Safety Data Sheet

5-Bromo-2'-deoxyuridine

Division of Safety
National Institutes
of Health

WARNING!

THIS COMPOUND IS MODERATELY TOXIC, TERATOGENIC, EMBRYOTOXIC, AND MUTAGENIC. IT IS 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 CLEANUP. AVOID SKIN CONTACT OR BREATHING OF AEROSOLS. USE WATER TO DISSOLVE COMPOUND. USE ABSORBENT PAPER TO MOP UP SPILL. WASH DOWN AREA WITH SOAP AND WATER. DISPOSE OF WASTE SOLUTIONS AND MATERIALS APPROPRIATELY.

A. Background

5-Bromo-2'-deoxyuridine (BrdU) is a white crystalline water-soluble compound. It is cytotoxic, strongly teratogenic, and mutagenic in some test systems. Carcinogenicity has not been demonstrated; in fact, it is a useful agent in the treatment of neoplasms because it sensitizes tumor cells to the lethal effects of X-rays to a greater degree than normal tissue cells. Its major mode of action is due to its incorporation into tissue DNA, substituting for thymine moieties. It is also a topical antiviral agent.

Issued: 7/88

Prepared by the Environmental Control and Research Program

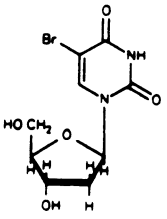
The mechanism of action of BrdU and related compounds has been reviewed (Goz, 1978).

B. Chemical and Physical Data

1. Chemical Abstract No.: 59-14-3.

2. Synonyms: BDU; 5-BDU; bromouracil deoxyriboside; bioxuridine; NSC 38297; uridine, 5-bromo-2'-deoxy-.[A]

3. Chemical structure and molecular weight



$C_9H_{11}BrN_2O_5$; 307.13

4. Density: No data.

5. Absorption spectroscopy: Ultraviolet absorption maxima (ε) are at 279 nm (10,250) in 0.1 N HCl and 276 nm (6,600) in 0.01 N NaOH (Garrett et al., 1966). Other UV, infrared, and NMR spectral data have been published (Jones et al., 1970; Sano et al., 1971).

6. Volatility: No data; may be regarded as essentially non-volatile.

7. Solubility: No quantitative data. Solubility in water or physiological saline must be adequate since BrdU is dissolved in these media in biological investigations.

8. Description: White needles when crystallized from absolute ethanol.

9. Boiling point: No data; melting point: listed as 181-3°C (Bardos et al., 1955) and 187-9°C (Beltz and Visser, 1955). No more recent data have been found. (The latter melting point may be more reliable since BrdU preparations are apt to contain trace contaminants).

10. Stability: Solid BrdU is stable in the dark to heat and humidity for 3 months at temperatures below 60°C. On exposure to sunlight there is discoloration to grayish-brown (Sano et al., 1971).[B] Ultraviolet irradiation of frozen aqueous

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[A]Chemical Abstracts name, used for listings in 6th Decennial Index and subsequently.

[B]This information is derived from an abstract of a Japanese article and could not be verified in detail. No other data available.

solutions ofBrdU results in liberation of bromide ion and formation of a debrominated dimer (Sasson and Wang, 1977), while γ-radiolysis of aqueous solutions in the presence of oxygen yields mainly bromide, isodialuric acid deoxyriboside, and smaller amounts of various oxygenated derivatives (Kourim et al., 1971).

11. Chemical reactivity: BrdU is hydrolyzed at the N-glycosyl bond, yielding bromouracil and 2-deoxyribose. The pH dependency of this reaction varies with the experimental conditions (Garrett et al., 1966; Shapiro and Kang, 1969). The rate of hydrolysis increases sharply at alkaline pH.

12. Flashpoint: No data.

13. Autoignition temperature: No data.

14. Explosive limits in air: No data.

Fire, Explosion and Reactivity Hazard Data

1. BrdU does not require special fire-fighting procedures or equipment and does not present unusual fire and explosion hazards.

2. The presence of strong alkali, acid, and/or oxidant probably contributes to instability of BrdU.

3. No incompatibilities are known.

4. BrdU 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 BrdU.

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: No validated method reported.

2. Decontamination: Turn off equipment that could be affected by BrdU 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. Wipe off surfaces with water, then wash with copious quantities of water. Glassware should be rinsed in a hood with soap and water. Animal cages should be washed with water.

3. Disposal: No waste streams containing BrdU shall be disposed of in sinks or general refuse. Surplus BrdU or chemical waste streams contaminated with BrdU 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 BrdU 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 BrdU 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 BrdU 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 BrdU shall be handled in accordance with the NIH radioactive waste disposal system.

4. Storage: Store solid BrdU and its solutions in dark-colored, tightly closed containers, preferably under refrigeration. Avoid exposure to light and moisture. Store working quantities of BrdU 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: Two methods have been described for the preparation of biological samples (plasma, cerebrospinal fluid, urine) for analysis; one involves ultrafiltration (Agarwal et al., 1982), while the other consists of ethyl acetate extraction of ammonium sulfate-deproteinized solutions (Stetson et al., 1985).

2. Analysis: The method of choice is high-performance liquid chromatography which allows for the separation of BrdU from its metabolites and their separate quantitation (Agarwal et al., 1982; Turturro et al., 1982; Stetson et al., 1985). Sensitivities of these procedures are not listed.

Biological Effects (Animal and Human)

1. Absorption: BrdU is absorbed from the gastrointestinal tract following parenteral injection and is presumably absorbed transplacentally (because of its teratogenic effects).

Distribution and pharmacokinetics: Intra-arterial injection of BrdU into rodents results in extensive degradation (see below). Most of the portion which is not so degraded is incorporated into DNA of various tissues, particularly the colon, stomach, bone marrow, and spleen (Kriss and Revesz, 1962). The label of intraperitoneally injected deuterated BrdU in pregnant mice is also found in the liver of both mothers and embryos (Skalko et al., 1971). The only study having a bearing on pharmacokinetics states that the peak blood concentration following subcutaneous implantation of BrdU tablets (amount not stated) in rats is reached in 5 hours (Maier et al., 1983).

Metabolism and excretion: As mentioned above, BrdU is degraded at a fairly rapid rate in mice and rats upon injection, in at least two metabolic pathways; one is hydrolysis at the glycosidic bond to yield bromouracil and 2-deoxyribose which is presumably then further metabolized. The other is debromination which is evidenced by liberation of bromide ion. The further fate of the remainder of the molecule has not been investigated (Kriss and Revesz, 1962). While debromination accounts for at least 80% of the metabolism in vivo, taking place mostly in the liver, incubation of BrdU in serum from various sources results in relatively little debromination and mostly production of bromouracil (Saffhill and Hume, 1986).

Toxic effects: The acute toxicity of BrdU appears to be quite low in rodents; various authors list acute LD50s by various parenteral routes in mice and rats to be in the range of 1.5-4 g/kg, and by the oral route 8.4 g/kg (Chaube and Murphy, 1968; Nakaguchi et al., 1971; RTCS, 1984). As with other halo-substituted pyrimidines, the fetus is 2-4 times as sensitive to lethal effects as the adult. No clinical or hematological signs of acute toxicity were noticed in rats receiving up to 500 mg/kg/day for 28 days in their drinking water (Phuphanich and Levin, 1985). In man, the highest tolerated intravenous infusion dose is 700 mg/m^2/day when given over a period of 12 hr/day (Russo et al., 1984). Subacute effects in rodents include inflammatory skin lesions, decreased weight and hair growth, and hematological effects (anemia, leukocytopenia, thrombocytopenia) (Nakaguchi et al., 1971).

The principal effects of BrdU in the animal body result from its incorporation into tissue DNA in place of thymidine (the 5-methyl analog of BrdU). Since chromosomal proteins have a greater affinity for BrdU-substituted DNA than for unsubstituted DNA (Goz, 1978), this results in a variety of chromosomal aberrations including chromosome lengthening, chromatid breakage, and effects on sister chromatid exchange frequency. Effects on meiosis as well as on mitosis have been reported (Mukherjee, 1968).

Carcinogenic effects: There is no evidence for BrdU carcinogenicity. On the contrary, it appears that incorporation of

BrdU into tissue DNA increases the susceptibility of mammalian cells to X-ray effects, and since tumor cells have a higher DNA turnover rate than normal cells, this results in BrdU being a useful adjunct to X-ray treatment of tumors.

6. Mutagenic and teratogenic effects: BrdU is not mutagenic in the standard Ames test, presumably because of its rapid metabolism to bromouracil (Rosenkranz and Poirier, 1979). It is however mutagenic in the micronucleus and sperm abnormality assay (Bruce and Heddle, 1979). BrdU is a strong teratogen in hamsters (Ferm, 1965), mice (Franz and Kleinebrecht, 1982), and other species.

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 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.

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