

# Safety Data Sheet

# Ifosfamide

Division of Safety  
National Institutes  
of Health



## WARNING!

THIS COMPOUND IS ACUTELY TOXIC, TERATOGENIC, EMBRYOTOXIC, MUTAGENIC, AND POSSIBLY CARCINOGENIC. 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, IRRIGATE 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 SOLUTION AND MATERIALS APPROPRIATELY.

### A. Background

Ifosfamide (IF) is a white crystalline water-soluble compound. It is toxic, possibly carcinogenic, mutagenic, and teratogenic in animals. Its mode of action consists of interference with DNA action by reaction with phosphodiester bridges. Its principal use is as an antineoplastic and immunosuppressive agent in the treatment of Lewis lung carcinoma, various leukemias, breast cancer, and non-Hodgkin's lymphoma.

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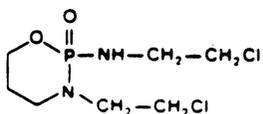
Prepared by the Environmental  
Control and Research Program

Recent review articles include IARC, 1981; Grochow and Colvin, 1981; Brade et al. 1985.

### 3. Chemical and Physical Data

Introductory note: The structure of IF reveals an asymmetric phosphorus atom, and therefore this compound exists as two optical isomers. To date there appear to be no studies concerning optical activity and possible differences in biological activity of the two isomers; such differences probably do exist in view of findings with the closely related cyclophosphamide (CP).

1. Chemical Abstract Nos: a. general: 3778-73-2; b. levo-IF: 66849-33-0; c. dextro-IF: 66849-34-1; d. racemic IF: 84711-20-6.
2. Synonyms: 1,3,2-oxazaphosphorine-2-amine, N-3-bis(2-chloroethyl)-tetrahydro, 2-oxide; <sup>A</sup> 3-(2-chloroethyl)-2-[(2-chloroethylamino]-perhydro-2H-1,3,2-oxazaphosphorine-2-oxide; iphosphamid(e); isophosphamid(e); A4942; Asta 24942; Holoxan; isoendoxan; NSC 109724.
3. Chemical structure and molecular weight:



C<sub>7</sub>H<sub>15</sub>Cl<sub>2</sub>N<sub>2</sub>O<sub>2</sub>P; 266

4. Density: No data.
5. Absorption spectroscopy: No data.
6. Optical rotation: No data on the optical isomers.
7. Volatility: No data; may be assumed to be low.
8. Solubility: Up to 10% in water. Soluble in ethanol, ether, dichloromethane, and dimethylsulfoxide.
9. Description: White crystals. A 5% solution in water has a pK<sub>a</sub> of 5.5.
10. Boiling point: No data; melting point: 48-51°C.
11. Stability: Considerably more stable to hydrolysis than CP. Approximately 50% remained unchanged after 119 days at 37°C (Brade et al., 1977).

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

2. Chemical reactivity: No data other than those for hydrolysis. IARC (1981) mentions "sensitive to...oxidation and heat" but no references to this effect were found. However, 2-chloroethylamino groups are usually subject to reaction with oxidizing agents.
3. Flashpoint: No data.
4. Autoignition temperature: No data.
5. Explosive limits in air: No data.

### Fire, Explosion, and Reactivity Hazard Data

1. IF 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 moderate instability 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 IF results in the production of acrolein (see F3) which is a flammable irritant to the eyes and mucosa; however, there are no data which indicate that acrolein is produced from IF under conditions of fire.
5. IF does not require non-spark equipment.

### 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 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 IF.

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.

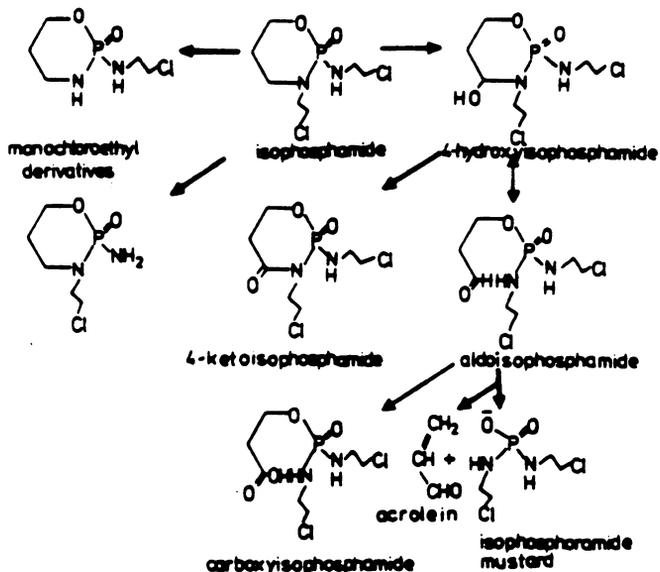
1. Chemical inactivation: Validated methods have been reported (Castegnaro et al., 1985).
2. Decontamination: Turn off equipment that could be affected by IF or the materials used for cleanup. If there is any uncertainty regarding the procedures to be followed for decontamination, call the NIH Fire Department (dial 116) 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 IF before disposal. For details, see Castegnaro et al. (1985). No waste streams containing IF shall be disposed of in sinks or general refuse. Surplus IF or chemical waste streams contaminated with IF 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 IF shall be handled and packaged for incineration in accordance with the NIH medical-pathological waste disposal system. Potentially infectious waste (e.g., animal carcasses and bedding) containing IF 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 IF 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 IF shall be handled in accordance with the NIH radioactive waste disposal system.
4. Storage: Store solid IF and its solutions in dark-colored, tightly closed containers, preferably under refrigeration. Avoid exposure to light and moisture. Store working quantities of IF and its solutions in an explosion-safe refrigerator in the work area.

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

1. Sampling: No data.
2. Analysis: The methods of choice are gas chromatography of trifluorocetyl (Pantarotto et al., 1974) or heptafluorobutyryl derivatives (Holdness and Morgan, 1983), the latter with a detection limit of 1 ng/ml of plasma or urine. Analysis for active metabolites of IF in addition to the parent compound by thin-layer chromatography (Norpoth et al., 1975) and by gas chromatography (Bryant et al., 1980) has been described.

## Biological Effects (Animal and Human)

1. Absorption: IF is absorbed from the intestinal tract and by parenteral injection. There is no evidence for absorption in organic solution through the skin, as is the case for CP, but this is likely, due to the similarity of structures. It is also transmitted transplacentally (Stekar, 1973).
2. Distribution and pharmacokinetics: There are no data on distribution of the intact molecule or its metabolites. Pharmacokinetic data have been published (Allen and Creaven, 1975; Allen et al., 1976; Brade et al., 1985) and indicate a multicompartment model. Plasma decay after intravenous infusion in man is biphasic, with a terminal half time of 15.2 hours.
3. Metabolism and excretion: The metabolism of IF has been reviewed (Bryant et al., 1980). It is outlined as follows:



(From Bryant et al., 1980)

Another scheme (Norpoth, 1976) also includes 2-dichloroethyl derivatives and products of side chain oxidation ( $-P-NH-CH_2CHOHC1$ ,  $-P-NH-CH_2COCl$ , and  $-P-NH-CHOHCH_2Cl$ ). Most of these compounds have been isolated from the urine of animals or humans (e.g., Norpoth et al., 1976).

4. Toxic effects: Acute LD50s have been reported as follows (in mg/kg): mouse, 500 iv, 540 ip; rat, 300-430 iv. In the rat (the only species thus studied) the toxicity is highly age-dependent: the LD50 (sc) is 55 and 350 mg/kg one and 30 days after birth (Stekar, 1973). The reason for and significance of this effect, particularly as it may apply to other species, is not known. It should be noted that this phenomenon was also found with CP and therefore may be a characteristic of oxazaphosphorines.

Toxic side effects of IF in animals and as a result of chemotherapy have been reviewed (Brade et al., 1985). The major symptom, as with CP, is hemorrhagic cystitis of the bladder and urinary tract, probably due to renal excretion of 4-hydroxy metabolites and of acrolein. This urotoxicity used to be dose-limiting for IF but is prevented by simultaneous administration of Mesna (sodium-2-mercaptoethane sulfonate). Other side effects are myelosuppression, nausea, vomiting, and alopecia (Creaven et al., 1976). The biochemical mechanism of action of IF is similar to that of CP, leading to inhibition of DNA and RNA synthesis. In vitro interaction with phosphodiester bridges of DNA, leading to phosphotriesters, has been demonstrated (Lindemann and Harbers, 1980).

5. Carcinogenic effects: These have been reviewed (IARC, 1981) on the basis of relatively few studies. While one of these (Mitrou et al., 1979) claimed that daily subcutaneous treatment of mice over a period of 14-16 months produced a dose-related increase in tumor frequency, the evidence for carcinogenicity is not very convincing. There are no human data.
6. Mutagenic and teratogenic effects: IF is mutagenic after activation in the Ames test and against E. coli (Ellenberger and Mohn, 1977; Benedict et al., 1977) and teratogenic and embryotoxic in mice and rats (Stekar, 1973; Bus and Gibson, 1973). This subject has been reviewed (Mohn and Ellenberger, 1976).

### Emergency Treatment

1. Skin and eye exposure: For skin exposure, remove contaminated clothing and wash skin with soap and water. Skin should not be rinsed with organic solvents. Since IF is probably absorbed through the skin, avoid rubbing of skin or increasing its temperature. For eye exposure, irrigate immediately with copious quantities of running 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 at once. Consider treatment for pulmonary irritation.

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