Chlornaphazine
(N,N-bis(2-chloroethyl)-2-naphthylamine)

Safety
Data
Sheet

Division of Occupational Health and Safety
National Institutes of Health

WARNING:

This compound is toxic and carcinogenic in animals and man. It may be absorbed into the body by inhalation, ingestion, or injection.

For eye exposure, irrigate immediately with water.

For skin exposure, wash with soap and water.

For ingestion, drink large amounts of milk or water.

In case of contact refer to a physician.

A. Background

Chlornaphazine (N,N-bis(2-chloroethyl)-2-naphthylamine) is a colorless crystalline solid. It is moderately toxic in rats but is carcinogenic in rats and man, with the bladder as the primary target organ. It is mutagenic for the fruit fly. It has been used clinically as an antineoplastic agent. Chlornaphazine has been identified by an IARC Working Group as being carcinogenic for humans (Group 1) (Althouse *et al.*, 1980).

B. Chemical and Physical Data

1. Chemical Abstract No.: 494-03-1.
2. Synonyms: N,N-bis(2-chloroethyl)-2-naphthylamine; chlornaphtin; chloronaphthine; dichloroethyl-β-naphthylamine; naphthylamine mustard; β-naphthyl-bis(2-chloroethyl)amine; Erysan; R-48; CB 1048; NSC 62209.
3. Chemical formula: $C_{14}H_{15}Cl_2N$.

   Molecular Weight: 268.2
4. Density: no data.
5. Absorption spectroscopy: Ultraviolet spectrum is shown by Lang (1966).
6. Volatility: no data.
7. Solubility: slightly soluble in water and glycerol; more soluble (in ascending order) in petroleum ether, ethanol, ether, acetone and benzene.
8. Description: colorless plates.

9. Boiling point: 210° C at 5 mm Hg; melting point: 54-66° C.
10. Stability: no specific data. Most aryl-2-halogenoethylamines are light sensitive and produce deep colors on exposure to air, particularly in dilute solution (Ross, 1949). This probably applies to chlornaphazine also.
11. Chemical reactivity: Hydrolysis in water-acetone mixtures is increased in presence of thiosulfate ion, decreased by chloride ion. Forms esters on incubation with organic anions (Ross, 1949). As an alkylating agent it reacts with nucleophiles with replacement of one or both chlorine atoms.
12. Flash point: no data.
13. Autoignition temperature: no data.
14. Explosive limits in air: no data.

C. Fire, Explosion, and Reactivity Hazard Data

1. Chlornaphazine does not require special fire-fighting procedures or equipment and does not present unusual fire and explosion hazards.
2. No conditions contributing to instability, other than (probably) oxidation in presence of air, are known to exist.
3. No incompatibilities are known.
4. No hazardous decomposition products have been identified.
5. Chlornaphazine does not require non-spark equipment. When handled in flammable solvents, the precautions required for such solvents will apply.

D. Operational Procedures

1. Laboratory operations should be carried out in a fume hood or glove box. Personnel should wear laboratory coats and surgical gloves which should be changed immediately upon suspected contamination.
2. Chemical inactivation may be accomplished by strong alkali at elevated temperature. In analogy with 2-naphthylamine, a preferable method may be oxidation by basic permanganate solution but this needs to be demonstrated.
3. Decontamination: (No specific methods have been described. The procedures suggested below should be experimentally verified.) Wash surfaces with acetone. The washings should be collected, allowed to evaporate (in a hood) and the residue decontaminated with basic aqueous permanganate. Glassware should be washed in the same way, followed by the usual washing procedures. (These procedures should be carried out in a hood, and operators should wear rubber gloves.) Animal cages should be decontaminated in a similar manner. Animal carcasses, feces, and Litter should be treated as carcinogenic toxic waste.
4. Disposal: Aqueous and organic waste solutions may be incinerated (temperatures of 1000°C or higher, with retention time of 2 sec, are satisfactory for most organic compounds). Waste solids, including animal carcasses and bedding should be collected to disposal containers and incinerated.
5. Storage: Store in sealed ampoules or in amber screw-capped bottles with Teflon cap liners under refrigeration. Avoid unnecessary exposure to light.

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

1. Sampling: no specific methods have been reported.

2. Analysis: no specific methods for analysis have been reported. General methods for the determination of alkylating agents are available (Preussman *et al.*, 1969; Sawicki and Sawicki, 1969; Truhaut *et al.*, 1973).

F. Biological Effects (Animal and Human)

1. Absorption: Chlornaphazine procedures toxic and carcinogenic effects in rodents and man when administered by mouth or intraperitoneally. No data on other routes of entry have been reported.
2. Distribution: no data.
3. Metabolism and Excretion: There are very few specific data; most of what is postulated below is based on analogy with the metabolism of aryl mustards in general and 2-naphthylamine. The main metabolism of aryl mustards in alkylation of proteins and nucleic acids, and successive dechlorination to the mono- and dihydroxy derivatives (detoxification). 2-Naphthylamine (and presumably chlornaphazine) is hydroxylated in the 1-, 5- or 6- positions, and these phenolic compounds are esterified in the liver with sulfuric or glucuronic acid to yield non-carcinogenic esters (thus accounting, it is believed, for the absence of liver tumors).

   The powerful esterases in the kidney can partially hydrolyze these esters and this may account for the formation of bladder tumors (Thiede *et al.*, 1964). In the process, the chloroethyl groups may be removed from the rest of the molecule, thus accounting for the finding that injection of chlornaphazine in rats results in the urinary excretion of 2-amino-1-naphthyl hydrogen sulfate and 2-acetamido-6-naphthyl hydrogen sulfate (Boyland and Manson, 1963).
4. Toxic Effects: The LD_{50} (rat, intraperitoneal) has been reported to be 708-891 mg/kg (Rosenoer *et al.*, 1966). Daily dosage of 50-400 mg in patients is "relatively nontoxic" (Rider and Warwick, 1958). Prolonged administration to rabbits results in changes in plasma coagulability (hypoprothrombonemia, mild increase in circulating inhibitors of coagulation but no hemorrhages). High doses in mice produced testicular atrophy and decrease in spermatogenic activity (Shimkin *et al.*, 1966). In patients dosed with chlornaphazine some anorexia, nausea, vomiting, and diarrhea, and the effects on the hematopoietic system characteristic of aryl mustards (bone marrow and lymphocyte depression with slow onset) have been noted (Rider and Warwick, 1958).
5. Carcinogenic Effects: Mice injected intraperitoneally with chlornaphazine three times weekly for 4 weeks developed dose-related increases in pulmonary adenoma (Shimkin *et al.*, 1966); rats and mice also exhibited sarcomas at the site of injection. Patients treated with chlornaphazine for polycythemia or leukemia show a high incidence of cancer of the bladder and other parts of the urinary tract, with an average induction time of 5-6 years (Thiede *et al.*, 1964; Thiede and Christensen, 1969).
6. Mutagenic and Teratogenic Effects: Chlornaphazine is mutagenic to *Drosophila*; no teratogenic effects have been reported.

G. Emergency Treatment and Medical Surveillance

1. In case of skin exposure, remove contaminated clothing and wash skin with soap and water. For eye exposure, irrigate immediately with water. Refer to a physician.
2. If ingested, drink plenty of milk or water.
3. If inhaled, remove promptly to clean air.
4. In a medical surveillance program, possible effects on the hematopoietic system should be noted. White blood cell and differential counts should be taken prior to chlornaphazine, and at regular intervals thereafter. This surveillance should be continued for a long time after termination of potential exposure. Because of the significant incidence of bladder cancer (with induction time of several years), cystoscopy should be performed prior to exposure, and the appearance of potential hematuria and of urinary tumor cells should be looked for.

5. Acute signs and symptoms (noted in patients only at relatively high dosages) are anorexia, nausea, vomiting, and diarrhea.

H. References:

Althouse, R., Huff, J. Tomatis, L. and Wilbourn, J. 1980. An evaluation of chemicals and industrial processes associated with cancer in humans based on human and animal data: IARC monograph volumes 1 to 20. Cancer Res., 40:1-12.

Boyland, E., and Manson, D. 1963. Metabolism of 2-naphthylamine and its derivatives. A. R. Brit. Emp. Cancer Campaign, 41:69; quoted in IARC monograph.