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Adverse events at research facilities

To the editor:

The Office of Laboratory Animal Welfare (OLAW) provides guidance and interpretation of the Public Health Service (PHS) Policy on Humane Care and Use of Laboratory Animals (Policy) to ensure oversight of humane care and use of animal models in biomedical research in the US. On behalf of the PHS, OLAW oversees compliance with the PHS Policy by institutions using live vertebrate animals for research, training, or testing activities that are funded by the PHS agencies: National Institutes of Health (NIH), the Centers for Disease Control and Prevention (CDC) and the Food and Drug Administration (FDA). OLAW also oversees activities funded by the National Science Foundation (NSF), the National Aeronautics and Space Administration (NASA), the Biomedical Advanced Research and Development Authority (BARDA), and the Veterans Administration (VA) under separate memoranda of understanding.

In their oversight of animal welfare in biomedical research, OLAW has encountered events that endanger the health and well-being of research animals. In this paper, we share OLAW's experience to encourage institutions to proactively plan appropriate measures to avoid or mitigate adverse events. OLAW defines adverse events as those unexpected incidents that lead to harm, or endanger the well-being of animals and humans at a research facility. This article also provides information to help institutions maintain optimal care for their research animal population during adverse events while complying with the federal regulations and guidelines. Many adverse events are preventable, but because they are unanticipated, steps for prevention and mitigation may not always be well developed. In this article we list, categorize, and describe serious adverse events that have been documented by OLAW while overseeing biomedical research. Identifying the various events that can endanger animal and human lives and lead to loss and damage of property is essential in planning efficient measures for prevention and mitigation.

Adverse events and reportable events

NIH Grants Policy Statement¹ requires institutions to negotiate an Animal Welfare Assurance (Assurance) with OLAW to receive PHS support for the conduct of animal activities. OLAW approves the Assurance for domestic institutions on the basis of compliance with the PHS Policy, the *Guide for the Care and Use of Laboratory Animals (Guide)*, and the Animal Welfare Act (AWA) Regulations^{2–5}. In the Assurance, the institution commits to promptly report non-compliance or reportable situations to OLAW. The PHS defines non-compliance as serious or continuing non-compliance with the PHS Policy, serious deviations from the provisions of the *Guide*, or any suspension of a protocol by the Institutional

Animal Care and Use Committee (IACUC)³. Reportable events include conditions that jeopardize the health or well-being of animals, including natural disasters, accidents, and mechanical failures, resulting in actual harm or death to animals³.

Assured institutions are advised to submit a preliminary report of a reportable event promptly, prior to the completion of a full investigation and implementation of a corrective plan. OLAW will provide guidance to the institution as they take corrective actions and institute corrective measures to prevent recurrence. Institutions are usually able to address noncompliant and reportable incidents appropriately and institute suitable actions to prevent recurrence. Institutions must provide a final report signed by the Institutional Official that includes a detailed explanation of the circumstances and corrective actions taken. Institutions are always given the opportunity to take corrective action, and only rarely is a grant or an award suspended or terminated due to failure of implementing corrective action⁶.

Risk management, prevention, and planning

Effective risk management typically requires assessment of two factors: the likelihood the risk will occur (probability) and the magnitude of the consequences if it does occur (impact). Although the probability of a serious adverse event at a research facility may be low, the impact can be very high. In addition to animal welfare consequences and the loss of data and research animal(s), the institution may suffer negative media attention.

OLAW assures a variety of domestic and foreign institutions, including colleges, universities, government agencies, small businesses, pharmaceuticals research, hospitals, contract and non-profit research organizations. The care and use of animals in research, testing, and training at these institutions includes live vertebrate animals, namely, laboratory rats and mice, birds, reptiles, amphibians, fish, ungulates (sheep, cattle, and pigs), non-human primates, and other vertebrate animals. The domestic entities Assured by OLAW (Fig. 1), broken down into percentages⁷, and the species involved in reportable events from these institutions are presented in Fig. 2.

Occurrence of adverse events

OLAW received 6,575 case reports of non-compliance from various domestic institutions from 2009 to 2016. Of these, 765 were new cases that were reported in 2016. While many of the reportable concerns fall under animal study protocol issues (32%) or institutional policy issues (15%), a significant number can be categorized as part of the various adverse events listed below. Adverse events caused by human error, accident, neglect, abuse, crime, training failure, equipment failure and natural disaster comprised about 17% of all non-compliance cases reported to OLAW between 2009 to 2016 (Fig. 3).

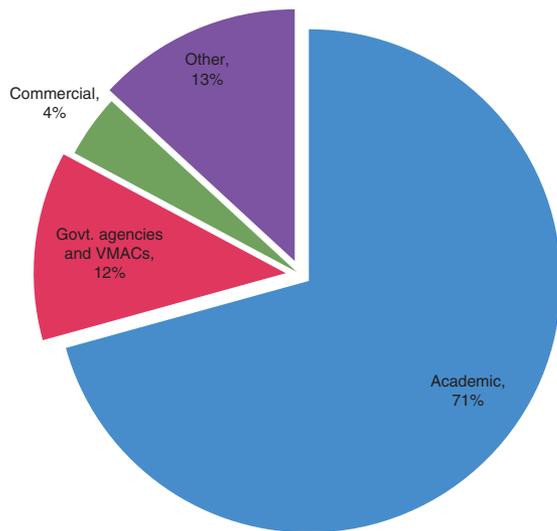


FIGURE 1 | Categories of OLAW assured institutions

Other events, such as mechanical issues (HVAC, emergency power and light issues), made up only about 2% of all non-compliance cases in the same time range. Similarly, biological adverse events (veterinary care issues, reaction to administered drugs) and animal husbandry-related adverse events (food and water availability, sanitation failure, enrichment issues) made up 13% and 12%, respectively, in the years 2009–2016.

As we can see from this data, unforeseen adverse events constitute an important portion of the issues encountered in the use of animals in research. Many adverse events are preventable, but because they are unanticipated, steps for prevention and mitigation may not be in place. This article describes serious adverse events that have been reported to OLAW so that institutions may engage in proactive planning to prevent such events and to have a suitable response action plan in place for events that cannot be prevented.

Definition and categorization of adverse events

Identifying the various events that can endanger animal and human lives and lead to loss and damage of property is essential in planning efficient measures for prevention and mitigation. Categorizing the possible events into groups based on their effects can help in coordinating and managing efforts to prevent and/or reduce the impact of such events.

The Federal Emergency Management Agency (FEMA) identifies and ranks hazards and risks by a standardized method of measurement that takes into account the likelihood and consequence of the event^{8,9}. OLAW has adapted these criteria for use in animal facility disaster management. Similarly, based on the number of animals that may be affected and the possible magnitude of loss or damage to the facility, adverse events can be classified as extensive or contained.

Extensive adverse events

Extensive adverse events cause large-scale damage to the area, the institution or the entire animal facility. Depending on the institution's capacity, a large number and multiple species of

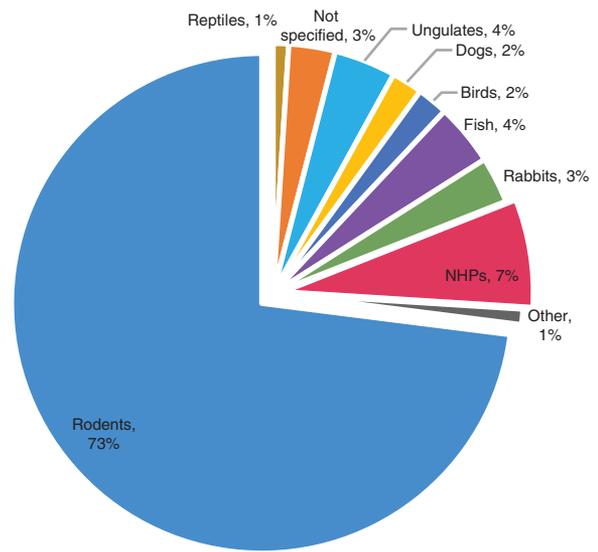


FIGURE 2 | Percentages of animal species in OLAW assured institutions

animals may be affected. Risk to personnel safety in such events is also serious and likely to be extensive (collective risk). Events of this type may be divided into three categories based on the causes, the systems affected and the likely consequences. These categories are:

- Natural
- Technical
- Intentional/civil

In order to allow better coordination of emergency action plans, extensive adverse events may be further ranked based on danger level and/or impact.

Often, adverse events may have sequelae that are unforeseen and hence produce unanticipated disruptions in animal welfare. Therefore, several of the events mentioned above might fall into multiple categories. For instance, fire can be an independent extensive adverse event or the secondary consequence of other disasters, such as an electrical malfunction. An example of an anticipated primary event leading to unexpected secondary consequences is the flooding at a large university in 1995 (ref. 10). That year, when the area was hit by a hurricane, although the university had several effective flood management plans in effect, malfunction of steam lines as an indirect effect of flooding resulted in the heat exhaustion deaths of about 30 rodents. This malfunction of steam lines was an unexpected outcome of cooling due to flooding in the streets that, in turn, caused disruption of ventilation systems in parts of the animal facility. Although the university had an overall flood management plan in place, the various secondary and tertiary outcomes were unanticipated. It is incumbent on institutions to develop action plans for each category of event so that when multiple, overlapping events occur, they can be dealt with promptly and effectively.

Natural events include, but are not limited to, weather-related emergencies such as snow storms, hurricanes, or droughts; oceanic/seismic events such as earthquakes or tsunamis; or other disasters such as disease outbreaks or infestations that may place the

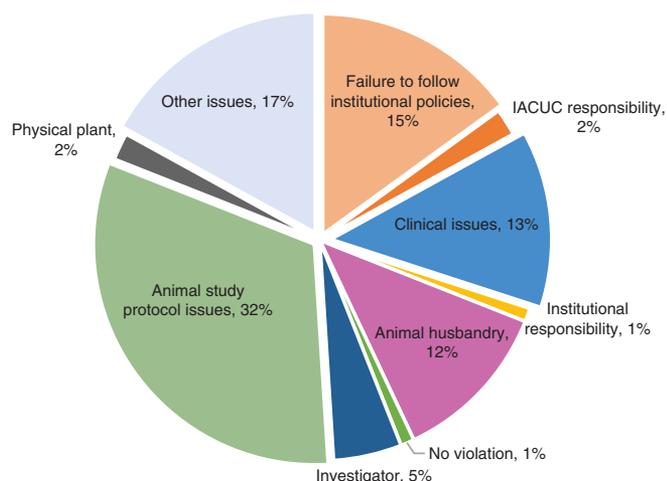


FIGURE 3 | Non-compliance cases reported to OLAW in the 2009–2016 period

entire animal population of the facility at risk. Massively destructive natural disasters occur infrequently. However, natural disasters do not have to be of enormous proportions to cause adverse events in animal facilities. For example, in 2014, OLAW received three reports of natural disaster-linked adverse events in animal facilities⁷. All three were relatively contained due to the prompt action of employees and investigators in accordance with the institutional disaster plan. However, there was some loss of animal lives due to unforeseen consequences during these events. For instance, one institution had measures in place for power failure and electrical surges and yet experienced equipment failure during a thunderstorm. This equipment failure (and consequent loss of animal lives) was traced back to their surge protectors being overwhelmed by powerful electrical surges from the thunderstorm. In this case, the institution

TABLE 1 | Natural extensive adverse events

Adverse event	Secondary effects
Weather	
Hurricane	Power outage
Tornado	Equipment failure
Winter storm	Temperature fluctuations
Thunderstorm	Disruption of the light/dark cycle
Drought	Inability to get supplies to facility Inaccessibility of facility for personnel
Seismic	
Earthquake	Power outage
Tsunami/flooding	Equipment failure
Landslides	Temperature fluctuations Disruption of the light/dark cycle Inability to get supplies to facility Inaccessibility of facility for personnel
Emergencies	
Fire	Damage to building, structures
Flood	Inaccessibility of facility Equipment malfunction
Environmental hazards	
Disease outbreak	Rapid spread
Infestations (mold, insects)	Mass culling required Possible zoonotic transmission

TABLE 2 | Technical extensive adverse events

Adverse event	Secondary effects
Hazardous materials	
Water supply contamination	Spread of hazardous materials
Chemical spills	Health hazard
Radiation leak	Long-term effects
Large scale failures	
Mechanical	Temperature fluctuations
Electrical	Disruption of the light/dark cycle

decided to disable automatic, electronically controlled equipment during severe weather. This example highlights the importance of understanding and preparing for secondary events. Other examples of natural events and their consequences are listed in **Table 1**.

Other natural adverse events include disease outbreaks that can affect, in addition to animal welfare and health, the research quality and outcome due to the introduction of additional variables. This is especially true for facilities housing wild-caught animals for research purposes, as these animals may harbor microbial and parasitic agents that may be transmitted to other animals in the facility^{11,12}. It is very important to maintain adequate care, isolation and quarantine, use of sentinel programs, quality control of feed and biologics, and sanitization programs to prevent introduction and spread of disease vectors in the animal population.

Technical events include, but are not limited to, large-scale equipment malfunction and hazardous materials contamination. Both of these types of events can pose long-term risks to the health of both animals and facility personnel. Examples of technical adverse events and their consequences are listed in **Table 2**. Large-scale facility-wide technical failures are rare, unless they occur in conjunction with severe weather catastrophes. However, flooding of animal facilities at one institution due to the rupture of the city's water main plumbing line is one such example of an adverse event caused by technical failure.

Intentional/civil events include, but are not limited to, large-scale deliberate events such as terrorist attacks, labor strikes, or protests that can place animals in danger and/or produce stress. In addition to physical assaults, vandalism and terrorist threats, animal rights activists have increasingly targeted stored data at various research facilities and educational institutions. Cyber attacks can lead to leaks of information such as employee and personnel records, travel records, proprietary information, and other sensitive data. An example of one such adverse event is the recent crusade of animal rights activists against childhood development studies at a federal agency whereby personal information of federal officials was posted in an effort to urge public harassment. Also, in recent years many animal facilities have moved to automated, centralized environmental control and access¹³, making them more susceptible to hacking. Examples of civil events and their consequences are listed in **Table 3**.

Contained adverse events

Contained adverse events cause damage to a specific area within the animal facility. Depending on the species housed, fewer animals may be affected. Generally, the damage is contained within one area/section of the facility, so other areas may be still be functional and can serve as alternate housing for the affected animals. Risk to personnel safety in such events is minimal. Contained adverse

TABLE 3 | Civil extensive adverse events

Adverse event	Secondary effects
Attack	
Terrorism	Access to facility limited
Assaults	Damage to building, people, animals
Bomb threats	Transportation systems affected
Strikes	
Demonstrations	
Computer security breach	
	Negative publicity
	Equipment malfunction

events may be divided into two broad categories based on their cause—deliberate or inadvertent. These categories may be further subdivided into sub-categories based on the systems affected, the nature of the adverse event, the risk, and the consequences.

- Deliberate/malicious events
- Inadvertent events
- Biological
 - Mechanical/technical/physical
 - Husbandry-related
 - Human error
- Adverse events due to animal nature

Deliberate events are those that are caused by humans for media attention and/or with the intent to harm the facility, animals, and personnel. These events include small scale incidents such as the theft and/or intentional release of specific animals, abuse or neglect, sabotage of equipment and/or records within the institution, vandalism or tampering with supplies or medicines, etc. Examples of deliberate events and their predicted secondary effects are listed in **Table 4**.

Inadvertent or accidental events that are limited in their effect are listed in **Table 5**. These events may be further sub-divided as the following:

(a) Biological events, such as problems in veterinary care, infestations, incomplete euthanasia, and adverse reactions to biologics, drugs, procedures or diseases.

(b) Mechanical or technical issues that are limited to a part or parts of the facility, such as problems with the electrical system, the water supply, the HVAC, the lighting.

(c) Husbandry-related events that may affect one or a few animals, such as absent or inadequate or tainted food/water, sanitation issues that can endanger the health of animals, and accidents like cage flooding.

(d) Adverse events brought about by human error and/or inadequate training, such as mishandling or unsatisfactory care during transportation.

(e) Events caused by the very nature of the animal, such as escapes, aggression, and development of stereotypical behavior.

TABLE 4 | Deliberate/Malicious contained adverse events

Adverse event	Secondary effects
Abuse/neglect	Harm to animals, negative publicity
Theft/crime	Protests
Sabotage/intentional damage	Damage to building, animals

Many of these events may be further categorized based on their potential consequences to simplify the creation of mitigation plans. However, many of these adverse events may overlap in their categorization and so care must be taken to prepare for possible secondary effects. Mostly, it requires daily monitoring of animals, enclosures and automated systems within the animal facility. While infrequent instances of cage flooding due to lixit malfunction are not reportable³, they do require immediate veterinary care to address hypothermia and a prompt repair of the mechanical device. Drowning of animals due to human error (such as rodent cages improperly placed in racks, activating a continuous flow of drinking water into cages), however, are reportable and require corrective action plans to be put in place immediately.

Similarly, distress and pain in individual animals constitute a contained adverse event that requires prompt care and corrective actions. This ranges from instances of overgrown teeth to dystocia. All such cases can be addressed by frequent monitoring and prompt action. However, it is important to be familiar with the IACUC-approved protocol as some problems may be included in the protocol as expected outcomes, such as tumor susceptibility in certain strains of rodents. There may be unexpected adverse phenotypical outcomes which may require revision of the protocol. For instance,

TABLE 5 | Inadvertent contained adverse events

Adverse event	Secondary effects
Biological	
Adverse reaction to biologics, drugs, chemicals	Reactions in other animals Interference with study results
Veterinary care issues; surgical, treatment, analgesia	
Disease/infestation	
Failed euthanasia	
Mechanical	
Electrical issues	Fire and related damage
Water supply	Flooding
HVAC	Potential for infections due to contaminated air
Lighting	Disruption of light/dark cycle
Construction/maintenance	Damage due to wear and tear
Husbandry-related	
Inadequate, inaccessible or spoiled food/water	Odors Aggression
Sanitation issues	Stereotypies
Overcrowding	Interference with study results
Insufficient enrichment	Morbidity and mortality
Accidents like cage flooding	
Human error	
Escapes	Negative publicity
Improper care during transportation	Interference with study results
Inadequate care/attention	Injury to people, animals
Mishandling due to inadequate training	
Animal nature	
Aggression toward other animals	Risk and injury to animals and people
Getting trapped, injured (e.g., chewing wires)	
Escapes	
Aggression toward people	

TABLE 6 | Commonly occurring adverse events at research facilities

Adverse event	Recommended preventive action
Non-human primates	
Strangulation on chain holding enrichment device	Ensure that the chain is too short to be pulled around neck Cover chain in PVC pipe
Injuries by escaped animals	Staff trained in appropriately latching cages Ensure locks are secure and undamaged
Mice	
Drowning due to improperly activated lixit by improperly placed cage	Staff trained in proper placement of cages Ensure proper cage placement during daily health checks Post pictures of correct placement for animal users
Incomplete euthanasia	Staff is trained in appropriate euthanasia techniques Secondary physical method of euthanasia to ensure death Special attention to newborn mice (more resistant to CO ₂)
Death after weaning separation	Provision of appropriate food Ensure mice can access water source
Improper monitoring at a satellite facility	Good communication between facilities personnel Daily monitoring of all approved spaces
Fish	
Large scale die-off due to poor water quality	Monitor oxygen, temperature and other critical elements Ensure that probes for environmental monitoring are functioning Ensure notification systems are working properly Have a backup source of water for tanks
Multiple species	
Death during transport	Ensure that climate controlled vehicles are used Ensure that all cages have air ventilation Ensure cages are stacked appropriately to prevent falling Check animals if trip is extended Ensure that animals are not left on loading docks, tarmacs or holding rooms for excessive time periods. Ensure shortest route is used and minimize time in transit
Death due to accidental cage wash	Train staff to do thorough checks prior to cage wash
Failure to provide analgesia postprocedurally	Post-approval monitors to specifically check for this Staff to follow protocol even in absence of pain symptoms
Failure of backup power supply or HVAC system	Frequent monitoring and testing of backup systems Preventive maintenance

in apolipoprotein knockout mice on a C57BL/6 background, it was noted that older mice were more likely to develop thickened, ulcerated skin lesions than other strains/lines of mice¹⁴. A well-organized clinical surveillance and monitoring program helped to identify this as one of the many phenotypic characteristics of these mice, rather than disease outbreak in the colony or a husbandry issue.

Many instances of distress to research animals arise from their biological behavior and instincts. Because a captive environment is not part of a natural habitat, many research animals are likely to develop abnormal behaviors such as aggression and stereotypic patterns such as pacing, head swaying, and self-injurious behavior. Aggression can also develop in the case of unstable social groups in many species such as macaques. In addition to harm to other animals and to personnel, abnormal behaviors in research animals can lead to stress in these animals and therefore, unreliable research data. The 1985 amendments to the AWA¹⁵ introduced environmental enrichment to reduce stress and to ensure humane treatment of research animals.

Social housing is another essential determinant of psychological well-being of research animals. Both the Animal Welfare Regulations¹⁵ and the *Guide for the Care and Use of Laboratory Animals*¹⁶ consider the housing of compatible social species as the default unless exempted for veterinary medical or scientific reasons justified in the protocol and approved by the IACUC. However, it is essential to understand the biology, group dynamics, and behavior in the wild of each species prior to setting up social housing in order to ensure optimum physical and psychological well-being¹⁷. For instance, female prairie voles have been shown to have pregnancy terminations if exposed to the urine and bedding material of unknown males¹¹. Therefore, care should be taken to minimize such exposures when housing breeding pairs.

Prevention and mitigation

Many types of adverse events are preventable. However, rigorous planning and effective communication are essential for an optimal prevention and mitigation scheme. Large scale disasters

resulting in institution-wide animal welfare issues are rare. Most adverse events in research facilities are contained, and often controllable. While delineating prevention strategies for each type of adverse event is not the primary focus of this article, it is worth pointing out that the majority of events reported to OLAW were easily correctable. Research institutions can work with their IACUCs to identify and correct commonly occurring deficiencies in their animal care program. Therefore, OLAW has put together an example of commonly reported issues that directly affect animal welfare in research facilities and the recommended preventive action for each (Table 6).

Conclusions

Serious adverse events are incidents that lead to significant injury or illness, unrelieved pain or distress, or the death of an animal. Adverse events are among the risks of conducting research at research facilities, and they should be addressed through effective risk management practices. The impact of a serious adverse event can be substantial, not only for the animal but also for the researcher and the facility. This article has explored adverse events that have occurred at institutions assured by OLAW, as an aid to assist other facilities in making plans to help prevent such events. For the sake of animal well-being, as well as institutional well-being, every facility should take into consideration possible adverse events and their sequelae, so as to be better prepared in the event of such occurrences in the future.

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Swapna Mohan, Lori L Hampton & Susan Brust Silk

Office of Laboratory Animal Welfare, National Institutes of Health, Bethesda, Maryland, USA. Correspondence should be addressed to S.M. (swapna.mohan@nih.gov)

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