

Working with Doxorubicin (Adriamycin)

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Background

Doxorubicin (DX), also commonly referred to as adriamycin, adriacin, and DX-HCL, is an antibiotic anthracycline compound derived from the fermentation of *Streptomyces peucetius* broth (NIH 1986). Doxorubicin has been used clinically as an antineoplastic drug for many years. It has been used successfully in the treatment of carcinomas including: breast cancer, lymphosarcoma, leukemia, bladder cancer, ovarian cancer, and a number of other carcinomas. In its pure state, DX occurs as an orange-red powder which is soluble in water, aqueous alcohols, and a number of solvents (NIH 1986). Its major vehicle of action involves intercalation and ionic binding to DNA, DNA double strand breakage, (NIH 1986, Mahon 2001) and alkylation of macromolecules (Hewitt 1997, Gianni et al 1983). Research has indicated that DX is cytotoxic, embryotoxic, carcinogenic, teratogenic, and mutagenic (NIH 1986l)). These potentially severe side effects make DX exposure a significant health and safety threat to laboratory staff, animal handlers and other personnel who may be subjected to accidental exposure. Due to this health and safety threat the [Institutional Biosafety Committee](#) (IBC) has classified DX as a [reportable hazardous chemical](#) that must be reported on all [Institutional Animal Care and Use Committee](#) IACUC protocols.

PURPOSE

The purpose of this page is to provide the research community sufficient information regarding specific health threats/exposure routes, implementation of proper work methods, and provision of suitable personal protective equipment for development of research protocols that include measures for effectively reducing risk of occupational exposure to DX.

OCCUPATIONAL EXPOSURE HAZARDS

Primary routes of occupational exposure to DX include: aerosol exposure, ingestion, accidental injection, and tissue/transplacental absorption (NIH 1986). Available industrial hygiene and epidemiology case studies are limited. The available scientific literature indicates the following potential consequences in relation to acute and chronic occupational exposure.

1. Cytotoxic Effects: Acute and chronic toxic effects including: cardiotoxicity, skin and eye tissue vesication, dermatitis, neutropenia, leucopenia, and anemia have been

documented (NIH 1986, FDA 2003, RxMed 2006). Case studies have indicated that chronic/cumulative exposure low doses or single exposures to greater doses of DX may result in deleterious morphological changes to the heart which may lead ultimately to congestive heart failure (FDA 2003, Ewer et al 2002). Exposure to skin and eye tissue has been linked to development of severe dermatitis and/or vesification. Case studies have associated some of these outcomes to insufficient use of proper personnel protective equipment by technicians during the preparation of DX drug doses (Hewitt 1997, Reich & Bachur 1975). Case studies have also indicated that injection of DX into intramuscular and subcutaneous tissue, and extravasion of intravenous fluid containing DX may lead to severe necrosis (FDA 2003).

2. Teratogenic and Mutagenic Effects: Research has indicated that DX induces lethal mutations in mice and can potentially induce human chromosomal damage (FDA 2005). Doxorubicin (adriamycin) is included on the “Dangerous Properties of Industrial Materials” listing of known and suspected human carcinogens (Sax and Lewis, 2004).

3. Reproductive Toxin: Case studies have documented that DX and its metabolites cross the placental barrier leading to highly variable effects on fetal development ranging from fetal death to healthy newborns with no discernable defects (Mahon 2001, Briggs et al 1994). While exposure to DX throughout the pregnancy is considered a risk, exposure to DX during the first trimester appears to pose the greatest potential for fetal toxicity (Selevan et al 1985, Germann 2004). Some studies have suggested that DX is excreted into breast milk, leading American Academy on Pediatrics to recommend that mothers undergoing DX treatment forego breast feeding (American Academy on Pediatrics, 1985, 2005). Case studies have indicated that nurses and other workers with occupational exposure to doxorubicin and other antineoplastic drugs have an elevated potential for experiencing pregnancies with birth defects and other complications (Hewitt 1997, Selevan 1985). Research has also indicated that DX is toxic to male sex organs, with evidence of oligospermia and azoospermia observed following exposure (FDA 2003).

4. Carcinogenicity: Exposure to DX, and to DX in conjunction with other chemotherapeutic drugs has been associated with greater incidence carcinomas including secondary acute myelogenous leukemia, myelodysplastic syndrome, and possibly other neoplasms (FDA 2003, Hewitt 1997, Boice et al 1983). The International Agency for Research on Cancer (IARC) lists DX (adriamycin) as a Group 2A probable human carcinogen (IARC 2005).

SAFE WORK METHODS

The list of potential DX related health hazards identified above make it imperative that PIs conduct thorough risk assessments and prepare protocols which include standard operating procedures (SOPs) which identify appropriate administrative controls, personal protective equipment (PPE), work methods, engineering controls, and waste disposal procedures for eliminating or sufficiently reducing exposure threat to all staff involved in the affected research. Research has indicated that implementation of suitable work methods greatly reduces the likelihood of significant exposure of personnel involved with the handling (preparation/mixture of drug doses, drug administration, handling of waste products, etc.) of DX (Tuffnell et al 1986).

1. Administrative Controls

a. Management considerations for DX and other potentially hazardous chemicals must be included in the laboratory [Chemical Hygiene Plan](#).

b. Protocols involving use of DX must include completion of [reportable hazardous chemical](#) form and approval through the [Institutional Animal Care and Use Committee](#).

c. Principal investigators will develop and implement standard operating procedures (SOPs) by which laboratory staff will prepare/administer DX with minimal potential for exposure.

d. All tasks having potential for occupational DX exposure (mixing of doses, dose preparation, administering of injections, etc.) will only be conducted by competent staff whom have received appropriate training (OSHA: “Worker Right to Know”) regarding the specific DX-related health and safety risks, SOPs, and procedures to be followed in event of an exposure incident.

e. Workers must be instructed to use extreme caution when performing injections involving DX, as accidental needle stick appears to present a serious exposure threat.

f. All staff engaging in processes identified above are also required to complete applicable modules of the [VCU Laboratory Safety Training Modules](#).

g. Research has indicated that persons with active varicella-zoster infections (chicken pox and shingles), liver disease, heart disease, gout, and kidney stones are more susceptible to harmful effects in relation to DX exposure (FDA 2003, American Cancer Society 2006). Principal investigators should consider removing any personnel with the above conditions from any duties involving significant risk of DX exposure.

h. Exposures involving DX or any other acutely hazardous material should be reported to Employee Health as soon as possible.

2. Personal Protective Equipment: Case studies have indicated that worker DX exposure is often attributable to the wearing of inadequate PPE. Staff involved with any tasks where potential for DX exposure exists must don the following PPE:

a. Examination gloves: Two pairs of powder-free latex or nitrile examination gloves which cover hands and wrists completely through overlapping sleeve of lab coat should be donned as a minimum level of protection whenever working with DX. Working should thoroughly wash hands with soap and water immediately upon removing examination gloves. *Polyvinyl chloride (PVC) gloves are not appropriate for use with DX (NIH 1986).*

b. Safety glasses or safety goggles (ANSI Z-87 approved) are considered the least appropriate level of protection. The IBC recommends donning of full-face shield when conducting tasks posing potential for any generation of aerosol or droplets.

c. Lab coat or disposable coveralls that provide complete coverage of skin.

d. Appropriate laboratory attire: workers handling DX should don attire which provides coverage of all skin surfaces.

e. If aerosol exposure threat exists suitable respiratory protection must be provided. Prior to instituting respiratory protection to personnel, the laboratory must participate in the university [Respiratory Protection Program](#).

3. Work Methods

- a. Procedures with the potential for producing DX aerosols should be conducted with a certified biosafety cabinet.
- b. Needles used for DX injection will be disposed of in approved sharps containers immediately following use.
- c. Needles used for DX injection should never be bent, sheared, or recapped. If recapping is absolutely necessary, a "[Needle Recapping Waiver](#)" must be submitted for IBC review/approval prior to proceeding.
- d. Areas where DX is prepared and/or administered should be cleaned immediately following each task completion utilizing a 20% (1 : 5) bleach/water solution (prepare fresh stock as needed).

4. Engineering controls

- a. In cases where the recommended level of PPE does not provide sufficient protection (e.g.: splash potential, aerosolization potential) tasks should be conducted within a biological safety cabinet or chemical fume hood utilizing sash for added protection.
- b. Syringes used for DX injection must be safety engineered (self-sheathing syringes, luer-lock syringes, etc.).
- c. Animals should be appropriately restrained and/or sedated prior to administering injections and other dosing methods.
- d. Research has indicated that analytical procedures involving DX should be conducted utilizing siliconized glassware or polypropylene vessels. Doxorubicin may degrade or be absorbed into standard glassware creating possible contamination and exposure issues (NIH 1986).
- e. Laboratories and other spaces where handling of DX occurs must be equipped with an eyewash station that meets the requirements of the American National Standards Institute (ANSI).

5. Waste Disposal

a. Surplus DX must be disposed of as a hazardous chemical through the OEHS [Chemical Waste Management Program](#).

b. Limited scientific literature is available regarding the metabolization of DX. The available studies indicate that excretion is of DX and its metabolites is via the fecal route, with lesser excretion via the urinary route with the primary excretion product being unchanged DX (RxMed 2006, NIH 1986). being responsible for a lesser available studies indicate that DX is The limited available literature regarding DX metabolism makes it imperative that all potentially contaminated carcasses, bedding, and other nonsharps materials be disposed of as [Regulated Medical Waste](#) (RMW) through incineration (National Institutes of Health 1986).

c. All contaminated sharps waste materials must be placed in proper sharps container and disposed of as RMW.

6. Spills: Small spills of DX should be deactivated with 20% bleach solution (allow minimum of 15 minute contact time). Following deactivation, spill area should be thoroughly cleaned with absorbent paper and soap and water. Don appropriate PPE during clean-up, dispose of all waste generated through OEHS. For larger spills of DX contact the OEHS emergency line (828-9834) for assistance.

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