

# Safety Data Sheet

# Doxorubicin

Division of Safety  
National Institutes  
of Health



## WARNING!

THIS COMPOUND IS TOXIC ON INGESTION, PARENTERAL INJECTION, AND ON CONTACT WITH 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

Doxorubicin (adriamycin, DX) is an antibiotic anthracycline, a member of the rhodomycin group. It has been isolated from fermentation broths of Streptomyces peucetius, var. caesius, first described by Arcamone et al. (1969). Its hydrochloride, the form in which it is used clinically, is a water soluble orange-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 and it has been used successfully against Ehrlich ascites carcinoma, lymphosarcoma, sarcoma 180, bronchogenic carcinoma, and others. Its therapeutic index is somewhat higher than that of daunorubicin, however, it shares with it the property of producing cardiomyopathy and other toxic effects on the hematopoietic system and gastrointestinal tract. Its mode of action on tumor and normal cells consists of intercalation and ionic binding to intracellular DNA.

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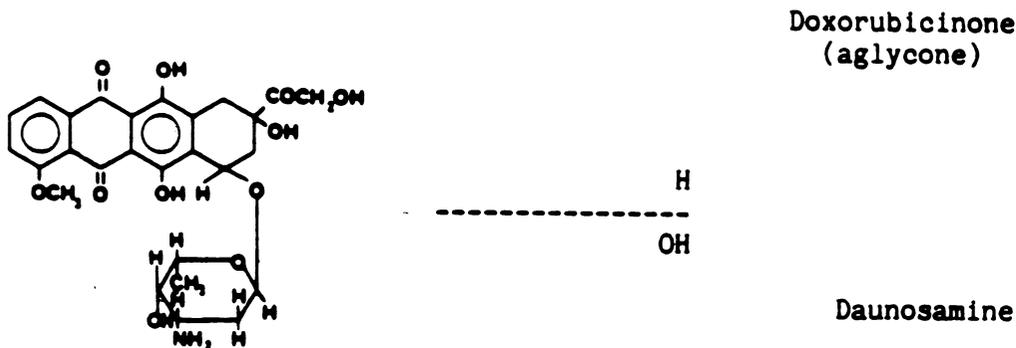
Prepared by the Environmental  
Control and Research Program

General recent reviews include: IARC (1976); Vigevani and Williamson (1980); Arcamone (1981); Perry and Yarbro (1984); Aibel-Sadron and Londos-Gagliardi (1984).

## B. Chemical and Physical Data

Note: All data in the literature refer to doxorubicin hydrochloride (DX·HCl); 1 mg DX  $\equiv$  1.07 mg DX·HCl

1. Chemical Abstract No. 22314-92-8 for the free base; 25316-40-9 for the hydrochloride.
2. Synonyms: Adriamycin; AM; 14-hydroxy daunomycin; DX; DXR; 5,12-naphthacenedione, [10-(3-amino-2,3,6 trideoxy- $\alpha$ -L-lyxo-hexapyranosyl)oxy]-7,8,9,10-tetrahydro-6,8,11-trihydroxy-8-(hydroxyacetyl-1-methoxy-(8S-cis)-);<sup>A</sup> F.I. 106; NCI-CO1514; NSC-123127.
3. Chemical structure<sup>B</sup> and molecular weight:



free base:  $C_{27}H_{29}NO_{11}$ ; m.w. 543.5

hydrochloride:  $C_{27}H_{29}NO_{11} \cdot HCl$ ; m.w. 580

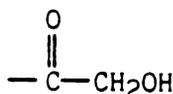
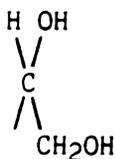
<sup>A</sup>Chemical Abstracts name; used for listing in 9th Decennial Index and subsequently.

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

# Structures of representative metabolites

Doxorubicinol:

instead of



Deoxydoxorubicin aglycone:



Density: No data.

Absorption spectroscopy: The visible, ultraviolet, infrared, NMR, mass, fluorescence (Vigevani and Williamson, 1980) and Raman spectra (Angeloni et al., 1982) have been published.

Volatility: No data. DX·HCl may be regarded as essentially nonvolatile.

Solubility: DX·HCl is soluble in water (approx. 2%), methanol, aqueous alcohols, acetonitrile, tetrahydrofuran. Slightly soluble or insoluble in less polar solvents.

Description: Thin orange-red needles. Dispensed commercially in vials of orange-red lyophilized powder of 10 or 50 mg DX·HCl containing 5 mg lactose/mg DX·HCl. The aqueous solution is orange-yellow at acid pH, orange-red at neutral pH, and blue-violet at alkaline pH (Arcamone et al., 1969);  $pK_a = 7.20$  (Arcamone, 1981). Spectral data at varying concentrations indicate dimerization in solution (Angeloni et al., 1982).

Boiling point: No data; melting point: 205°C with decomposition.

Stability: Vials of solid DX·HCl are stable for years at room temperature if protected from light (Vigevani and Williamson, 1980). Aqueous solutions, if protected from sunlight, are stable for one month at 5°C but are unstable at higher temperatures and at acid or alkaline pH (Arcamone et al., 1969). Better than 90% of original concentration remains after 48 hours at 21°C after addition to infusion fluid (5% dextrose or 0.9% NaCl) (Poochikian et al., 1981). Solutions of DX in buffered or unbuffered solutions are unstable on exposure to light; all fluorescence is lost in 30 hours in intensive sunlight, 67% in 144 hours in subdued light (Tavoloni et al., 1980). DX is

strongly adsorbed from solution by glass or Teflon but not by polypropylene, PVC, or siliconized glass (Benvenuto et al., 1981; Tomlinson and Malspeis, 1982).

11. Chemical reactivity: Acid hydrolysis results in production of doxorubicinone and daunosamine as indicated in B3. The kinetics of this reaction indicates that under the conditions of pH in the stomach and an assumed gastric emptying time, 86-98% of oral DX should remain intact and that therefore the ineffectiveness of oral administration is probably due to other factors (Wassermann and Bundgaard, 1983). The anthracycline ring is subject to reduction, e.g., with sodium borohydride. From the physiological point of view the most important reaction of DX is that with DNA by intercalation of DX in the double helix, hydrogen bonding, and electrostatic interaction between the ionized amino group of DX and phosphate moieties of DNA (DiMarco, 1975).
12. Flash point: No data.
13. Autoignition temperature: No data.
14. Explosive limits in air: No data.

#### Fire, Explosion and Reactivity Hazards

1. DX 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 or alkali, elevated temperatures, and exposure to ultraviolet light.
4. Hazardous decomposition products under conditions of fire are 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 DX.

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

1. Chemical inactivation: Validated methods have been reported (Castagnarò et al., 1985).

2. Decontamination: Turn off equipment that could be affected by DX or the materials used for clean up. 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 DX before disposal. For details, see Castegnaro et al. (1985). No waste streams containing DX shall be disposed of in sinks or general refuse. Surplus DX or chemical waste streams contaminated with DX 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 DX 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 DX 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 DX 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 DX shall be handled in accordance with the NIH radioactive waste disposal system.
4. Storage: For information on storage stability see B10. Solid DX may be stored at room temperature in the dark.

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

Note: All analytical procedures should be carried out in polypropylene or siliconized glassware to avoid surface adsorption (e.g., Oosterbaan, 1984). Degradation has also been noted when using some brands of silica gel on TLC plates (Watson and Chan, 1976).

1. Sampling: No data.

2. Analysis:

- a. Sample extraction and preparation: For plasma analysis, blood samples should be cooled immediately in an ice bath and separated. Plasma samples may be stored in frozen form if analysis is delayed, or at 4°C for 24 hours. In 0.1 M phosphoric acid (used for extraction in some procedures) plasma samples are stable for several months at 4°C (Eksborg et al., 1981). Tissue should be frozen in dry ice-ethanol and macerated, kept cool, and protected from light during subsequent manipulations (Schwartz, 1973). Advantages and

disadvantages of various extraction procedures have been evaluated (Schwartz, 1973; Vigevani and Williamson, 1980; Arcamone, 1981). Extraction with butanol (Finkel et al., 1969)<sup>A</sup> 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 tissues (Chan and Wong, 1979; Shinozawa et al., 1980) or of plasma (Pierce and Jatlow, 1979; Bots et al., 1983) 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 DX from linkage with DNA and therefore gives a truer picture of tissue DX (Schwartz, 1973).

- b. Analytical methods: The three principal methods used in the analysis of DX 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 or disadvantages, and these have been critically reviewed (Sepaniak and Yeung, 1980; Arcamone, 1981). Fluorimetry, which does not distinguish between DX, doxorubicinone, and metabolites unless coupled with TLC (Chan and Harris, 1973; Benjamin et al., 1977), has been used in plasma, urine and tissue analysis (Schwartz, 1973; Watson and Chan, 1976; Benjamin et al., 1977). HPLC is particularly applicable to the study of metabolite distribution and has been coupled with fluorometric detectors (Andrews et al., 1980; Sepaniak and Yeung, 1980; Shinozawa and Oda, 1981; Bots et al., 1983). Detection limits are of the order of 10 ng/ml plasma or urine. RIA, with a lower limit of detection of 1 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 crossreact with daunorubicin and daunorubicinol (Bachur et al., 1977). A combination of HPLC and RIA has been described (Langone et al., 1975) for the separation of DX, DX aglycones, and doxorubicinol in the urine of patients. An apparently very simple procedure, applicable to urine samples, consists of immersing carbon paste electrodes in the sample (thereby producing adsorption of DX and probably also some metabolites) and measuring concentration by differential pulse voltammetry, with a sensitivity of less than  $10^{-8}$  M (~ 5 ng/ml) (Chaney and Baldwin, 1982). This method might be useful in routine clinical monitoring.

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<sup>A</sup>This paper addresses procedures for daunomycin but the results probably apply to DX also.

## Biological Effects (Animal and Human)

**Absorption:** DX 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 slipping during treatments; however, whether systemic toxic effects are produced by this route is not known.

**Distribution:** Intravenously injected DX is rapidly cleared from the blood stream. This clearance has been described as either biphasic ( $t_{1/2} = 1.1$  and 16.7 hours; Carter et al., 1981) or triphasic ( $t_{1/2} = 12$  minutes, 3.3 hours, and 29.6 hours; Benjamin et al., 1977) in man. After reaching tissues it crosses cell membranes rapidly by an active process against a concentration gradient (Bachur, 1975). Highest concentrations are found in kidney and lungs, with lower amounts in heart, spleen, and liver. DX does not cross the blood-brain barrier, presumably because of the charged nature of the compound, but passes to areas of the somatic and autonomic peripheral nervous system outside of this barrier (Bigotte et al., 1982a, 1982b). Pharmacokinetic models for the distribution of DX have been developed (Yesair et al., 1972; Reich et al., 1979; Arcamone, 1981; Sonneveld and Mulder, 1981).

**Metabolism and excretion:** The metabolism of DX in mammalian species has been reviewed (Loveless et al., 1978). Initially it proceeds via two pathways: reduction to doxorubicinol by a cytoplasmic aldo-reductase and reductive glycosidic cleavage to deoxydoxorubicin aglycone by microsomal enzymes (see B3 for structures). These steps are followed by further hydrolyses, reductions, demethylation at position 4, and conjugation with glucuronic acid and/or sulfate at positions 4 and 13. Schemes for the metabolism of DX have been outlined (Asbell 1972; Takanashi and Bachur, 1976). Excretion of DX is mainly via the bile (Israel et al., 1978; Tavoloni and Guarino, 1980, 1981) but there is little or no evidence for enterohepatic circulation (Tavoloni and Guarino, 1982), and the major route of excretion is via feces (Arcamone et al., 1984); smaller amounts are excreted in the urine. The major excretion product is unchanged DX. The chief mechanism of action of DX is by intracellular intercalation with DNA (reviewed by DiMarco, 1975 and Arcamone, 1981), resulting in inhibition of DNA-dependent RNA synthesis. This may not be the only mechanism since recent evidence indicates cytotoxic action of DX without cell penetration (Tritton and Yee, 1982).

4. Toxic effects: The acute LD50 of DX<sup>A</sup> in the mouse is 4.6, 12-20, 13.5, and 570 mg/kg by intraperitoneal, intravenous, subcutaneous, and oral administration (Goldberg et al., 1983). Intravenous toxicity in the rat is of the same order as for the mouse, while the dog appears to be more sensitive with an intravenous LD50 of 2.5 mg/kg (Bertazzoli et al., 1985). On repeated intravenous injection of DX in mice there appears to be a steep dose/toxicity curve since 15-day mortality for 5 and 6.67 mg/kg/day for 8 days has been reported to be 0 and 80%, respectively (DiMarco et al., 1969).

Toxic effects in man have been reviewed (e.g., Carter et al., 1981; Perry and Yarbrow, 1984). Briefly, these effects are on the hematopoietic system (leukopenia, thrombocytopenia), nausea vomiting, diarrhea, anorexia, and alopecia. Neurotoxicity involving the peripheral nervous system has been noted in rats (Cho, 1977; Jortner and Cho, 1980) at otherwise compatible dosage, and nephropathy in rabbits (van Vleet and Ferrans, 1980; Fajardo et al., 1980). The most important effects are on the cardiopulmonary system in animals and man which may lead to congestive heart failure. The possible mechanism of this cardiotoxicity has been intensively investigated and reviewed (Olson et al., 1981; Perry and Yarbrow, 1984). It is believed that DX forms a reactive free radical species with hydrogen peroxide, possibly OH<sup>+</sup>, which can oxidize cellular components. This reaction is prevented by intracellular sulphhydryl donors (glutathione) and the reason for the specific action of DX on heart tissue may be the much lower concentration of glutathione in heart muscle compared with liver or kidney (Olson et al., 1981; Nohl and Jordan, 1983). The fact that reducing substances such as cysteamine,  $\alpha$ -tocopherol or coenzyme Q<sub>10</sub> reduce the lethality of DX (Yamanaka et al., 1979) is evidence in favor of this theory. Topically, DX has a vesicant action when applied intradermally (Bartkowski-Dodds and Daniels, 1980) or inadvertently by extravasation in patients during intravenous infusion.

5. Carcinogenic effects: The literature through 1975 has been summarized (IARC, 1976) and indicates little if any evidence for carcinogenicity. Mammary fibroadenomas and adenocarcinomas (Marquardt et al., 1976; Solicia et al., 1978; Bucciarelli, 1981) are induced in rats by intravenous DX. Subcutaneous tumors have been noted at the point of subcutaneous or intraperitoneal injection.

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<sup>A</sup>It is not clear whether toxicity figures in the literature are in terms of mg DX·HCl/kg or have been recalculated as mg DX/kg. The difference is not likely to be significant for parenteral and probably also not for oral toxicity.

6. Mutagenic and teratogenic effects: DX is mutagenic in the Ames test (Benedict et al., 1977; Marzin et al., 1983) and against Drosophila (Clements et al., 1984). It is teratogenic in the rat (in which species it is more potent than daunorubicin) but not in the rabbit (Thompson et al., 1978).

### Emergency Treatment and Medical Surveillance

1. Skin and eye exposure: For skin exposure, remove contaminated clothing and wash with soap and water. For eye exposure, irrigate immediately with copious quantities of warm water or boric acid solution.
2. Ingestion: Give milk or sodium bicarbonate solution to reduce gastric irritation.
3. Inhalation: Remove to clean air and avoid further contact.
4. Medical surveillance: Preemployment and periodic surveillance should include liver and kidney function tests, hematological workup, and cardiovascular examination. It is recommended that personnel with preexisting dermatitis and cardiovascular impairment, as well as women during the first three months of pregnancy, not be exposed to DX except in very small amounts. Drugs have been suggested for the treatment of DX toxicity (Yamanaka et al.; 1979, Banks et al., 1983). 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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