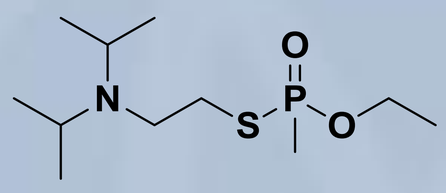
ORGANISATION FOR THE
PROHIBITION OF CHEMICAL WEAPONS

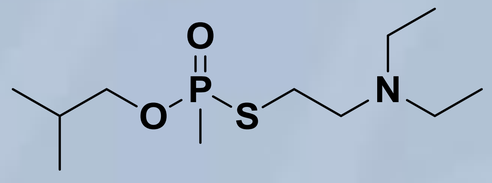
Working Together For a World Free of Chemical Weapons

Organophosphorus (OP) Nerve Agents and their Countermeasures

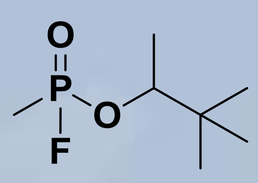
Examples of stockpiled nerve agents:



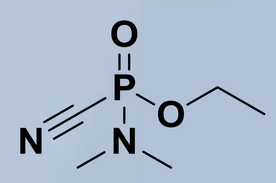
VX



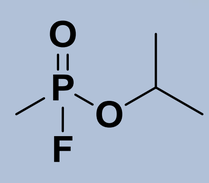
Russian VX



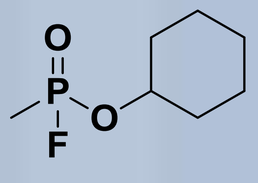
Soman (GD)



Tabun (GA)

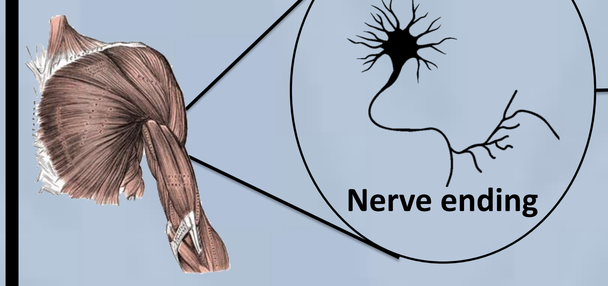


Sarin (GB)



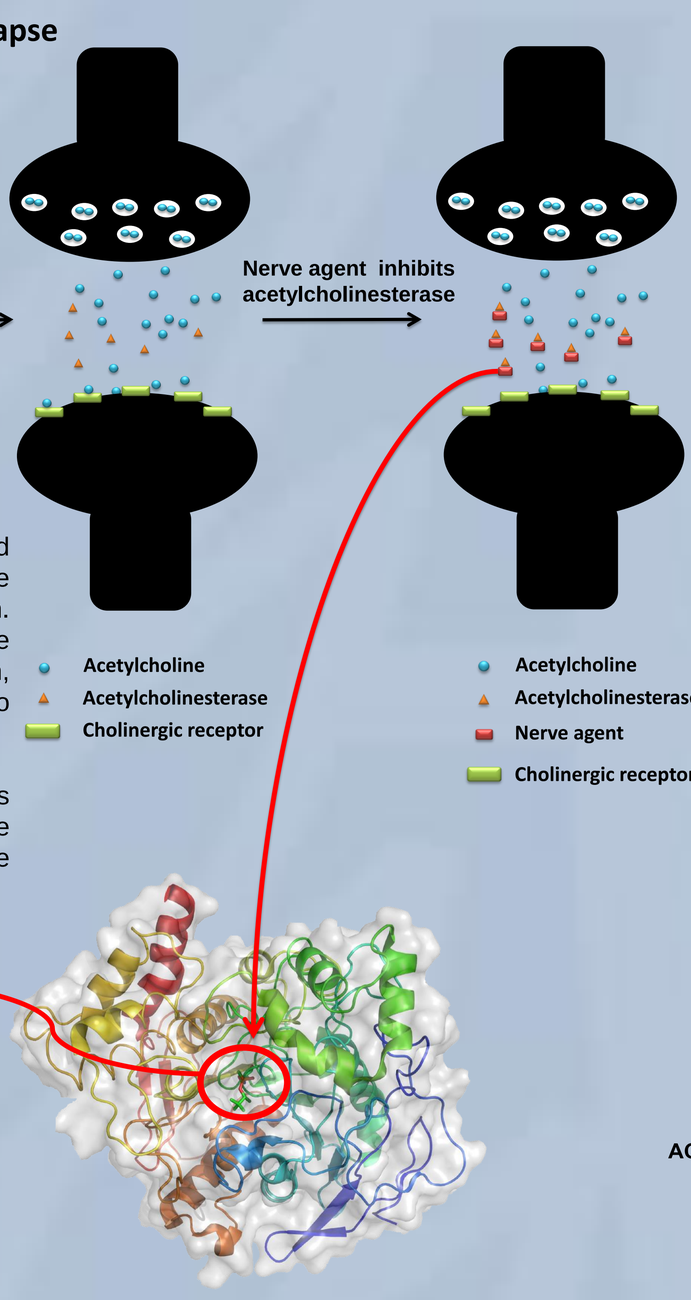
Cyclosarin (GF)

Mechanisms



The neurotransmitter acetylcholine (ACh) is released into the synapse followed by binding to acetylcholine receptors which results in muscle contraction. Immediately after ACh binding, the enzyme acetylcholinesterase (AChe) breaks down ACh, removing it from the synapse to allow the muscle to relax.

Nerve agents inhibit AChE, which results in an excess of acetylcholine and over-stimulation of the neuromuscular junction. SLUDGE syndrome followed by paralysis and death results.



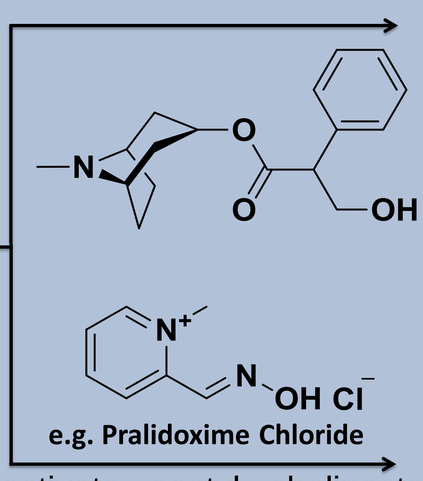
Soman ( ) adduct

Non-aged soman (GD) conjugate of *Torpedo californica* acetylcholinesterase

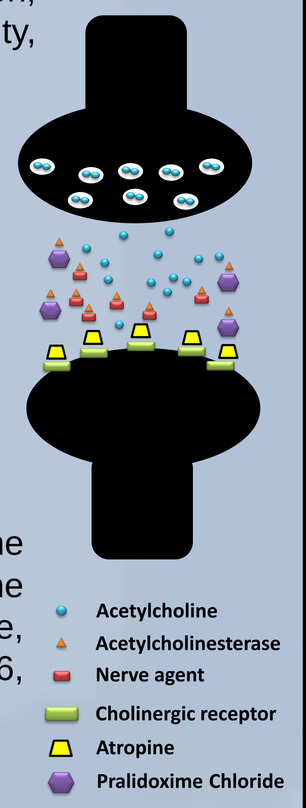
(Protein Data Bank structure 2WFZ)

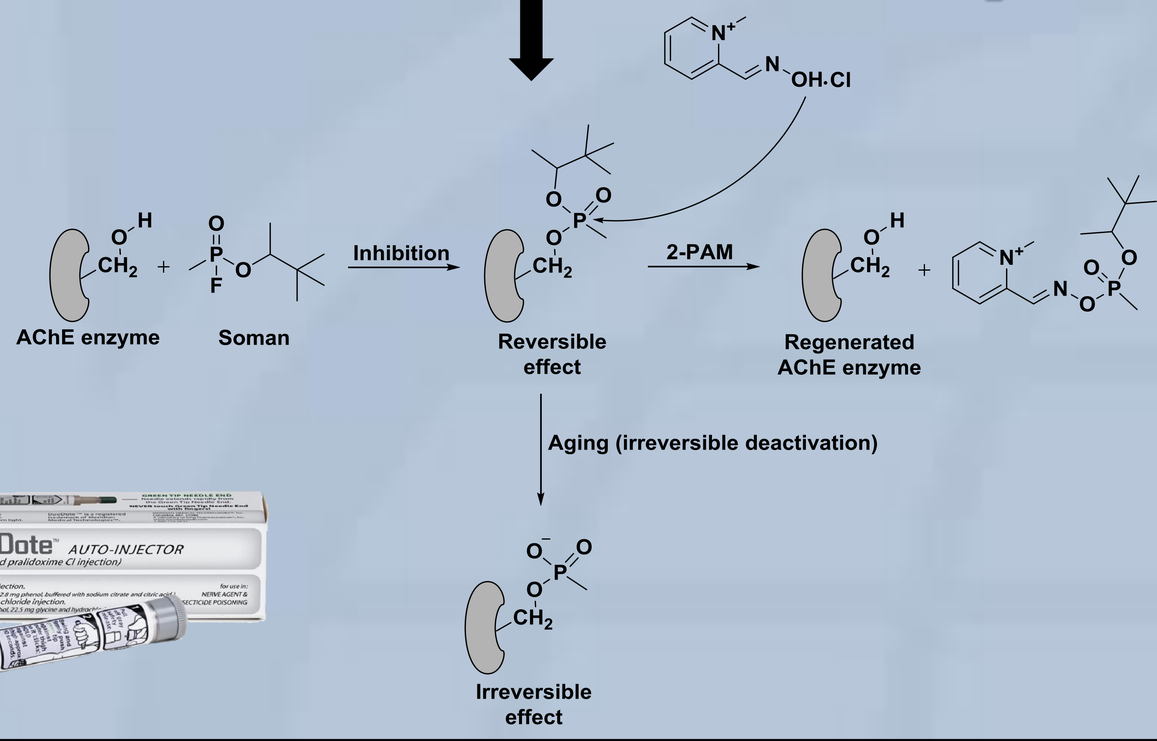
- Inhalation toxicity
- Dermal toxicity
- Neurological complications

Atropine, blocks the action of acetylcholine at muscarinic receptors and treats SLUDGE syndrome (salivation, lacrimation, urination, diaphoresis, gastrointestinal motility, emesis)



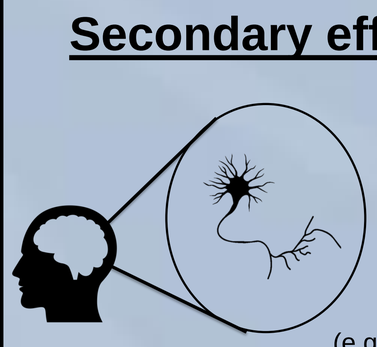
Oximes, Reactivate acetyl cholinesterase before the process of aging (e.g. irreversible inhibition of the enzyme. Oximes can be co-administered with atropine, commnly used oximes include pralidoxime chloride, HI-6, trimedoxime and obidoxime

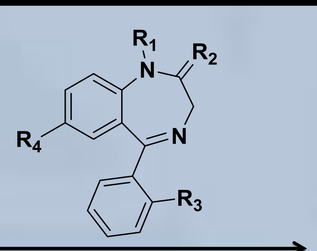




Nerve agent countermeasures Atropine and Pralidoxime Chloride auto injector

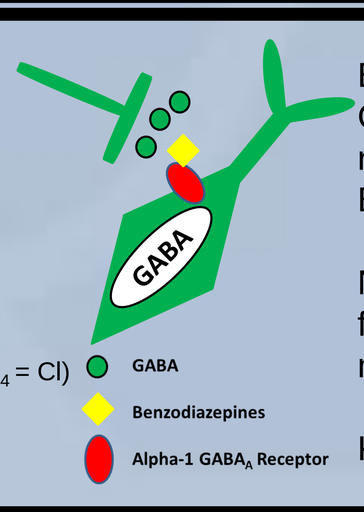
Secondary effect





Benzodiazepines

(e.g. Diazepam; $R_1 = CH_3$, $R_2 = O$, $R_3 = H$, $R_4 = Cl$)

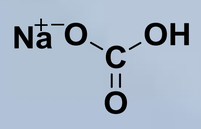


Benzodiazepines (BDZs, a class of anticonvulsants) bind to the gamma sub-unit of the $GABA_A$ receptor. Binding results in an allosteric (structural) modification of the receptor that increases receptor activity and inhibits excessive nerve cell activity. BDZs used for this purpose include diazepam, lorazepam and midazolam.

Neuroprotective substances that bind to the $GABA_A$ receptor such as BDZs are helpful for preventing neurological damage in the brain (atropine and oximes are targeted at muscle tissue).

Ketamine has also been studied as a neuroprotective substance.

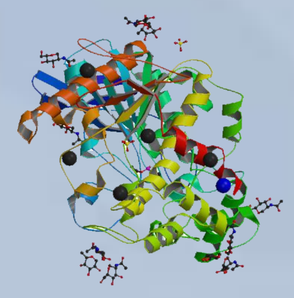
Other reported countermeasures



Sodium bicarbonate infusion has been reported to neutralize nerve agents. This is not a generally recommended procedure but there are reports of its use. *Iran J Med Sci. 2012 Jun; 37(2): 74–91*

Hemoperfusion and **fresh frozen plasma** can also be used to increase the excretion rate of nerve agent from the body. *Arch Toxicol. 2014 Feb;88(2):301-7*

Bioscavengers are enzymes that detoxify OPs by stoichiometric reaction or by catalytically cleaving the OPs into biologically inert products. Butyrylcholinesterase (illustrated below) represents an example of a stioichiometric bioscavenger.
Chem Biol Interact. 2013 Dec 5;206(3):536-44



Non-aged form of human butyrylcholinesterase inhibited by the tabun analogue TA1.
(Protein Data Bank structure 2WID).

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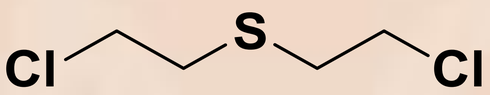
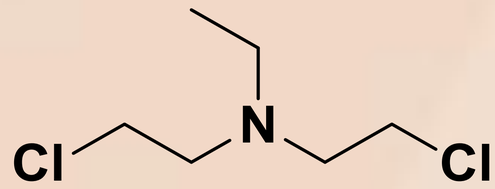
Blister Agents and their Countermeasures

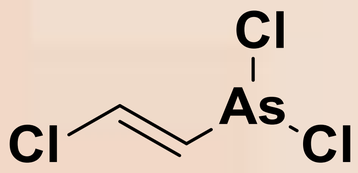
Examples of stockpiled blister agents:



Sulfur Mustard (HD)

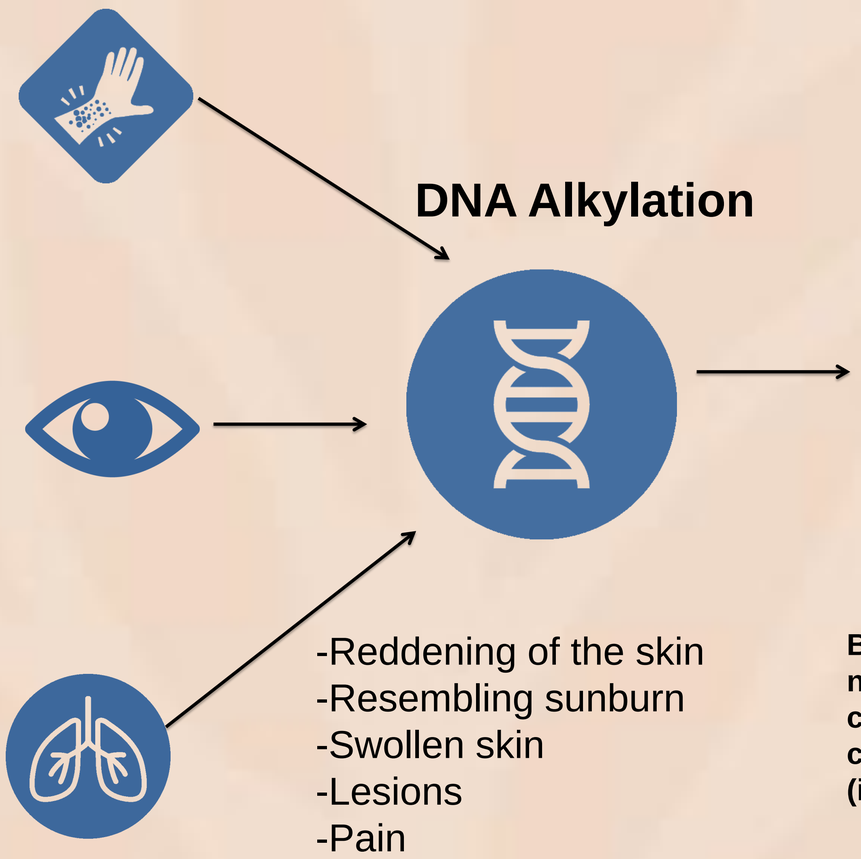


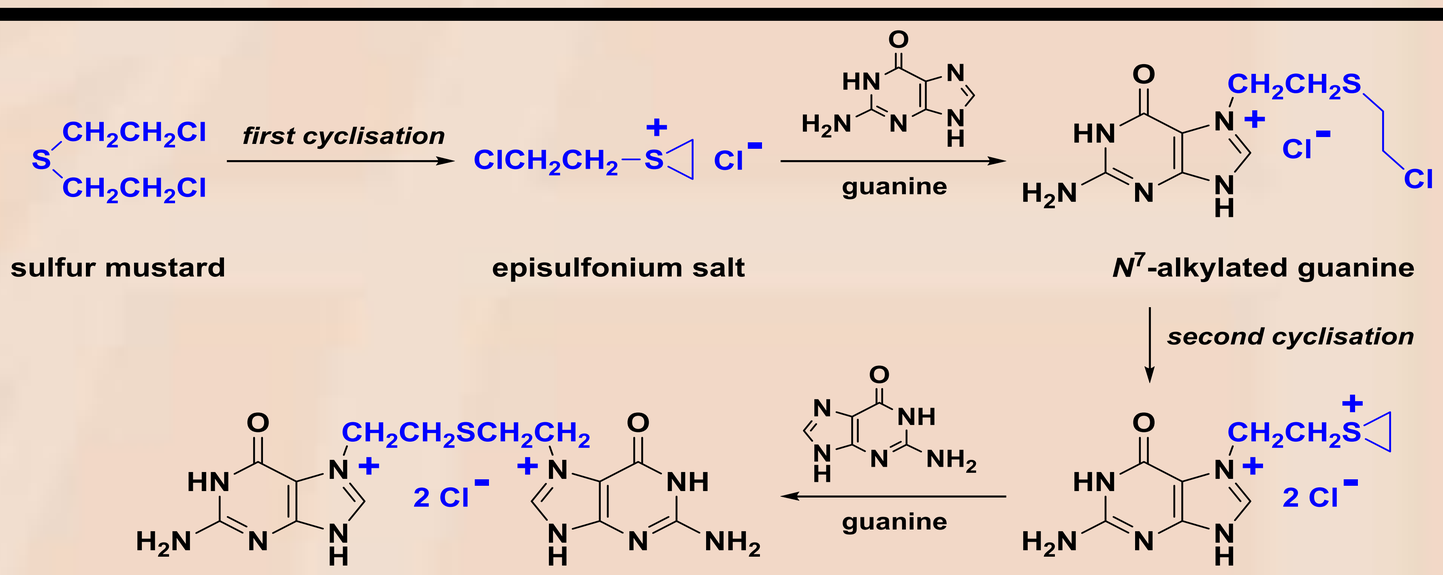
Nitrogen Mustard (HN-1)



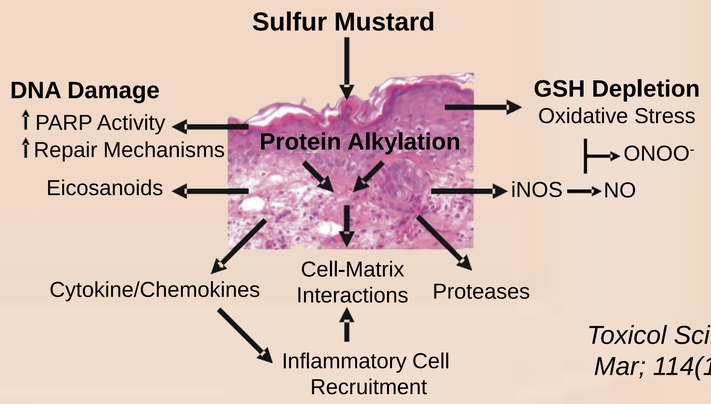
Lewisite (L)

Effects of sulfur mustard



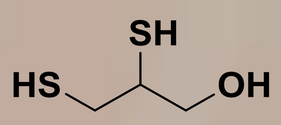
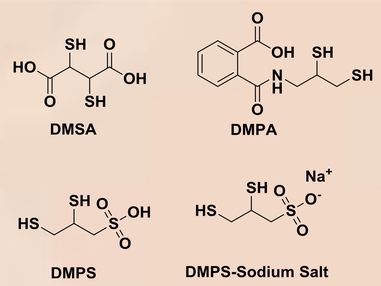
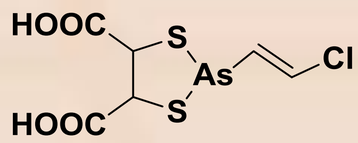
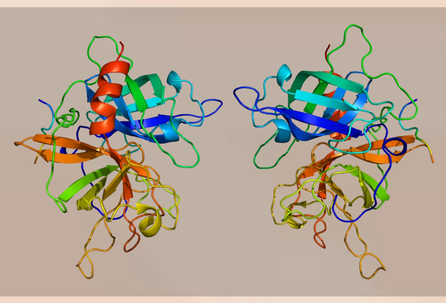
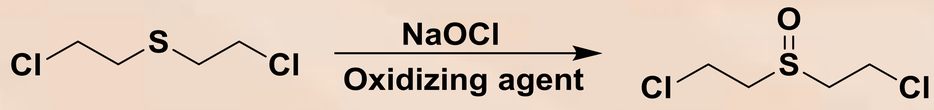


Blister agents alkylate biological molecules such as nucleic acids, proteins and cellular membrane components. This results in a cascade of complications. Alkylation and cross linking of DNA (illustrated above) can lead to a risk of cancer.



Toxicol Sci. 2010 Mar; 114(1):5-19

Countermeasures including supportive measures

		Effect
Sodium Thiosulfate (administered intravenously)	$Na_2S_2O_3$	Prevents lethality by reacting with mustard (scavenger). $R-Z(CH_2)_2 + Cl^- \xrightarrow{Na_2S_2O_3} R-Z-CH_2-CH_2-S-S(=O)_2-O^-Na^+ + NaCl$ R = $ClCH_2CH_2$ and Z = S (HD) R = Et and Z = NCH_2CH_2Cl (HN-1)
Reactive Skin Decontamination Lotion - RSDL A Mixture of Dekon 139 and 2,3, butanedione monoxime (DAM) in a polyethylene glycol monomethyl ether (MPEG) and water solvent system (also works as a countermeasure against organophorphorus agents). Commercially available, www.rsdl.com.		Prevents dermal absorption and rapidly neutralizes the vesicant chemical.
BAL (British Anti Lewisite) (administered intramuscularly)		Chelating agent that binds to Lewisite to form a water soluble complex. Lewsite + BAL → 5 membered ring complex + 2 HCl
DMSA DMPS DMPA DMPS-Sodium Salt (used for Lewisites)		These chelating agents bind to Lewisite to form water soluble complexes. 
Tissue plasminogen activator (tPA) (Experimental therapeutic, administered intravenously) *Am J Respir Cell Mol Biol. 2013 Apr; 48(4): 439–447*		Diminishes airway obstructive fibrin–containing casts; this improves clinical respiratory distress, pulmonary gas exchange and tissue oxygenation.
Sodium Hypochlorite Can be used as a skin decontaminant. However, it is not a recommended treatment due to caustic properties.	NaOCl	Oxidizes (and inactivates) blister agents. 

The effects of blister agents appear within minutes of exposure. To minimize injury, decontaminate immediately!

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Blood Agents and their Countermeasures

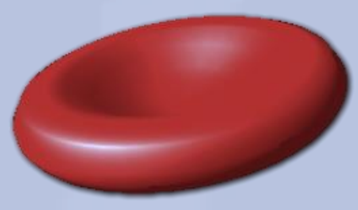
$N\equiv C-H$	$N\equiv C-C\equiv N$	$N\equiv C^{-}{}^{+}Na$	$N\equiv C-Br$
Hydrogen Cyanide	**Cyanogen**	**Sodium Cyanide**	**Cyanogen Bromide**
LD_{50}*	LD_{50}*	LD_{50}*	LD_{50}*
Inhalation 300 mg/kg	**Inhalation** 350 mg/kg	**Ingestion** 64 mg/kg	**Inhalation** 39 –52 mg/kg
Ingestion 50 – 200 mg/kg	**Skin** 10 - 15 mg/kg	**Skin** 77 mg/kg	**Ingestion** 25-50 mg/kg
Skin 100 mg/kg			**Skin** 250-1000 mg/kg

** LD_{50}: Median lethal dose in humans extrapolated from animals, toxicological profile of Cyanide, Agency for Toxic Substances and Disease Registry, U.S. Department of Health & Human Services.*

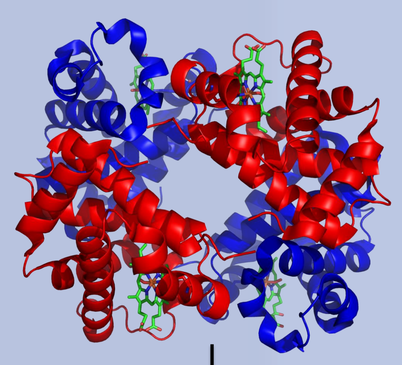
Effect

Cyanide ion (CN^-)
Produced by blood agents

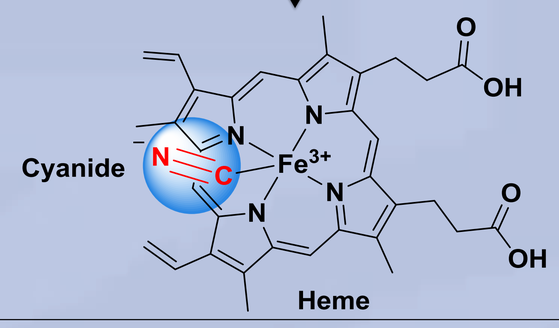
Red Blood Cells →



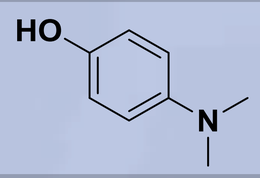
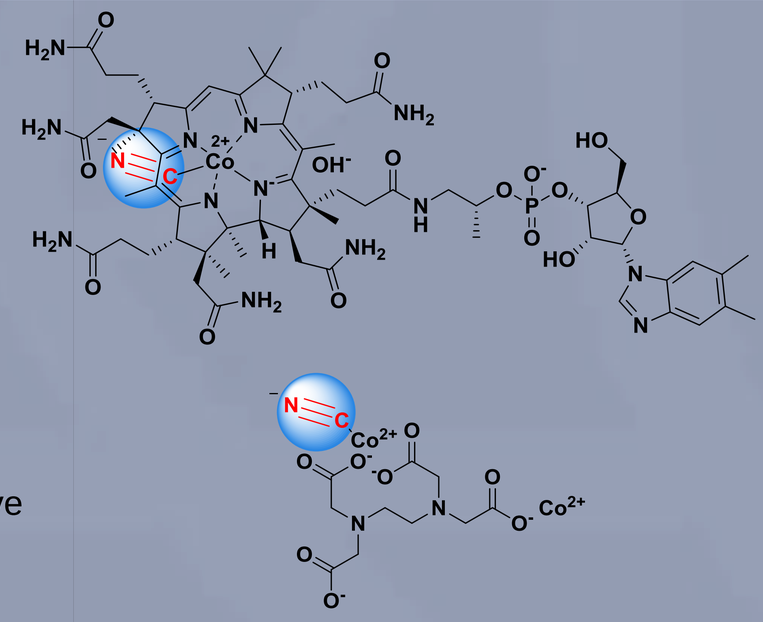
Hemoglobin →



Heme-Cyanide Complex



- Cyanide ion (CN^-) binds to hemoglobin, the oxygen-carrying molecule in red blood cells.
- It distributes throughout the body via the bloodstream where it binds to the metabolic enzyme cytochrome c oxidase. This prevents cells from using oxygen and producing energy.
- Symptoms of hydrogen cyanide poisoning:
  - Headache, nausea, dizziness (mild doses)
  - Convulsions and coma (high doses)
  - Respiratory and cardiac arrest (very high doses)

Countermeasures including supportive measures	Structure	Effect
Sodium nitrite/ Sodium Thiosulfate (administered intravenously)	$NaNO_2$/ $Na_2S_2O_3$	Nitrite oxidizes iron from the ferrous (+2) state to the ferric (+3) state, increasing the concentration of circulating ferric ion which competes for cyanide binding to the ferric ion of cytochrome c oxidase. Sodium thiosulfate binds to cyanide to produce thiocyanate, which is less toxic and eliminated via the kidneys.
4-Dimethylaminophenol (4-DMAP) (administered intravenously)		Oxidizes iron from ferrous (+2) to ferric (+3) at a faster rate then sodium nitrite.
Hydroxocobalamin (a form of Vitamin B_{12} , administered intravenously) Dicobalt EDTA Caution: High incidents of side effects have been observed in patients receiving this treatment.		Binds to cyanide to form a complex that can be cleared from the body via the kidneys.
Nitrocobinamide	NO_2-vitamin B_{12}	Reverses cyanide inhibition of the enzyme cytochrome c oxidase.
Hyperbaric Oxygen Therapy		Potentiates activity of other counter-measures by displacing CN^- from heme.

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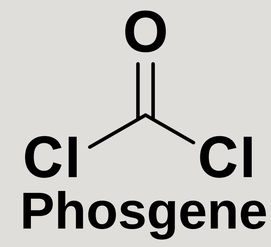
Choking Agents and their Countermeasures

Chlorine

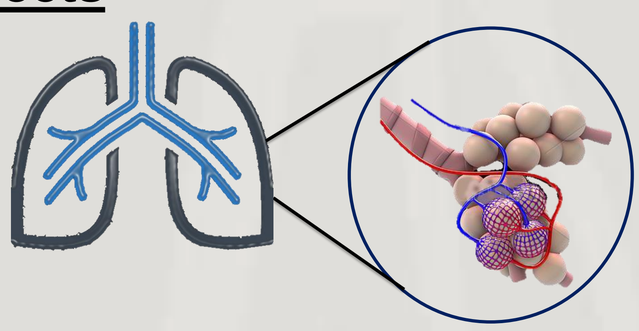
Chlorine is a yellow green gas with a strong, bleach like odour. Soldiers describe its smell as a distinct mix of pepper and pineapple. Its density (3.21 kg/m^3) is about three times that of air.



Phosgene

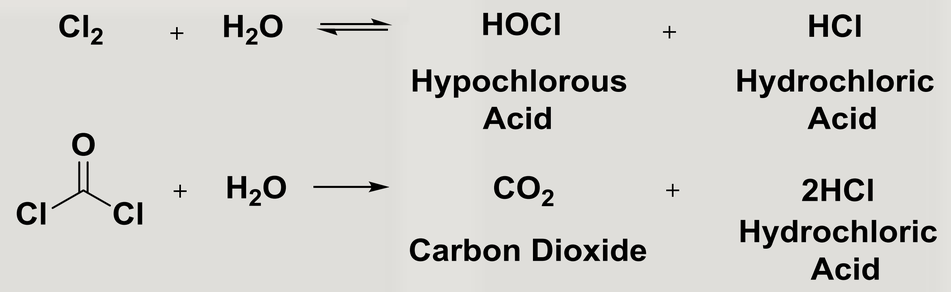
Phosgene is a colourless gas with a musty odour. Its density (4.25 kg/m^3) is about four times that of air.

Effects



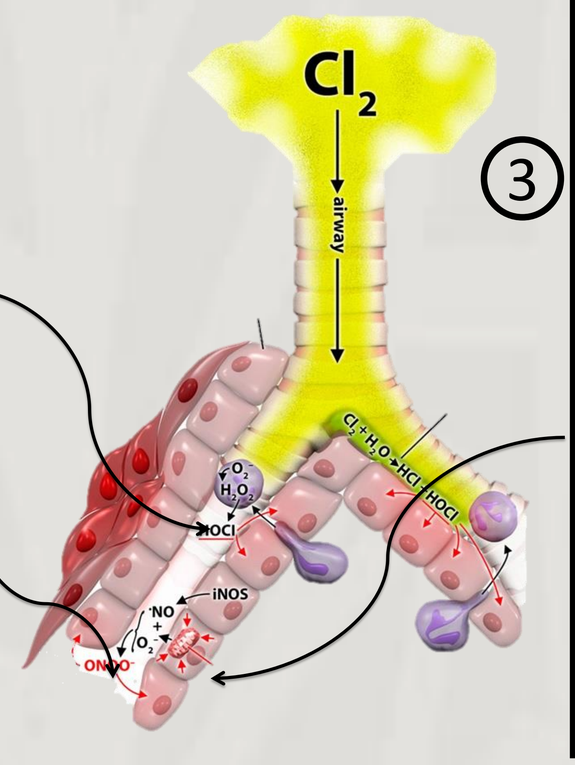
Choking agents react instantly with biological fluids, skin and eyes

- Chest Discomfort
- Shortness of breath
- Irritation of nose and throat
- Lachrymation



① Both **Cl_2** and HOCl react with airway lining constituent molecules. Reactive oxygen species (ROS) such as superoxide (O_2^-), hydrogen peroxide (H_2O_2) and hydroxy radicals (·OH) also form, and cause irreversible biochemical changes.

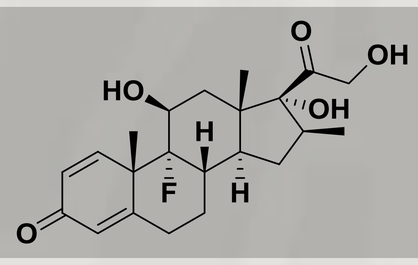
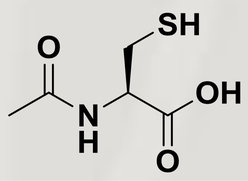
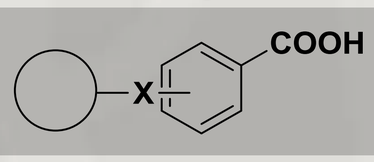
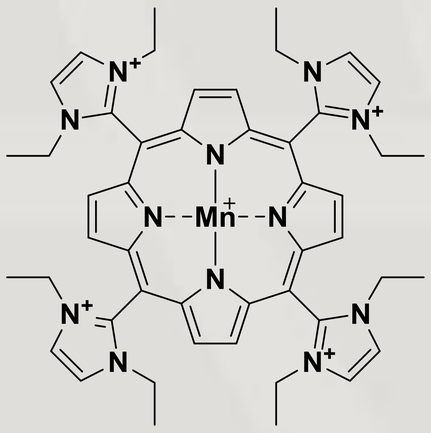
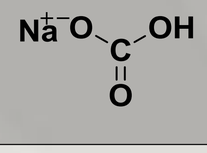
② Induction of nitric oxide synthase (iNOS) can lead to formation of nitric oxide (NO) and, secondarily, peroxynitrite ($ONOO^-$).



③ These reactive species damage DNA repair enzymes; activate some inflammatory cascades; and induce vascular dysfunction, oxidative stress, mitochondrial damage, and arterial plaque formation.

Bronchospasm, increased mucous production causes damage of alveoli-capillary membranes, in addition to a life-threatening build-up of fluid on the lungs (pulmonary edema).

Phosgene rapidly hydrolyses in water to form carbon dioxide and hydrochloric acid which produces ocular, naso-pharyngeal, and central airway irritation. The carbonyl group (C=O) of phosgene can undergo acylation reactions with amino (-NH_2), hydroxyl (-OH), and sulfhydryl (-SH) groups. These reactions account for the major pathophysiological effects of phosgene (severe dyspnoea and clinically evident pulmonary edema).

Countermeasures including supportive measures	Structure	Indication
Steroids (Inhaled or intravenous) e.g. Betamethasone (illustrated on the right)		Decrease respiratory complications by inhibiting inflammatory responses.
N-Acetyl cysteine (NAC)		Prevents cells from oxidative damage (anti-oxidant)
Non Steroidal Anti Inflammatory Drugs (NSAIDs)		Reduce pulmonary oedema
AEOL 10150 Newly available countermeasure *Curr Opin Investig Drugs. 2006 Jan;7(1):70-80*		This countermeasure has multiple mechanisms of action that include: anti-oxidant, anti-inflammatory and anti-angiogenic activity; and the catalytic consumption of reactive oxygen and nitrogen species (free radicals)
Nebulized Sodium Bicarbonate (is not generally recommended but there are reports of its use). *Inhal Toxicol. 2006 Oct;18(11):895-900*		Neutralization of the choking agent in the affected area.