

Safety Data Sheet

6-Mercaptopurine

Division of Safety
National Institutes
of Health



WARNING!

THIS COMPOUND IS ACUTELY TOXIC, TERATOGENIC, EMBRYOTOXIC, AND MUTAGENIC. IT MAY BE WEAKLY CARCINOGENIC. IT IS READILY ABSORBED BY VARIOUS BODY TISSUES, THROUGH THE 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 AND EXPOSURE TO UV LIGHT. 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 CLEAN-UP. AVOID SKIN CONTACT OR BREATHING OF AEROSOLS. SEE CASTEGNARO ET AL. (1985) FOR DETAILS. DISPOSE OF WASTE SOLUTIONS AND MATERIALS APPROPRIATELY.

A. Background

6-Mercaptopurine (6-MP) in its usual form as the monohydrate consists of yellow, practically odorless prisms. It is toxic, weakly carcinogenic, mutagenic, teratogenic, and embryotoxic in animals. After activation (conversion into one or more nucleotide derivatives) its mode of action consists of incorporation into cellular RNA and DNA and consequent inhibition of normal RNA and DNA biosynthesis. Its principal use is as an antineoplastic agent in

Issued: 4/87

Prepared by the Environmental
Control and Research Program

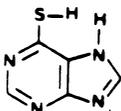
the treatment (alone or in combination with radiotherapy and/or other antineoplastics) of acute lymphocytic anemia and acute and chronic myelogenous leukemia. As an immunosuppressive agent it has been largely supplemented by its derivative azathioprine, the methyl-nitro-imidazolyl derivative of 6-MP, which is converted in the body to 6-MP. Azathioprine has lower liver toxicity than 6-MP and is being used extensively in renal transplants.

Recent review articles include IARC, 1981; van Scoik et al., 1985.

B. Chemical and Physical Data

Introductory note: Unless otherwise noted, all data are for the monohydrate, which is the usual form.

1. Chemical Abstract No.: 50-44-2 for anhydrous form, 6112-76-1 for monohydrate.
2. Synonyms: Mercaptopurine; 6-mercapto-1^H-purine; purine-6-thiol; ^A6-purinethiol; 6^H-purine-6-thione, 1,7-dihydro-; ^B6-thiohypoxanthine; 6-thiopurine; IND 1226; Leukerin; Mercapurin; NSC 755.
3. Chemical structure and molecular weight



$C_5H_4N_4S \cdot H_2O$
170.19

[Note: This is the usually accepted form; however, there is NMR evidence that at least the ribotide derivative exists in the thio rather than the mercapto form (Evans and Sarma, 1975)].

4. Density: No data.

^AChemical Abstracts name, used for listings in 7th and 8th Decennial Index.

^BChemical Abstracts name, used for listings in 9th Decennial Index and as subsequently.

Absorption spectroscopy: Ultraviolet absorption maxima (ϵ) in 0.1 N NaOH: 230 (14,000) and 312 (19,600)nm; in 0.1 N HCl: 222 (9,240) and 327 (21,300)nm. Data for infrared, NMR, and mass spectra have been published (Benezra and Foss, 1978), as have data on fluorescence at liquid nitrogen temperature (Al-Mosawi et al., 1980).

Volatility: No data; may be assumed to be low.

Solubility: Practically insoluble in water, acetone, and ether; slightly soluble in dilute sulfuric acid; soluble in hot ethanol and dilute alkali (with autoxidation which may be prevented by addition of the antioxidant dithioerythritol or dithiothreitol) (de Abreu et al., 1982). Data on water solubility as a function of temperature (van't Hoff plot) indicate that the monohydrate is the only stable form in the range 6-54°C (Arakawa et al., 1976).

Description: Yellow, nearly odorless prisms as the hydrate. Acid dissociation constants are $pK_{a1}=7.77$ and $pK_{a2}=11.17$.

Boiling point: No data; melting point: changes to anhydrous form at 140°C, melts at 313-314°C with decomposition.

Stability: Stable in solid form. Stable in injection solution (0.5 g/150 ml 0.9% NaCl or 5% dextrose) for 7 days in the refrigerator (Gallelli, 1967). Stable to UV irradiation in rigorously deoxygenated solution but oxidized in oxygenated solution on irradiation (Hemmens and Moore, 1984, 1986). This photochemical oxidation is accelerated by the presence of alkali (Benezra and Foss, 1978).

Chemical reactivity: The mercapto group is oxidized to sulfinate in alkaline iodine solution and to sulfonate in alkaline permanganate. Neutral iodine solution oxidizes 6-MP to the disulfide (Doerr et al., 1961). For reactions in biological systems see F3.

Flash point: No data.

Autoignition temperature: No data.

Explosive limits in air: No data.

Fire, Explosion, and Reactivity Hazard Data

6-MP 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 susceptibility to alkali, light, and oxidizing agents.
3. No incompatibilities are known.
4. When heated to decomposition, 6-MP emits vapors of SO_x and NO_x.
5. 6-MP 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 6-MP.

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 6-MP penetrate various glove materials (Laidlaw et al. 1984). This factor should be taken into account when handling 6-MP.

1. Chemical inactivation: Validated methods have been reported (Castegnaro et al., 1985).
2. Decontamination: Turn off equipment that could be affected by 6-MP 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 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 6-MP before disposal. For details, see Castegnaro et al. (1985). No waste streams containing 6-MP shall be disposed of in sinks or general refuse. Surplus 6-MP or chemical waste streams contaminated with 6-MP 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 6-MP 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 6-MP 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 6-MP shall be handled as potentially infectious waste and packaged for incineration, as above. Absorbent materials (e.g., associated with spill clean-up) grossly contaminated shall be handled in accordance with the chemical waste disposal system. Radioactive waste containing 6-MP shall be handled in accordance with the NIH radioactive waste disposal system.

4. Storage: Store solid 6-MP and its solutions in dark-colored, tightly closed containers, preferably under refrigeration. Avoid exposure to ultraviolet light and moisture. Store working quantities of 6-MP 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

Earlier methods of analysis have been reviewed (Benezra and Foss, 1978; IARC, 1981).

1. Sampling: Urine samples are acidified, passed through a cation exchange column, and eluted with ammonia (Chalmers, 1975). Plasma samples are usually deproteinized with tungstic acid (Finkel, 1967; Rosenfeld et al., 1977). Low recoveries in many earlier procedures (particularly when fluorimetry is used) are considerably improved by addition of dithiothreitol and performing extractions at low temperature (De Abreu et al., 1982) and/or conversion to the phenylmercury derivative prior to extraction (Maddocks, 1979; Jonkers et al., 1982). For analysis of 6-MP metabolites in cellular material, perchloric acid extraction has been used (Breter and Zahn, 1979).
2. Analysis: The main methods of analysis are fluorimetry after oxidation to the sulfonate, high performance liquid chromatography, and gas chromatography-mass spectrometry. An original fluorimetric procedure (Finkel, 1967) has been criticized for lack of specificity and high blanks, and improved (Maddocks, 1979; Hirose and Tawa, 1983). Sensitivity of these methods is about 2-5 ng/ml plasma. HPLC has been used extensively (Ding and Benet, 1979a; De Abreu et al., 1982; Narang et al., 1982; Jonkers et al., 1982) using the above mentioned precautions, which improve recoveries considerably. Gas chromatography of methylated derivatives (Pantarotto et al., 1974; Bailey et al., 1975; Rosenfeld et al., 1977) is convenient, particularly for simultaneous measurement of metabolites, but suffers from recoveries in the 70% range and high blank corrections.

Absorption: 6-MP is poorly and variably absorbed from the intestinal tract after oral administration (Hamilton and Elion, 1954; Ravis et al., 1984); in spite of this, most administrations to patients are via this route. It is absorbed on parenteral injection and also transplacentally.

Distribution and pharmacokinetics: Uncertainty exists concerning the distribution of 6-MP following oral or parenteral administration because of its rapid metabolism in the animal body. Radioactivity due to ^{35}S -6-MP has a half-life in plasma of about 1.5 hours (Hamilton and Elion, 1954). 6-MP is transferred across the blood-brain barrier slowly whether it is administered intravenously or intracerebrally (Nelson et al., 1974; Covell et al., 1985). Pharmacokinetic data for the rhesus monkey (Ding and Benet, 1979b; Narang et al., 1983) and rat (Tterlikkis et al., 1977) have been published.

Metabolism and excretion: The metabolism of 6-MP has been worked out in detail and has been reviewed (Brockman, 1963; Zimmerman et al., 1974; Zimm et al., 1985; van Scoik et al., 1985), and these reviews should be consulted for details of enzymatic involvement in the various transformations. Briefly, it comprises anabolism to 6-MP-9-nucleoside, nucleotide, di- and tri-phosphate sequentially, and catabolism which consists of the following four pathways: (a) conversion to hypoxanthine and sulfate, (b) oxidation to 6-thioxanthine and 6-thiouric acid, (c) S-methylation followed by the same reaction sequence as outlined under anabolism, and (d) sequential conversion to thioinosine, thioxanthosine, and thioguanosine monophosphate followed by incorporation into cellular RNA and DNA. It is this last reaction which appears to constitute the mechanism of toxic and antineoplastic action of 6-MP. Nearly all of the above-named metabolites have been identified in the urine or tissues of animals and patients treated with 6-MP. Major urinary excretion products are unchanged 6-MP, 6-thiouric acid, and sulfate.

Toxic effects: The acute LD₅₀ has been reported as follows (in mg/kg): mouse, 250 iv, 280 oral; rat, 250 ip; hamster, 364 ip. The LD₅₀ is considerably lower when 6-MP is given in divided daily doses (for details see Phillips et al., 1954). Toxic side effects in man are a gradually developing bone marrow depression, with anorexia, nausea, and vomiting in some patients. In experimental animals there is also necrosis of the liver and damage to the intestinal epithelium. There is no cutaneous irritation in rabbits on topical application (Murphy et al., 1979). As stated above, the major biochemical lesion produced by 6-MP metabolites is due to their incorporation into tissue DNA and RNA and consequent disruption of normal nucleic acid biosynthesis.

5. Carcinogenic effects: These have been reviewed (IARC, 1981) and with the exception of one study (Weisburger, 1977) in which a 1.5-2 fold increase in tumor incidence over controls was noted in female but not in male rats, it is concluded that "there was no evidence for the carcinogenicity of 6-MP in the limited studies in experimental animals."
6. Mutagenic and teratogenic effects: 6-MP is mutagenic in the Ames test after activation (Benedict et al., 1977) and teratogenic in the mouse, rat, rabbit (Mercier-Parot and Tuchmann-Duplessis, 1967; Holden et al., 1973), and hamster (Shah and Burdett, 1979).

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 or scanned with UV light. Avoid rubbing of skin or increasing its temperature. For eye exposure, irrigate immediately with sodium bicarbonate solution, followed by 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.

References

- Al-Mosawi, A.I., J.N. Miller, and J.W. Bridges. 1980. Determination of 6-mercaptopurine and related compounds by phosphorescence spectroscopy. *Analyst* 105:448-454.
- Arakawa, J., M. Nakano, K. Juni, and T. Arita. 1976. Physical properties of pyrimidine and purine antimetabolites. I. The effects of salts and temperature on the solubility of 5-fluorouracil, 1-(2-tetrahydrofuryl)-5-fluorouracil, 6-mercaptopurine and thioinosine. *Chem Pharm Bull* 24:1654-1657.
- Bailey, D.G., T.W. Wilson, and G.E. Johnson. 1975. A gas chromatographic method for measuring 6-mercaptopurine in serum. *J Chromatog* 111:305-311.
- Benezra, S.A., and P.R.B. Foss. 1978. 6-Mercaptopurine, in: Florey, K. (ed.), *Analytical Profiles of Drug Substances*, 7:343-357. Academic Press, NY.
- Breter, H.-J., and R.K. Zahn. 1979. Quantitation of intracellular metabolites of [³⁵S]-6-mercaptopurine in L5178Y cells grown in time-course incubates. *Cancer Res* 39:3744-3748.

- Brockman, R.W. 1963. Biochemical aspects of mercaptopurine inhibition and resistance. *Cancer Res* 23:1191-1201.
- Castegnaro, M., J. Adams, M.A. Armour, J. Barek, J. Benvenuto, C. Confalonieri, U. Goff, S. Ludeman, D. Reed, E.B. Sansone, and G. Telling. 1985. Laboratory Decontamination and Destruction of Carcinogens in Laboratory Wastes: Some Antineoplastic Agents. IARC Scientific Publications No. 73. World Health Organization, Geneva, Switzerland.
- Chalmers, A.H. 1975. A spectrophotometric method for the estimation of urinary azathioprine, 6-mercaptopurine, and 6-thiouric acid. *Biochem Med* 12:234-241.
- Covell, D.G., P.K. Narang, and D.G. Poplack. 1985. Kinetic model for the disposition of 6-mercaptopurine in monkey plasma and cerebrospinal fluid. *Am J Physiol* 248:R147-R156.
- De Abreu, B.A., J.M. van Baal, T.J. Schouten, and D.A.M. Schretlen. 1982. High-performance liquid chromatographic determination of plasma 6-mercaptopurine in clinically relevant concentrations. *J Chromatog* 227:526-533.
- Ding, T.L., and L.Z. Benet. 1979a. Determination of 6-mercaptopurine and azathioprine in plasma by high-performance liquid chromatography. *J. Chromatog* 163:281-288.
- Ding, T.L., and B.Z. Benet. 1979b. Comparative bioavailability and pharmacokinetic studies of azathioprine and 6-mercaptopurine in the rhesus monkey. *Drug Metab Disp* 7:373-377.
- Doerr, I.L., I. Wempen, D.A. Clarke, and J.J. Fox. 1961. Thiation of nucleosides. III. Oxidation of mercaptopurines. *J Org Chem* 26:3401-3409.
- Evans, F.E., and R.H. Sarma. 1975. Comparative study of the structure and conformation in aqueous solution of the antileukemic agent 6-thiopurine ribonucleoside 5'-phosphate to that of common purine 5'-nucleotides. *J Am Chem Soc* 97:3215-3218.
- Finkel, J. 1967. A fluorimetric method for the estimation of 6-mercaptopurine in serum. *Anal Biochem* 21:362-371.
- Gallelli, J.R. 1967. Stability studies of drugs used in intravenous solutions. Part 1. *Am J Hosp Pharm* 24:425-433.
- Hamilton, L., and G.B. Elion. 1954. The fate of 6-mercaptopurine in man. *Ann NY Acad Sci* 60:304-314.
- Hemmens, V.J., and D.E. Moore. 1984. Photo-oxidation of 6-mercaptopurine in aqueous solution. *J Chem Soc (Perkin Trans II)*, 209-211.
- Hemmens, V.J., and D.E. Moore. 1986. Photochemical sensitization by azathioprine and its metabolites. I. 6-Mercaptopurine. *Photochem Photobiol* 43:247-255.
- Hirose, S., and R. Tawa. 1983. An improved method for micro-fluorimetric determination of 6-mercaptopurine. *Anal Lett* 16:209-218.
- Holden, H.E., V.A. Ray, M.G. Wahrenburg, and J.D. Zelenski. 1973. Mutagenicity studies with 6-mercaptopurine. I. Cytogenetic activity in vivo. *Mut Res* 20:257-263.
- IARC. 1981. International Agency for Research on Cancer. 6-Mercaptopurine. IARC Monographs 26:249-266.

- Jonkers, R.E., B. Oosterhuis, R.J.M. ten Berge, and C.J. van Boxtel. 1982. Analysis of 6-mercaptopurine in human plasma with a high-performance liquid chromatographic method including post-column derivatization and fluorometric detection. *J Chromatog* 233:249-255.
- Laidlaw, J.L., T.H. Connor, J.L. Theiss, R.W. Anderson, and T.S. Matney. 1984. Permeability of latex and polyvinyl chloride gloves to 20 antineoplastic drugs. *Am J Hosp Pharm* 41:2618-2623.
- Maddocks, J.L. 1979. Assay of azathioprine, 6-mercaptopurine and novel thiopurine metabolite in human plasma. *Brit J Clin Pharmacol* 8:273-278.
- Mercier-Parot, L., and H. Tuchmann-Duplessis. 1967. Obtentions de malformations des membres par la 6-mercaptopurine chez trois espèces: Lapin, rat et souris. [Production of limb malformations by 6-mercaptopurine in three species: rabbit, rat and mouse]. *C Rend Soc Biol* 161:762-768.
- Murphy, J.C., E.S. Watson, P.W. Wirth, P. Skierkowski, R.M. Folk, and G. Peck. 1979. Cutaneous irritation in the topical application of 30 antineoplastic agents to New Zealand white rabbits. *Toxicol* 14:117-130.
- Narang, P.K., R.L. Yeager, and D.C. Chatterji. 1982. Quantitation of 6-mercaptopurine in biologic fluids using high-performance liquid chromatography: A selective and novel procedure. *J Chromatog* 230:373-380.
- Narang, P.K., D.C. Chatterji, D. O'Neill, and D.G. Poplack. 1983. Pharmacokinetics of 6-mercaptopurine (6-MP) in the monkey. I. Disposition from plasma and cerebrospinal fluid following iv bolus. *Drug Metab Dispos* 11:5-9.
- Nelson, J.A., H.F. Cserr, and S.H. Chu. 1974. Distribution of 6-mercaptopurine ribonucleoside and other purine analogs to brain. *Cancer Res* 34:1889-1891.
- Pantarotto, C., A. Martini, G. Belvedere, A. Bossi, M.G. Donelli, and A. Frigerio. 1974. Application of gas chromatography-chemical ionization mass fragmentography in the evaluation of bases and nucleoside analogues used in cancer chemotherapy. *J Chromatog* 99:519-527.
- Philips, F.S., S.S. Sternberg, L. Hamilton, and D.A. Clarke. 1954. The toxic effects of 6-mercaptopurine and related compounds. *Ann NY Acad Sci* 60:283-296.
- Ravis, W.R., J.S. Wang, and S. Feldman. 1984. Intestinal absorption and metabolism of 6-mercaptopurine in the rat small intestine. *Biochem Pharmacol* 33:443-448.
- Rosenfeld, J.M., V.Y. Taguchi, B.L. Hillcoat, and M. Kawai. 1977. Determination of 6-mercaptopurine in plasma by mass spectrometry. *Anal Chem* 49:725-727.
- Shah, R.M., and D.N. Burdett. 1979. Developmental abnormalities induced by 6-mercaptopurine in the hamster. *Can J Physiol Pharmacol* 57:53-58.
- Tterlikkis, L., E. Ortega, R. Salomon, and J.L. Day. 1977. Pharmacokinetics of mercaptopurine. *J Pharm Sci* 66:1454-1457.

- van Scoik, K.G., C.A. Johnson, and W.R. Porter. 1985. The pharmacology and metabolism of the thiopurine drugs 6-mercaptopurine and azathioprine. Drug Metab Revs 16:157-170.
- Weisburger, E.K. 1977. Bioassay program for carcinogenic hazards of cancer chemotherapeutic agents. Cancer 40:1935-1949.
- Zimm, S., G.E. Johnson, B.A. Chabner, and D.G. Poplack. 1985. Cellular pharmacokinetics of mercaptopurine in human neoplasia: cells and cell lines. Cancer Res 45:4156-4161.
- Zimmerman, T.P., L.-C. Chu, C.J.L. Buggé, D.J. Nelson, G.M. Lyon, and G.B. Elion. 1974. Identification of 6-methylmercaptopurine ribonucleoside 5'-diphosphate and 5'-triphosphate: metabolites of 6-mercaptopurine in man. Cancer Res 34:221-226.