Working With Doxorubicin and Treated Animals
University of Toronto
Office of Environmental Health and Safety

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Introduction/Uses	Doxorubicin, also known by the trade name Adriamycin or hydroxydaunorubicin is a chemotherapeutic drug. Doxorubicin works by inserting itself into (intercalating) DNA and preventing replication. The drug is used to treat a broad range of cancers. The drug is usually administered intravenously as the Doxorubicin hydrochloride salt or encapsulated as a polyethylene glycol coated liposomal particle.
Adverse Health Effects:	In the clinical setting life-threatening heart damage is the most serious side effect of the drug. Other effects seen clinically are nausea, vomiting, a decrease in white blood cells (neutropenia), as well as hair loss. Urine can turn bright red after treatment. The mechanisim of the cardiotoxic action involves the generation of reactive oxygen species upon the interaction of Doxorubicin and Iron (III). Since the amounts used in animal research are far smaller than clinical doses, it is unlikely that anyone working with Doxorubicin or Doxorubicin treated animals would be exposed at the level that produces these effects. Effects such as severe tissue death (necrosis) have been seen where Doxorubicin has been injected improperly and has leaked out of veins or been injected into surrounding tissue (extravasion).
Routes of Entry	Routes of entry include skin contact, inhalation of aerosols or particulate through the nose or mouth, injection and injestion (eating).
Irritant:	Yes. Acute exposure can result in eye, skin and respiratory irritation. Proper handling should prevent all of these endpoints.
Sensitizer:	Allergic reactions have been seen in clinical usage.
Carcinogen:	The IARC (International Agency for Research on Cancer) classificaton is Group 2A probably carcinogenic to humans due to inadequate evidence in humans and sufficient evidence in animals.
Mutagen:	Evidence of mutagenicity and genotoxicity in animals, human cell lines and nurses using doxorubicin and other neoplastics in a clinical setting.
Teratogen:	Reproductive effects such as fetal harm have been seen in animals, but have not been confirmed in humans. FDA pregnancy class D.
Physical Properties:	Chrystalline red solid
Elimination:	Doxorubicin is excreted in urine and faeces with a half life of ~16hrs in the mouse.
Note:	Prior to Working with the chemical or treated Animals, the Principal Investigator (PI) and Area Manager must ensure all employees and students: a. Have been trained and are familiar with the contents of this procedure
PREPARATION	
Engineering Controls:	Solutions must be prepared in a certified chemical fume hood or biosafety cabinet (minimum class II type A2). Personal protective equipment (PPE) must be worn – double gloves, goggles, and lab coat (or double gown) at a minimum. All work surfaces must be covered with absorbent, plastic-backed, disposable bench paper. If it is not possible to weigh in a certified chemical fume hood or biosafety cabinet, then: - Tare an empty container with its cap; - In a certified chemical fume hood or biosafety cabinet, transfer an approximate quantity of of chemical into the container; - Cap and weigh the container; - In a certified chemical fume hood, add an appropriate amount of solvent to achieve the desired concentration.
Administrative Controls:	The pure chemical and its solutions must be stored in labeled, tightly capped containers. The container must be properly labeled with the identity of the hazardous contents and the appropriate hazard warning. The primary container for must be placed in a sealed, leak proof, unbreakable secondary container, which must also be labeled as described above. The chemical as received from the manufacturer/vendor in its original undiluted or powder form must be stored separately from other chemicals in a labeled, sealed, leak proof secondary container. The storage area must be posted with an appropriate hazard label. To minimize the risk of exposure to during reusing and storage, the chemical should be procured in the appropriate volume to ensure all chemical is used up after opening container. Disposable labware should be used when preparing solutions. Solutions must always be transported in a labeled, sealed, primary container within a sealed, leakproof, unbreakable secondary container. Adequate absorbent material must be placed within the secondary container, around the primary container, to absorb all the solution in the event of a spill.
Personal Protective Equipment:	Two pairs of chemical-resistant gloves (e.g., nitrile), disposable lab coat or double gown, wrist-guards or gloves taped to sleeves and mucous membrane protection (e.g. chemical goggles, face shield and surgical mask) must be worn before commencing this step.
Waste Disposal:	If non-disposable glassware is used, it must be triple washed with lab detergent. Solutions must be collected and disposed of as chemical waste. Refer to the Laboratory Hazardous Waste Management and Disposal Manual for specific instructions or contact EHS Environmental Protection Services for further information. When all work is complete, carefully remove all bench paper and dispose of as chemical waste. Wipe all surfaces with detergent solution and wipe clean with water.
ADMINISTRATION	
Engineering Controls:	Administration to rodents must be conducted in a certified chemical fume hood, certified class II type A2 biological safety cabinet at a minimum or at a certified down draft table.

Administrative Controls:	Animals must be chemically or physically restrained prior to starting the procedure. All work surfaces, except the down-draft table, must be covered with absorbent, plastic-backed, disposable bench paper.
Personal Protective Equipment:	Both the personnel administering the chemical, and those in the immediate vicinity of the procedure must wear appropriate PPE. Two pairs of chemical-resistant gloves (e.g., nitrile), disposable lab coat or gown, wrist-guards or gloves taped to sleeves and mucous membrane protection (e.g., chemical goggles, face shield and surgical mask) must be worn before commencing this task.
Waste Disposal:	After the completion of each injection, immediately place the syringe-needle unit in a sharps disposal container.
Note:	Use only needle-locking syringes or disposable syringe-needle units (i.e., needle is integral to the syringe). Used disposable needles must not be bent, sheared, broken, recapped, removed from disposable syringes, or otherwise manipulated before disposal.
ANIMAL HOUSING	**First 4 Days After Dosing**
Engineering Controls:	For rodents, use disposable cages; cover the cages with filter bonnets If cages are not filtered, they should be ventilated (i.e. via certified chemical fume hood, certified class II type A2 biological safety cabinet at a minimum or ventilated rack)
Administrative Controls:	The door(s) to a room containing treated animals must be posted in such a manner that it is clear that the room contains treated animals, including the name of the chemical. The animal cages must also be properly labeled.
Personal Protective Equipment:	If handling/working with treated animals, changing cages, disposing cages or disposing cage waste: Wear disposable gown on top of gown, wrist-guards, head and foot covering, two pair chemical-resistant gloves (e.g., nitrile), N-95 disposable respirator, and chemical goggles.
Waste Disposal:	Carefully remove the pads and place in a waste container for disposal. If pan liners are not used, adequately wet the bedding with water to keep the dust down. Place bedding in a waste container, using care not to aerosolize dust from the bedding.
Note:	If entering room with treated animals without handling treated animals (cage closed): Wear a standard gown, foot covering and chemical-resistant gloves (e.g., nitrile).
ANIMAL HOUSING	**After 4 Days**
Administrative Controls:	The animals may be transferred to clean, standard caging and the door signs and cage tags may be removed.
Note:	Procedures used should be the same as for untreated animals from this point onwards.
EMERGENCY RESPONSE	**In the event of an exposure:**
	1. Flush body area for a minimum of 15 minutes. a. For an injection exposure seek medical attention immediately as tissue death (necrosis) can result from injection. Inform Hospital personnel that you have accidentally injected **Doxorubicin Hydrochloride**. Surgery can be required if the exposure is significant and medical action is not taken promptly. b. Contaminated skin should be washed with copious amounts of soap and water. c. Contaminated eyes and mucous membranes should be irrigated using normal saline or water. 2. Notify the supervisor, if immediately available. Supervisor to fill out an online accident/incident for employees or for students/contractors/visitors depending on the role of the person at the time of the exposure incident. Both forms are available at www.ehs.utoronto.ca. 3. Seek medical attention as soon as possible. 4. If in doubt, call EHS Occupational Hygiene & Safety at 416-978-4467 to determine further steps.
EMERGENCY RESPONSE	**In the event of a spill:**
Small Spill	1. Only employees trained in the handling of spills of the chemical should clean up spills. 2. Wear appropriate PPE as per preparation above. 3. If a spill occurs occurs on linings and underpads place them in a chemical hazardous waste bag. 4. If a liquid spill occurs on an unlined surface, clean the area with plastic-backed pads to prevent contamination of gloves. The area should be washed with detergent, rinsed with water and dried with pads. Then the washing process should be repeated a second time. 5. If a solid spill occurs on an unlined surface, cover the spill with disposable towel dampened with a detergent/water solution. Collect the wetted solid and place carefully in a hazardous waste bag. 6. Discard contaminated linings, underpads and materials in hazardous waste bags. 7. If in doubt, call EHS Environmental Protection Services at 416-978-7000.
Large Spill	1. Evacuate people from the immediate area 2. During business hours, call EHS Environmental Protection Services at 416-978-7000. 3. During off-hours, contact the Campus Police.

Further Infromation/References	1. Doxoorubicin, National Library of Medicine HSDB Database entry, accessed June 2012, http://toxnet.nlm.nih.gov/cgi-bin/sis/search/a?dbs+hsdb:@term+@DOCNO+3070 2. J van Asperen, O van Tellingen, F Tijssen, AH Schinkel and JH Beijnen,Increased accumulation of doxorubicin and doxorubicinol in cardiac tissue of mice lacking mdr1a P-glycoprotein, British Journal of Cancer (1999) 79(1), 108–113. 3. Doxorubicin Hydrochloride MSDS, Sigma Aldrich, revision date April 23/2012, accessed June 2012. 4. Mariana C. Castells, Nichole M. Tennant, David E. Sloane, F. Ida Hsu, Nora A. Barrett, David I. Hong, Tanya M. Laidlaw, Henry J. Legere, Samridhi N. Nallamshetty, Ross I. Palis, Jayanti J. Rao, Suzanne T. Berlin, Susana M. Campos, and Ursula A. Matulonis. Hypersensitivity reactions to chemotherapy: Outcomes and safety of rapid desensitization in 413 cases, J ALLERGY CLIN IMMUNOL VOLUME 122, NUMBER 3 5. Ijeoma F. Uchegbu, John A. Double, John A. Turton, Alexander T. Florence. Distribution, Metabolism and Tumoricidal Activity of Doxorubicin Administered in Sorbitan Monostearate Niosomes in the Mouse. Pharmaceutical Research, Vol. 12, No. 7, 1995 6. Georgy Hartmann, Vessela Vassileva, and Micheline Piquette-Miller. Impact of endotoxin-induced changes in p-glycoprotein expression on Disposition of doxorubicin in mice. Drug Metabolism and Disposition, 33:820–828, 2005. 7. Felix Kratz, André Warnecke. Finding the optimal balance: Challenges of improving conventional cancer chemotherapy using suitable combinations with nano-sized drug delivery systems. In Press, Journal of Controlled Release (2012). 8. Vural Kesik, Bulent Kurt, Turan Tunc, Yıldırım Karslioglu, E. Caglar Citak, Erol Kismet, Vedat Koseoglu. Melatonin Ameliorates Doxorubicin-induced Skin Necrosis in Rats. Annals of Plastic Surgery 2010;65: 250–253.