Cyclophosphamide

Safety Data Sheet

Division of Occupational Health and Safety
National Institutes of Health

WARNING!

This compound is acutely toxic, carcinogenic, teratogenic, embryotoxic, and mutagenic. It is readily absorbed by various body tissues, through the skin, intestinal tract, and transplacentally. Avoid formation and breathing of aerosols.

Laboratory operations should be conducted in a fume hood, glove box, or ventilated cabinet.

Avoid skin contact: if exposed, wash with soap and cold water. Avoid washing with solvents. Avoid rubbing of skin or increasing its temperature.

For eye exposure, irritagate immediately with large amounts of water. For ingestion, induce vomiting. Drink milk or water. Refer for gastric lavage. For inhalation, remove victim promptly to clean air. Administer rescue breathing if necessary. Refer to physician.

In case of laboratory spill, wear protective clothing during cleanup. Avoid skin contact or breathing of aerosols. See castegnaro *et al.* (1985) for details. Dispose of waste solutions and materials appropriately.

A. Background

Cyclophosphamide (CP) in its hydrated (usual) form is a white odorless powder with slightly bitter taste. It is toxic, carcinogenic, mutagenic, and teratogenic in animals and probably in man. Its mode of action is that of an alkylating agent after activation. Its principal uses are as an antineoplastic agent, as an immunosuppressive agent in a varity of non-malignant diseases, as an insect chemosterilant, and as a defleecing agent for sheep.

CP has been identified by an IARC Working Group as being probably carcinogenic for humans (Group 2A) (Althouse *et al.*, 1980).

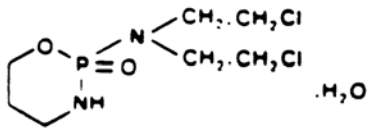
Recent review articles include IARC, 1981; Colvin and Hilton. 1981.

B. Chemical and Physical Data

Introductory notes: (a) The structure of CP reveals an asymmetric phosphorus atom and, therefore, this compound exists as two optical isomers. The levo- and dextro-rotary enantiomers have been identified by x-ray analysis as the S- and R-forms, respectively (Sato *et al.*, 1983). Commercial preparations are unresolved but there are indications that differences exist in the relative abundances of these enantiomers in such

preparations (Mruzek and Shaw, 1984). With the exception of a few studies dealing with their optical or biological properties, which are mentioned in the text, no attention has been paid by investigators to the existence of isomers or the isomeric composition of their material. (b) Unless otherwise noted, all data are for the monohydrate which is the usual form.

1. Chemical Abstract Nos.: a. general: 50-18-0; b. levo-CP: 60007-96-7; c. dextro-CP: 60030-72-0; d. racemic CP: 6007-95-6.
2. Synonyms: 2H-1,3,2-oxazaphosphorine, 2-[bis-(2-chloroethyl)-amino)tetrahydro-2-oxide[A]; 2H-1,3,2-oxazaphosphorine-2-amine,N,N-bis-(2-chloroethyl)tetrahydro-2-oxide[B]; 1-bis(2-chloroethyl0amino-1-oxo2-aza-5-oxaphosphoridine monohydrate; [bis(chloro-2-ethyl)-amino]-2-tetrahydro-3,4,5,6-oxazaphosphorine-1,3,2-oxide-2-monohydrate[C]; B518; Cyclophosphan(e); Cytoxan; Endoxan; Genoxal; Mitoxan; Procytox; Sendoxan; NSC 26271.
3. Chemical structure and molecular weight: $C_7H_{15}Cl_2N_2O_2P{\cdot}H_2O$; M.W. 279.1.



4. Density: No data.
5. Absorption spectroscopy: Ultraviolet absorption maximum (long ε) at 198 nm (2.667) in methanol (Wantland and Hersh, 1979). The mass spectrum has been reported (Schulten, 1974).
6. Optical rotation: $[\alpha]_D^{25}$ = +2.48 and -2.46 for the two optical isomers (Sato *et al.*, 1983).
7. Volatility: No data; may be assumed to be low.
8. Solubility: In water and physiological saline, 40 g/L. Soluble in ethanol, methanol, chloroform, dioxane, ethylene glycol; slightly soluble in ether and acetone.
9. Description: The monohydrate is a white colorless crystalline powder with a slightly bitter taste. The anhydrous material is an oily semisolid.
10. Bioling point: No data; melting point: variously reported as 1-45°C and 49.5-53°C. (The latter range appears to be more reliable.) Melting point of both optical isomers: 67-68°C.
11. Stability: Decomposition in aqueous solution (physiological saline) at room temperature for 8 and 24 hours and 1 week is: less than 1.5%, 3.5% and 11.9%, respectively; less than 1.5% decomposition in the refrigerator in 6 days (Gallelli, 1967; Brooke *et al.*, 1973). Stable (less than 10% change in 24 hours at room temperature) in 5% dextrose in plastic containers (Benvenuto *et al.*, 1981). Hydrolyzes at temperatures above 30°C (Arnold and Kose, 1960; Zon *et al.*, 1971; Kensler *et al.*, 1979). Anhydrous CP decomposes slowly on standing at room temperature. At temperatures above 30C and relative humidity of less than 70% the hydrate slowly changes to the anhydrous form (Laine *et al.*, 1983).
12. Chemical reactivity: No data other than those for hydrolysis. Note that liberation of chloride ion in aqueous solution is very much slower than from alkyl nitrogen mustards under comparable conditions. 2-Chloroethylamino compounds are usually subject to reaction with oxidizing agents.
13. Flashpoint: No data.

[A] Chemical Abstracts name, used for listings in the 7th and 8th Decennial Index.

[B] Chemical Abstracts name, used for listings in 9th Decennial Index and subsequently.

[C] For other chemical names see IARC (1981).

14. Autoignition temperature: No data.
15. Exposive limits in air: No data.

C. Fire, Explosion, and Reactivity Hazard Data

1. CP does not require special fire-fighting procedures or equipment and does not present unusual fire and explosion hazards.
2. No conditions contributing to instability are known to exist, other than its instability to light, to water at elevated temperatures, and probably to oxidizing agents.
3. No incompatibilities are known
4. No hazardous decomposition products have been identified. The metabolism of CP results in the production of acrolein, which is a flammable irritant to eyes and mucosa; however, there are no data indicating that acrolein is produced under conditions of fire from the solid material.
5. CP does not require non-spark equipment.

D. Operational Procedures

The NIH Guidelines for the Laboratory Use of Chemical Carcinogens describe operational practices to be followed when potentially carcinogenic chemicals are used in the NIH laboratories. The NIH Guidelines should be consulted to identify the proper use conditions required and specific controls to be implemented during normal and complex operations or manipulations involving CP.

IT should be emphasized that this data sheet and the NIH Guidelines are intended as starting points for the implementation of good laboratory practices when using this compound. The practices and procedures described in the following sections pertain to the National Institutes of Health and may not be universally applicable to other institutions. Administrators and/or researchers at other institutions should modify the following items as needed to reflect their individual management system and current occupational and environmental regulations.

Solutions of CP penetrate various glove materials (Laidlaw *et al.*, 1984; Slevin *et al.*, 1984). This factor should be taken into account when handling CP.

1. Chemical inactivation: Validated methods have been reported (Castegnaro *et al*., 1985).
2. Decontamination: Turn off equipment that could be affected by CP or the materials used for cleanup. If there is any uncertainty regarding the procedures to be followed or decontamination, call the NIH Fire Department (dial 911) for assistance. Consult Castegnaro *et al.* (1985) for details concerning decontamination of surfaces, glassware, and animal cages.
3. Disposal: It may be possible to decontaminate waste streams containing CP before disposal. For details, see Castegnaro *et al.* (1985). No waste streams containing CP shall be disposed of in sinks or general refuse. Surplus CP or chemical waste streams contaminated with CP shall be handled as hazardous chemical waste and disposed of in accordance with the NIH chemical waste disposal system. Nonchemical waste (*e.g.*, animal carcasses and bedding) containing CP shall be handled and packaged for incineration in accordance with the NIH medical pathological waste disposal system. Potentially infectious waste (*e.g.*, tissue cultures) containing CP shall be disinfected by heat using a standard autoclave treatment and packaged for incineration, as above. Burnable waste (*e.g.*, absorbent bench top liners) minimally contaminated with CP shall be handled as potentially infectious waste and packaged for incineration, as above. Absorbent materials (*e.g.*, associated with spill cleanup) grossly contaminated shall be handled in accordance with the chemical waste disposal system. Radioactive waste containing CP shall be handled in accordance with the NIH radioactive waste disposal system.

4. Storage: Store solid CP and its solutions in dark-colored, tightly closed containers, preferably under refrigeration. Avoid exposure to light and moisture. Store working quantities of CP and its solutions in an explosion-safe refrigerator in the work area.

E. Monitoring and Measurement Procedures Including Direct Field Measurements and Sampling for Subsequent Laboratory Analysis

1. Sampling: Biological samples are frozen (if analysis is delayed) and extracted with organic solvents from alkaline solution (Nayar *et al.*, 1979; van den Bosch and De Voss, 1980). For large samples, such as 24 hour urine collection, concentration prior to purification on Amberlite columns is useful (Evelo *et al.*, 1986).

2. Analysis: The current methods of choice are by gas chromatography of trifluoroacetyl (Pantarotto *et al.*, 1974; Jardine *et al.*, 1978; Juma *et al.*, 1979; van den Bosch and De Voss, 1980) or heptafluorobutyryl derivatives (Nayar *et al.*, 1979), using electron capture, flame ionization, or nitrogen-phosphorus detectors. The latter is the most sensitive procedure, with detection limits of 10 ng/ml. A highly specific method (involving, however, considerable sample preparation) is isotope dilution mass spectrometry (Jarman *et al.*, 1975; Bahr *et al.*, 1980). Simultaneous analysis for active metabolites of CP in addition to the parent compound has been accomplished with gas (Jardine *et al.*, 1978) and thin layer chromatography (Norpoth *et al.*, 1975). Other less frequently used methods are HPLC with detection by ultraviolet at 200 nm (not sensitive enough for biological media; Kensler *et al.*, 1979), infrared analysis (ditto), and a modification of the 4(4'-nitrobenzyl)pyridine colorimetric method (CP reacts with this reagent only after preliminary hydrolysis to nor-nitrogen mustard).

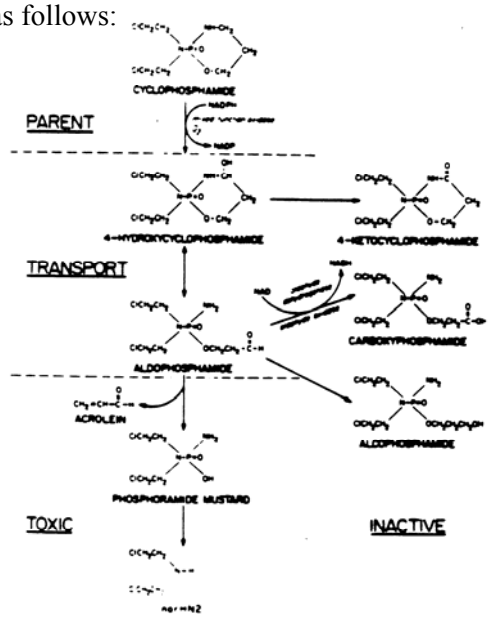
F. Biological Effects (Animal and Human)

1. Absorption: CP is absorbed from the intestinal tract, by parenteral injection, and through the intact skin (in organic solution(Hirst *et al.*, 1984; Wagner and Fenneberg, 1984). It is also transmitted transplacentally.

2. Distribution and pharmcokinetics: There are no data on the distribution of intact molecule. The ^{14}C label of side chane labeled CP is rapidly distributed throughout the human body after intravenous injection; 70% of the label is subsequently excreted in the urine (Bagley *et al.*, 1973).

   Pharmacokinetic data have been published (Grochow and Colvin, 1983; Wagner and Fenneberg, 1984).

3. Metabolism and excretion: The metabolism of CP has been worked out in detail and has been worked out in detail and has been reviewed (Colvin, 1978; Domeyer and Sladek, 1980; Przybylski, 1982). It is outlined as follows:



i. (From Domeyer and Sladek, 1980.)

All intermediates have been identified as metabolites in animals, and most of them in man. 4-Hydroxy CP and its tautomer aldophosphamide are regarded as transport forms and may not be active in themselves, although 4-hydroxy CP is regarded as representing the major contributor to cytotoxic effects of CP by being the major cell entrant (Powers and Slader, 1983). Additional metabolites, which have not as yet been fitted into the above pathways, are 2-chloroacetaldehyde (Shaw *et al.*, 1983), and three phosphorus-free oxazolin-2-one ring structures (Chan *et al.*, 1986). Of these, the highly reactive 2-chloroacetaldehyde may be responsible at least partly for the toxic effects of CP in the bladder. It is noteworthy that CP recovered from the urine of patients who were administered racemic CP is levorotatory, indicating a stereo- selective metabolism of CP (Cox *et al.*, 1976).

The metabolites which are probably the active alkylating agents, responsible for toxic and carcinogenic effects, are phosphoramide mustard, nor-nitrogen mustard, and acrolein. Urinary excretion products are mianly unmetabolized CP, 4-hydroxy CP, acrolein (both as conjugation products with sulfhydrl compounds such as glutathione), 4-keto CP, phosphoramide mustard, and carboxy-phosphamide (Biles, 1979; Wagner *et al.*, 1980).

4. Toxic effects: Acute LD50s have been reported as follows (in mg/kg): mouse, 580 iv, 400 ip, 780 oral; rat, 196 iv, 182 ip, 180 oral; guinea pig, 400 iv; dog, 40 iv ,44oral. These figures apply to adult animals; it should be noted that in the newborn rat (the only species thus studied) toxicity is highly age-dependent: the LD50 (sc) is 35 and 320 mg/kg one and 30 days after birth (Stekar, 1973) which is in line with even higher embryotoxicity. The reason for and significance of this effect, particularly as it may apply to other species, is not known.

   Toxic side effects of CP in animals and as a result of chemotherapy have been reviewed (Colvin and Hilton, 1981). There is depression of the hematopoietic system, leucopenia, alopecia, and hemorrhagic cystitis, probably due to renal excretion of 4-hydroxy metabolites and of acrolein (brook *et al.*, 1981). In early studies the urinary tract damage due to hemorrhagic cycstitis was dose limiting, but it can be prevented by simultaneous administration of Mesna (sodium-2-mercaptoethane sulfonate) (Grochow and Colvin, 1983).

   Early toxic signs in man are nausea, vomiting, and water retention. Compared with other alkylating agents, CP has exceptionally high immunosuppressive activity which makes it the agent of choice in the treatment of autoimmune diseases and in renal and bone marrow transplants. The biochemical lesion produced by CP metabolites is inhibition of thymidine incorporation into tissue DNA and of RNA synthesis.

5. Carcinogenic effects: These have been reviewed in detail (IARC, 1981) and it is concluded that there is sufficient evidence for carcinogenicity in mice, rats, and man. Examples are: In a life time experiment, administration of 0.63, 1.25, or 2.5 mg/kg of CP 5 times per week in drinking water resulted in dose-dependent incidence of carcinoma of the bladder and tumors of the lymphoid and the hematopoietic system (Schmähl and Habs, 1979). Pulmonary tumors were induced in mice after intraperitoneal administration, but only in doses 300 times higher than those of nitrogen mustard producing an equivalent response (Simkin et al., 1966). Application of CP (0.5 ml of a 0.4% acetone solution) to the skin of mice resulted in a significant incidence of mammary tumors (Matsuyama et al., 1966). There are several reports of tumor induction in patients treated with CP for nephrosis or malignancies; most often seen were bladder carcinomas. These reports are difficult to evaluate since in most cases, there was only concomitant radiation or other chemotherapy.

6. Mutagenic and teratogenic effects: CP is mutagenic after activation in the Ames test and against E. coli and Drosophila (Ellenberger and Mohn, 1975; Seino et al., 1978), and teratogenic and embryotoxic in the chick, rabbit, mouse, and rat. Since metabolites of CP (4-hydroxy CP, phosphoramide mustard) are mutagenic without activation being required, these are presumably the direct mutagens and teratogens. Acrolein may also play a role in the mutagenicity and teratogenicity of CP (Hales, 1982).

G. Emergency Treatment

1. Skin and eye exposure: For skin and eye exposure, remove contaminated clothing and wash skin with soap and water. Skin should not be rinsed with organic solvents or scanned with UV light. Since CP is readily absorbed through the skin, avoid rubbing of skin or increasing its temperature. For eye exposure, irrigate immediately with copious quantities of water for at least 15 minutes. Obtain ophthalmological evaluation.
2. Ingestion: Drink plenty of water or milk. Induce vomiting. Refer for gastric lavage.
3. Inhalation: Remove victim promptly to clean air. Administer rescue breathing if necessary.
4. Refer to physician. Consider treatment for pulmonary irritation.

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