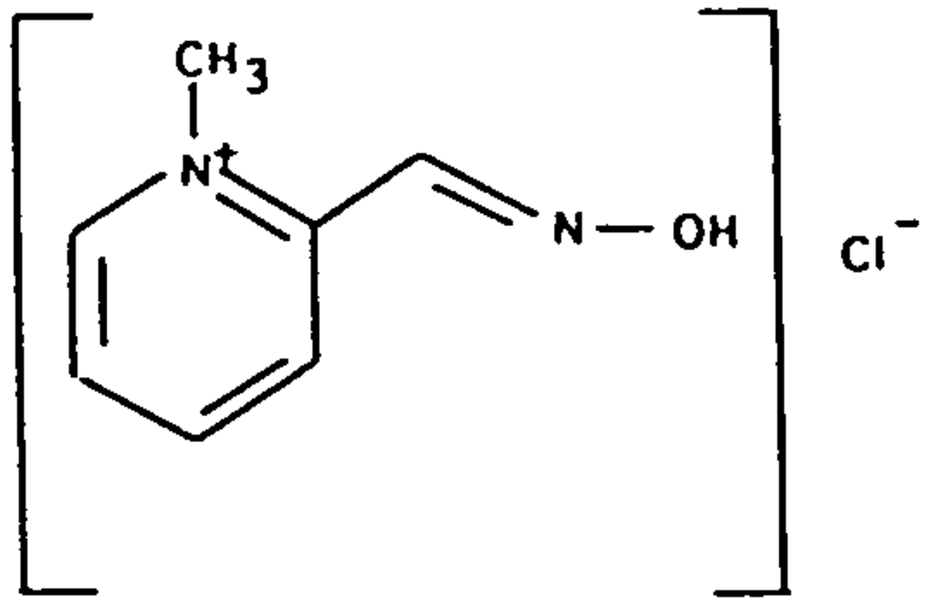
Clinical

A Seizure disorder

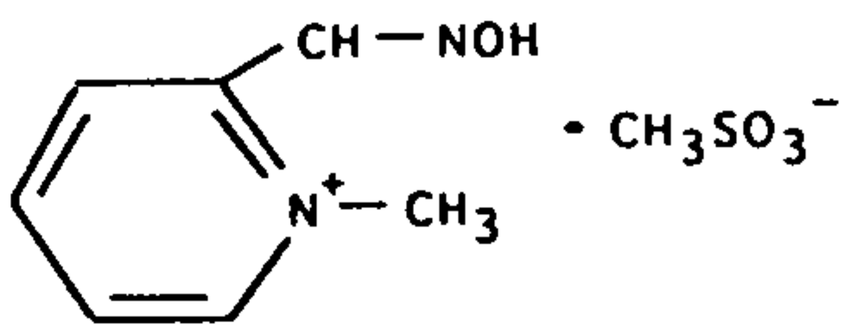
B Peripheral neuropathy



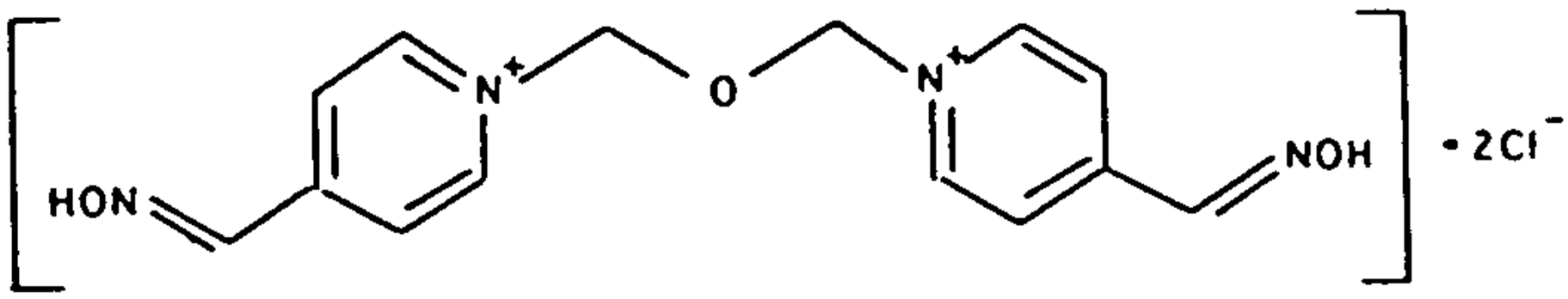
PYRIDOSTIGMINE BROMIDE



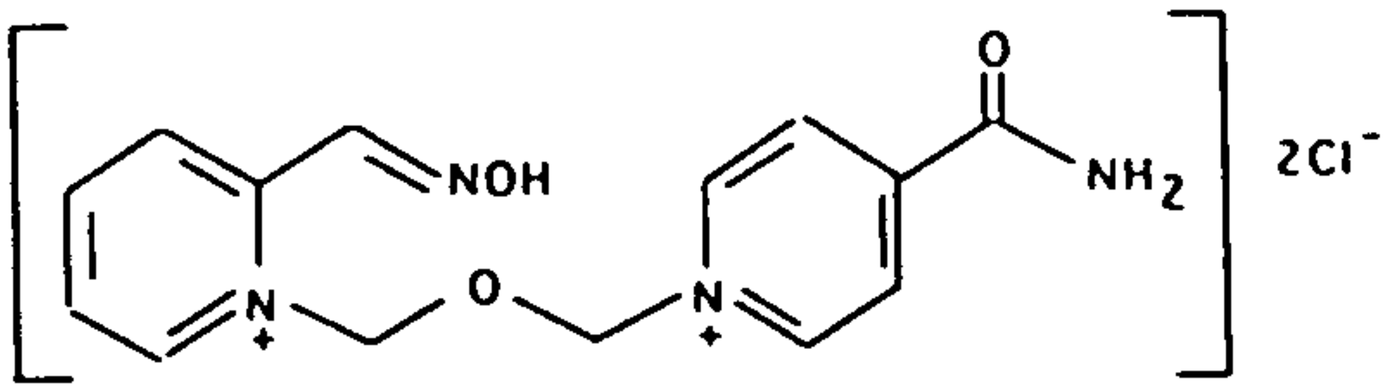
PRALIDOXIME CHLORIDE



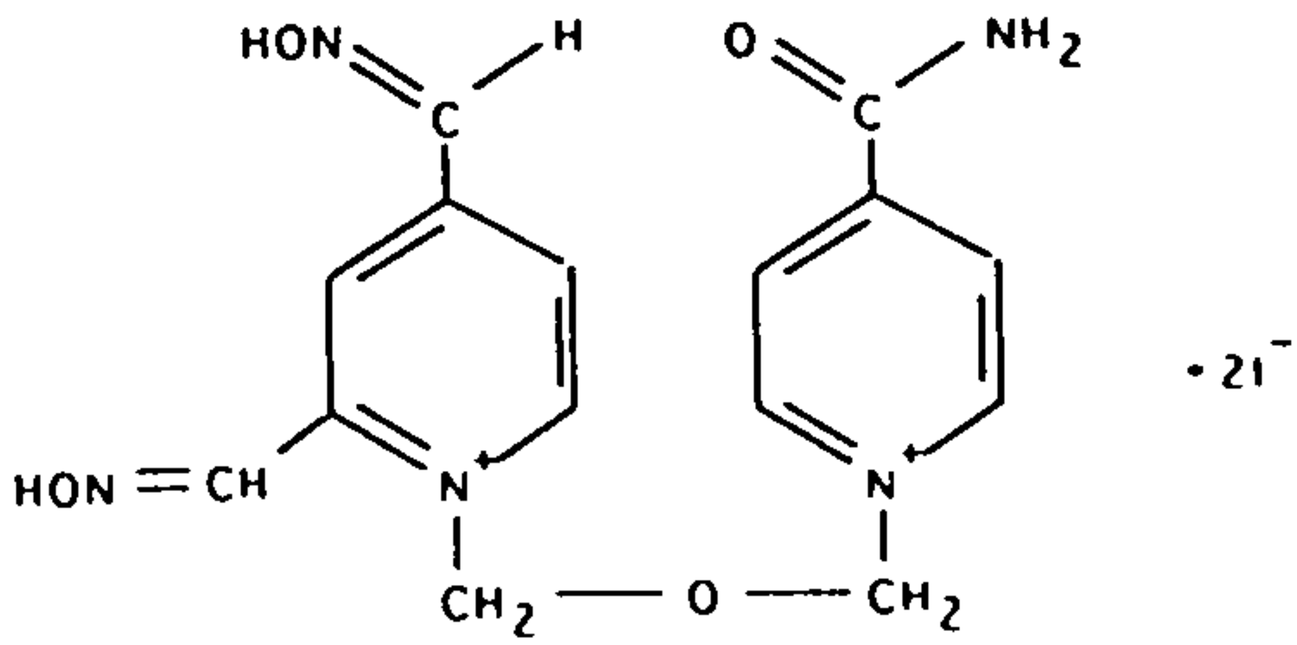
PRALIDOXIMINE METHANESULPHONATE;
N-METHYLPYRIDINIUM-2-ALDOXIME METHANESULFONATE; (P2S)



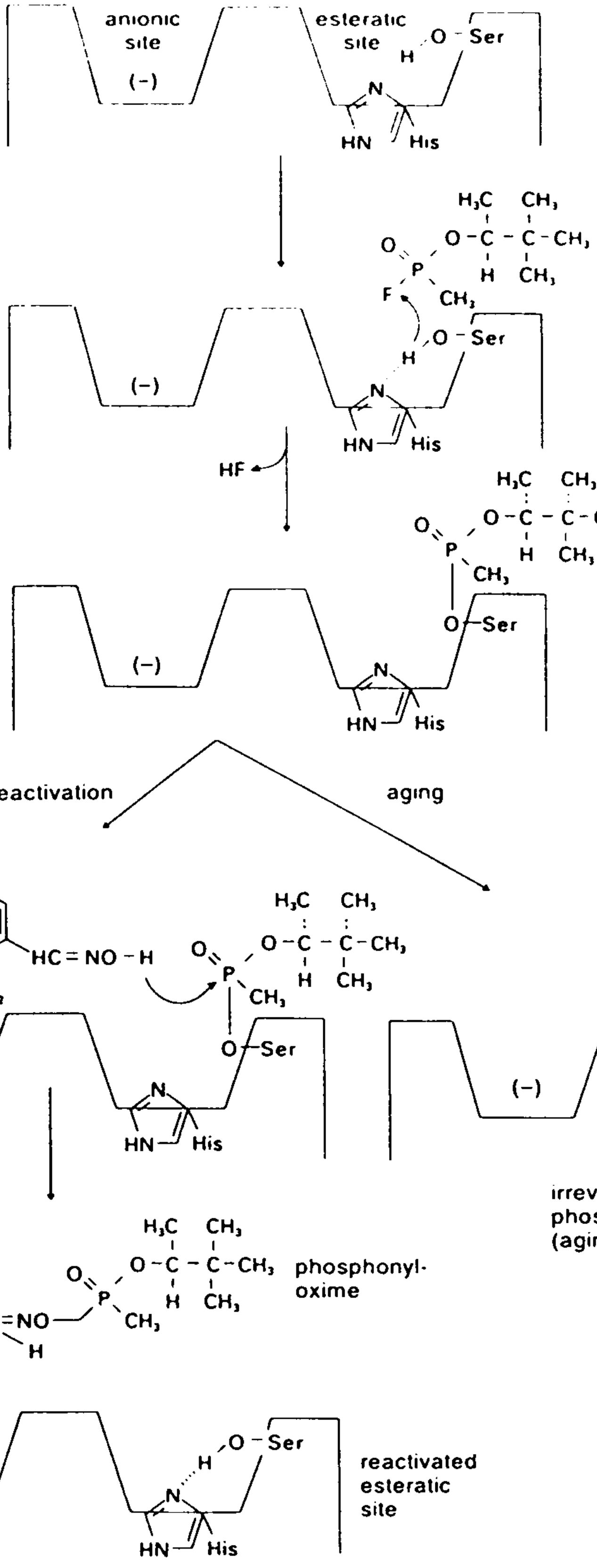
OBIDOXIME; TOXOGONINE DICHLORIDE



1-[[[4-(AMINO-CARBONYL)PYRIDINIO]METHOXY]METHYL]-2 [HYDROXYIMINO)METHYL]-
PYRIDINIUM DICHLORIDE; ASOXIME CHLORIDE; HI-6



PYRIMIDOXIME DIODIDE; Hlo7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His
HF
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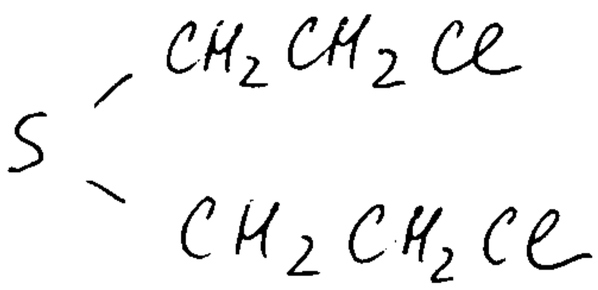
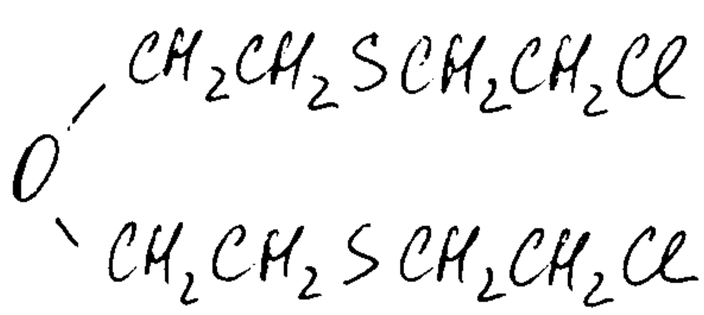
O − C − C − CH₃
H CH₃
O
P
CH₃
CH₃
O − Ser
(−)
N
HN
His
reactivation
aging
H₂N − CO
HC = NO − H
H₂C
CH₂
O
H₃C CH₃
O − C − C − CH₃
H CH₃
O
P
CH₃
O − Ser
(−)
N
HN
His
H₃C CH₃
H − C − C − CH₃
OH CH₃
OH
O = P − CH₃
O − Ser
(−)
N
HN
His
irreversible phosphonylation (aging)
H₂N − CO
H₃C CH₃
O − C − C − CH₃
H CH₃
O
P
CH₃
C = NO
H
H₂C
CH₂
O
phosphonyl-oxime
O − Ser
H
N
(−)
HN
His
reactivated esteratic site

Structures of vesicant agents.



HD



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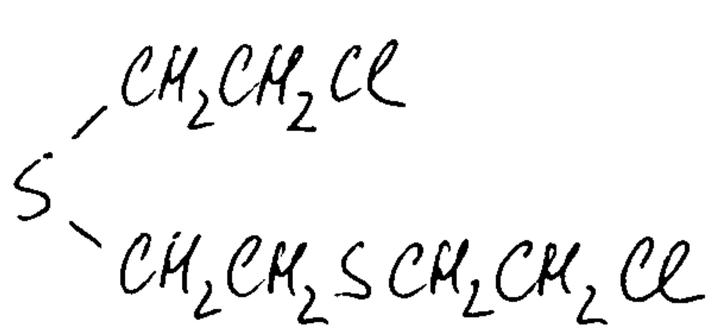

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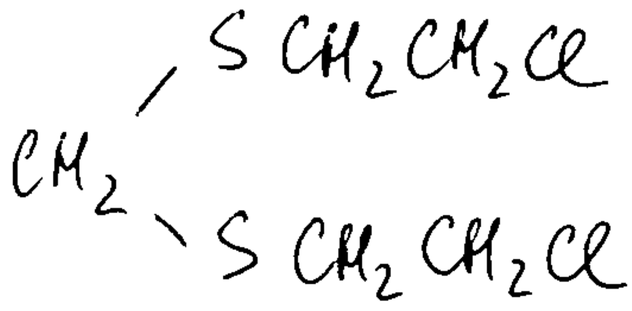
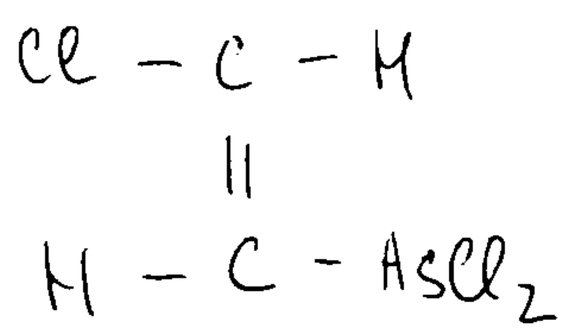
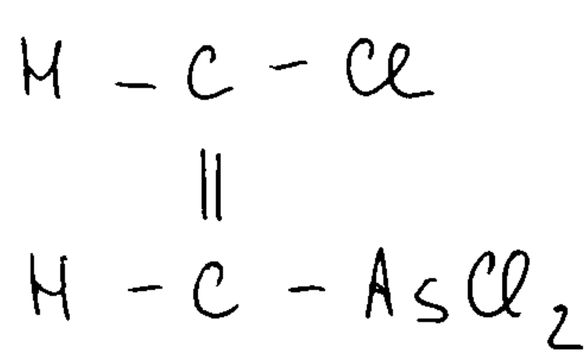


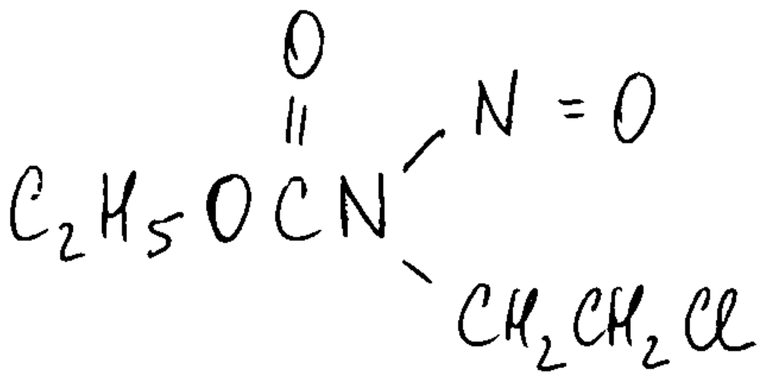
Double HD



L – trans



L - cis



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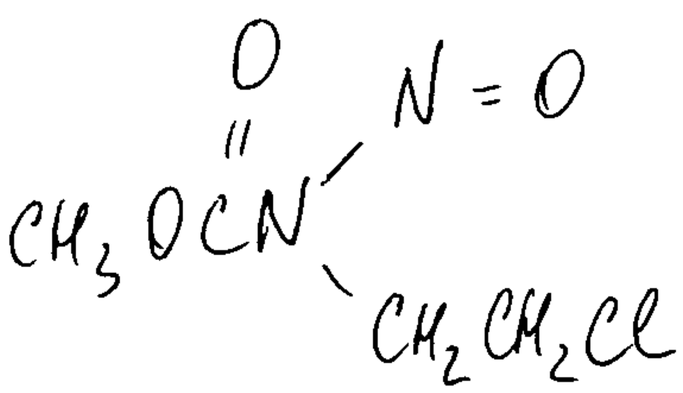

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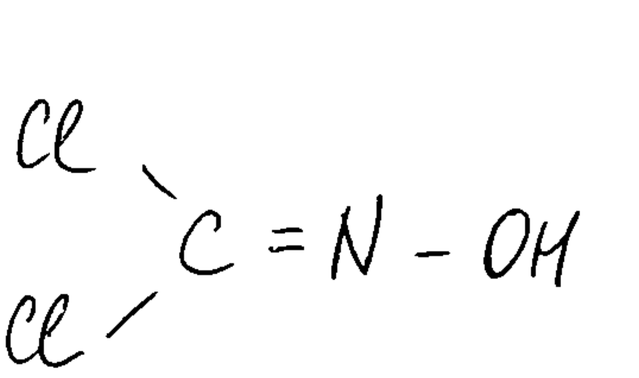
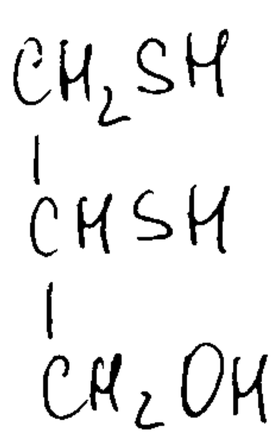
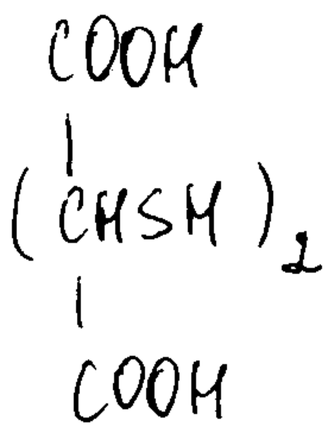


CX

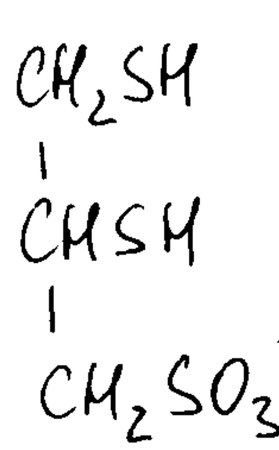
L antidotes:



BAL



DMSA



DMPS

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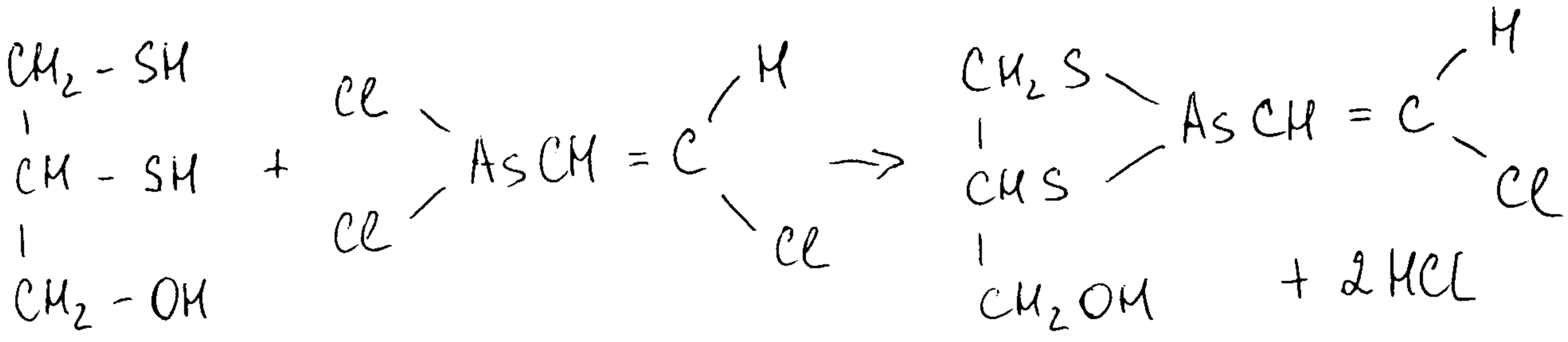
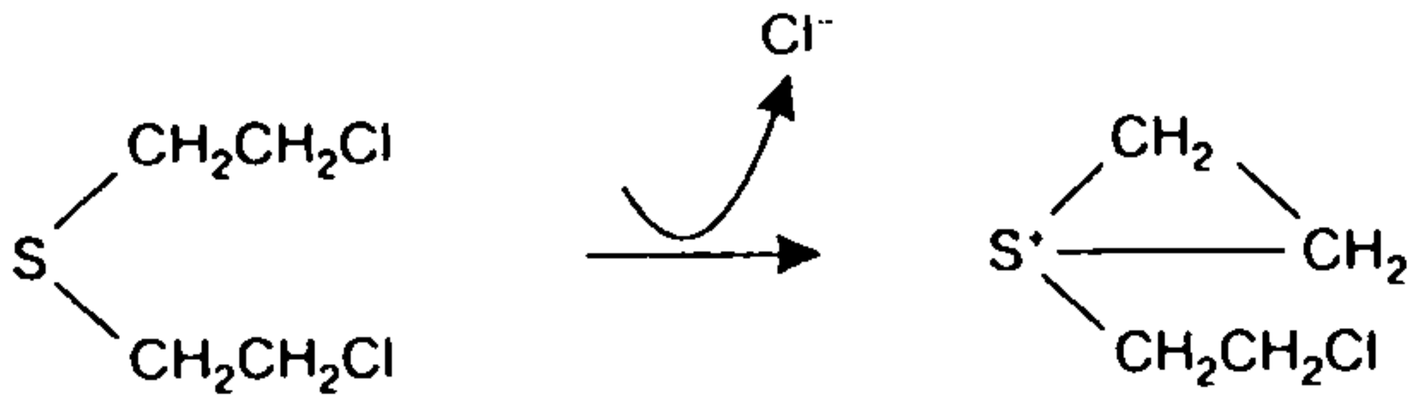
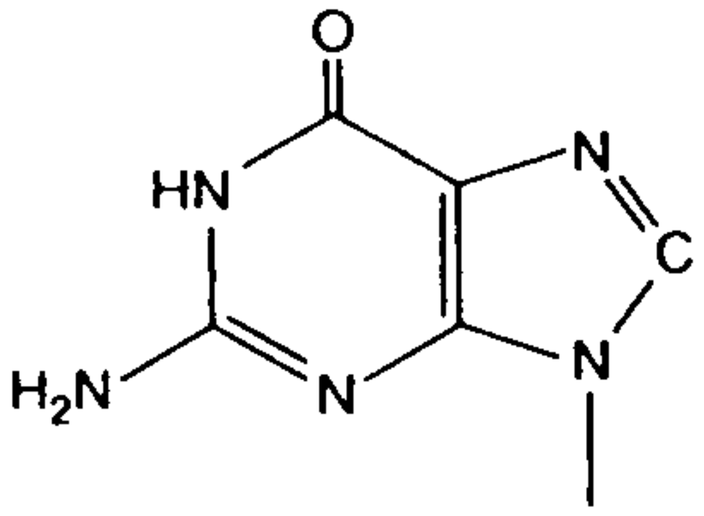




1st Cyclization



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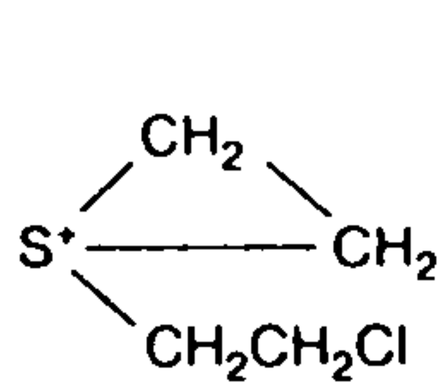
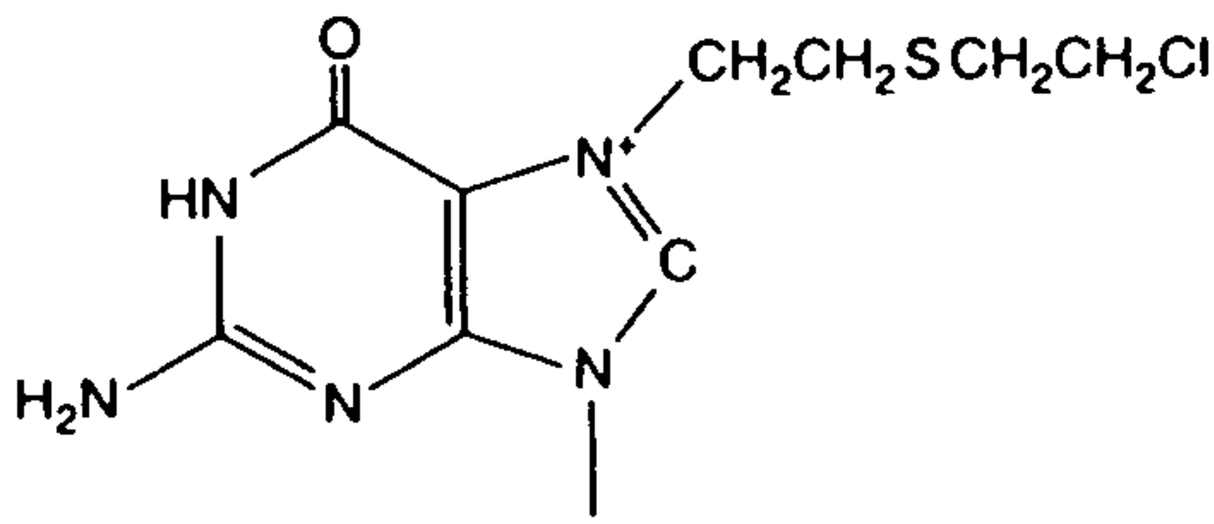
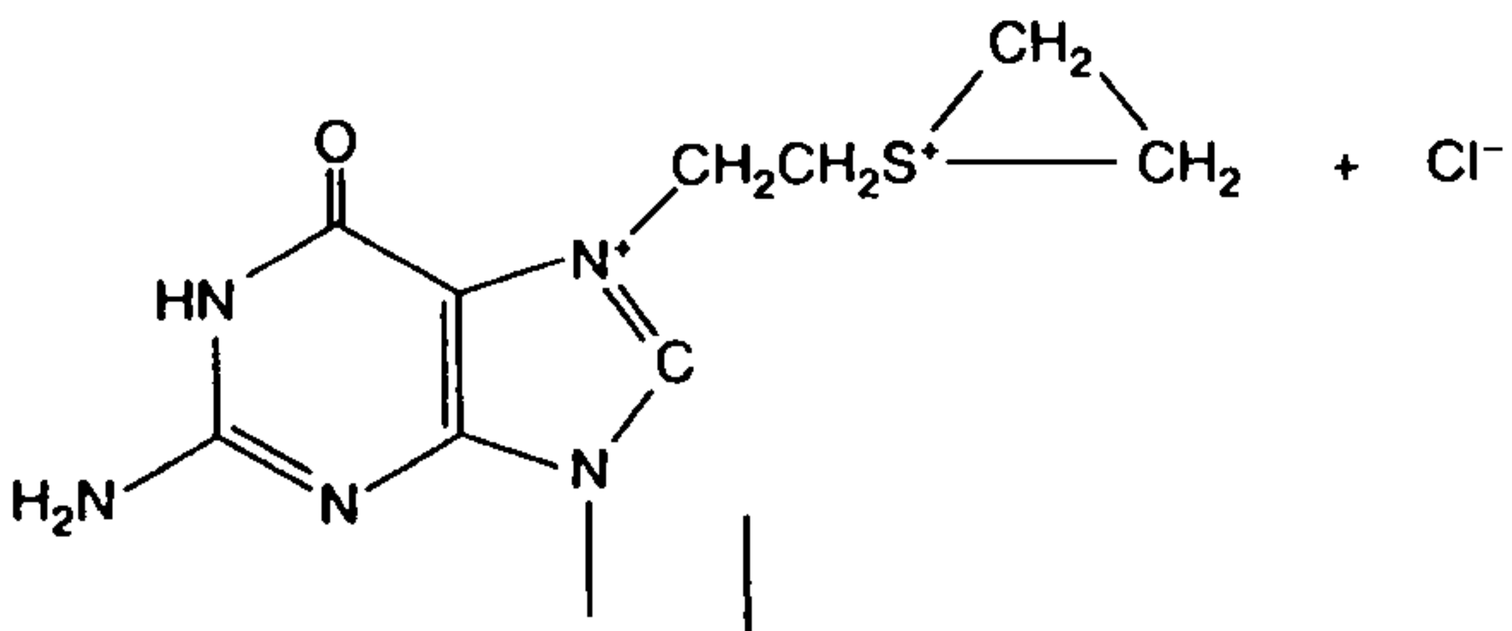
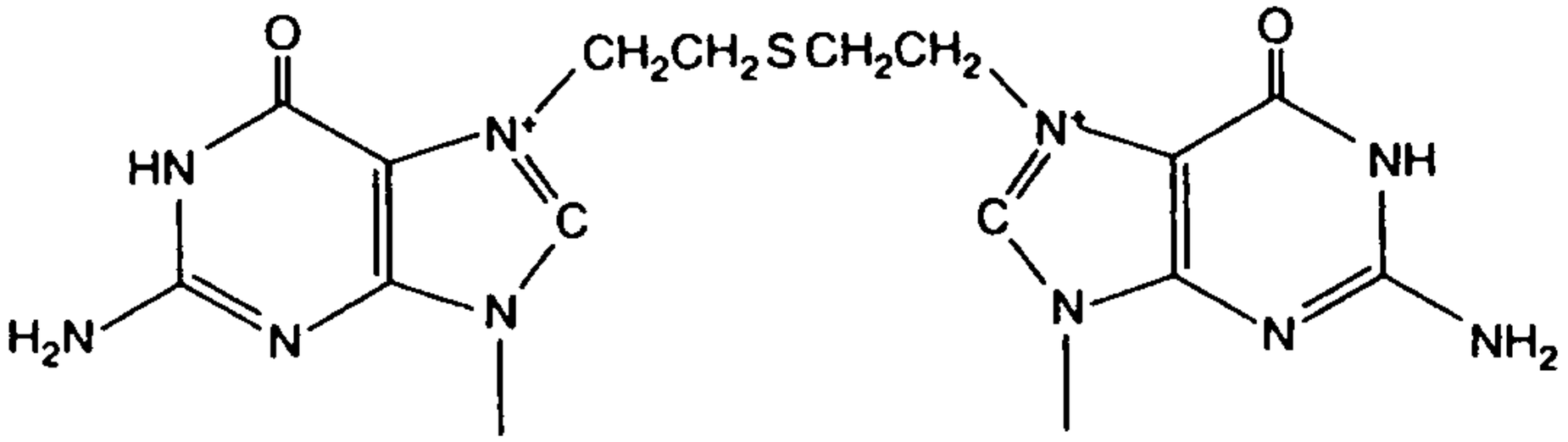


Ethylenesulphonium ion binds to guanine





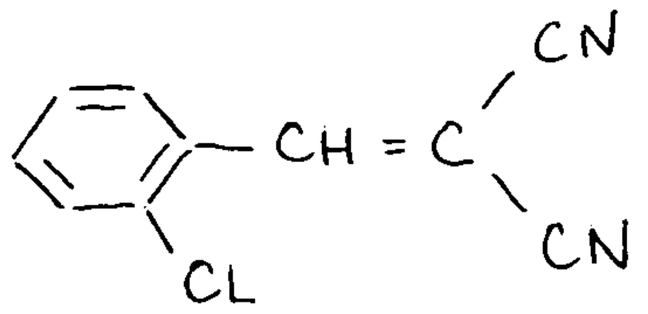
2nd Cyclization



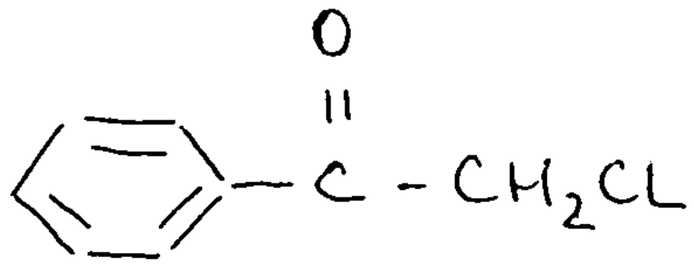
Cross-linked guanine residues

Reactions occurring in cross-linking of DNA

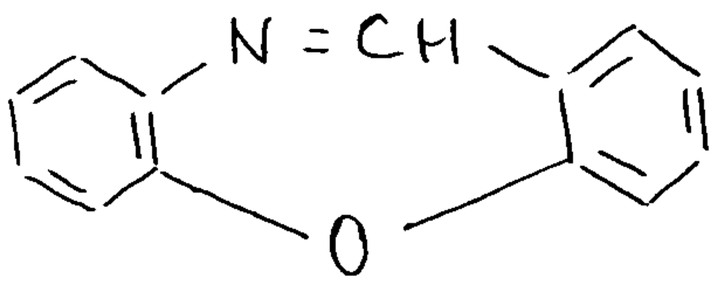
Chemical Structure of Riot Control Chemical Warfare Agents.



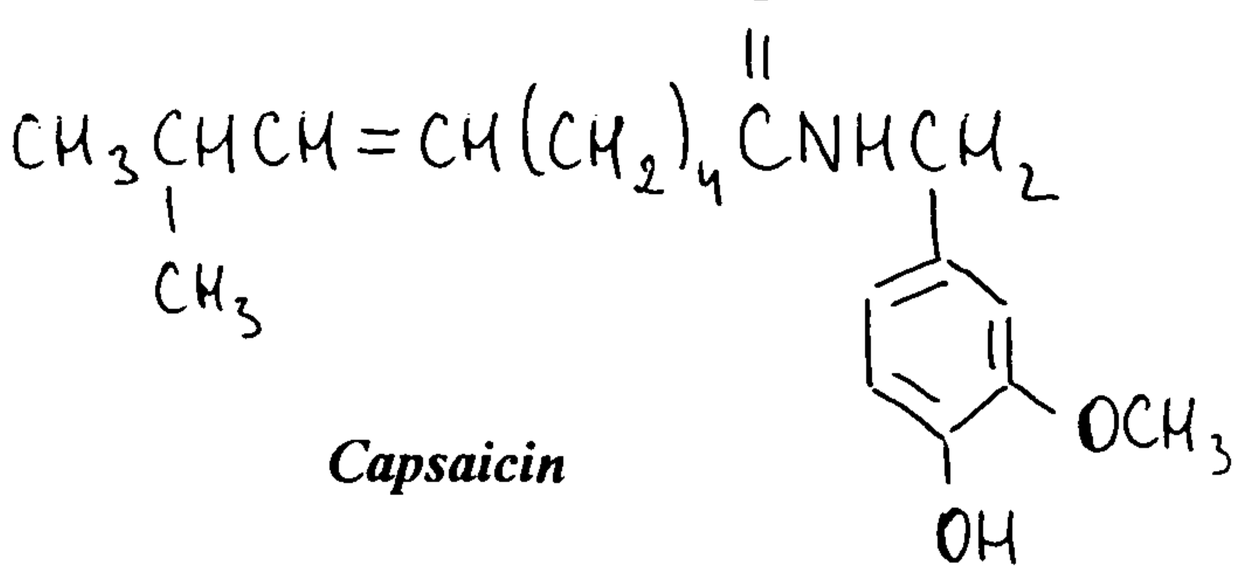
CS (o-chlorobezlylidenmalonodinitrile)



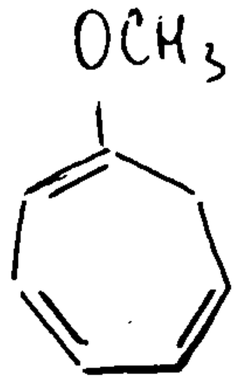
CN (α-chloroacetophenone)



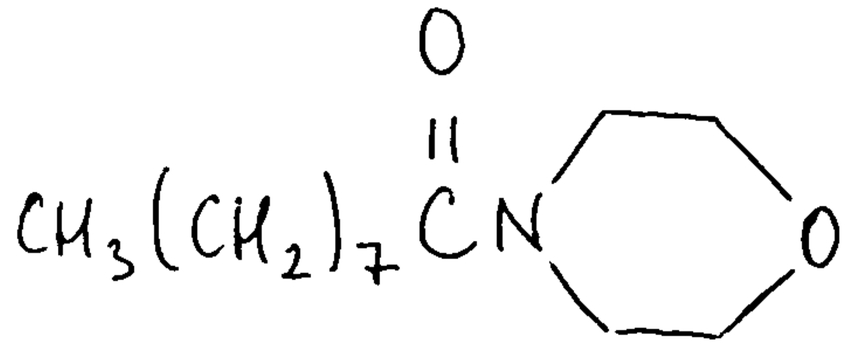
CR (dibenz[b,f][1,4]oxazepine)



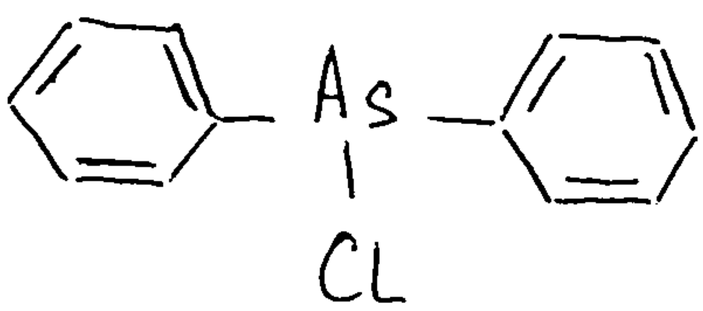
Capsaicin



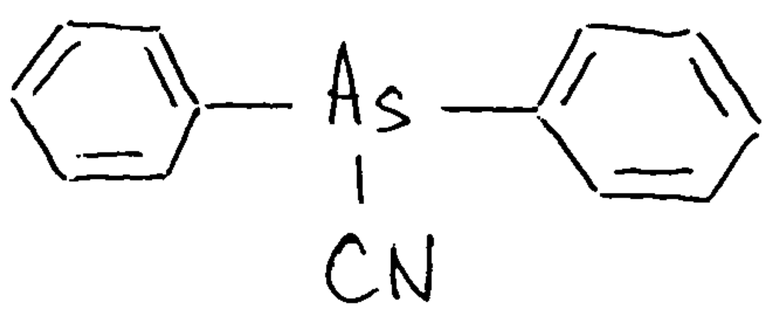
CH (1-metoxy-1,3,5-cycloheptatriene)



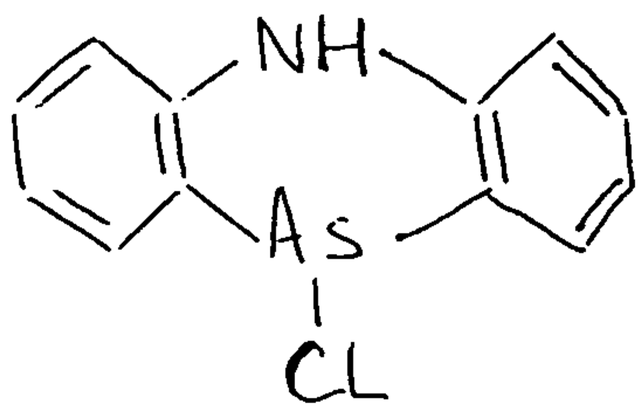
Pelargonic acid morpholide



DA (Diphenylchloroarsine)



DC (Diphenylcianoarsine)



DM (Adamsite, Diphenylamine chloroarsine)

Agent/desease	Likely method of dissimination	Transmissible human to human	Infective dose	Incubation period	Duration of illness	Lethality	Persistence	Vaccine efficacy (aerosol exposure)
Bacillus anthracis/ inhalation anthrax	Spores in aerosol	No (except cutaneous)	8–10,000 spores	1–5 days	3–5 days	High	Very stable (spores remain viable for years in soil)	2 doses of vaccine protect against 200–500 LD_{50} in monkeys
Vibrio cholerae/ cholera	Sabotage (food and water); aerosol	Rare	$>10^6$ organisms	12 hours–6 days	≥1 week	Low	Unstable in aerosols and freshwater; stable in saltwater	No data on aerosol
Yersinia pestis/ pneumonic plague	Aerosol	High	<100 organisms	1–3 days	1–6 days	High unless treated within 12–24 hours	For up to 1 year in soil; 270 days in bodies	3 doses not protective against 118 LD_{50} in monkeys
Francisella tularensis/ tularemia	Aerosol	No	1–50 organisms	1–10 days	≥2 weeks	Moderate if untreated	For months in moist soil or other media	80% protection against 1–10 ID_{50}
Coxiella burnetii/ Q fever	Aerosol; sabotage (food and water)	Rare	10 organisms (aerosol)	14–26 days	Weeks	Very low	For months on wood and sand	94% protection against 1–3500 ID_{50} in guinea pigs
Ebola virus/Ebola fever	Direct contact (endemic); aerosol (BW)	Moderate	1–10 plaque forming units for primates	4–16 days	Death between 7–16 days	High for Zaire strain, moderate for Sudan	Relatively unstable	No vaccine
Variola virus/ smallpox	Aerosol	High	Assumed low	10–12 days	4 weeks	High to moderate	Very stable	Vaccine protects against large doses in primates
Venezuelan equine encephalitis virus/VEE	Aerosol; infected vectors	Low	Assumed very low	1–6 days	Days to weeks	Low	Relatively unstable	TC 83 protects against 30–500 LD_{50} in hamsters
Botulinum toxin/ botulism	Aerosol; sabotage (food and water)	No	Human LD_{50} p.o. 1 ng/kg	Hours to days	Death in 24–72 h; lasts months if not lethal	High without respiratory support	Weeks in food and nonmoving water	3 doses efficacy of 100% against 22–250 LD_{50} in primates
T-2 mykotoxins	Aerosol; sabotage	No	Moderate	2–4 hours	Days to months	Moderate	Years at room temperature	No vaccine
Ricin	Aerosol; sabotage (food and water)	No	LD_{50} 3–5 μg/kg	Hours to days	Days, death 10–12 days after ingestion	High	Stable	No vaccine
Staphylococcal enterotoxin B	Aerosol; sabotage (food and water)	No	Clinical illness from pico-gram range	1–6 hours	Hours	<1%	Resistant to freezing	No vaccine