

# Safety Data Sheet

# Daunorubicin

Division of Safety  
National Institutes  
of Health



## WARNING!

THIS COMPOUND IS TOXIC ON INGESTION, PARENTERAL INJECTION, AND ON CONTACT WITH THE SKIN AND EYES. IT IS CARCINOGENIC, MUTAGENIC, AND TERATOGENIC.

HANDLE WITH EXTREME CARE. AVOID SKIN AND EYE CONTACT AND BREATHING OF DUST. ON EXPOSURE, WASH SKIN IMMEDIATELY WITH SOAP AND WATER.

IF INHALED, MOVE TO CLEAN AIR. CALL PHYSICIAN.

DO NOT TAKE INTERNALLY.

### A. Background

Daunorubicin (daunomycin, DM) is an antibiotic anthracycline, a member of the rhodomycin group. It has been isolated from fermentation broths of Streptomyces caerulorubidus and S. peucetius. Its hydrochloride, the form in which it is used clinically, is a water soluble red crystalline compound. It is highly toxic in all mammalian species tested (parenteral LD50 in the mg/kg range) and carcinogenic, mutagenic, embryotoxic, and teratogenic in some. Exposure of skin and eyes may produce vesication. Its major use is as an antineoplastic, mainly against acute lymphocytic and myelogenous leukemias, but it is not promising in adult solid tumors and not effective in maintenance therapy. In patients the major toxic effects are on the heart, hematopoietic system, and gastrointestinal tract. Its mode of action on tumor and normal cells consists of intercalation and ionic binding to intracellular DNA.

General reviews, of which there are many, include: DiMarco, 1975 a,b; IARC, 1976; von Hoff et al., 1978; Aibel-Sadron and Londos-Gagliardi, 1984.

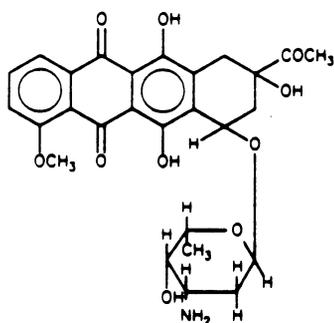
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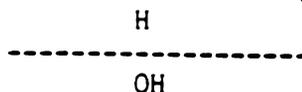
## B. Chemical and Physical Data

Note: All data in the literature are those for daunorubicin hydrochloride (DM·HCl); 1 mg DM  $\equiv$  1.07 mg DM·HCl

1. Chemical Abstract No.: 20830-81-3 for the free base; 23541-50-6 for the hydrochloride.
2. Synonyms: Acetylauriamycin; cerubidin; daunomycin; DM; leukaemomycin C; 5,12-naphthacene dione, 8-acetyl-10-[(3-amino--2,3,6-trideoxy- $\alpha$ -L-lyxo-hexapyranosyl)oxy]-7,8,9,10-tetrahydro-6,8,11-trihydroxy-1-methoxy-, (8S-cis)-<sup>A</sup>; NCI-CO4693; NSC-82151; RP 13057; rubidomycin; rubomycin C. Synonyms of DM·HCl: Daunoblastin, NDC 0082-4155; Ondena.
3. Chemical structure<sup>B</sup> and molecular weight:



Daunomycinone  
(aglycone)

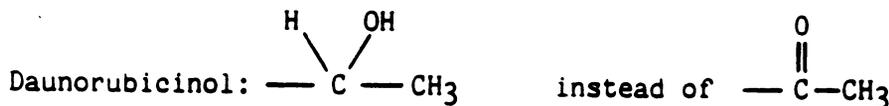


Daunosamine

free base:  $C_{27}H_{29}NO_{10}$ ; m.w. 527.5

hydrochloride:  $C_{27}H_{29}NO_{10}\cdot HCl$ ; m.w. 564

### Structures of representative metabolites



4. Density: No data.

5. Absorption spectroscopy: The ultraviolet, infrared (Bachur et al., 1974), and fluorescence spectra (Bachur et al., 1970)

<sup>A</sup>Chemical Abstracts name; used for listing in 9th Decennial Index and subsequently.

<sup>B</sup>Position assignments marked in this structure are those commonly used in the literature dealing with metabolic transformation of DM (see F3); they differ from the Chemical Abstracts assignments.

have been published. There is a broad UV absorption maximum in the 480-495 nm region (Dubost et al., 1963); fluorescent spectral data are:  $\lambda_{exc} = 470$  nm,  $\lambda_{em} = 554, 585$ nm.

6. Volatility: No data. DM·HCl may be regarded as essentially nonvolatile.
7. Solubility: Solubility in water: 450 mg/ml; soluble in methanol, insoluble in chloroform, ether, benzene (von Hoff et al., 1978)
8. Description: Thin red needles. Dispensed by NCI in vials containing 21.4 mg DM·HCl ( $\equiv$  20 mg DM) + 100 mg mannitol. The aqueous solution (0.1 mg/ml) has a pH of ca. 6.4; its color is pink at acid pH and blue at alkaline pH (von Hoff et al., 1978)
9. Boiling point: No data; melting point: 188-190°C with decomposition.
0. Stability: Vials of solid DM·HCl, if protected from light, are stable for at least 3 years at room temperature (von Hoff et al., 1978). Aqueous solutions, if kept protected from sunlight, are stable for one month at 5°C; better than 90% of original concentration remains after 48 hours at 21°C in a variety of infusion fluids (Poochikian et al., 1981), although it is recommended that solutions prepared for therapy should be used within 8 hours (von Hoff et al., 1978). Solutions of DM in buffered or unbuffered solution are unstable on irradiation with ultraviolet light; decomposition products include daunomycinone and a deacetylated derivative (Gray and Phillips, 1981).
1. Chemical reactivity: Acid hydrolysis results in production of daunomycinone and daunosamine as indicated in B3. The anthracycline ring is subject to reduction, e.g., with sodium borohydride. From the physiological point of view the most important reaction of DM is that with DNA by intercalation of two DM molecules in the double helix and hydrogen bonding (Calendi et al., 1965; Quigley et al., 1980). Enzymatic reduction by daunorubicin reductase yields daunorubicinol, a major metabolite (Felsted et al., 1974).
2. Flash point: No data.
3. Autoignition temperature: No data.
4. Explosive limits in air: No data.

#### Fire, Explosion, and Reactivity Hazards

1. DM is likely to be inactivated under conditions of fire. Because of its vesicant action 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 are acid, elevated temperature, and exposure to ultraviolet light.
4. Hazardous decomposition products on heating are fumes of nitrogen oxides and hydrochloric acid.

### 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 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 DM.

DM·HCl solutions penetrate PVC gloves (Laidlaw et al., 1984). This factor should be taken into account when handling DM·HCl.

1. Chemical inactivation: Validated methods have been reported (Castegnaro et al., 1985).
2. Decontamination: Turn off equipment that could be affected by DM or the materials used for cleanup. If more than 1 g has been spilled or if there is any uncertainty regarding the procedures to be followed for decontamination, call the NIH Fire Department (dial 116) for assistance. For details of procedures, see Castegnaro et al. (1985).
3. Disposal: It may be possible to decontaminate waste streams containing DM before disposal. For details, see Castegnaro et al., (1985). No waste streams containing DM shall be disposed of in sinks or general refuse. Surplus DM or chemical waste streams contaminated with DM 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 DM 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 DM 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 DM 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 DM shall be handled in accordance with the NIH radioactive waste disposal system.
4. Storage: For information on storage stability see B10. Solid DM may be stored at room temperature in the dark.

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

1. Sampling: No data.

2. Analysis:

- a. Sample extraction and preparation: Advantages and disadvantages of various extraction procedures have been evaluated (Schwartz, 1973). Extraction with butanol (Finkel et al., 1969) is adequate for blood and urine but not for tissues; ethanolic HCl (Bachur et al., 1973) results in variable hydrolysis to the aglycone and therefore cannot be used in metabolic studies. More recent methods involve extraction with organic solvents of tissue homogenates (Cradock et al., 1973) or of plasma (Hulhoven and Desager, 1976) or direct introduction of urine samples into an HPLC system (Sepaniak and Yeung, 1980; Andrews et al., 1980). Treatment of tissue homogenates with silver nitrate solution releases DM from linkage with DNA and therefore gives a truer picture of total tissue DM (Schwartz, 1973).
- b. Analytical methods: The three methods used in the analysis of DM and its metabolites in tissues and biological fluids are fluorimetry, high performance liquid chromatography (HPLC), and radioimmunoassay (RIA), either singly or in combination. Each has its advantages and disadvantages, and these have been critically reviewed (Sepaniak and Yeung, 1980; Brown et al., 1981). Fluorimetry (which does not distinguish between DM, daunomycinone, and metabolites unless coupled with TLC [Cradock et al., 1973]) has been used in plasma and urine (Finkel, 1969) and tissue analysis (Bachur et al., 1970), with a lower detection limit of 0.05-0.5  $\mu\text{g/g}$  for the latter. HPLC is particularly applicable to the study of metabolite distribution and has been coupled with fluorimetric (Sepaniak and Yeung, 1980; Andrews et al., 1980) or electrochemical detectors (Akporfure et al., 1982). Detection limits are of the order of 10  $\text{ng/ml}$  plasma or urine. RIA, with a lower limit of detection of 1  $\text{ng/ml}$  plasma or urine (van Vunakis et al., 1974) is the most sensitive procedure but requires expensive counting equipment and collection of chromatographic fractions. The antisera cross react with doxorubicin and doxorubicinol (Bachur et al., 1977).
- c. Stability of tissue preparations: Several authors stress that tissue samples should be kept cool and protected from light during work-up for analysis.

## F. Biological Effects (Animal and Human)

1. Absorption: DM is absorbed and produces biological effects after parenteral (intravenous [the usual clinical method] and intraperitoneal) injection, and by ingestion. It acts as a vesicant and may produce contact dermatitis as a result of handling or by extravasation due to needle slippage during treatments; however, there is no evidence whether systemic toxic effects are produced by this route.
2. Distribution: Intravenously injected DM is rapidly cleared from the bloodstream (half time in the hamster = 15 minutes [Mhatre et al., 1972]) and is transported into tissues, where it crosses cell membranes rapidly by an active process, against a concentration gradient (Bachur, 1975). Highest concentrations are found in kidney and lungs, lower amounts in heart, spleen, and liver in the rabbit (Hulhoven and Harvengt, 1982). DM apparently does not cross the blood-brain barrier, presumably because of the charged nature of the compound, in animals and man (DiFronzo and Bonadonna, 1969).
3. Metabolism and excretion: The metabolism of DM in mammalian tissues has been reviewed (Loveless et al., 1978). Initially, it proceeds via two pathways: reduction to daunorubicinol, and reductive glycosidic cleavage to deoxydaunorubicin aglycone (see B3 for structures). These steps are followed by further hydrolyses, reductions, demethylation at the 4-position, and conjugation with glucuronic acid and/or sulfate at positions 4 and 13. Schemes of metabolic pathways can be found in publications by Asbell et al. (1972) and Takahashi et al. (1975), among others. Excretion of unchanged DM and its metabolites is via urine and bile, with daunorubicinol as the major excretion product in urine, and glucuronide conjugates of DM, daunorubicinol, and aglycones in bile. It appears that the metabolism of DM is geared towards production of compounds of higher polarity (Cradock et al., 1973).
4. Toxic effects: The acute LD50s of DM<sup>A</sup> by the intravenous or intraperitoneal route are in the range of 4-25 mg/kg for mouse, rat, guinea pig, hamster, rabbit, and dog (Dubost et al., 1963; Maral and Jouanne, 1981). The subcutaneous LD50 in the mouse is 47 mg/kg (Dubost et al., 1963) and the oral LD50s of DM·HCl in mouse and rat are considerably higher (205 and 290 mg/kg, respectively [RTECS, 1983]) and its physiological action by this route is slight. The "highest non-toxic dose" in the monkey (i.v.) is 0.5 mg/kg (Priour et al., 1972).

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<sup>A</sup>It is not clear whether toxicity figures in the literature are in terms of mg DM·HCl/kg or have been recalculated as mg DM/kg. Since only ranges are given here the difference is not significant for parenteral administration and probably also not for oral toxicity.

Toxic effects of DM vary greatly with species and dose. In the mouse and rat, intraperitoneal injection produces mainly diarrhea and other gastrointestinal symptoms (von Hoff et al., 1978) with nephrosis noted in rats (Sternberg 1970). High doses of DM i.v. result in fatal respiratory depression in the guinea pig (Herman et al., 1969). In most species the effects are cardiopulmonary: tachypnea, dyspnea, and hypotension leading to cardiac arrhythmia in hamsters, dogs, and monkeys (Herman and Viok, 1970; Mhatre et al., 1972) and other cardiomyopathy in the rabbit (Bachur et al., 1974).

In man, antineoplastic treatment with DM results in effects on the hematopoietic system (leukopenia, thrombocytopenia), nausea, vomiting, anorexia, diarrhea, phlebitis, and alopecia and cardiotoxic symptoms which may lead to congestive heart failure (Bonadonna and Monfardini, 1969; von Hoff et al., 1978).

**Carcinogenic effects:** The literature through 1975 has been summarized (IARC, 1976). Mammary fibroadenomas and adenocarcinomas (Marquardt et al., 1976; Solicia et al., 1978) and renal tumors (Sternberg et al., 1972) are induced in rats by intravenous DM (Bucciarelli, 1981) but not in BALB/c mice (Bucciarelli et al., 1982). Subcutaneous sarcomas have been noted in several species at the point of subcutaneous or intraperitoneal injection.

**Mutagenic and teratogenic effects:** DM is mutagenic in the Ames test (Benedict et al., 1977; Marzin et al., 1983). Teratogenicity has been noted in the rat (Thompson et al., 1978) and chick (DeBernardi et al., 1967). DM does not appear to be teratogenic in the rabbit but produces a high incidence of spontaneous abortions (Maral and Jouanne, 1981).

### Emergency Treatment and Medical Surveillance

**Skin and eye exposure:** For skin exposure, remove contaminated clothing and wash with soap and water. For eye exposure, irrigate immediately with copious amounts of warm water or boric acid solution.

**Ingestion:** Give milk or sodium bicarbonate solution to reduce gastric irritation.

**Inhalation:** Remove to clean air and avoid further contact.

**Medical Surveillance:** Preemployment and periodic surveillance should include liver and kidney function tests, hematological work up, and cardiovascular examination. It is recommended that personnel with preexisting dermatitis and cardiovascular symptoms, as well as women during the first three months of pregnancy, not be exposed to DM except in very small amounts.

The treatment of skin dermatitis due to extravasation during injection, as well as accidental exposure of laboratory workers, has been reviewed (Ignoffo and Friedman, 1980; Cox, 1984).

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