Chloroform

Synonyms: trichloromethane; methylidine trichloride
CAS: 67-66-3
MF: $CHCl_3$
MW: 119.4
Solubility: in water, 10 g/l at 15°C; soluble in ethanol and diethyl ether [1].

Major uses
Chloroform is a solvent in laboratories and in the chemical industry. It is also an inhalation anesthetic agent; however, the medical use is restricted because it is both hepatotoxic and cardiotoxic [2].

Human toxicity
Chloroform can be poisoning by ingestion and inhalation. The acute toxicity of chloroform is a combination of the central nervous system (CNS) depression, heart collapse, and hepatic and kidney toxicity.

General symptoms of exposure include: a) neurologic: anesthesia; headache, anorexia, loss of consciousness, psychotic behavior etc.; b) cardiovascular: cardiac dysrhythmias; cardiac arrest (e.g. during chloroform anesthesia), and coma; c) respiratory: chemical pneumonitis, respiratory depression, and pulmonary edema; d) gastrointestinal: nausea, vomiting, and abdominal pain; e) hepatic: central hepatic necrosis, 10 to 48 h post-ingestion [1].

Death has been reported with ingestions of as little as 10 ml orally, due to the CNS depression [1].

Blood concentrations of 5 mg/l lead to dizziness, intracranial pressure, and nausea 7 min after exposure, with fatigue and headache felt later. The concentration about 20 mg/l leads to vomiting and a sensation of fainting; concentrations of 70-80 mg /l are the narcosis limiting concentrations [3]. Post-mortem blood concentrations ranged between 17 and 390 mg/l in 10 described cases [4].

Threshold Limit Value/Time Weighted Average (OSHA, 2005): 10 ppm (49 mg/m^3) [1].

Carcinogenicity: chloroform is listed as a suspected carcinogen; carcinogen rating 2B, possibly carcinogenic to humans (IARC, 2004; EPA, 2004) [1].

Kinetic data
Absorption: chloroform is rapidly absorbed from the lungs, gastrointestinal tract, and from the skin [1].

Kinetics: possibly, first-order kinetics? [5].

Volume of distribution (Vd): 2.6 l/kg [5].

Distribution: Chloroform is readily distributed to all tissues of the body. It is highly lipid-soluble and can accumulate in adipose tissue [6].

Time to peak blood concentration was 1 h after a single oral dose of 500 mg chloroform [6].

Elimination half-life is 1.5 h [5].

Protein binding: not reported [5].

Passage of blood-brain barrier: free [5].

Chloroform diffuses readily across the placenta [1].

Metabolism and excretion

Chloroform undergoes considerable biotransformation in the liver, where it is metabolized enzymatically with help of cytochrome P450 to the following compounds: chlormethanol, hydrochloric acid, phosgene, chloride, carbon dioxide, and diglutathionyl dithiocarbonate. The main end products are carbon dioxide and hydrochloric acid [2, 8].

Phosgene is a highly reactive electrophylic compound. It is produced by the hydroxylation of chloroform to trichloromethanol, which spontaneously dehydrochlorinates to produce phosgene. Phosgene reacts with water to produce carbon dioxide and chloride ion, and with glutathione to produce diglutathionyl dithiocarbonate [2, 8].

Excretion: mainly via lungs, but also via the liver and kidney. In one study about 50% of a single oral dose was exhaled as carbon dioxide within 8 hours, and about 43% was exhaled unchanged in the same period. Less than 0.01% of the dose was found in 8 hour urine (reviewed in [6]).

Toxicological mechanisms

Chloroform is highly cytotoxic compound, which, due to its high lipid solubility, penetrates rapidly into the cells, causing cellular and tissue damage. The main effects of chloroform are the CNS and cardiac depression.

Phosgene, the toxic metabolite of chloroform, can covalently bind to liver and kidney proteins and deplete the liver and kidney of glutathione, resulting in hepatic and renal necrosis [7].

High concentrations of chloroform can cause cardiac arrhythmias and cardiac arrest apparently due to sensitization of the myocardium to epinephrine.

Post-mortem examination of fatal cases has shown fatty degenerative changes in the liver, kidney and heart [2, 7].

Target organs: CNS; histopathological organ lesions in the heart, liver and kidney [5].

References

1. Poisindex, Thomson Micromedex (2005).
2. Haddad, L.M. & Winchester, J.F. (1990) *Clinical Management of Poisoning and Drug Overdose*. 2nd ed., pp. 1173-114. W.B. Saunders Company.
3. Bingham, E., Cohrssen, B., Powell, C.H. (2001) *Patty's Toxicology*. 5th ed., John Wiley & Sons, New York, NY.
4. Hallander, S.& Ekwall, B. (1997) *Chloroform, MEIC Monograph*. . http://www.cctoxconsulting.a.se/33_chloroform.pdf

5. Ekwall, B., Clemedson, C., Crafoord, B., Ekwall. Ba., Hallander, S., Walum, E., Bondesson, I. (1998) MEIC evaluation of acute systemic toxicity. Part V. Rodent and human toxicity data for the 50 reference chemicals. ATLA 26, 571-616.
6. Baselt, R.C.& Cravey, R.H. (1995) *Disposition of Toxic Drugs and Chemicals in Man*. 4th edn., pp. 146-148. Chemical Toxicology Institute, Foster City, CA, USA.
7. *Casarett and Doull's Toxicology (The Basis Science of Poisons)* (1986) Klaassen, C.D., Amdur, M.O., Doull, J., eds., Macmillan Publishing Company.

Written by Ada Kolman, January 2006; revised March 2007
ada.kolman@telia.com