

Tel-Aviv University –Safety Unit

Standard Operating Procedure for Fluorouracil in Animals

1. Health hazards	<p>Fluorouracil or 5-FU (trademarked as Aduvicol (IV), Carac (topical), Efudex and Efudix (topical)) is a drug that is a pyrimidine analog which is used in the treatment of cancer. It is used to treat many types of cancer including, breast cancer, head and neck cancers, anal cancer, stomach cancer, colon cancer and some skin cancers.</p> <p>Fluorouracil is part of a group of chemotherapy drugs known as anti-metabolites. Anti-metabolites are similar to normal body molecules but they have a slightly different structure. Antimetabolite drugs work by inhibiting essential biosynthetic processes, or by being incorporated into macromolecules, such as DNA and RNA, and inhibiting their normal function. The 5-fluorouracil (5-FU) does both.</p> <p>5-Fluorouracil is combustible when exposed to high temperatures and is reactive to oxidizers such as bleach.</p> <p>*Pregnant women should not be exposed to or handle this cytotoxic in any form - May damage fertility or the unborn child - May cause genetic defects.*</p>
2. Designated Area	ABSL-2 facility.
3. Training	Hazardous cytotoxic training and training on this SOP is required before working with Fluorouracil. This should include but is not limited to reviewing the MSDS, training on the physical hazards of the cytotoxics, symptoms of exposure, appropriate work practices, and proper use of PPE.
4. Personal Protective Equipment (PPE)	<p>Double nitrile gloves or compatible cytotoxic-resistant gloves, Cytotoxic safety goggles, Lab coat and mask. Appropriate PPE should also be used for lower arms such as sleeve covers or securing gloves over the sleeves of laboratory coat. <i>Pregnant women should not be exposed to or handle this cytotoxic in any form.</i></p> <p>There are no established safe levels of exposure to cytotoxic drugs. Medical opinion is that even small quantities of cytotoxic drugs and their metabolites should be avoided as much as possible.</p>

	<p>The safest approach therefore is to reduce occupational exposure to levels as low as reasonably achievable.</p>
<p>5.General . Precautions for Animal Use</p>	<p>The main routes of exposure to cytotoxic drugs are through the inhalation of drug particles or aerosols, skin absorption, inadvertent ingestion through contact with contaminated food or cigarettes, and needle stick injuries .</p> <p>Exposure may occur during preparation and administration of the drugs, handling of body fluids from animals receiving cytotoxic drugs, handling and disposal of cytotoxic wastes and related trace contaminated material, and transportation of cytotoxic drugs. Some cytotoxic drugs have a direct irritant effect on the mucous membranes, eyes and skin.</p> <p>Spills onto skin surfaces that have cuts or abrasions and punctures of the skin with a contaminated needle or broken glass can lead to severe soft tissue injury. They should be treated immediately and observed for potential problems.</p> <p>Tools (as, syringe, blades and safety needles where possible) should be adapted for BSL-2. Have a sharps container in close vicinity.</p> <p>Animals should be restrained or anesthetized during injection.</p> <p>Fluorouracil may be excreted by the animals within the first 72 hours post injection therefore the lab must change the bedding 72 hours after administration.</p> <p>5-Fluorouracil can be absorbed through the skin- May cause an allergic skin reaction, or skin irritation.</p> <p>Toxic if swallowed. May cause allergy or asthma symptoms or breathing difficulties if inhaled, may cause respiratory irritation.</p> <p>Causes serious eye irritation -</p>
<p>6. Environmental / Ventilation Controls</p>	<p>The preparation of Fluorouracil including reconstitution, weighing, and diluting should be performed in a fume hood or biological safety cabinet (class II Type B). Work should be done over absorbent pads.</p> <p>Following preparation of Fluorouracil, the work area should be thoroughly cleaned with soap and water or with virusolve.</p> <p>Work should be conducted in ABSL-2 facility, over absorbent pads in a class II type A1</p>

	or A2 biological cabinet.
<p>5. Special Handling Procedures & Storage Requirements</p>	<p>Handling: Fluorouracil should be handled in containment and done over absorbent pads.</p> <p>Any visible contamination or spills should be cleaned with virusolve and then washed with water. Any wipes contaminated with Fluorouracil must be disposed as Cytotoxic hazardous waste.</p> <p>Utilize safe sharps procedures (i.e. sharps container in the immediate vicinity, Leurlock syringes are recommended). The fume hood or other approved containment must be cleaned upon completion of tasks.</p> <p>Any laboratory equipment or surfaces that have come in contact with Fluorouracil must be disposed of (cytotoxic cytotoxic waste) or decontaminated (wipe with virusolve follow by water soaked paper towels) Non-porous material (e.g. glassware) can be decontaminated by soaking in virusolve for 24 hours.</p> <p>Upon completion, soak all surgical equipment in 80%(v/v) ethanol for at least one hour before washing with soap and water and autoclaving.</p> <p>When transporting Fluorouracil, the vials should be placed in secondary, sealed, plastic, labeled, non-breakable containers.</p> <p>All equipment must be decontaminated prior to removal from the room housing the infected animals.</p> <p>DO NOT use bleach for disinfection of work surfaces where 5-Fluorouracil has been used.</p> <p>Hands must be washed upon exiting animal room.</p>
<p>8. Precautions for Animal Use</p>	<p>No recapping needles. Have a sharps container in close vicinity. Animals should be restrained or anesthetized during injection. Once Fluorouracil is injected, animals , animal waste and cages are considered hazardous for a minimum of 72 hours.</p> <p>Approximately 7-20% of the drug is excreted unchanged in the urine, 90% of it within the first hour after treatment. The remaining drug is metabolized to CO₂, urea, and α-fluoro-β-alanine, which are inactive and non-hazardous. Because 90% of the drug is excreted and accounted for in the first 24 hours, cages are changed after 72 hours and animals can be housed in conventional caging provided there is no other Biohazardous agent used.</p> <p>Hands must be washed upon exiting animal room.</p>

7. Animal handling practices

1. Animals must be housed in **filter top cages** marked as biohazards (including the name of the pathogen/biohazard). Handling the cages (including bedding) will be done only by the researchers.

2. Use a class II Biological Safety Cabinet at all times (especially during injection or any surgical procedure), when performing work on these animals and/or when moving animals from dirty to clean cages.

3. Injecting animals with Fluorouracil: Animals will be injected IP with Fluorouracil within Class II Biosafety cabinet or designated cytotoxic fume hood.

All needles will be disposed of in sharps container – do not recap or bend needles.

4. Infected animals considered hazardous for a minimum of 72 hours after each administration of Fluorouracil; take precautions to avoid the creation of aerosols when changing or washing cages, or cleaning the room.

A respirator is recommended for personnel that are immunocompromised and for healthy personnel if work is done outside the ventilated cabinet.

5. Care should be taken to avoid exposure to bedding dust when handling exposed animals and their waste materials during this time.

6. Dead animals must be placed in primary plastic bags, which are then placed in biosafety bags for infectious waste incineration.

7. All surfaces and racks that may be contaminated will be decontaminated with virusolve followed by water ASAP.

8. The first cage change after each drug administration is to be done no sooner than 72 hours after the administration. The bedding is considered contaminated and requires special handling.

When changing cages, use the following technique:

- Transfer the animals to clean cages .
- Decontaminate the used cages with virusolve.
- Insert the used cages in a plastic bag .
- Twist the ends of full bags, and seal with tape. Label with wide tape or other type of label marked “toxin- Fluorouracil.
- Transport the bags of cages to a HEPA filtered dumping station that draws air away from the use (or BSC Type II), it is recommended to use a fume hood.

	<ul style="list-style-type: none"> • If local ventilation controls are not available for opening cages or dumping bedding, an N-99 respirator and safety goggles must be worn. • All contaminated bedding will be labeled as hazardous materials and handled accordingly : incinerated or placed in cytotoxic waste bags for disposal. • After this first cage change there is no need for further special precautions to be taken regarding the animals or the cages as long as the animals have not received any more Fluorouracil. • Use virusolve to decontaminate the cages, then put in plastic bags (marked “toxin- Fluorouracil) and sealed for transport to the washroom. • In the washroom ,cages should be unloaded from the bags with the appropriate PPE as mentioned above and run through the cage wash in the conventional manner. Note- cage wash personnel that meet the criteria for extra precautions above (pregnant exc.) should take extra precautions (additional PPE) when handling cages that may have Fluorouracil contamination.
<p>9. Spill and Accident Procedures</p>	<ol style="list-style-type: none"> 1. Spills must be cleaned immediately by properly protected trained personnel wearing a gown, goggles, two pairs of gloves (nitrile) and respirator mask covering the mouth and nose . 2. Minor Liquid Spills: should be cleaned immediately by personnel wearing a PPE. Use absorbent pads to wipe liquid. The spill area should then be cleaned thoroughly with virusolve (<i>allow at least 15 minutes</i>) and then wash the area with soap and water. Place waste in plastic bag and then in the cytotoxic waste container. 3. Powder/Major Spills: should be cleaned immediately by personnel wearing a PPE. For powder or major liquid spills outside of a fume hood or approved containment, personnel should be instructed to leave the laboratory and entrance should be restricted for at least 30 min. In addition to the above specified PPE, a respirator and safety goggles, should also be worn. Contain or absorb spill with absorbent material, it may be helpful to lightly wet the absorbent material. Wipe the area with virusolve 1-2 times (<i>allow at least 15 minutes</i>) and then wash the area with soap and water.

	<p>Collect and place waste in plastic bag and then in the cytotoxic waste container.</p> <p><u>Exposure:</u></p> <ol style="list-style-type: none"> 4. In case of skin contact or injection with Fluorouracil, wash the affected area with soap and water for at least 15 minutes. Consult with Employee Health Center. 5. For eye exposure, flush with water for at least 15 minutes. Consult with Employee Health Center, Report incident to supervisor. Supervisor reports the accident/injury to the Biosafety Unit.
<p>10. Waste Disposal</p>	<p>Dispose all waste material in the appropriate cytotoxic waste container.</p> <p>Unused solutions of Fluorouracil and contaminated solid waste will be disposed of as hazardous cytotoxic material.</p>
<p>I hereby confirm that I have read the SOP (Standard Operating Procedure) for Working with Fluorouracil in Animals, and agree to follow these procedures.</p>	
<p>Name:</p>	<p>Title:</p>
<p>Signature:</p>	<p>Date:</p>

Dr. Esther Michael - Biological Safety Office, : 640-9966