INDIANA UNIVERSITY

OFFICE OF THE VICE PRESIDENT
FOR RESEARCH

Institutional Animal Care and Use Committee (IACUC)

IACUC Policy for Dose Volumes in Laboratory Animals

FULL POLICY CONTENTS

Effective: May 23, 2017
Last Updated: February 28, 2022

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Policy Owner:
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Policy Statement

This document is designed to provide information about the volume or amount of a substance to be given to laboratory animals depending on route of administration. All procedures must be approved by the Institutional Animal Care and Use Committee (IACUC). The method of administration to be performed, the intervals between substance administration, and the volume to be given must be listed in the approved protocol specific to each study. Contact the LAR office (x5-2356) or email lar@iu.edu if training is needed on these techniques.

Reason for Policy

In the conduct of studies utilizing laboratory animals, various compounds or substances may be administered to the animal to see its response to the treatment. Table 1 provides ideal maximum dose volumes to be used by species and route (the bolded numbers). The guidelines also give an indication of the maximum volume that may be administered to an animal by route. If dosing beyond the recommended volume up to

the maximum volume, justification for using the higher dose and IACUC approval must be obtained before dosing.

Procedures

Abbreviations Used in Tables 1 and 2:

Orally (**PO**)- per os- given by mouth alone or in food or water.
Intragastric- given via a gastric gavage needle for rodents or stomach tube for larger species.
Intravenous (**IV**)- administered through a blood vessel directly into the blood stream.
Subcutaneous (**SC**)- administered under the skin.
Intradermal (**ID**)- administered directly into the dermal layer of skin.
Intramuscular (**IM**)- administered into the muscle.
Intraperitoneal (**IP**)- administered into the abdomen for exposure by the peritoneal cavity and lymphatic system.
Intranasal (**IN**)- administered into the nose.
Transcorneal- administered onto the eye.
Intraocular- administered into the eye.
Intracerebral (or other structures of the brain)- administered into the brain.
Epidural- administered into the space surrounding the dura mater.
Intrathecal- administered into the space surrounding the spinal cord (subarachnoid space).
Intraosseous- administered into the bone marrow cavity.
Inhalation- administered into the lungs.
Enteral- administered into the mouth, in the diet or food, orogastric or nasogastric gavage, per rectum.
Intratracheal (**IT**)- administered into the trachea.
Topical (epicutaneous)- Application of substance directly to the skin for topical effect.
Transdermal (percutaneous)- application of substances directly to the skin for systemic effect.

Table 1: Recommended locations for administration of substances by listed route of administration

	Mouse, Rat, Hamster, Voles	**Rabbit**
PO gavage	Oral, intragastric (gavage needle)	Oral, intragastric (nasopharyngeal tube)
IV	Tail, saphenous	Ear, cephalic
IP	Lower right abdominal quadrant	Not used
SC	Intrascapular, neck, shoulders, flank, lower back	Intrascapular, neck, shoulders, flank
IM	Not recommended	Triceps, quadriceps, dorsal lumbar, semimembranosus, semitendinosus
IN*	Nose	Nose
IT*	Trachea	Trachea
ID	Skin	Skin

*Usually requires sedation or anesthesia for administration

Please use the following volumes (in bold) for the maximum dose volumes and routes of administration.

Table 2: Maximum Volumes to be used for dosing of species by route of administration
All volumes are ml/kg unless otherwise noted

Species	PO gavage/intragastric	IV* (bolus)	IV** (ml/kg/h)	IP@	SC@	IM***@	IN*** IT***	ID***
Mouse	**10** (20)	**5** (20)	**1** (4)	**10** (20)	**5** (10)	**0.03** (0.05)$	**0.03-0.05**[a]	**0.05** (0.1)
Rat	**10** (20)	**5** (20)	**1 or 2** (4)	**10** (20)	**5** (10)	**0.05** (0.1)$	**0.03-0.05**[a]	**0.05** (0.1)
Hamster	**10** (20)	**5** (10)	2-4	**10** (20)	**1-5** (10)	**0.05** (0.1)$	**0.03-0.05**	**0.05** (0.1)
Guinea pig	**10** (20)	**1** (5)	2-4	**10** (20)	**5** (10)	**0.05** (0.1)	**0.03-0.05** (0.2)	**0.05** (0.1)
Rabbit	**10** (20)	**1** (5)	**2-4**	Not recommended	**2.5** (10)	**0.05** (0.5)	**0.2** (0.5)	**0.05** (0.1)

Ideal maximum dose volumes are bolded, absolute maximum dose volumes are (smaller in parenthesis)

*An IV bolus injection is typically dosed in less than 1 min.

**Continuous IV infusions are typically dosed over 3-10 minutes. Solution properties such as tonicity, pH, etc. must be taken into account when approaching the volume limits or determining the volume to be infused IV. The recommended working range for pH is 4.5-8.0. The order of degree of tolerance of pH for different dosing routes is oral>intravenous>intramuscular>subcutaneous>intraperitoneal. Animal health must also be taken into consideration, such as kidney function and cardiovascular function. These systems must be normal to handle increased fluid volume.

***The values listed in this column are the total volume in ml per site, total of 2 sites/day.

@When administering a solution IP, SC, or IM, the viscosity, concentration, tonicity and pH of the solution need to be taken into account.

$IM dosing in mice, rats, hamsters and voles is NOT recommended.

[a]In mice, volumes less than 35µl have been reported to be distributed primarily to the upper respiratory tract, whereas a 50 µl volume was predominantly deposited in the lower respiratory tract.

1. The first dose listed in **bold** is the **ideal maximum dose volume**. However, the dose can range up to the second value given in parentheses with justification. Volumes up to or less than the ideal dose volume should be used. Dose volumes should be the minimum compatible with compound formulation and accuracy of administration. **If dose volumes are between the ideal and maximum volumes, this needs to be noted in the protocol along with justification for the higher dose to be included in the protocol and approved by the IACUC.**
2. **The physiochemical properties of the substance to be administered will markedly affect the volumes that are tolerated.** For example, lower volumes than those listed in the table may need to be used for highly viscous or irritating substances.
3. If dosing parenterally toward the maximum quantities listed, ensure that your dosing solution is isotonic, close to physiologic pH (6.8-7.2), stable, not viscous, has appropriate osmolality, biocompatibility, sterility, and does not contain quantities of diluent that could be toxic when dosed. Dosing solutions given parenterally can have a **pH range of 4.5-8**, but when dosing intravascularly should be administered through a central (jugular v., femoral v., etc.) rather than a peripheral (cephalic v., saphenous v.) vessel. When substances are given by IV infusion, the volume should not exceed 5% of the circulating blood volume over 2 hours or 4 ml/kg/h.
4. The **maximum recommended injection volume** for a dosing solution that is given **rapidly IV is 1 ml/kg body weight** for most laboratory animal species. If dosing a larger quantity of solution is necessary, infusion of the dose IV over greater than 5 minutes should be considered and should not exceed 10% of the circulating blood volume over 2 hours. Rats may be given daily IV injections of isotonic saline at up to 80 ml/kg at 1 ml/min. for 4 days. Intraarterial administration should be avoided since it can result in blindness, cerebrovascular stroke, permanent motor deficits and limb gangrene.
5. When administering by the IV route, asepsis is critical both with the solution and preparation of the site of administration. Extravascular delivery of compounds that are irritating may result in local soft tissue damage, infection, pain and tissue

sloughing. In all species**, injection of compounds that contain particulate material or are of low pH** that precipitate when mixed with blood can result in vascular occlusion, emboli, and thrombosis of local and distant capillary beds such as those found in ears, tail, toes, or lungs.

6. When administering large volumes subcutaneously, 2-3 sites of administration should be used.
7. **No more than 2 IM sites should be used per day.** In small rodents (mice, voles and hamsters) the IM route is not preferred because of the mouse's small muscle mass and possibility for side effects like paresis, paralysis, muscle necrosis, localized muscle sloughing and self-biting of injected areas.
8. The anatomy of the pharynx in the rabbit and guinea pig species makes gavaging difficult. Nasogastric tubes 3-8 French soft rubber pediatric feeding tubes can be used instead. Please contact LAR to learn or obtain assistance with this technique.
9. The **smallest volume possible** is recommended for the oral route of administration, 5 ml/kg or less should be administered via the oral or gastric route to avoid gastric distension especially in species unable to vomit like rodents. Limitations of oral dosing may include slower onset of action compared with parenteral delivery, potentially significant first-pass effect by the liver resulting in reduced efficacy, lack of absorption due to chemical polarity or interference with absorption by ingesta, poor compliance with voluntary consumption because of poor palatability or local irritation, lack of systemic absorption from the digestive tract, degradation of substances by digestive enzymes and acid, and inability to use this route in animals that are unconscious or have clinically significant diarrhea or emesis.
10. The intraperitoneal (IP) route of administration is not used in rabbits.
11. All substances given **parenterally (not by the oral route) must be sterile**. If preparation is not a commercially manufactured solution, it should be mixed in a laminar flow hood or biosafety cabinet and **filtered through a 0.2 µm filter**.
12. If a route or species you are considering is NOT on this list, please consult the veterinary staff.
13. In all cases, consult the veterinary staff if you have questions about your dosing material, dose route, or technique.
14. The following routes of administration are acceptable but there are no current recommendations on dose volumes. Information may be obtained from the literature or by contacting LAR veterinarians- epicutaneous/transcutaneous/topical/percutaneous, transcorneal, intraocular, intracerebral, epidural, intrathecal, intraosseous, inhalation, enteral.

Sanctions

Failure to comply with IACUC policies may result in noncompliance reports to the Institutional Official, the Office of Laboratory Animal Welfare (OLAW), the U. S. Department of Agriculture (USDA), and/or the suspension of animal use privileges. In addition, the availability of sponsored research funds may be affected when an investigator is found to be in violation of these policies.

Additional Contacts

Subject	*Contact*	*Phone*	*Email*

Veterinary Concerns	LAR Veterinarian	855-2356	lar@indiana.edu
Policy	IACUC Manager	855-5138	biacuc@indiana.edu

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