Distribution Agreement

In presenting this thesis or dissertation as a partial fulfillment of the requirements for an advanced degree from Emory University, I hereby grant to Emory University and its agents the non-exclusive license to archive, make accessible, and display my thesis or dissertation in whole or in part in all forms of media, now or hereafter known, including display on the world wide web. I understand that I may select some access restrictions as part of the online submission of this thesis or dissertation. I retain all ownership rights to the copyright of the thesis or dissertation. I also retain the right to use in future works (such as articles or books) all or part of this thesis or dissertation.

Signature:

_____ _____

Leslie M. Hubble Date

The Development and Implementation of a Chemical Banding Program to Minimize Worker Risk Associated with the Use of Chemicals in Research Animals

By

Leslie M. Hubble
Master of Public Health

Environmental Health

_____

Gary W. Miller, Ph.D.
Committee Chair

_____

Paige Tolbert, Ph.D.
Committee Member

The Development and Implementation of a Chemical Banding Program to Minimize Worker Risk Associated with the Use of Chemicals in Research Animals

By

Leslie M. Hubble

B.S.E.H.
University of Georgia
2002

Thesis Committee Chair: Gary W. Miller, Ph.D.

An abstract of
A thesis submitted to the Faculty of the
Rollins School of Public Health of Emory University
in partial fulfillment of the requirements for the degree of
Master of Public Health
in Environmental Health
2010

Abstract

The Development and Implementation of a Chemical Banding Program to Minimize Worker Risk Associated with the Use of Chemicals in Research Animals

By Leslie M. Hubble

Chemical and pharmaceutical industries have led the way in chemical risk classification systems also known as chemical banding systems. Industry primarily uses chemical banding for quantitative exposure monitoring. Chemical industries can approach chemical risk management in this fashion, because they typically work with a finite number of chemicals which often have established occupational exposure limits. In contrast, scientific research at a University with an academic medical center can involve thousands of chemicals, many with unknown exposure limits and unknown monitoring methods. The frequent use of chemicals for this research can increase the relative risk and increases the need for qualitative chemical risk assessment and mitigation. Exposure risk becomes more difficult to assess, quantify, and control when these chemical are used animal research. The chemicals used in animal research are typically toxic, carcinogenic, etc. and are often used to induce or treat adverse health outcomes.

The following paper outlines a program that was designed and implemented in conjunction with Emory University's Environmental Health and Safety Office (EHSO) and Division of Animal Resources (DAR) to meet the intent of Occupational Health and Safety Administration (OSHA) standards and the recommendations of Association for Assessment and Accreditation of Laboratory Animal Care International (AAALAC). This Chemical Banding program establishes a qualitative risk assessment method for controlling risk in the animal facility associated with chemical research in animals. The program establishes appropriate exposure controls to match each level of presumed risk. The program has been implemented with such control measures as protocol approval, personnel training, and hazard signage to identify areas where chemicals are being administered to animals.

Chemicals of unknown toxicity and nanomaterials present a challenge as the risk associated with these materials is not well characterized. Since quantifying this risk is resource intensive in terms of time and cost; the risk assessment and control method presented in this document is a good foundation for mitigating the potential chemical risk to workers in animal research.

The Development and Implementation of a Chemical Banding Program to Minimize Worker Risk Associated with the Use of Chemicals in Research Animals

By

Leslie M. Hubble

B.S.E.H.
University of Georgia
2002

Thesis Committee Chair: Gary W. Miller, Ph.D.

A thesis submitted to the Faculty of the
Rollins School of Public Health of Emory University
in partial fulfillment of the requirements for the degree of
Master of Public Health
in Environmental Health
2010

Acknowledgements

This thesis would not have been possible without the valuable professional input of:
Gary W. Miller, Ph.D.
Scott Thomaston, MS, MPH
Michael J. Huerkamp, DVM, DACLAM
Vanessa Lee, DVM, DACLAM

I am forever grateful to my family for their full support while attending RSPH.

Table of Contents

List of Tables and Figures

List of Appendices

Introduction

Potential worker risk

In the course of conducting research, many principal investigators employ the use of hazardous chemicals in animal models to induce disease, treat disease, and/or inhibit certain physiological systems in an attempt to understand and develop cures for a variety of diseases and pathologies. Examples of elicited effects include the induction or treatment of: cancer, nervous system disorders, or other conditions such as diabetes. Other effects involve immune system suppression, often used in transplantation research. While the doses administered to these animals are small relative to typical human doses, these chemicals are often toxic, carcinogenic, teratogenic, or have the ability to induce adverse health effects in animals as well as humans. Because these chemicals are being intentionally used to produce or treat adverse health effects in animals, one should assume that these chemicals present a certain amount of risk to workers. Many investigators add complexity to assessing worker risk by using newly developed chemicals for which toxicity has not been fully studied. Administration of hazardous chemicals to animals raises various concerns for the health and safety of the researchers and animal care staff that work with or around these animals.

There is an obvious direct risk to researchers and laboratory personnel at the time of administration. However, various control measures can be employed to reduce or eliminate this risk. A combination of risk reduction controls can be employed to adequately protect laboratory workers before and during administration. These controls include engineering controls (i.e. a chemical fume hood, ventilation), administrative controls (i.e. training, procedures), and personal protective equipment (i.e. goggle, gloves, and lab coat) appropriate for use with a particular chemical. The less understood risk to workers arises following

chemical administration to an animal. It is often difficult to find adequate pharmacokinetic data to fully understand the risk post administration. Parent chemical compounds and/or their metabolites can be excreted through urine, feces, sputum, skin, and exhalation of research animals all of which present risk to workers.

The challenge

Chemical risks to workers must be mitigated under Occupational Safety and Health Administration (OSHA) regulations.[1,2] Accrediting organizations such as the Association for Assessment and Accreditation of Laboratory Animal Care International (AAALAC) strongly encourage risk mitigation.[3] The Guide for the Care and Use of Laboratory Animals states generally that "In selecting safeguards for animal experimentation with hazardous agents, careful attention should be given to procedures for animal care and housing, storage and disbursement of the agents, dose preparation and administration, body-fluid and tissue handling, waste and carcass disposal, and personal protection." [3] The Guide does not provide specific guidance on how these safeguards should be assessed for chemically contaminated animals. A major risk assessment problem arises because the risk to workers from chemically contaminated animals is not as straightforward or as easy to manage as direct chemical exposure risk. In order to fully assess the risk to the worker post animal administration, one would have to conduct chemical exposure monitoring in consideration of the potential health effects from the parent chemical(s) and there metabolites. In addition to being time and cost prohibitive, exposure monitoring would have to be conducted for multiple chemicals and all of their metabolites. Most of these chemicals would not have appropriate monitoring methods or could be below the detection limits. Due to the

problems associated with quantifying this risk, one must use a qualitative risk assessment matrix combined with appropriate exposure controls.

Chemical banding

Chemical and pharmaceutical industries have led the way in chemical risk classification systems, also known as chemical banding systems.[4] Industry primarily bases chemical banding on quantitative exposure monitoring. Chemical industries can approach chemical risk management in this fashion for two primary reasons. First, they typically work with a finite number of chemicals which often have established occupational exposure limits and detection methods. Second, industry rarely deals with chemically contaminated animals. In contrast, scientific research can involve thousands of chemicals, many with unknown exposure limits, monitoring methods, and toxicity.

There is an obvious need for a chemical banding system that reaches beyond industry and is based on qualitative risk. The Centers for Disease Control and Prevention's (CDC) Office of Environmental Health and Safety (OHS) submitted a proposal in 2004 for a system that would have established Chemical Safety Levels, the equivalent of Biological Safety Levels as described in *Biosafety in Microbiological and Biomedical Laboratories (BMBL)* for chemical safety, including the use of chemicals in animals.[5,6] The proposal has not been implemented at this time. More recently, the National Institute for Occupational Health and Safety (NIOSH) submitted a literature review and analysis of the need for a chemical banding system. NIOSH acknowledges that "One such emerging strategy has gained increasing attention among safety and health practitioners: a qualitative risk characterization and management strategy, also referred to as control banding (CB)."[7] Research institutions

need set standards of practice and control methods for the use of chemicals in laboratories and associated animal research facilities.

Applicability at a research university

Large research universities, particularly academic medical centers, have a very diverse scope of research. Research at Emory extends from the basics of cellular function to searching for cures to life threatening diseases such cancer and amyotrophic lateral sclerosis. In many research protocols, it becomes necessary to employ the use of hazardous chemicals in animals. It becomes a difficult task to track all of the animal research involving chemicals. Since many of the chemicals are being used in animal models to determine the potential to progress into human clinical trials, the toxicities are often unknown or not fully understood. The primary goal of this project is to develop a chemical banding system that is functional across the university in minimizing worker risk, but more specifically addresses risk to animal researchers and animal facility workers.

The development of this risk assessment program and the associated controls were beyond the typical scope of duties and responsibilities of an Environmental Compliance Specialist. The design of the Chemical Banding program required much research and review of the literature to ensure that the program was based on appropriate chemical risk criteria and exposure controls. The planning and implementation of the program occurred gradually over a two year period to ensure proper function for the University.

Program Design

The Chemical Safety program at Emory, in conjunction with Animal Resources, was tasked to develop a qualitative risk assessment matrix. The matrix and the associated risk reduction controls were agreed upon through a committee of colleagues from the Environmental Health and Safety Office (EHSO), Division of Animal Resources (DAR), Institutional Animal Care and Use Committee (IACUC), and a Principal Investigator in toxicology. The matrix assigns chemicals to risk groups called Chemical Bands. These bands are based on a variety of criteria such as the toxicological properties and carcinogenic potential of the chemical. The risk matrix then assigns chemically contaminated animals to certain risk levels based on various criteria such as dose, route of administration, metabolism, and species. These risk levels, named Animal Control Levels (ACL), mandate particular controls for employees who work with or around these animals. It is important to note that the basic structure of the Chemical Bands can be used to assess and control risk in basic laboratory bench research. However, this project concentrates on the unique factors that affect animal research using hazardous chemicals, and the subsequent management of husbandry and clinical care of these animals.

Developing Chemical Banding Levels

Each chemical is first classified into a Chemical Band based on the toxicological properties of the chemical. These bands are numbered 1, 2, 3, or 4 with increasing risk and controls as the numbers increase. A ranking of 1 applies to chemicals with the least potential for harm, and a ranking of four applies to chemicals with the greatest potential for harm. This numbering system was chosen to mirror the equivalent concept used with biological hazards outlined in the BMBL. The project captures a range of toxicological characteristics to ensure that chemicals were properly categorized by risk. Characteristics considered in the

Chemical Bands range from LD_{50} values, to carcinogenic potential, sensitization, teratogenic and mutagenic potential, and degree of regulatory control. Most chemicals used by researchers in animals possess more than one of these characteristics. Chemicals are ranked by their highest risk criteria. *See Table 1.*

Table 1: Chemical Banding Criteria

	Chemical Band			
Criterion	4	3	2	1
Toxicity Values (Non-human) [1,2]	• LD_{50} (oral rat) < 50 mg/kg • LD_{50} (dermal rabbit) < 200 mg/kg • LC_{50} (rat) < 2 ppm • Acute organ toxicity	• LD_{50} (oral rat) = 51 -500 mg/kg • LD_{50} (dermal rabbit) = 201 -1000 mg/kg • LC_{50} (rat) = 2 -200 ppm • Chronic organ toxicity	• LD_{50} (oral rat) = 500 -1000 mg/kg • LD_{50} (dermal rabbit) = 1000 - 2000 mg/kg • LC_{50} (rat) 200 – 2,000 ppm	• Considered non-toxic
Carcinogenicity [2-11]	• NTP Part A Carcinogen • IARC Group 1 Carcinogen • OSHA carcinogen • TD_{50}< 100 ug/kg/day	• NTP Part B Carcinogen • IARC Group 2A or 2B Carcinogen • TD_{50}= 100 ug –10 g/kg/day	• IARC Group 3 Carcinogen • TD_{50}= 10 – 100 g/kg/day	• IARC Group 4 • Does not possess carcinogenic properties
Teratogenicity & Mutagenicity [1,2]	• Known or suspected human teratogen or mutagen	• Known animal teratogen or mutagen	• Suspected animal teratogen or mutagen	• Not known to be a mutagen or teratogen
Regulatory Oversight [12-14]	• A U.S. EPA PIC Banned Pesticide • RCRA P-listed	• A U.S. EPA PIC Severely Restricted or SHPF Pesticide • RCRA U-listed	• N/A	• N/A
Other Health Effects [1,2]	• Causes an irreversible illness in humans • Acetyl cholinesterase inhibitors • Strong sensitizer	• Weak sensitizer • Strong irritant • Causes a severe, but reversible illness in humans	• Weak irritant	• N/A
Drug Classes	• Chemotherapeutic	• Immuno-suppressant	• Anesthetics	• Standard of care medication

Laboratory Practices Associated with Each Chemical Band

Each chemical band is assigned to a set of laboratory practices to help minimize the risk to workers leading up to and including chemical administration. These practices can be used for general laboratory chemical safety controls as well.

Table 2: Chemical Bands and Associated Laboratory Exposure Controls[1,2,5,15]

Chemical Band (CB)	Exposure Controls
1	• Safety glasses, appropriate gloves, and lab coats must be worn while working. • Chemicals may be used on the bench top. However, a Chemical Fume Hood may be needed for use with volatile chemicals. • Chemicals must be stored safely on a sturdy shelf or in an appropriate cabinet and kept off the floor. • Chemicals must be stored by compatibility. • Eyewash and sink must be available. • MSDSs must be available. • Chemicals must be labeled with the chemical name and hazards.
2	Use lab practices for Chemical Band 1 at a minimum plus: • A Chemical Fume Hood must be used for volatile chemicals and fine powders. • Emergency shower must be available in the lab or hallway.
3	Use lab practices for Chemical Bands 1 and 2 at a minimum plus: • A Chemical Protocol is required. • Safety goggles must be worn while working. • Chemicals must be used in a Chemical Fume Hood whenever possible. When not possible, the Chemical Safety Officer must be consulted to ensure that lab practices minimize the potential for chemical exposure.

	• A PPE assessment must be performed to determine if more protective PPE should be worn.
4	Use lab practices for Chemical Bands 1-3 at a minimum plus: • Chemicals must be used in a Chemical Fume Hood, Chemical Glove Box, or with appropriate respiratory protection. • Chemicals must be stored in a secure area (i.e. in a locked lab room). • The area where the chemical is used must be appropriately labeled (i.e. label the Chemical Fume Hood).

Transforming Chemicals Bands into Animal Control Levels

Once a particular chemical is classified into a Chemical Band, one must then consider how the chemical will be used in animal research. During the risk evaluation to assign a control level, a number of questions must be answered to determine the potential risk to workers following chemical administration to an animal. The answers to the following questions aid in determining the final risk group which is called an Animal Control Level (ACL).

1. Is the chemical itself inside the animal cage?

   If the chemical itself in the animal cage, one must consider both the hazards of the parent chemical and any metabolites. This circumstance most often occurs from the administration of the chemical through the animal's food or water. One must also consider that the concentrations of the chemical(s) will be much greater when administered in this manner. A hazardous waste stream determination must be conducted on the food or water.

2. What is the administered dose?

Dose is an important piece of information needed to assess the potential for worker exposure.

3. What is the route of administration?

   Examples of routes of administration include: intraperitoneal, oral, oral gavage, intracranial, intraocular, etc. Chemicals injected into the brain or eyes are rarely excreted from the animal. Other methods of administration will more likely lead to excretion of the chemical and its metabolites.

4. What species of animal is the researcher working with?

   Metabolism, absorption, distribution, and excretion of a particular chemical may vary across species.

5. What are the metabolites and are they more or less toxic than the parent compound?

   Chemicals may have metabolites that are either more toxic or less toxic than the parent chemical.

6. How is the chemical distributed in that particular species of animal?

   Distribution will affect metabolism and excretion.

7. Are the metabolites excreted and by what route?

   Chemicals may be excreted through urine, feces, sputum, respiration, sweat, etc.

8. What is the rate of metabolism or biological half-life in the body? What is the rate of excretion?

   These rates will affect how long the workers may be exposed. Rate of metabolism must be considered to determine appropriate husbandry methods. The rate of metabolism and excretion will relate to animal housing, cage changing cycles, and the length of time the animal is kept in an ACL.

9. Are there multiple chemicals being administered in the same animal?

Chemicals administered jointly may have synergistic or antagonistic effects. For example, the carcinogenic effects of etoposide and azoxymethane used in combination are worse than either one when used independently.

Exemption List

In the course of animal care and research, there is often a need to administer chemical agents that are beyond the intent of the research. Veterinarians use standard of care medications in the course of caring for an animal. Researchers will use anesthetics to perform surgery on an animal or may use fixatives to preserve the animal post mortem. For feasibility of program implementation, these 3 groups of chemicals are exempt when used for their intended purpose and in appropriate doses.

Table 3: Exemption Table

Exemption Category	Examples
Standard of care medications	Acetaminophen, Amiodarone, Aspirin, Heparin, Meloxicam, Prozac, Saline, Sodium bicarbonate
Anesthetics & Analgesics	Buprenorphine, Isoflurane, Ketamine, Telazol, Tricaine
Perfusion / tissue fixatives	Acrolein, Formalin, Formaldehyde, Glutaraldehyde, Paraformaldehyde

Designation of Animal Control Levels & Associated Controls

The combination of the chemical banding criteria, exposure controls, and the risk factors associated with chemical research in animals has been consolidation into a risk classification tool. This tool named the Chemical Banding Flowchart (*Figure 1*) assisted in the risk assessment process for each chemical. The flowchart, along with answers to the risk assessment questions above, correlates the chemical use with an Animal Control Level or

ACL numbered 1- 4. The ACL designation is then used in animal areas in a similar manner to Biosafety Levels (BSL).[5] ACL 1 has the least restrictive risk controls, and ACL 4 has the most restrictive controls. *Table 4* displays the exposure control measures that are implemented at each level. As with any risk assessment, there are potential exceptions to the controls outlined in *Table 4*.

Table 4: Animal Control Levels and Associated Controls[1,2,3,5,15]

Animal Control Level (ACL)	Exposure Controls
1	Standard signage and PPE required in animal resources areas.
2	Corresponding Lab Practices must be followed plus: • A Notice of Intent is required • Cages may be on a static rack based on hazard assessment • Entrance door(s) must be labeled to warn of the chemical hazard • Cages must be labeled to warn of the chemical hazard • Cage changes must occur in a Biological Safety Cabinet or a Cage Changing Station • Bedding may be managed as conventional waste • Standard PPE required • Materials Safety Data Sheets must be available • Chemical-Specific Training • Chemical-Specific guidelines
3	Animal Control 2 Practices and Corresponding Lab Practices must be followed plus: • Cages must be on a static rack • Cage changes must occur in a Biological Safety Cabinet • Bedding / excreta must be managed as contaminated and disposed of appropriately (use controls & send for incineration) until the chemical hazard is not longer present Minimum PPE required: nitrile gloves and gowns
4	Animal Control 2 & 3 Practices and Lab Practices 4 must be followed plus: • Animals must be isolated in their own room or animal bay • Dust-free bedding should be used or bedding should be moistened before disposal • Chemical administration should occur in fume hood, glove box, or with appropriate respiratory protection • Luer-lock syringes must be used for chemical injection(s) • PPE required: nitrile gloves, appropriate respiratory protection, shoe covers, and gowns • Double-gloving is highly recommended

Program Implementation

Chemical Protocols & Hazard Assessments

The Chemical Notice of Intent Guideline (*Appendix 1*) was developed to assist Principal Investigator in determining which chemicals require an approved protocol. When a Principal Investigator proposes to use a hazardous chemical in animals they are required to submit a Chemical Notice of Intent (NOI) form (*Appendix 2*). This NOI is reviewed by committee before the researcher is allowed to use hazardous chemicals in animal research. The NOI form requests the information required to determine the Animal Control Level. The Chemical Banding Flowchart (*Figure 1*) is then used as a tool to classify each chemical according to its use.

Once approved, the Chemical NOI is converted into a Chemical Protocol. Researchers must have an approved Chemical Protocol in order to use these chemicals under their IACUC protocol. An approved Chemical Protocol is a prerequisite for IACUC protocol approval. The Chemical Protocol must be reviewed annually or when the researcher needs to alter their current protocol through the submission of a Chemical Protocol Amendment or Renewal Form (*Appendix 3*). Annual review and approval presents an opportunity to ensure that the proper controls are in place and that all personnel have attended the appropriate training. Upon protocol approval, each Principal Investigator is provided with a completed Chemical Protocol Hazard Assessment and Approval Form (*Appendix 4*) which outlines which exposure controls must be used in the laboratory and in the animal research facility.

Training program

Protocols are required to list all personnel that will handle the chemical or handle animals contaminated with the chemical. The success of this project is dependent on having trained protocol personnel and animal care staff. The training also assists in compliance with OSHA regulations and AAALAC recommendations.[1,2,3] Therefore, all personnel assigned to ACL 2, 3, or 4 are required to attend Animal Chemical Safety Training in addition to basic Laboratory Safety Training or Chemical Hygiene Training. Chemical Protocols are not approved until all listed personnel have received Animal Chemical Safety Training.

Room Hazard Signage and Cage Cards

All rooms and cages assigned to ACL 2, 3, or 4 are posted with a hazard sign (*Figure 2*) to assist with compliance and adequately warn employees entering the area of the potential for chemical exposure.[1,2,3] The room hazard sign contains the following information: Animal Control Level, all chemicals and the associated hazards, the personal protective equipment required for both room entry and animal handling, and emergency contacts. The emergency contacts section of the sign includes the contact name and phone number for the Principal Investigator, Animal Resources, Environmental Health and Safety, and the Emory Police Department. The sign also notifies entrants that each cage containing chemically contaminated animals is individually labeled. The cages containing chemically contaminated animals are tagged with a cage card that contains the following information: Principal Investigator, Chemical Protocol Number, approved chemical(s) being used in that cage, the date of initial chemical administration, the date of final chemical administration, the date through which the bedding must be managed as contaminated, and the route of administration (*Figure 3).*

Animal Control Level 1

Chemicals assigned to ACL 1 have been evaluated through the Chemical Banding Flowchart and are determined to be relatively safe based on a variety of factors. The classification of ACL 1 indicated that there is little need for signage or addition training above and beyond regular Laboratory Safety Training which covers Chemical Hygiene and Hazard Communication standards.

Program Obstacles

Chemicals of unknown toxicity and nanomaterials

It is the nature of research that Principal Investigators often use newly developed chemicals and / or nanomaterials. Most of these compounds have yet to be studied for their toxicological properties. Therefore, assessing the risk associated with these chemicals is difficult and does not often fit within the chemical banding scheme.

It becomes imperative when researchers want to use a newly developed chemical to work closely with the researchers to understand the mechanism of action of the chemical and / or the elicited effects that they intend to get from use of that chemical. While toxicity values, carcinogenic potential and metabolic products may not be known, it is the practice to make conservative assumptions about the risk associated with the chemical based on the intent of use.

Toxicological properties of many nanomaterials are also not known and were not originally part of our risk assessment matrix. As the program has moved forward, it has become apparent that nanomaterials must be included in this process. Nanomaterials can be composed of anything from inert materials to highly toxic materials.

Disposal issues

During the course of implementing this program, the University began assessing the ability to compost animal bedding as part of a Sustainability program. The composting program is fully underway and is diverting around 22 tons of animal bedding per month from the landfill. A risk assessment was conducted to determine if the bedding that would normally go to landfill in the lowest Animal Control Levels could go to compost. There was concern that the University could face a publicity issue even though de minimus

concentrations of chemicals may be found in the animal bedding. The solution to this issue was to increase the Animal Control Level for particular chemicals to ensure that the bedding would be collected for incineration.

Chemical administration through food or water also presented another disposal issue. We conduct a waste stream determination to ensure that all food or water containing these research chemicals is properly collect and disposed. Food that is used to administer a chemical is collected and managed as hazardous waste when appropriate per Environmental Protection Agency regulations.[12] Water that is used as a method of administration of chemicals that are not appropriate for sewer disposal are collected and managed as hazardous or regulated waste to maintain compliance with local ordinance, state regulation, or the Clean Water Act.

Conclusions and Recommendations

The risk to workers associated with hazardous chemicals administered to research animals is often unknown and unquantifiable. Knowledge of chemical toxicity and the risks associated with animal administration are often unknown or not fully understood. Conservative risk estimates should be used specifically when dealing with new chemicals or chemical of unknown toxicity.

Worker risk exists in this setting and can be mitigated through qualitative risk assessment and controls. Risk to workers can be reduced through the banding classification of chemicals and implementation of exposure controls. This project implements the use of administrative controls such as protocol approvals, training, and signage to control and warn of the potential risk. Risk can also be reduced through the use of personal protective equipment which is provided in the animal research facilities and outlined on the Room Hazard Sign. Potential risk can be further reduced through engineering controls such as chemical fume hoods and biological safety cabinets.

Implementation of similar programs at other institutions requires a collaborative effort and the professional experience and knowledge of researchers and animal care staff at your institution. Animal protocols that intend to administer hazardous chemicals should be evaluated by a committee of peers and associated professionals. This committee collaboratively evaluates and makes decisions on how to structure your program and how to rank chemicals by risk. The committee should include veterinarians, environmental health and safety staff, IACUC staff, and a toxicologist at minimum.

References

1. *Occupational Exposure to Hazardous Chemicals in Laboratories.* 2010. 29 CFR 1910.1450
2. *Hazard Communication.* 2010. 29 CFR 1910.1200
3. National Research Council. *Guide for the Care and Use of Laboratory Animals.* 1996. National Academy of Sciences.
4. Zalk DM and Nelson DI. *History and Evolution of Control Banding: A Review.* May 2008. Journal of Occupational and Environmental Hygiene, 5:5, 330-346.
5. Hill RH, Gaunce JA, Whitehead P. *Chemical Safety Levels (CSLs): A Proposal for Chemical Safety Practices in Microbiological and Biomedical Laboratories.* Oct 2004. Centers for Disease Control and Prevention Office of Health and Safety.
6. Department of Health and Human Services. *Biosafety in Microbiological and Biomedical Laboratories.* 5th edition. Dec 2009.
7. Department of Health and Human Services. *Qualitative Risk Characterization and Management of Occupational Hazards: Control Banding (CB).* Aug 2009. DHHS (NIOSH) Publication No. 2009–152.
8. *13 Carcinogens.* 2010. 29 CFR 1910.1003
9. *11th Report on Carcinogens.* [Internet]. 2010. National Toxicology Program. [Cited 17 Nov 2010] Available at: http://ntp.niehs.nih.gov/index.cfm?objectid=32BA9724-F1F6-975E-7FCE50709CB4C932
10. *Agents Classified by the IARC Monographs, Volumes 1–100.* [Internet]. 2010. International Agency for Research on Cancer. [Cited 17 Nov 2010] Available at: http://monographs.iarc.fr/ENG/Classification/index.php
11. Peto R, et al. *The TD50: A Proposed General Convention for the Numerical Description of the Carcinogenic Potency of Chemicals in Chronic-Exposure Animal Experiments.* 1984. Environmental Health Perspectives, 58: 1-8.
12. *Identification and Listing of Hazardous Waste.* 2010. 40 CFR 261.
13. *Annex III Prior Informed Consent Pesticide List.* [Internet]. 2004. Rotterdam Convention. [Cited 17 Nov 2010] Available at: http://www.pic.int/home.php?type=t&id=29&sid=30
14. Restricted and Canceled Uses. [Internet]. 2010. United States Environmental Protection Agency. [Cited 17 Nov 2010] Available at: http://www.epa.gov/pesticides/regulating/restricted.htm
15. *Personal Protective Equipment.* 2010. 29 CFR 1910.132 – 1910.138

Figure 1: Chemical Banding Flowchart

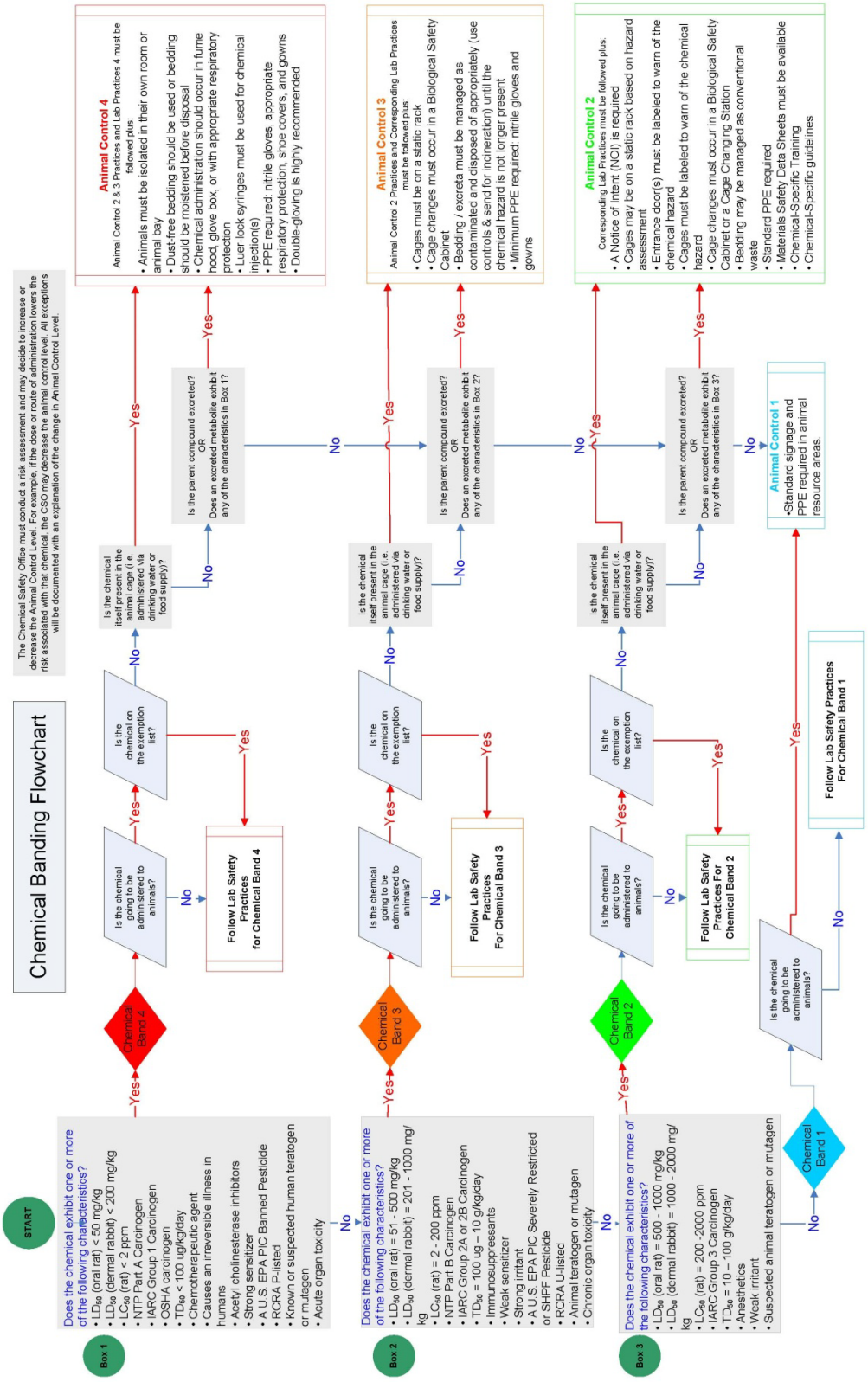
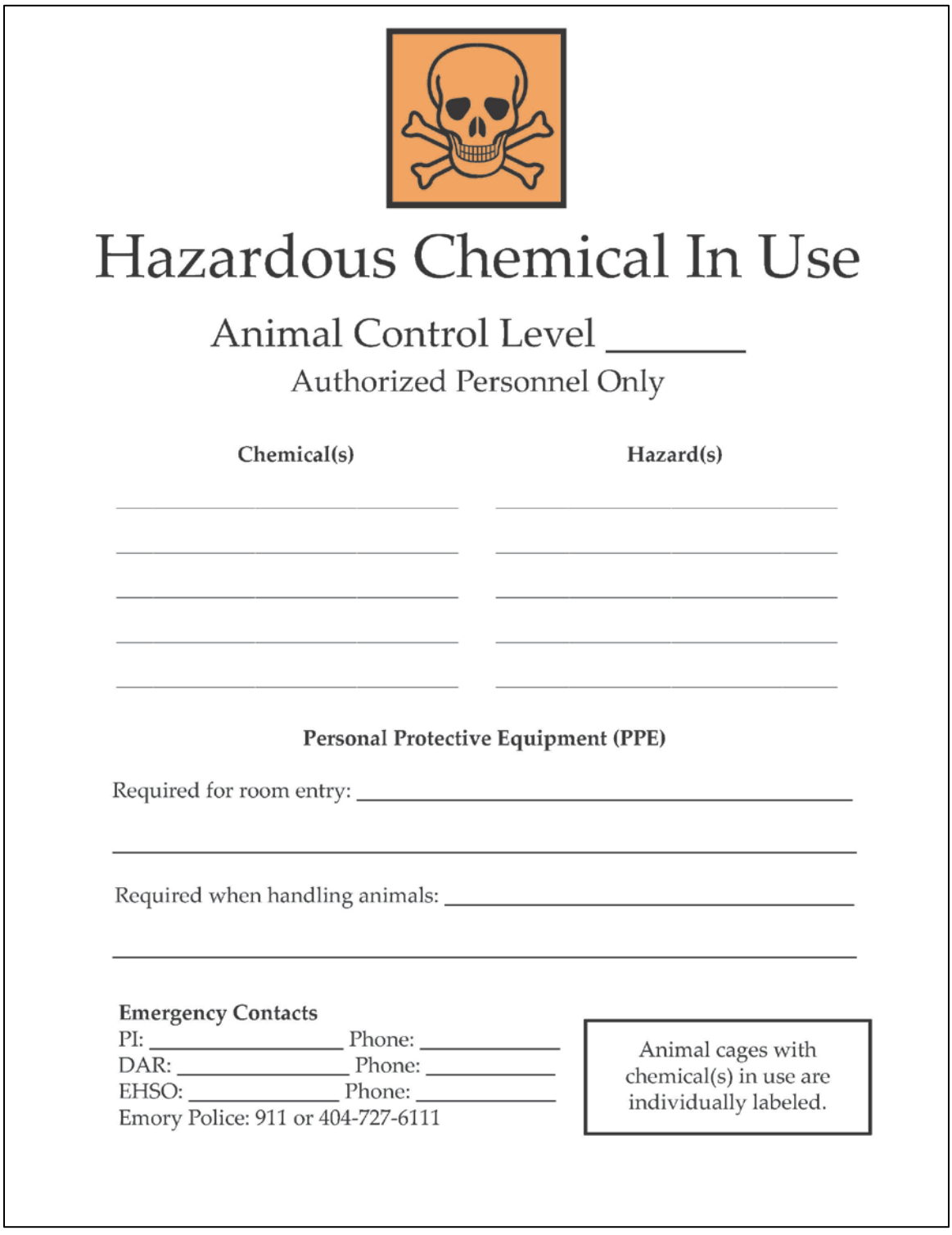


Figure 2: Room Hazard Sign



Hazardous Chemical In Use

Animal Control Level _____

Authorized Personnel Only

Chemical(s)	Hazard(s)
_____	_____
_____	_____
_____	_____
_____	_____
_____	_____

Personal Protective Equipment (PPE)

Required for room entry: _____

_____

Required when handling animals: _____

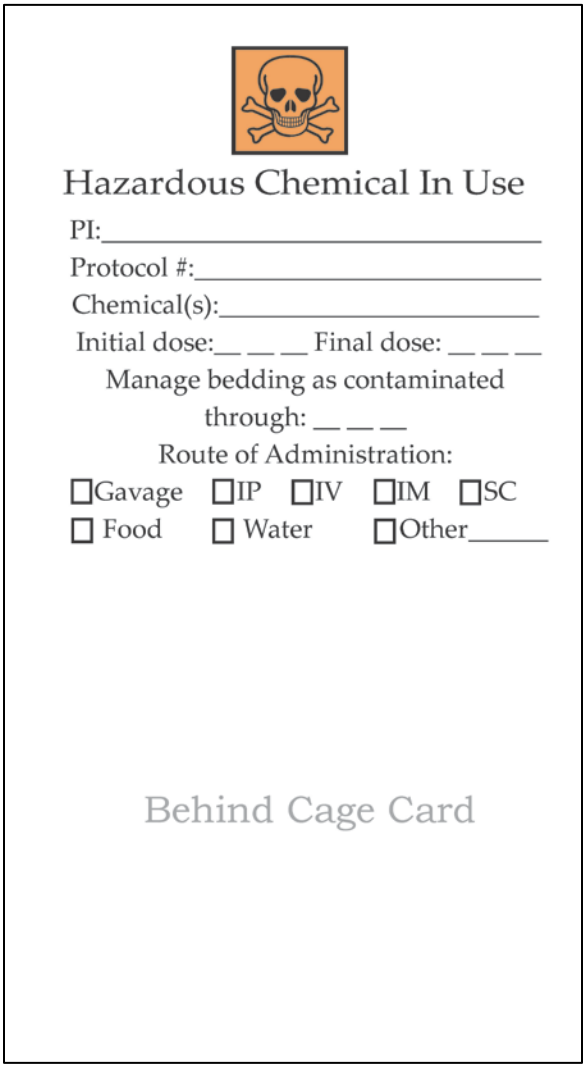
_____

Emergency Contacts

PI: _____ Phone: _____
DAR: _____ Phone: _____
EHSO: _____ Phone: _____
Emory Police: 911 or 404-727-6111

Animal cages with chemical(s) in use are individually labeled.

Figure 3: Cage Card



Appendix 1: Chemical Safety Notice of Intent (NOI) Guideline

CHEMICAL SAFETY NOTICE OF INTENT (NOI) GUIDELINE

A Chemical Safety Notice of Intent (NOI) is required when:

- A chemical is administered (via IP, IV, food, water, etc.) to a research animal for experimental purposes.
  NOTE*: EHSO exempts standard of care medications, anesthetics, and perfusion fixatives from the NOI process as long as they are used for their intended purpose.*

And

- The chemical has - or is expected to have - one or more of the characteristics listed in the following table.

HAZARD	CRITERIA	EXAMPLES
Acetyl cholinesterase inhibitors	All	Parathion, Physostigmine, Diisopropylfluorophosphate
Carcinogens	Regulated as an OSHA carcinogen	Benzidine, Ethyleneimine
	Listed by NTP as a Part A or Part B carcinogen	Cyclophosphamide, Tamoxifen, Doxorubicin HCl, ENU, MNU, PCBs, Streptozotocin
	Listed by IARC as a Group 1, 2A, or 2B carcinogen	Nickel compounds, Dimethyl sulfate, Etoposide (VP-16), Urethane
	Other known carcinogens	Azoxymethane
Chemotherapeutics	All	Busulfan, Cisplatin, Paclitaxel, Erlotinib, Fludara, Sutent, Pentostatin
Highly regulated chemicals	RCRA P-Listed chemicals	Heptachlor, Physostigmine
	RCRA U-Listed chemicals	DDT, ENU, MNU, Streptozotocin
	RCRA D-listed chemicals	Cadmium, Chromium, Lead, Mercury
	EPA PIC banned or severely restricted pesticides	DDT, Aldrin, Dieldrin, Heptachlor
	Severe environmental hazards	PCBs
Irritants (cause a severe reversible inflammatory effect at the site of contact)	Strong irritants	5-FU, Phosgene
Irreversible illness	All	MPTP, Thalidomide
Mutagens	Known or suspected to cause mutations in humans	BRDU
	Known to cause mutations in animals	Bleomycin Sulfate

HAZARD	CRITERIA	EXAMPLES
Nanoparticles	All	Carbon nanotubes, polystyrene, titanium dioxide
Sensitizers (can cause an allergic reaction after repeated exposure)	All	Paclitaxel, Malathion, Isocyanates, Nickel salts
Teratogens	Known or suspected to cause teratogenic effects in humans	BRDU, Busulfan, 5-FU, Rotenone, RU 486, Thalidomide
	Known to cause teratogenic effects in animals	Bleomycin Sulfate, Erlotinib, Fludara
Toxics and Toxins	LD50 (oral, rat) < 500 mg/kg	Tetrodotoxin, Picrotoxin, 5-FU, Rotenone, Chlorpyrifos, DMBA
	LD50 (dermal, rat) < 1,000 mg/kg	Aldrin, Chlorpyrifos, Dieldrin
	LC50 (rat) < 200 ppm	Acrolein, Diisopropyl fluorophosphates, Dimethyl sulfate, Parathion, Phosgene
	Acute or chronic organ toxicity	Potassium Cyanide, PCBs, Nickel Sulfide

Examples of exempt chemicals include, but are not limited to:

- Standard of care medications: Acetaminophen, Amiodarone, Aspirin, Heparin, Meloxicam, Prozac, Saline, Sodium bicarbonate
- Anesthetics & Analgesics: Buprenorphine, Isoflurane, Ketamine, Telazol, Tricaine
- Perfusion/tissue fixatives: Acrolein, Formalin, Formaldehyde, Glutaraldehyde, Paraformaldehyde

The Chemical Safety Protocol NOI Submission and Approval Process:

NOTE: the required forms are electronically writable

1. The principal investigator (PI) must complete a Chemical Safety Notice of Intent Form and submit to EHSO.

   NOTE*: All personnel must have taken Lab Safety Training within the past year to obtain approval.*
2. The Environmental Compliance Officer will review the NOI, conduct a risk assessment, and ask any applicable questions before submitting the NOI to the Chemical Safety Subcommittee of the IHBC.
3. The Subcommittee will assign the chemical to an Animal Control Level between 1 and 4 (1 is the lowest risk; 4 the highest risk) which specifies the health and safety controls that must be in place while conducting the research.

   The assignment is based on the hazards of the chemical and/or its metabolites, the route of administration, dosing information, etc. Animal Control Level 4 is applied to the highest risk chemicals and has the most restrictive requirements.

4. Depending on the Animal Control Level assigned, the personnel listed on the protocol may be required to attend further training. The PI will be notified via email if further training is required.
5. The Environmental Compliance Officer and the veterinarian will approve the NOI when all requirements have been met. The approved NOI is then sent to the IHBC for final approval.
6. An electronic copy of the Chemical Safety Protocol Approval Letter and Chemical Safety Protocol Hazard Assessment & Approval Form will be returned to the PI and specify any procedures (wearing certain personal protective equipment, using certain ventilation devices, posting signs, etc.) that must be followed in order to maintain approval.
7. The EHSO or IACUC retains the right to inspect compliance with these procedures and suspend a protocol, if necessary.

Chemical Safety Protocol Amendments and Renewal Processes:

NOTE: the required forms are electronically writable

1. The Chemical Safety Protocol must be amended if any of the following circumstances arise during the current approval year:
    a. Adding or removing personnel
    b. Changing, adding, or deleting a title
    c. Adding a chemical agent
    NOTE: Chemical Safety may request that another NOI be submitted.
    d. Changing routes of administration, dose, experiment duration, or days of treatment for the approved chemical agent.
    e. Changing animal species, lab location, or animal housing location.
    f. Transferring the protocol to another PI at Emory
    g. Terminating the protocol
2. Chemical Safety Protocols must be renewed annually.
    NOTE: The EHSO will notify the PI (via email) two months prior to protocol expiration date.
3. Complete the Chemical Safety Protocol Form: Amendment or Renewal electronically and submit to Environmental Compliance via email.

Appendix 2: Chemical Safety Notice of Intent Form

CHEMICAL SAFETY NOTICE OF INTENT

TO WORK WITH HAZARDOUS CHEMICALS IN RESEARCH ANIMALS

Instructions:

- Access the 'Chemical Safety Notice of Intent Guideline' on the EHSO website to determine which chemicals require a Notice of Intent when used with animals.
- Complete this form electronically & save as <CS NOI-PIname> (e.g., CS NOI-SThomaston)
  - Use the mouse, tab, or scroll to move through this form *(page up/down arrows will not work)*
- E-mail the completed document to Environmental Compliance
  - **To authenticate, the PI must send from his/her Emory mail account.**

For EHSO input only	
Date Submitted:	
Chemical Safety #:	

SECTION 1: ADMINISTRATIVE INFORMATION					
PI & LAB INFORMATION					
PI name:			Dept:		
Campus address:			Room #:		
E-mail address:			Phone #:		
Alternate Contact Name*:*			Phone #:		
E-mail address:					
Lab Building Name:				Lab Room #:	
Has an EHSO laboratory self inspection been conducted in the last 12 months?	☐ Yes ☐ No – See www.ehso.emory.edu <Current Initiatives>			Lab Phone #:	
PROJECT INFORMATION					
Project Title(s):					
Associated IACUC Protocol Titles and/or Numbers (if known):					
Non-technical abstract (a summary) of planned work of <500 words: *insert here or attach a separate document to the e-mail*					
Lab procedures involving the chemical agent of interest. (i.e. 2 mg of BrdU powder will be weighed & dissolved in saline for injection)					

Name *Note: List only those individuals that will handle chemicals or work with animals following chemical administration.*	**Student/Employee ID**	**Lab Safety Training Date** *Note: Training documentation should be located in the Lab Safety Binder and/or on Peoplesoft Self Service.*

PI -		

HAZARD COMMUNICATION – Entry notifications are required for laboratories and animal housing areas when acutely hazardous chemicals are in use	
Chemicals are labeled as to their contents	☐ Yes ☐ No
Appropriate door signage is posted at the lab which includes emergency contact information	☐ Yes ☐ No
MSDSs are available for all chemicals & employee know how to access them *(refer to http://www.ehso.emory.edu)*	☐ Yes ☐ No
EXPOSURE MANAGEMENT / EMERGENCIES	
First aid procedures have been determined and are posted.	☐ Yes ☐ No
An Emergency Plan has been created which includes a call list of responsible personnel who can be contacted in the event of an emergency (on/off shift)	☐ Yes ☐ No

SECTION 2: CHEMICAL ADMINISTRATION

Animal Species	
Total number of animals planned	
Maximum number of animals housed per day	
Will chemical(s) be administered in the Animal Research Facility or Lab (or both)?	☐ Animal Research Facility ☐ Laboratory ☐ Both
List all labs or other areas in which chemical administration may occur by building / room number.	/ ☐ Currently unknown / /
Will animals be transported between the lab and any other area (DAR, MRI, etc.) post chemical administration?	☐ Yes ☐ No If yes, indicate the method of transportation:
Areas (such as MRI) where animals will be taken post chemical administration by building / room.	/ ☐ Currently unknown /
Location of animal housing post chemical administration by building / room.	/ ☐ Currently unknown /
Will you be conducting perfusions?	☐ Yes ☐ No
Will you use isoflurane?	☐ Yes ☐ No

Chemical-specific training has been provided & documented by the PI to all personnel working with the listed agents. *NOTE: Training documentation must be kept in the Lab Safety Binder.*	☐ Yes ☐ No

Chemical Name	Routes of Administration	Dose & Dose Frequency	Experiment Duration (days)	Days of Treatment

SECTION 3: ACKNOWLEDGEMENT & SIGNATURE

I have read and am familiar with the Chemical Hygiene Plan, applicable Material Safety Data Sheets, safety practices, containment equipment, and laboratory facilities recommendations for the chemicals used in this project. I understand that EHSO approval is contingent upon all personnel having completed annual Lab Safety Training. I also understand that all personnel listed on this protocol may be required to attend additional training upon review of this Chemical Safety Notice of Intent.

I agree to ensure that all faculty, staff, and students working on this project will follow all safety recommendations as a condition of the EHSO approval of this project.

Principal Investigator	*Date*

- *Save the form as <CS NOI-PI name>*
- *Attach the Non-Technical Abstract to the e-mail if not inserted into this document*
- *Submit electronically to Environmental Compliance*

Appendix 3: Chemical Safety Protocol Amendment or Renewal Form

CHEMICAL SAFETY PROTOCOL FORM: AMENDMENT OR RENEWAL

Instructions:

- Complete this form electronically & save as <CS AR-PIname> (e.g., CS AR-SThomaston)
  - Use the mouse, tab, or scroll to move through this form *(page up/down arrows will not work)*
- E-mail the completed document to Environmental Compliance
  - **To authenticate, the PI must send from his/her Emory mail account.**

For EHSO input only	
Date Submitted:	

SECTION 1: ADMINISTRATIVE INFORMATION			
Current Chemical Protocol Title:			
Current Chemical Protocol File #:		Associated IACUC Protocol #:	
Currently Approved Chemical(s):		Animal Species:	
PI name:		Dept:	
Campus address:		Phone #:	
E-mail address:			
Alternate Contact Name*:*		Phone #:	
E-mail address:			
Lab Building Name:		Lab Room #:	
Animal Housing Building:		AH Room #:	

SECTION 2: PROTOCOL STATUS	
☐ Renew Protocol **without** changes. This project will continue as is.	*Complete Sections 3 & 6*
☐ Renew Protocol **with** changes.	*Complete Sections 3, 4, & 6*
☐ Amend Protocol.	*Complete Sections 3, 4, & 6*
☐ Terminate or Transfer Protocol.	*Complete Sections 5 & 6*

SECTION 3: PERSONNEL INFORMATION

☐ Add Personnel

Note: List only those individuals that will handle chemicals or work with animals following chemical administration.

Name	**Student/Employee ID**	**Lab Safety Training Date** *Note: Training documentation should be located in the Lab Safety Binder and/or on Peoplesoft Self Service.*

☐ Continuing Personnel *(only complete for a renewal)*

Name	Student/Employee ID	Lab Safety Training Date

☐ Remove Personnel

Name	Student/Employee ID

SECTION 4: PROTOCOL CHANGES

TITLE CHANGES

☐ Change Title(s) – *a title to an existing, approved protocol may be changed only if the research project procedure remain exactly the same*

☐ Add Title(s) - *a title may be added to an existing, approved protocol only if the research project procedure remain exactly the same*

Justification for addition:	
Describe the aims and procedures used in the new protocol title:	

☐ Delete Title(s) – *a title may be deleted from an existing, approved protocol if the funding has ended*

CHEMICAL CHANGES

☐ Add Agent(s)
☐ Change routes of administration, dose, experiment duration, and/or days of treatment

Chemical Name	Routes of Administration	Dose & Dose Frequency	Experiment Duration (days)	Days of Treatment

OTHER CHANGES
Please describe any other changes regarding your protocol below. Examples of information to include are changes in animal species, lab location, animal housing location, etc.

SECTION 5: TERMINATIONS & TRANSFERS			
☐ Terminate Protocol			
Reason for termination:			
Date termination should go into effect:			
☐ Transfer Protocol to another PI at Emory			
Date transfer should go into effect:			
PI name:		Dept:	
Campus address:		Phone #:	
E-mail address:			
Alternate Contact Name*:*		Phone #:	
E-mail address:			
Lab Building Name:		Lab Room #:	

SECTION 6: ACKNOWLEDGEMENT & SIGNATURE
I have read and am familiar with the Chemical Hygiene Plan, applicable Material Safety Data Sheets, safety practices, containment equipment, and laboratory facilities recommendations for the chemicals used in this project. I understand that EHSO approval is contingent upon all personnel having completed annual Lab Safety Training. I also understand that all personnel listed on this protocol may be required to attend additional training upon review of this Chemical Safety Protocol Amendment / Renewal. I agree to ensure that all faculty, staff, and students working on this project will follow all safety recommendations as a condition of the EHSO approval of this project.

Principal Investigator	*Date*

- *Save the form as <CS Renew-PI name>*
- *Submit electronically to Environmental Compliance*

Appendix 4: Chemical Safety Protocol Hazard Assessment and Approval Form

CHEMICAL SAFETY PROTOCOL HAZARD ASSESSMENT & APPROVAL

The Environmental Health and Safety Office (EHSO), in conjunction with the Division of Animal Resources (DAR), has conducted this hazard assessment upon review of the following Chemical Safety Protocol.

Principal Investigator:	
Chemical Protocol Title:	
Chemical Protocol File #:	
Approved Chemicals:	

SECTION 1: LABORATORY PRACTICES		
Engineering Controls to be used. *Note: This equipment must be certified annually.*	☐ Chemical fume hood ☐ Biological Safety Cabinet ☐ Glove box ☐ Other:	
Secondary Containment for reagent to be used:	☐ Double container (overpack) of chemical ☐ Other:	
Personal Protective Equipment (PPE) to be used: *(refer to the Personal Protective Equipment Guideline on the EHSO web site)*	☐ Gloves	☐ Nitrile ☐ Latex ☐ Neoprene ☐ Butyl ☐ Other
	☐ Eye Protection	☐ Goggles ☐ Safety glasses ☐ Face shield
	☐ Protective Clothing	☐ Lab coat ☐ Disposable Gown ☐ Coveralls ☐ Apron ☐ Sleeve covers ☐ Shoe Covers ☐ Boots ☐ Bouffant ☐ Other
	☐ Respiratory Protection	☐ None ☐ Surgical-type mask ☐ N-95 or PAPR ☐ Cartridge Respirator ▪ *Wearer must be examined by a health care professional to determine medical fitness to wear a respirator. Contact Employee Health Services.* ▪ *EHSO will provide training, fit test the user & select the appropriate respirator.*
Special Lab Practices:		

SECTION 2: ANIMAL RESEARCH FACILITY PRACTICES	
Animal Care Provider	☐ DAR ☐ Yerkes ☐ Other:
Hazard Signage (provided by the animal facility) must be posted on:	☐ Animal Cages ☐ Animal Housing Room Door ☐ Other:

Personal Protective Equipment (PPE) to be used:	☐ Gloves	☐ Nitrile ☐ Latex ☐ Neoprene ☐ Butyl ☐ Other
	☐ Eye Protection	☐ Goggles ☐ Safety glasses ☐ Face shield
	☐ Protective Clothing	☐ Lab coat ☐ Disposable Gown ☐ Coveralls ☐ Apron ☐ Sleeve covers ☐ Shoe Covers ☐ Boots ☐ Bouffant ☐ Other
	☐ Respiratory Protection	☐ None ☐ Surgical-type mask ☐ N-95 or PAPR ☐ Cartridge Respirator ▪ *Wearer must be examined by a health care professional to determine medical fitness to wear a respirator. Contact Employee Health Services.* ▪ *EHSO will provide training, fit test the user & select the appropriate respirator.*
Animal Management	General Animal Housing	☐ Acute experiment *(animal housed in lab less than 12 hours)* ☐ Maintenance in colony room ☐ Isolation in special room ☐ Other:
	Rodent housing	☐ Filter top, ventilated cage ☐ Filter top, non-ventilated cage ☐ Open, solid-bottom cage ☐ Dust-free bedding ☐ Isolation
		☐ Other Animal Management Practices: Describe:
	Non-human primate housing	☐ Single cage housing ☐ Pair housing ☐ Protected contact housing ☐ Group housing ☐ Other:
	Non-rodents housing	☐ Cage standard for species ☐ Pen ☐ Other:
Waste Management	Bedding Collection	☐ Normal means ☐ Ventilated dump station
	Housing Decontamination	☐ Standard cage washing ☐ Decontamination solution: ☐ Other - Describe:
	Carcass Disposal	☐ Normal means ☐ Collected for incineration ☐ Collected for chemical waste disposal
	Excreta Disposal	☐ Normal means ☐ Collected for incineration

		☐ Collected for chemical waste disposal
	Food Disposal	☐ Normal means ☐ Collected for incineration ☐ Collected for chemical waste disposal
	Water Disposal	☐ Normal means ☐ Collected for incineration ☐ Collected for chemical waste disposal
	Personal Protective Equipment Disposal	☐ Normal means ☐ Collected for incineration ☐ Collected for chemical waste disposal
Special Animal Research Facility Practices:		

SECTION 3: CHEMICAL WASTE DISPOSAL	
Disposal method for unused chemical reagents and/or other chemical waste accumulated during the project.	☐ Call EHSO for a chemical waste pickup Special Waste Disposal Instructions:

SECTION 4: EHSO AND DAR APPROVAL	
The NOI has been assigned to Animal Control Level	☐ **1** ☐ **2** ☐ **3** ☐ **4**
All required personnel have attended Animal Chemical Safety Training through DAR or Yerkes	☐ Yes ☐ No ☐ N/A
Chemical Safety Approval	*Date*
Veterinary Approval	*Date*