

## Paraldehyde

Synonym: paracetaldehyde

CAS: 123-63-7

MF: C<sub>6</sub>H<sub>12</sub>O<sub>3</sub>

MW: 132.2

LogKow=0.67

Paraldehyde is a colorless, transparent liquid.

Solubility: 1 part in 10 parts water at 30°C; miscible with alcohols, chloroform, ether and oils [1].

### Major use

Paraldehyde is a cyclic acetaldehyde trimer, first synthesized in 1872 and first used therapeutically in 1882. Paraldehyde is used as a sedative or hypnotic agent, as anticonvulsant, and to treat epilepsy. It is also included in some cough medicines [2, 3].

Industrial applications: paraldehyde is used in resin manufacture, as a preservative, and in other processes as a solvent [3].

### Human toxicity

Paraldehyde is irritating to the eyes, skin, respiratory tract, and gastrointestinal tract. It may be toxic by inhalation, ingestion, dermal, rectal, and intravenous exposure.

Paraldehyde overdose produces signs and symptoms which may include mydriasis (dilation of the pupil), metabolic acidosis, severe hypotension, tachycardia, respiratory depression, pulmonary edema, coma, cerebrovascular accident, and cardiac failure. Pulmonary edema is a frequent factor in death due to paraldehyde.

Therapeutic oral doses of paraldehyde in adults are between 5 and 250 ml (0.25 ml/kg). Intravenous therapeutic dose is 2 to 3 ml (reviewed in [4]).

Death presumably from respiratory failure is usually preceded by prolonged coma which may be seen with doses ranging from 31 to 120 ml orally. Deaths have been reported with ingestion of as little as 25 ml of paraldehyde, and have been reported with ingestion of 31, 45, 75 and 120 ml. Intravenous paraldehyde was fatal at doses of 35 ml [4]. Approximate lethal dose of paraldehyde is 1-2 g/kg [5].

Therapeutic blood plasma concentrations in ten obstetric patients who received 30 ml of paraldehyde orally were 110 to 332 mg/l (average 220 mg/l) within 0.5-4.0 h after ingestion; these concentrations declined to an average of 75 mg/l by 16 h [2].

Maximum tolerated exposure: As much as 100 to 150 ml of paraldehyde has been ingested with recovery (reviewed in [4]). Mechanisms by which paraldehyde may cause fatality in one case and not in another with a similar exposure are still under investigation [4]. Several fatalities have occurred when paraldehyde has been used in association with alcohol [2].

Toxic blood concentrations are various, from 200 mg/l up to 1300 mg/l. One patient who ingested 120 ml of paraldehyde, developed levels of 1300 mg/l and became comatose, but recovered. Fatal blood concentrations were in the range of 543 to 1480

mg/l (average 936 mg/l) in one study; in another study fatal concentrations in blood ranged 490-1600 mg/l in several patients (reviewed in [4]).

### **Kinetic data**

*Absorption:* rapidly and effectively absorbed in the body.

*Bioavailability:* 95% of oral dose is absorbed [4].

*Kinetics:* possibly multiphasic (? , AK\*), because patients given paraldehyde have a rapid rise in serum levels and slow rate of decline (reviewed in [4]).

*Volume of distribution:* 0.9 l/kg [2].

*Distribution:* paraldehyde is distributed to brain, liver and kidney (post-mortem analyses) [2].

*Passage of blood brain barrier:* possibly free, because paraldehyde was found post-mortem in brain (245 mg/kg, range 115-480 mg/kg) in 3 fatal cases [2].

*Plasma half-life:* 3-10 h [2].

*Time to peak blood concentration:* 30 min after ingestion; 20-60 min after injection (reviewed in [4]).

*Plasma protein binding:* no data available.

*Elimination half-life:* 7 h (3-10 h) [6].

### **Metabolism and excretion**

Paraldehyde is depolymerized in the liver to acetaldehyde (CH<sub>3</sub>CHO), which is then oxidized to acetic acid. Acetic acid is then metabolized to carbon dioxide.

With hypnotic doses, 70 to 80% is metabolized in the liver, most of the remainder is exhaled, and a small amount is excreted in the urine [2].

*Excretion:* approximately 3% of paraldehyde is excreted unchanged in the urine; approximately 28% is eliminated by the pulmonary route (reviewed in [2]).

### **Pharmacological mechanisms**

Paraldehyde has a depressant action on the nervous system including the peripheral, spinal, and cerebral systems. However, its action is especially marked on the cerebral cortex [4].

### **Toxicological mechanisms**

Hypothetical mechanism: depression of postsynaptic potentials in the CNS by toxic metabolite of paraldehyde, acetaldehyde [7].

It is not excluded, that paraldehyde, as well as acetaldehyde, can interfere with cell membrane fluidity, leading to “displacement of critical membrane enzymes and alterations in membrane functions” [8].

**Target organs:** CNS, PNS, heart, liver, kidney [4].

## References

1. Hazardous Substances Data Bank, HSDB (2006)
2. Baselt, R.C. & Cravey, R.H. (1995) *Disposition of Toxic Drugs and Chemicals in Man*. 4<sup>th</sup> ed., pp.579-581. Chemical Toxicology Institute, Foster City, California.
3. Wikipedia, The Free Encyclopedia (2006), via Internet.
4. Poisindex, Thomson Micromedex (2006).
5. Haddad, L.M. & Winchester, J.F. (1990) *Clinical Management of Poisoning and Drug Overdose*. 2<sup>nd</sup> ed., p.669. W.B. Saunders Company.
6. Ellenhorn, M., Schonwald, S., Ordog, G., Wasserberger, J. (1997) *Ellenhorn's Medical Toxicology: Diagnosis and Treatment of Human Poisoning*. 2<sup>nd</sup> ed., p. 604-605. Williams & Wilkins.
7. Ekwall, B., Clemenson, 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.
8. *Casarett and Doull's Toxicology (The Basic Science of Poisons)*, (1986) Klaassen, C.D., Amdur, M.O., Doull, J., eds., pp. 648-654. Macmillan Publishing Company.

\*A. Kolman

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