

Safety Data Sheet

5-Fluorouracil

Division of Safety
National Institutes
of Health



WARNING!

THIS COMPOUND IS MODERATELY TOXIC AND TERATOGENIC. IT IS READILY ABSORBED BY VARIOUS BODY TISSUES THROUGH THE SKIN, THE INTESTINAL TRACT, AND TRANSPLACENTALLY. IT MAY IRRITATE THE SKIN. 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 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, DRINK MILK, SODIUM BICARBONATE SOLUTION, OR WATER. FOR INHALATION, REMOVE VICTIM PROMPTLY TO CLEAN AIR. REFER TO PHYSICIAN.

IN CASE OF LABORATORY SPILL, WEAR PROTECTIVE CLOTHING DURING CLEAN UP. AVOID SKIN CONTACT OR BREATHING OF AEROSOLS. DISPOSE OF WASTE SOLUTIONS AND MATERIALS APPROPRIATELY.

A. Background

5-Fluorouracil (5-FU) is a white to almost white odorless crystalline compound, soluble in polar solvents. It is absorbed by ingestion, parenteral injection, and through the skin. Its synthesis and first evaluation as an antineoplastic compound in Heidelberger's laboratory (Duschinsky et al., 1957) was based on the rationale that (a) hepatoma cells use uracil for RNA synthesis at a rate higher than that of normal liver cells, (b) fluorine-substituted organic compounds are generally more toxic than the

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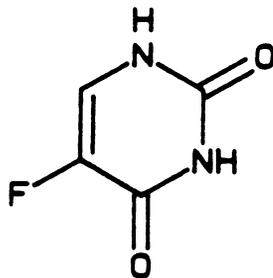
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corresponding unsubstituted ones, and (c) the 5 position of uracil is that of normal methylation to thymine. Its major use is in human medicine in the management of many carcinomas (either singly or in combination with other drugs such as cyclophosphamide and/or methotrexate), and topically in the treatment of precancerous dermatoses. 5-FU is moderately toxic on parenteral administration but the effects in patients (mainly on the hematopoietic system and the gastrointestinal tract) are reversible. It does not appear to be carcinogenic or mutagenic but has a strong teratogenic and embryotoxic effect.

General reviews of the physical, chemical, and biological properties of 5-FU include: IARC, 1981; Heidelberger, 1972, 1982; Rudy and Senkowski, 1973; Valerioti and Santelli, 1984.

B. Chemical and Physical Data

1. Chemical Abstract No.: 51-21-8.
2. Synonyms: 2,4(1H, 3H)-pyrimidinedione, 5-fluoro;^A 5-fluoropyrimidine-2,4 dione; 5-fluracil; fluorouracil; FU; FUra. Trade names: NSC-19-893; Ro-2-9757; Adrucil; Efudex; Fluroplex; Fluoro Uracil; Fluril; Timazin.
3. Chemical structure and molecular weight:



$C_4H_3FN_2O_2$; 130.08

The monoanion exists in a number of tautomeric forms whose relative abundance varies with the solvent (Wempen and Fox, 1965; Wierzchowski et al., 1965).

4. Density: No data.
5. Absorption spectroscopy: The ultraviolet absorption spectrum shows a maximum at 265-266 nm ($\epsilon = 7,070$) and a minimum at 232 nm (in acetate buffer, pH 4.7). This, as well as IR, NMR (proton and ^{19}F), and fluorescence spectral data ($\lambda_{max exc} = 315$, $\lambda_{max em} = 391$) are described by Rudy and Senkowski, 1973.
6. Volatility: No data; may be regarded as essentially non-volatile.

^AChemical Abstracts name, used for listing in 9th Decennial Index and subsequently.

7. Solubility: The solubility of 5-FU in 22 solvents has been tabulated (Hsu and Marss, 1980). Solubility decreases with decreasing polarity of the solvent. Representative figures are (in g/l): dimethylformamide:28.50; water:13.26; methanol 7.69; slightly soluble in ethanol, practically insoluble in chloroform, benzene, ether. Aqueous solubility appears to increase with pH since PDR (1980) lists an injectable solution for clinical use of 500 mg in 10 ml aqueous solution adjusted to pH 9.
8. Description: White to nearly white crystals. No odor. In aqueous solution 5-FU exists in several ionic species with $pK_{a1} = 8.0^A$ and $pK_{a2} = 13.0$
9. Boiling point: No data; melting point: 282-283°C with decomposition. Sublimes at 199-200°C (0.1 mm Hg).
10. Stability: There are no data on stability of solid 5-FU but it may be considered to be stable at room temperature in dark bottles. Solutions of 5-FU are stable if the pH is below 9. For instance, it is stable in 1 N HCl at 100° for 3.5 hours and for at least 16 weeks in injectable form as a 1% solution in 5% dextrose in PVC drug reservoirs at room temperature (Quebbeman et al., 1984). In alkaline solution 5-FU is degraded to urea, fluoride, and an aldehyde, the rate of hydrolysis increasing with pH and temperature (Rudy and Senkowski, 1973). Hydrolysis profiles at 80°C for the pH range 5.9-12.7 have been published (Garrett et al., 1968). 5-FU solution should be stored in the absence of light since UV irradiation of solutions of 5-FU results in changes in the UV spectrum (Kahn et al., 1973). (1,3-Dimethyl-5-FU is reversibly hydrated at the 5 and 6 positions on irradiation [Fikus et al., 1964] and the same may apply to 5-FU). 5-FU shows significant adsorption on glass surfaces from methanol solution though there is no indication that this occurs with aqueous solutions also (Driessen et al., 1978). However, as a precaution it is recommended that only plastic or silanized glassware is used in experimental (particularly analytical) work.
11. Chemical reactivity: None has been described other than the hydrolytic reactions discussed above, and the biological reactions of anabolism and catabolism to be described later. 5-FU may be converted to uracil by hydrogenation, and the secondary amino groups may be alkylated.

This is the usually quoted figure; Valerioti and Santelli lists $pK_a = 8.15$.

12. Flash point: No data.
13. Autoignition temperature: No data.
14. Explosive limits in air: No data.

Fire, Explosion, and Reactivity Hazards

1. 5-FU is likely to be inactivated under conditions of fire. However, because of its effects of producing erythema on exposed skin, it is recommended that fire-fighting personnel wear protective clothing and face masks.
2. Flammability is likely to be low.
3. Conditions contributing to instability (and detoxification) are alkali and elevated temperatures.
4. No hazardous decomposition products are known.

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 5-FU.

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 5-FU penetrate various glove materials (Laidlaw et al., 1984). This factor should be taken into account when handling 5-FU.

1. Chemical inactivation: No validated method reported.
2. Decontamination: Turn off equipment that could be affected by 5-FU or the materials used for clean up. 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 10% NaOH, then wash with copious quantities of water. Glassware should be rinsed (in a hood) with 10% NaOH, followed by soap and water. Animal cages should be washed with ammonia solution followed by water.

3. Disposal: No waste streams containing 5-FU shall be disposed of in sinks or general refuse. Surplus 5-FU or chemical waste streams contaminated with 5-FU 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 5-FU 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 5-FU 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 5-FU 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 5-FU shall be handled in accordance with the NIH radioactive waste disposal system.
4. Storage: Store solid 5-FU and its solutions in dark-colored, tightly closed containers, preferably under refrigeration. Store working quantities of 5-FU and its solutions in a safety 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 earlier methods of 5-FU assay in biological material were microbiological, using Strep. fecalis (Clarkson, 1964; Brandberg et al., 1977) or E. coli (Hunt and Pitillo, 1968). A spectrophotometric method has also been described (Morimoto et al., 1981), based on formation of an ion pair complex of the monoion with alkylammonium ion, extraction into an organic solvent, addition of perchlorate and reextraction of liberated 5-FU into the aqueous phase (range 0-100 µg/ml plasma). More commonly used methods are chromatographic, either by GC/MS or HPLC; in a critical comparison of these two (Aubert et al., 1981) it was concluded that HPLC had lower sensitivity but was easier to carry out particularly when used in routine plasma analysis. Conversion to silyl derivatives after extraction and GLC using either electron capture or flame ionization detectors (sensitivity limit 50 ng/ml plasma) has been used (e.g., Pantarotto et al., 1979) but this method has been criticized because it requires frequent reconditioning of columns (Hsu and Marss, 1980). HPLC, using a variety of internal standards (³H-5-FU [Buckpitt and Boyd, 1980, sensitive to less than 1 µM], 5-bromo-uracil [Sampson et al., 1982, limit 0.3 µmol/ml; especially useful to monitor intravenous infusion],

5-chlorouracil [DeLeenheer and Cosyns-Duyk, 1979, limit 2 µg/ml]) is a recommended procedure. Major interferences may be due to metabolites (nucleotides or nucleosides) but they can be eliminated by suitable choice of extraction procedures (e.g., Finn and Sadée, 1975). Highest sensitivity (in the ng/ml range) is achieved by GC/MS after methylation (Hillcoat et al., 1976; Min and Garland, 1978; Cano et al., 1979).

Biological Effects (Animal and Human)

Absorption: 5-FU is absorbed and produces biological effects after parenteral (intravenous [the usual clinical method] and intraperitoneal) administration and by ingestion. Topical treatment of keratoses is by application to skin in the form of creams from which it is absorbed (Cohen and Staughton, 1974); there is however no evidence whether systemic toxic effects are produced by this route.

Distribution: Intravenous 5-FU is cleared rapidly from the blood stream (91 and 98% within 5 minutes and 1 hour, respectively) and is apparently distributed to all tissues, with larger amounts in bone marrow, intestine, spleen, liver, and kidney. Significant amounts are found in the central nervous system and cerebrospinal fluid (Bourke et al., 1973). In man, the half time of intravenous or oral 5-FU (15 mg/kg) in plasma is 12 minutes (Finn and Sadée, 1975).

Metabolism and excretion: 5-FU is metabolized by both anabolism and catabolism. Detailed schemes of these processes are shown and discussed in several reviews (IARC, 1981; Heidelberger, 1972, 1982; Sadée and Wong, 1977; Ardalan and Glazer, 1981; Valerioti and Santelli, 1984) and are only outlined here.

Catabolism involves reduction to 5,6-dihydro-5-FU and subsequent conversion to NH_3 , CO_2 , urea, and α -fluoro- β -alanine. In normal animals this amounts to about 60-80% of total metabolism (as judged by excretion of respiratory CO_2 from labelled 5-FU) with 15-20% urinary excretion of unchanged 5-FU. In tumor tissues catabolism is greatly reduced (which may be the reason for the selective action of 5-FU against tumors). It has been hypothesized that α -fluoro- β -alanine is metabolized further to fluoracetate and/or fluorocitrate which could be responsible for some of the toxic symptoms associated with 5-FU through Krebs cycle inhibition ("lethal synthesis"). Anabolism involves conversion to 5-fluorouridine and 5-fluoro-2'-deoxyuridine and further to their mono-, di-, and tri-phosphates which are then incorporated as antimetabolites into RNA and DNA, respectively. 5-fluoro-2'-deoxyuridine monophosphate, regarded as the active form of 5-FU, is a potent inhibitor of thymidilate synthetase, forming a covalent ternary complex with it and the coenzyme $\text{N}^5, \text{N}^{10}$ -methylene tetrahydrofolate. This complex formation, though reversible, has a sufficiently long half life to prevent

synthesis of thymidylic acid and therefore DNA. The mechanism of inhibition of RNA synthesis is not as well understood, neither is the relative importance of these two pathways in nucleic acid synthesis and cell death.

4. Toxic Effects: LD50s in the rat and mouse by various routes are in the range of 190-500 mg/kg (Heidelberger et al., 1958; Murphy, 1962; Scherf et al., 1970), the intravenous figures usually being higher than intraperitoneal, subcutaneous, or oral ones.

In mice and man, early symptoms of parenteral intoxication are stomatitis and esophago-pharyngitis followed by diarrhea, anorexia, nausea, and emesis. On continued administration this leads to leucopenia, hemorrhage, gastrointestinal ulceration, alopecia, and dermatitis (Harrison et al., 1978; Heidelberger, 1982). All these are temporary effects and disappear after discontinuation of treatment. Reversible cerebellar ataxia has also been described (reviewed by Weiss et al., 1974). Skin application of 5-FU (as solution or in creams) in the treatment of actinic keratosis may produce local pain, hyperpigmentation, and burning sensations (Falkson and Schultz, 1962).

5. Carcinogenic Effects: There is no clear cut evidence for carcinogenicity of 5-FU in either animals or man. The few reported studies were either negative or suffered from too short a duration of the experiments or else from simultaneous administration with known or suspected carcinogens. These data have been reviewed (IARC, 1981).

6. Mutagenic and Teratogenic Effects: No mutagenic effects have been found in the Ames test (Seino et al., 1978; Yajima et al., 1981). However, 5-FU is a strong teratogen in hamsters (Shah and MacKay, 1978), mice (Dagg, 1960), rats (Wilson et al., 1969), and rhesus monkeys (Wilson, 1971). In the rat at least the dose-effect profile is quite steep (non-teratogenic at 10 mg/kg, highly teratogenic at 20 mg/kg).

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. Since 5-FU is 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 sodium bicarbonate solution, water, or milk.

3. Inhalation: Remove victim immediately to clean air.

4. Refer to physician.

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