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Preventing Adverse Events at Research Facilities

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In this article, adverse events are defined as events that lead to significant injury or illness, unrelieved pain or distress, or the death of an animal, excluding those caused by IACUC-approved research procedures. The ability to identify possible adverse events is an essential step in planning for risk prevention and mitigation. Using data from news sources and the Animal and Plant Health Inspection Service (APHIS) website, this article provides guidance to research facilities regarding various types of adverse events to consider in risk management plans because these events might occur or have occurred and, in some cases, have been documented as noncompliances at APHIS-regulated research facilities. APHIS classifies noncompliances as 'direct' when they currently (at the time of the inspection) have a serious or severe adverse effect on the health and wellbeing of animals. Not all direct noncompliances are associated with adverse events, and not all adverse events are documented as direct noncompliances (for example, a past adverse event that does not currently affect the wellbeing of animals is not a direct noncompliance). However, because APHIS does not require reporting of adverse events, the information regarding direct noncompliances was the only APHIS data available to study adverse events at research facilities. Direct noncompliances documented by APHIS were 4% of all documented noncompliances from 2010 through 2014. The greatest number of direct noncompliances was in the category of veterinary care issues (44%), followed by animal husbandry issues (34%), 'other issues' (15%), and physical plant issues (7%). The category of other issues included events due to human error, equipment failures, and accidents.

Abbreviations: APHIS, Animal and Plant Health Inspection Service; AWA, Animal Welfare Act; OLAW, Office of Laboratory Animal Welfare; PHS, Public Health Service

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Two federal agencies have primary responsibility for the oversight of animals in biomedical research in the United States—the USDA Animal and Plant Health Inspection Service (APHIS) and the NIH Office of Laboratory Animal Welfare (OLAW). Using examples of reported events, OLAW previously published an article on adverse events from the OLAW perspective,[8] with an emphasis on the categorization of possible events. Similarly, the current article discusses the various types of adverse events that might occur, that actually have occurred, and, in some cases, that have been documented as noncompliances at research facilities regulated by APHIS, using data from news sources and from the APHIS website before the Public Search Tool[22] was modified in 2017. The ultimate goal of the current article—as with the OLAW article[8]—is to provide data on adverse events that have occurred previously at research facilities to assist institutions in creating proactive plans to prevent or mitigate such events in the future. In addition, the current article will present some resources and ideas to help in making plans more effective in preventing or managing the wide variety of possible adverse events at research facilities.

Although APHIS data are compared with OLAW data as a matter of interest, differences between the agencies, their data sources, and their methods of collecting data prevent the data from being directly comparable. Under the Animal Welfare Act (AWA), APHIS regulates facilities that use animals in biomedical research, tests, experiments, or teaching. The implementing regulations of the AWA are established in the Code of Federal Regulations, Title 9, Chapter 1, Subchapter A, Parts 1 through 4.[21] In both the AWA and the regulations, 'animal' is defined as "any live or dead dog, cat, monkey (nonhuman primate mammal), guinea pig, hamster, rabbit, or such other warm-blooded animal, as the Secretary may determine is being used, or is intended for use, for research, testing, experimentation, or exhibition purposes, or as a pet; but such term excludes (1) birds, rats of the genus *Rattus*, and mice of the genus *Mus*, bred for use in research, (2) horses not used for research purposes, and (3) other farm animals, such as, but not limited to, livestock or poultry, used or intended for use as food or fiber, or livestock or poultry used or intended for use for improving animal nutrition, breeding, management, or production efficiency, or for improving the quality of food or fiber. With respect to a dog, the term means all dogs, including those used for hunting, security, or breeding purposes."[21] APHIS noncompliance data are documented by APHIS inspectors during periodic (at least annual) inspections.[16] In contrast, OLAW uses continual institutional self-reporting to monitor compliance with the Public Health Service (PHS) Policy on Humane Care and Use of Laboratory Animals with regard to research conducted or supported by any component of the PHS on any live vertebrate animal.[26]

The current article will focus on adverse events having a negative effect on animal welfare. In this article, 'animal welfare' is defined as the state of the animal, as affected by the provision or availability of appropriate shelter, management, nutrition, handling, veterinary care, and so forth.[10] Good welfare occurs when both an animal's physical and mental needs are fulfilled.[1]

The ability to proactively identify events that may lead to negative outcomes, including damage or loss of lives (animal and human) and property, is an essential step in making plans that put appropriate prevention and mitigation measures in place. A description of events that are possible and some that

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have actually been documented by APHIS can help facilities ascertain the efforts needed to prevent or reduce the effects of such events. The identification, analysis, assessment, control, and avoidance, minimization, or elimination of unacceptable risks is known as risk management.[4] Effective risk management typically requires an assessment of 2 factors: the likelihood that the risk will occur (probability) and the magnitude of the consequences when it does occur (effect).[7] Although the probability of a serious adverse event at a research facility might be slight, the effect can be great. In addition to animal welfare consequences, including possible animal deaths, the institution may suffer the loss of research data, negative media attention, Freedom of Information Act requests for details of the event by animal advocacy groups, and possible significant enforcement actions by APHIS. Each institution will have its own level of risk acceptance for each of these factors, but for most, if not all, institutions, the prevention and mitigation of serious adverse events involving animals will be prioritized in the risk management plan.

Adverse Events and APHIS Citations

APHIS defines serious adverse events as incidents that lead to significant injury or illness, unrelieved pain or distress, or the death of a regulated animal.[13] That definition is used in this paper, with the understanding that it excludes those events caused by IACUC-approved research procedures. Not every adverse event is preventable, but institutions are expected to take reasonable steps to try to prevent them. For example, social housing of compatible NHP is required by Section 3.81(a) of the AWA regulations,[21] but it involves the risk of possible injuries from fighting. This risk must be assessed for every NHP that is socially housed. For some NHP, the likely magnitude of the risk may be only minor injuries, and the probability of injury may be close to 0. For others, the likely magnitude of the risk might be major injuries or even death, and the probability of injury might be close to 100%. Most NHP will be in a category somewhere between these 2 extremes, and institutions can take steps to minimize injuries that occur due to social housing. When a primate suffers major injuries because of social housing, an APHIS inspector has to evaluate whether the facility took all reasonable steps to ensure that the socially housed animals were compatible, with the understanding that the decision regarding what is considered reasonable will be a judgment call. Examples of clear failures to take reasonable steps include animal injuries due to inadequate facilities, staffing, or training (for example, inadequate preparation for or oversight of social housing, insufficient training in recognizing signs of impending problems).

When evaluating the magnitude of the effect of a possible adverse event, the effect on animal welfare is of primary concern, but additional potential factors might also be important to an institution, including loss of research data, negative media attention, Freedom of Information Act requests for details of the event by animal advocacy groups, and APHIS actions, such as citations or enforcement actions. However, documentation of direct noncompliances at research facilities is rare. In the 5 y from 2010 through 2014, only 149 direct noncompliances (among 3587 total noncompliances) were documented, involving only 56 (of more than 1100) research facilities. Clearly, some inspection reports documented multiple direct noncompliances, and some facilities had direct noncompliance categories repeated on subsequent reports. One such facility paid the largest fine ever levied by APHIS under the AWA.[11]

An adverse event must result in noncompliance with an AWA regulation or standard to be cited on an inspection report. Noncompliances that currently (at the time of the inspection) have a serious or severe adverse effect on the health and wellbeing of the animal are categorized as direct noncompliances.[17] Because APHIS does not require reporting of adverse events, the data on direct noncompliances were the only APHIS data available for study of adverse events at research facilities during the chosen time period (2010 through 2014) and therefore are used in this article.

However, not all direct noncompliances are associated with adverse events, and not all adverse events are documented as direct noncompliances (that is, when a past adverse event does not currently affect animal wellbeing, it is not a direct noncompliance). For that reason, in 2016, APHIS began documenting some citations as 'critical noncompliant items.' Noncompliant incidents noted to have had serious or severe animal welfare consequences previously but that pose no current risks to animals are 'critical noncompliances.'[17] In addition, direct noncompliances (that is, noncompliances affecting current animal wellbeing) are considered to be critical noncompliances.[17] All noncompliances resulting from adverse events, therefore, are critical noncompliances, although not all critical noncompliances are associated with adverse events. Examples of critical noncompliances that are not necessarily associated with adverse events include inspection refusals, threatening an APHIS inspector, falsifying records, knowingly obtaining animals from prohibited sources, and obtaining animals by use of false pretenses, misrepresentation, or deception.[17]

Critical noncompliances are even more serious when they are repeated noncompliances. A repeat noncompliance is one that is the same as or similar to an earlier-cited noncompliance; that is, a noncompliance cited in the same section and subsection of the last full inspection or cited multiple times within the last 3 y even if it was not cited on the last full inspection.[17] In addition, the recurring noncompliance can be a noncompliance with a similar section and subsection of the regulations or standards but identified for a different species[17] (for example, not providing a sufficient quantity of nutritious food for hamsters, followed by the same noncompliance involving rabbits).

As noted earlier, registrants are generally not required to report noncompliances—including adverse events—to APHIS. Only when the event results in the suspension of an animal activity by the IACUC is it required to be reported, according to Section 2.31(d)(7) of the AWA regulations.[21] However, institutions may voluntarily choose to report such events, to inform the agency about the situation, provide documentation of corrective actions, and demonstrate their 'good faith' intention to comply with the AWA and regulations. In addition, APHIS may learn of adverse events from whistleblower accounts or media reports.

In December 2017, APHIS published new guidance (revised in May 2018) regarding its handling of reported noncompliances,[18] including reports of adverse events. When an institution reports an incident, APHIS first assesses whether it is a noncompliance. When the incident does not involve a noncompliance, APHIS shares its assessment with the institution and concludes its review. However, when the incident does involve a noncompliance, APHIS does not document the noncompliance on an inspection report when it is not a critical noncompliance, it was discovered by the institution in a timely fashion by use of its own compliance monitoring program, and the institution immediately takes appropriate corrective action and swiftly establishes measures to prevent recurrence. When the noncompliance is a critical noncompliance, APHIS does not cite it on an inspection report providing that it does not constitute a repeat noncompliance and that the institution (1) discovers it in a timely fashion

by use of its own compliance monitoring program, (2) immediately takes appropriate corrective action and swiftly establishes measures to prevent recurrence, (3) promptly (that is, generally within 5 d of discovery) reports the noncompliance, orally or in writing, to its Animal Care inspector or any Animal Care office and cooperates with the inspector reviewing the incident, (4) has no repeat or critical noncompliance on any inspection report at the involved site during the preceding 12 mo, and (5) has not voluntarily reported a noncompliance at the involved site that falls within the same section and subsection of the AWA regulations or standards during the preceding 24 mo.

When a noncompliance will not be documented as a citation, APHIS shares this assessment with the institution and makes a note of the voluntary reporting by using the institution's customer number, the date the voluntarily reported incident occurred, and the section and subsection of the applicable AWA regulation or standard.[18] Otherwise, the APHIS inspector will document the noncompliance on an inspection report during the next inspection of the involved site. If the institution has already taken appropriate steps to prevent similar problems in the future, the inspector will note the noncompliance as corrected. When the noncompliance has not been corrected and it is not a repeat noncompliance, a correction deadline will be imposed. The institution must then evaluate the incident and take suitable corrective action to prevent future such problems; that is, institutions are expected to correct program problems resulting in noncompliances, in addition to specific cited noncompliances. When a noncompliance remains uncorrected, is repeated, or results from a situation that an institution should have known could seriously affect animal welfare, the institution is subject to possible enforcement action, ranging from a warning to a fine.[12] In determining an appropriate penalty, APHIS is required by Section 2149(b) of the AWA to consider the size of the business, the gravity of the violation, the 'good faith' of the institution, and the history of previous violations.[21]

Almost every citation made by an inspector involves a judgment call, and reasonable people may arrive at different judgments regarding the same set of circumstances. When a difference of opinion occurs, the inspector and institutional representatives may be able to resolve their differences at the time of the inspection. If not, the institution may appeal any citation with which it disagrees; the appeals process is described on the APHIS website.[19] When a citation is appealed, the inspection report will not be publicly available until a final decision regarding the appeal is made.[20]

Animal Species Involved in Direct Noncompliances

APHIS regulation of animals used in biomedical research excludes purpose-bred *Rattus* species, *Mus* species, and birds. Notably, most of the animals involved in cases of noncompliance reported to OLAW from 2009 through 2016 were rodents (73%).[8] Fish were involved in 4% of noncompliance reports.[8] Therefore, about 3/4 of the animals involved in noncompliances reported to OLAW are animals not regulated by APHIS.

Figure 1 A shows the data regarding types of animals used in research regulated by APHIS for the period from 2010 through 2014. Figure 1 B shows the percentages of species involved in direct noncompliances for the same period; the category of 'other' includes ferrets (3%) and rodents other than guinea pigs and hamsters (11%). This rodent category includes gerbils, chinchillas, and wild rodents. Overall, including guinea pigs and hamsters, rodents represent 15% of the animals involved in direct noncompliances from 2010 through 2014. Carnivores (dogs, cats, and ferrets) represent 33%, and ungulates (all of the farm animals) represent 19%. These data are very different from the data on adverse events reported to OLAW during this time period.[8] In fact, the APHIS and OLAW data are almost mirror images of each other. Most of the animals involved in direct noncompliances documented by APHIS were carnivores (33%), followed by ungulates (19%), rabbits (18%), and NHP and rodents (15% each). Published OLAW data from 2009 through 2016 have rodents at 73%, 'other' (reptiles, birds, rabbits, and 'other') at 7%, NHP at 7%, ungulates at 4%, carnivores (dogs) at 2%, fish at 4%, and unknown at 3%.[8] The difference in percentages of rodents is an expected result, given that OLAW data include purpose-bred *Rattus* and *Mus* species, whereas APHIS data do not.

Interestingly, although guinea pigs and hamsters represented most of the research animals APHIS regulated from 2010 through 2014 (33%), they comprised the fewest number of animals involved in direct noncompliances (4%). Conversely, dogs and cats represented the fewest of the research animals regulated (9%) but the greatest percentage of animals involved in direct noncompliances (30%). The other species were involved in direct noncompliances in percentages similar to those for their rankings in regard to usage.

Occurrence of Direct Noncompliances

Most noncompliances at research facilities are administrative or only slightly influence animal welfare. Of the research facility citations documented by APHIS from 2010 through 2014 (3587 total, averaging 717 per year), the greatest proportion of citations (39%) related to the administrative functions of IACUC. Total APHIS citations were outnumbered by total OLAW case reports (6575 from 2009 through 2016,[8] averaging 822 per year), but a majority of OLAW case reports similarly involved institutional and IACUC functions. Protocol, policy, IACUC, institutional, and investigator issues made up 55% of noncompliances reported to OLAW from 2009 through 2016.[8] Adverse events categorized by OLAW as 'other issues' (human error, accident, neglect, abuse, crime, training failure, equipment failure and natural disaster) accounted for 17% of all reported noncompliance cases during this time period.[8] Finally, husbandry issues comprised 12%, biologic issues 13%, and mechanical issues 2% of reported noncompliances for the time period.[8]

For APHIS, during 2010 through 2014, there were 149 direct noncompliances (about 4% of all citations) on 87 inspection reports involving 56 research facilities (about 5% of all registered research facilities). Figure 2 shows the data on direct noncompliances documented by APHIS from 2010 through 2014, in categories created to allow comparison with OLAW data.[8] Of the direct noncompliances, veterinary care issues comprised about 44%, animal husbandry issues (monitoring, water availability, space issues, enrichment issues) were 34%, physical plant issues (ventilation, drainage, construction, maintenance) were 7%, and 'other' direct noncompliances (caused by human error, training failure, mishandling, and so forth) totaled 15%.

Figure 3 is an actual comparison of APHIS direct noncompliance data with OLAW data after case reports involving only institutional and IACUC functions are removed. Most of the remaining OLAW reports involved 'other issues' (39%). Clinical issues (30%) occurred slightly more often than husbandry issues (27%), and physical plant issues accounted for only 5% of the case reports not involving institutional and IACUC functions.[8] For both APHIS and OLAW, physical plant issues occurred relatively infrequently compared with issues involving personnel.

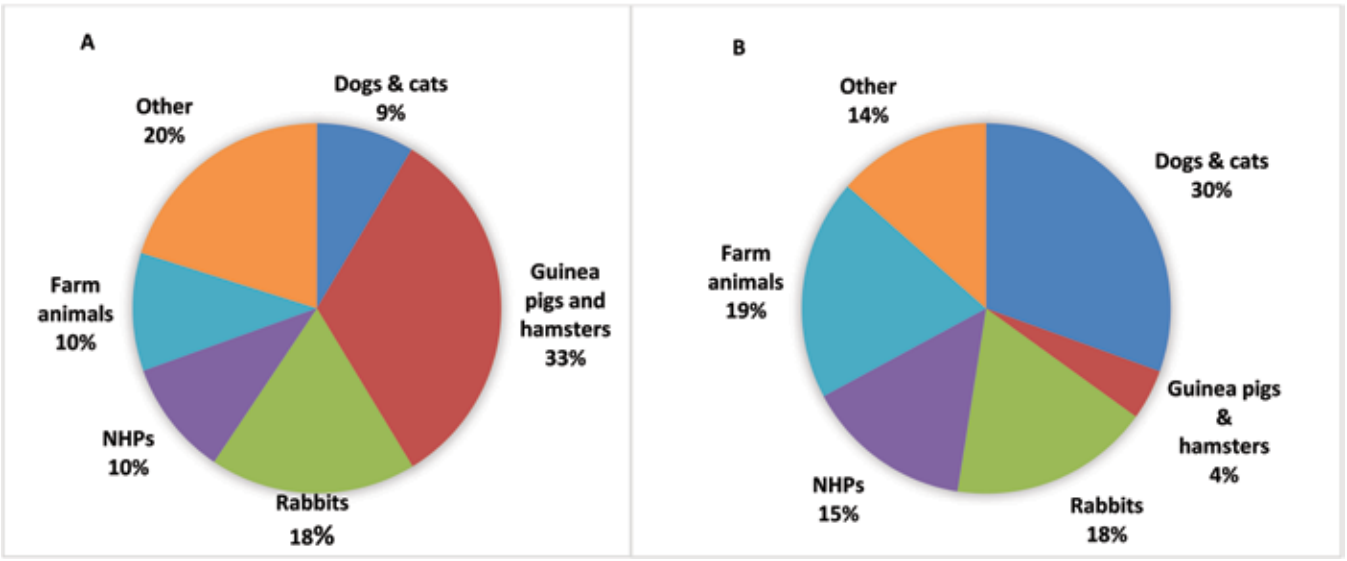

Figure 1. (A) Distribution of the types of animals used in APHIS-regulated research from 2010 to 2014. (B) Distribution of animals involved in direct noncompliances on APHIS inspection reports from 2010 to 2014. The category of 'other' includes ferrets (3%) and rodents other than guinea pigs and hamsters (11%). APHIS regulates the use of warm-blooded animals in biomedical research, excluding purpose-bred *Rattus* species, *Mus* species, and birds.

As these data indicate, successful prevention and mitigation of adverse events require responsive monitoring of animals and enclosures. APHIS has recently published a tech note describing best practices for monitoring.[15] In addition, many adverse events are preventable when they have been anticipated and when steps for prevention are in place. The aim of this article is to help institutions engage in the proactive planning needed to prevent such events and to have suitable action plans in place to mitigate events that cannot be prevented.

Ensuring Comprehensive Planning

It is important to have comprehensive action plans in place so that, when an event occurs, all facets of the event can be dealt with promptly and efficiently. Risk management plans sometimes suffer from a failure to consider the secondary effects of various risks. For example, in planning for disasters (natural or human-caused), institutions might expect and plan for damage and power outages, but they may not have effective plans should the facility become inaccessible. In planning for flooding, institutions might not consider the possibility of contamination of drinking water or electrical malfunction. An electrical malfunction, whatever the cause, might trigger an unanticipated fire, in addition to the expected power outage. Generators—or the gas to run them—may be unobtainable immediately after a disaster.

Human error leading to an animal escape may involve unexpected injury or death of the animal, other animals, or even humans, in addition to the expected necessity of recapture. Poor husbandry leading to overcrowding may result not only in expected aggression and injury to animals but also in unexpected mortality for animals and injury to humans from the aggressive animals. An animal disease outbreak may result in expected morbidity and mortality among the animals as well as in unexpected zoonotic infections in humans, some of which might have long-term effects on human health. Animal injuries or deaths resulting from lack of preparation for adverse events often result in negative publicity if they make the news, and all of the examples just listed interfere with the results of studies using the affected animals. These examples, therefore, highlight the importance of identifying and preparing for secondary, as well as primary, adverse events.

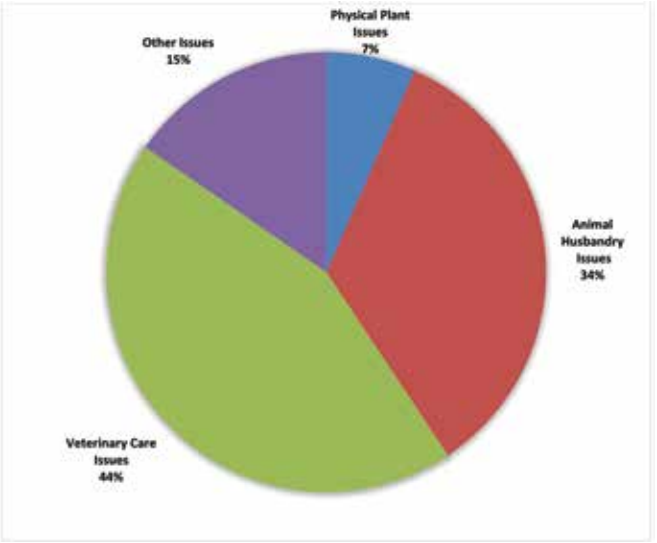

Figure 2. Direct noncompliances documented by APHIS were 4% of all documented noncompliances from 2010 to 2014. The greatest number of direct noncompliances was in the category of veterinary care issues (44%), followed by animal husbandry issues (34%), 'other issues' (15%), and physical plant issues (7%). 'Other issues' included human error, equipment failures, accidents, and so forth.

Types of Adverse Events

To allow comparison with OLAW data, direct noncompliances (including—but not solely consisting of—adverse events) were classified as veterinary care issues, animal husbandry issues, physical plant issues, and 'other' issues. The category of other issues includes adverse events caused by natural disasters or by human intent or errors, such as animal abuse or other crimes, accidents, neglect, training failures, poor handling, and so forth. Additional 'other' types of events involve environmental threats (such as environmental temperature extremes and large-scale disease outbreaks or infestations) and events caused by the very

	APHIS 2010-2014	OLAW 2009–2016
Total no. of citations (APHIS) or case reports (OLAW)	3587 (717/y average)	*6575* (822/y average)
No. of citations or case reports involving institutional or protocol issues	1399 (280/y average) 39% of total citations	3616 (452/y average) 55% of total reports
Total no. of direct citations (APHIS) or adverse event case reports (OLAW)	149 (30/y average) 4% of total citations	2893 (362/y average) 44% of total reports
No. of 'other' citations (APHIS) or case reports not involving violations (OLAW)	2039 (408/y average) 57% of total citations	66 (8/y average) *1%* of total reports
No. of veterinary care adverse events (APHIS direct citations) or adverse event case reports (OLAW)	66 (13/y average) 44% of direct citations 2% of total citations	855 (107/y average) 30% of adverse event report *13%* of total reports
No. of animal husbandry adverse events (APHIS direct citations) or adverse event case reports (OLAW)	51 (10/y average) 34% of direct citations 1% of total citations	789 (99/y average) 27% of adverse event reports *12%* of total reports
No. of physical plant adverse events (APHIS direct citations) or adverse event case reports (OLAW)	10 (2/y average) 7% of direct citations 0.3% of total citations	132 (17/y average) 5% of adverse event reports *2%* of total reports
No. of 'other' adverse events (APHIS direct citations) or adverse event case reports (OLAW)	22 (4/y average) 15% of direct citations 0.6% of total citations	1118 (140/y average) 39% of adverse event reports *17%* of total reports

Figure 3. Comparison of categories in APHIS citations and OLAW case reports. Note that the differences between the agencies, their data sources, and their methods of collecting information prevent these data from being compared directly. These differences alone cause divergent results, which nevertheless are a matter of interest. Regarding the OLAW data, those actually reported by OLAW[8] are in italics; nonitalicized values were calculated from reported data. Because of rounding, discrepancies exist in both numerical and percentage totals. OLAW[8] categorized 44% of case reports received from 2009 to 2016 as involving 'adverse events;' that is, those due to human error, accident, neglect, abuse, crime, training failure, equipment failure, or natural disaster. APHIS 'other' citations are those that are not reported elsewhere in the chart; that is, citations that are neither direct citations nor those that involve institutional or protocol issues. Note that the data for APHIS 'other' citations and OLAW case reports not involving violations are not comparable; these data were included simply to account for all of the data points for each agency.

nature of the animal (such as escapes, aggression, and development of stereotypical behaviors). In the rest of this article, these same classifications are used to organize examples of adverse events for discussion, although some overlap between categories is apparent.

Many of these examples are simply adverse events that might be anticipated to occur at research facilities. Others are examples of events that have actually occurred and been reported in the media. A few are examples documented on APHIS inspection reports. Although direct noncompliances at research facilities are rare, some types of direct noncompliances have occurred at multiple facilities, and the causes of some direct noncompliances might arise at any facility, so a discussion of these examples will likely help facilities to make proactive plans that prevent or mitigate adverse events.

As noted earlier, issues involving personnel outnumber physical issues. Personnel issues involve many categories of adverse events, including veterinary care, animal husbandry, and 'other' issues. For example, human-caused issues in the 'other' category include both deliberate events and those due to human error.

Deliberate events are those that are caused by humans with the intent to harm research facilities or personnel. Examples include attacks (including physical assaults, terrorism, and cyber-attacks), threats (such as bomb threats), the theft or intentional release of animals, arson, animal abuse, sabotage of equipment or records within the institution, vandalism, tampering with supplies or medicines, and strikes. These events may be caused by an institution's own employees or by outside personnel. The stored data of research facilities is becoming increasingly susceptible to compromise. Cyber-attacks can lead to leakage of stored data, including personnel records as well as research data.[8] Likewise, automated, centralized environmental control systems are susceptible to hacking.[8] Facilities may wish to take advantage of free 'assist visits' and security surveys offered by the US Department of Homeland Security, which will provide a detailed assessment of the security and resilience of a facility.[27]

Human error includes events such as accidents, neglect, training failures, poor handling, and so forth. Transportation is especially hazardous. Failure to control temperatures or to provide appropriate ventilation (that is, adequate fresh air without exposure to exhaust fumes) can result in animal deaths. Temperature and air-quality monitoring (preferably with associated records and possibly with associated alarm systems) may help prevent such incidents. A camera that allows the driver or a passenger to view the animals provides increased assurance of animal safety, including the ability to recognize injured or ill animals expeditiously. Road accidents during transportation can result in many animals escaping or needing veterinary care simultaneously in an unexpected location. Contingency plans should be in place to help handle such incidents.

Inadequate care and mishandling can occur during transportation, at a satellite facility, or at the main facility. Animals might be provided inadequate care or mishandled due to inadequate employee training, carelessness, or poor anger management. For example, animals have been forgotten and left in inappropriate places while being moved for transportation or cleaning purposes. Rabbits have received serious spinal injuries because of poor handling by employees, even after training in proper handling procedures. In some cases, recumbent animals have received inadequate care. In several cases, anesthetized animals have suffered thermal burns from incorrectly used heating devices. In one case, an NHP died because it was returned to the wrong group enclosure after a procedure. In another, a rabbit

was bled to death when protocol procedures were not followed, and in yet another, a goat was bled for antibodies despite showing signs of illness. Animals have escaped and been injured (or injured others) when employees failed to secure an enclosure properly or removed animals from their enclosures for transport, veterinary care, transfer to another enclosure, and so on. Because of the risk inherent in the process of removing animals from their enclosures, it is important to make provisions for secondary containment, when possible. In addition, animals have been injured (for example, incurred broken limbs) when equipment (such as, squeeze equipment, guillotine doors) was operated incorrectly. In several cases, animals have been killed by being run through cage washers accidentally. Events involving human error are serious because they can result in injury or even death of animals and people, interference with study results, and negative publicity.

Animal husbandry issues are often a special category of human-caused events, especially in short-staffed facilities. Husbandry-related events may affect one or more animals, and they include situations such as absent, inadequate, inaccessible, or tainted food or water; failure to monitor animals appropriately; sanitation issues endangering the health of animals; overcrowding resulting in injuries due to aggression; inadequate or inappropriate enrichment; and miscellaneous problems, such as cage flooding. No employee is infallible, and a system for random back-up checks can help ensure that appropriate types and amounts of uncontaminated food and water are available to animals. Enough clean and safe receptacles should be available to provide access for all animals, without fighting; receptacles should be positioned to minimize possible contamination, and they should be secured to prevent spillage. Checking water sources at least daily helps to ensure that sufficient uncontaminated water is available. During 2010 through 2014, there were 7 citations on APHIS inspection reports (among 3587 total citations) regarding the lack of available water; several of these cases resulted in animal deaths. Animals unable to obtain water will stop eating, but water problems should be identified before uneaten food becomes obvious. In outdoor enclosures, water is especially important on hot days, but provisions also are needed to keep it from freezing on cold days. Animals that have been without water for extended periods are vulnerable to water intoxication when water accessibility is not carefully and slowly restored. Too much water in the enclosure itself can be a problem as well. Cage flooding may occur due to a water system malfunction or to employee error when linking up the system. Planning should be aimed at preventing such problems and, when necessary, identifying and dealing with them as quickly as possible.

One problem often associated with serious animal incidents is the failure of employees to monitor animals appropriately. In one instance, 2 voles died with empty water bottles after 5 d of no observation. In several cases, employees failed to monitor animals as prescribed in protocols; for example, by not tracking weights or by not monitoring restrained or anesthetized animals. In other cases, employees failed to note ill or injured animals, or they insufficiently monitored animals under treatment for injury or illness. In some cases, animals were found unresponsive or dead during APHIS inspections, from unnoted chronic conditions, or from study procedures that were supposed to include close monitoring for possible ill effects. In one memorable case, 3 autolyzed NHP carcasses were found during an inspection. Institutions can avoid such adverse events by ensuring that correctly trained and supervised employees appropriately monitor all animals.

Section 1752(a)(2) of the 1985 amendments[24] to the AWA introduced environmental enrichment for the psychologic wellbeing of NHP. Appropriate enrichment is important to help prevent distress in research animals, which may manifest in unwanted behaviors (such as aggression) or stereotypic activities (such as pacing, head swaying, and self-injurious behavior). Unrelieved distress also leads to unreliable research data. However, enrichment devices can themselves present possible dangers. Assessment of enrichment devices for possible dangers to animals is similar to the assessment of toys for small children. Problems may occur with devices that have sharp points or edges; have toxic components (for example, lead paint); contain strings or other parts that animals could swallow; allow animals to get entangled or strangled; allow escape from an enclosure (for example, a box that could be used to climb over an enclosure fence), or encourage fighting among group-housed animals. The safety concerns of enrichment devices are discussed in *Environmental Enrichment for Captive Animals*,[29] and the discussion is summarized (with a safety checklist) in the "Environmental Enrichment" section of the *Orangutan Husbandry Manual*, available on the website of the Center for the Science of Animal Care and Welfare of the Chicago Zoological Society.[6] A brief discussion of some risks of environmental enrichment is included in a recent article on the subject.[5]

Social housing is a component of the environmental enrichment requirements. The AWA regulations for NHP require social housing of compatible animals of social species unless an animal is exempted for veterinary medical reasons or for scientific reasons justified in a protocol and approved by the IACUC. [21] However, an understanding of the normal group dynamics of a species is essential in setting up social housing, to try to ensure safe and appropriate housing in pairs or groups. Aggression is probably the most common problem caused by the formation of inappropriate social groups. Institutions must be careful to avoid social housing situations that might negatively affect the welfare of NHP.

Veterinary care issues include issues involving surgeries, treatments, anesthesia, analgesia, and use of paralytics; incomplete euthanasia; adverse reactions to biologics, drugs, chemicals, procedures, or diseases; and disease or infestation outbreaks within the facility. Like animal husbandry issues, many veterinary care adverse events are a special category of human-caused events. Veterinary care issues involve not only poor veterinary care itself but also related problems, including an inadequate number of people to provide care, lack of authority on the part of the veterinarian, failure to notify the veterinarian of a problem, and failure to follow the veterinarian's instructions regarding treatment or euthanasia—all of which may result in delayed, absent, or failed treatments or distressful deaths. The provision of wallet cards with contact information for key employees (such as the veterinarian) may facilitate prompt attention to identified problems.

Unalleviated distress or pain in individual animals that is not IACUC-approved as a scientifically necessary component of a protocol constitutes a direct noncompliance that requires prompt care and corrective actions when institutional planning is unsuccessful in preventing it altogether. This category includes issues involving body care (such as matted coats causing sores, overgrown toenails or hooves causing foot problems, and overgrown teeth interfering with eating). Efforts to minimize distress and pain include frequent monitoring and appropriate action to prevent problems.

Incomplete euthanasia is a recurring problem that is easily preventable. When the primary euthanasia method (for example,

the use of carbon dioxide) may result in failure, secondary methods will ensure death prior to disposal. Secondary steps to ensure the death of euthanized animals include thoracotomies, exsanguination, decapitation, pithing, and in some cases, cervical dislocation.[2] Random backup checks on employee performance help to ensure sufficient training and correct implementation of euthanasia techniques.

Physical plant issues include failures of mechanical and electrical equipment (such as the lighting, the entire electrical system, water supply, drainage system, HVAC, and backup systems), hazardous material spills or leaks internal to the facility, and issues with the construction or maintenance of the facility. Such issues also include problems with transportation vehicles, such as inadequate climate and ventilation control. Inadequate climate control in vehicles can lead to frostbite or deaths due to hypo- or hyperthermia, and inadequate ventilation can cause either illness due to the introduction of exhaust fumes into animal areas or asphyxiation when insufficient fresh air is provided. In fixed facilities, physical plant issues may cause secondary problems such as fires, isolated flooding, diseases due to contaminated air, and so forth. Frequent monitoring, preventive maintenance, and regular testing of backup systems are important to prevent such problems.

Fires caused by physical plant issues can spread rapidly, and drills on how to respond to possible fires will help employees to quickly identify and react to problems. For example, breakers can be switched off when smoking wiring is noticed, to help prevent an actual fire. A small fire may be put out with a fire extinguisher before it spreads, when employees are able to respond properly. Once a fire reaches a stage requiring mass evacuation, it is likely too late for staff to try to save the animals. However, first responders might be able to take protective actions if the institution regularly coordinates with them prior to emergencies to ensure they know where the animals are located. The smoke, heat, and gases from a fire usually are more dangerous than the flames. Smoke may make it hard to see, and it can kill both humans and other animals. The heat of a fire can also kill. Inhaling the superheated air can scorch lungs, and the heat can melt objects onto bodies. In addition, fire consumes the oxygen needed for breathing and produces carbon monoxide gas, making people and animals disoriented and drowsy. Asphyxiation is the leading cause of fire deaths, exceeding burns by a 3:1 ratio.[28] Institutions need working smoke and carbon monoxide detectors as well as procedures to ensure that people are alerted by and respond promptly to alarms, even at night and during weekends and holidays. Planned responses must take into account all of the dangers of fire, not just those due to flames. Institutions should regularly test prevention and response procedures and equipment (including smoke alarms, fire alarms, fire extinguishers, sprinkler systems, emergency lighting, and fire doors) to ensure that they—as well as procedures and equipment involved with other life-safety parameters (such as electrical power system alarms, HVAC system alarms, emergency gas shut-off valves, security cameras, and others)—will function correctly in an emergency.

In addition, institutions should ensure that construction materials in animal facilities support appropriate animal care. The use of inappropriate flooring materials is a relatively common construction issue. Mesh floors must prevent feet from slipping through, be strong enough not to sag, and have wide enough strands (or coated strands) to prevent foot injuries. Solid enclosure floors must be of nonslippery materials.

Inadequate maintenance can similarly result in problems, such as broken wires, with sharp ends protruding into the enclosure; obstructed ventilation, leading to a build-up of ammonia or insufficient fresh air; and clogged drains, causing animals to stand in water contaminated with urine and feces. Institutions must try to ensure that employees promptly notice and report construction and maintenance problems and that those problems are fixed rapidly, to avoid further complications. Frequently scheduled maintenance inspections can help to prevent serious facility problems.

One recurring problem is malfunctioning thermostats, which can cause inadequate or excessive heat. The most common problem is excessive heat, when the thermostat fails to cut off the heater, causing animals to die of hyperthermia. HVAC systems can be set to fail in the off position, which may help prevent such overheating. Another safeguard is the use of temperature sensors that raise an alarm when temperatures drop below or exceed an acceptable range, but personnel must be available to receive and respond to such alarms at all times, including nights, weekends, holidays, and weather emergencies. When a thermostat or heater malfunctions during an ice storm, for example, animals might die of hypothermia if provisions have not been made to help ensure that employees can respond during such an emergency.

Natural disasters include events due to weather (hurricane, tornado, winter storm, thunderstorm, drought), seismic incidents (earthquake, landslide, tsunami), and other emergencies (fires and floods originating outside the facility). Secondary effects of such events include power outages, equipment failures, building damage, and the inability to get supplies and personnel to the facility. An effective facility disaster plan should address all of the types of events— as well as all of the facets of such events—likely to affect the facility. Weather particularly poses problems for animals kept outdoors. Lightning, hail, blowing debris, and falling trees or tree limbs may cause injuries or even deaths. In any disaster, employees have to be willing and able to get to the facility to provide care for the animals. In some disasters, employees may need to take care of their own problems rather than those of the institution. In others, roads may be impassable (for example, due to flood or earthquake damage, flood or tornado debris, ice and snow), or law enforcement may limit who is allowed into disaster areas. Emergency plans must be considered carefully to try to ensure that every aspect will actually function in a real disaster. Tabletop exercises, especially when conducted by experienced emergency managers, may be helpful in identifying plan deficiencies. Further information on planning for disasters is available on the Animal Welfare Information Center website.[25] An archived document available from that website has an excellent article and checklist to help animal facilities prepare for disasters.[23] In addition, the National Academies of Sciences, Engineering, and Medicine recently published a report by an expert committee convened to develop recommendations and guidance to enhance the disaster resilience of the academic biomedical research community.[3] Furthermore, when creating disaster plans, it is often helpful to contact institutions that have previously experienced disasters, to learn from their experiences. The research community as a whole might consider creating a hub through which institutions can share knowledge, experiences, and resources with regard to disasters and disaster planning—similar to the Zoo and Aquarium All Hazards Preparedness, Response and Recovery Fusion Center created by the exhibitor community.[30]

Floods have been a relatively common disaster for research facilities, and animals kept in basements are particularly susceptible to drowning during floods of any type; consequently such housing is problematic. Animals kept in outdoor enclosures,

especially in low-lying areas, are also susceptible to drowning, from both unexpected (for example, broken water mains) and anticipated sources of flood water. In addition, these animals might become able to escape their enclosures and possibly be injured or killed, if the fencing is damaged or if high waters allow them to swim over the fence. Storms without flooding may enable animals to escape when fencing is damaged or downed branches allow animals to climb from their enclosures. In such cases, effective secondary containment may prevent loose animals from escaping the property.

Damage from fires originating outside the facility may be preventable by keeping a defensible space around the property. Smoke and ash problems from nearby fires must be considered also. Evacuation plans for animals as well as humans should be developed and practiced, whenever feasible. For urban facilities, there is a danger that fires may spread from adjacent properties. Abandoned properties are especially subject to arson attacks. Information on protecting homes and buildings from wildfires is readily available on the Internet. The National Fire Protection Association has a Standard on Fire and Life Safety in Animal Housing Facilities that is freely available online.[9] In addition, institutions can coordinate with local fire departments to help assess what might be done to prevent or mitigate dangers from fires. When animals cannot be evacuated, means to protect them from the effects of nearby smoke and fires may be available.

Environmental threats include such things as extreme environmental temperatures and problems originating outside the facility, including hazardous materials contamination and large-scale disease outbreaks or infestations. Environmental temperature extremes can cause problems when shelter is inadequate. What constitutes an excessively cold or hot temperature depends on the animal, relative humidity, wind speed, and other factors. Sometimes, obvious steps to prevent problems, such as shearing outdoor sheep before hot weather arrives, have been overlooked. Problems originating outside the facility, such as hazardous materials contamination (chemical spills, radiation leaks, water supply pollution), can pose both short- and long-term risks to the health of animals and facility personnel. Such contamination is especially possible when highways, rail lines, or pipelines are nearby. In addition, disease outbreaks can spread rapidly and may affect not only animal welfare and health but also human health (with zoonotic diseases) as well as interfere with the results of studies using affected animals. It is important to have adequate disease prevention and control programs to help prevent the introduction and spread of disease vectors in the animal populations of research facilities.

The types of environmental hazards that might affect animals depend on their environments. For example, indoor animals in old buildings may be exposed to asbestos or lead paint. Outdoor animals can be exposed to toxic plants or herbicides. Air, water, and soil pollution may all cause problems. In buildings, molds may be problematic. Outdoors, fungal growth in water sources may be a problem. Pesticides may cause problems indoors or outdoors, and parasites may be acquired from contaminated environments. In pastures, burrowing animals (for example, gophers, prairie dogs) may create holes that endanger livestock. Stinging insects (including fire ants) and poisonous snakes may be a concern, especially during particular seasons. Safe and effective pest control practices are essential, and minimizing pest populations minimizes food sources for snakes. Institutions should carefully evaluate the environments in which their animals live, identify possible problems that might occur, and take appropriate actions to prevent them.

Events caused by animal nature include things such as escapes, aggression toward other animals or people, development of stereotypical behavior, and entrapment or injury (for example, by chewing electrical wires). Some animals, such as NHP, are particularly prone to escaping their enclosures. For example, NHP have escaped by opening latches, unscrewing screws, swimming moats, and using branches or enrichment devices as ladders or springboards. In one case, NHP escaped by removing an unsecured food hopper and exiting their enclosure through the resulting hole. Escaped animals may be injured or killed, and they may injure or kill humans or other animals. Provisions for secondary containment help to prevent loose animals from escaping the property. Institutions should have plans for dealing with escapes, in addition to measures to prevent them.

Aggression toward people may result in injury or death (including euthanasia) for the animal as well as for the human (including death from zoonotic disease). Aggression toward other animals may result in the injury or death of several animals. Institutions must use careful monitoring, especially during introductions, to try to ensure that cohoused animals are compatible. Enclosures should allow subordinate animals to avoid and escape from aggression. Neighboring animals that are incompatible must not be able to injure each other through the sides of their enclosures or to gain access to each other through unsecured panels. In addition, employees must be trained and supervised appropriately. In one case, a primate died because an employee returned it to the wrong group enclosure after a procedure. Employees responsible for animal care should be sufficiently trained in animal behavior to recognize the circumstances and signs likely to lead to aggression, so they can prevent foreseeable attacks.

Furthermore, institutions must be alert for design elements that could result in animal injuries or deaths. For example, V-shaped elements, such as angled support poles, can strangle an animal if its head becomes stuck in the V, with livestock being especially susceptible. Ropes, cables, chains, and similar devices added to enclosures, including those used to suspend enrichment devices, can injure or kill animals also. Other enclosure areas or furnishings in which an animal's head or limbs could become entrapped might similarly cause serious injuries or death. NHP in mesh enclosures may reach through one part of the mesh and back in through another. If they are startled while in such a position, they might injure their arms as they try to pull loose quickly. When enclosures have bars, the spacing between bars must be appropriate to avoid causing entrapment injuries. Flighty animals may need enclosures that are small enough to prevent them from being injured by colliding at speed with enclosure walls or ceilings when trying to escape. To prevent electrocutions caused by electrical shorts or chewing on wires, electrical wires and outlets must be out of animals' reach. Employees must be alert to identifying elements of enclosures that might cause injuries or deaths, but bringing in 'fresh eyes' to make such examinations can be helpful, because people frequently overlook possible problem areas in facilities that they see every day.

Summary

Many types of adverse events are preventable, but meticulous planning is required to establish a successful prevention and mitigation strategy. Figure 4 includes a list of issues of particular concern because they have been documented at multiple research facilities and have especially severe negative consequences on animal welfare. Many of these issues also are listed in a similar table published by OLAW,[8] emphasizing the

Recurring Major Direct Noncompliances
NHP
Strangulation by a rope, cable, chain, or other item holding an enrichment device
Death or injury by or to escaped animals
Rodents
Incomplete euthanasia
Death by drowning due to malfunction of a watering system
Rabbits
Spinal injuries due to inappropriate handling
Multiple species
Thermal burns due to the incorrect use of heating equipment on anesthetized animals
Death during transport
Death by drowning during a storm; for example, animals in a basement
Death by dehydration due to malfunction of a watering system or failure to fill receptacles
Death due to putting an animal through a cage wash
Death or injury due to inappropriate monitoring
Death or injury due to faulty or mishandled equipment; for example, guillotine doors, squeezes
Death due to the failure of thermostats

Figure 4. Recurring major direct noncompliances at research facilities as documented in news reports or by APHIS (or both).

need for institutions to include them in prevention and mitigation plans. It is highly recommended that such adverse events be reported to APHIS, to inform the agency about the situation (before the reporters call), provide documentation of corrective actions, and demonstrate a 'good faith' intention to comply with the AWA and regulations. In addition, reporting enables APHIS to work with the institution to identify and correct deficiencies in the animal care program.

Conclusions

Adverse events are those that lead to significant injury or illness, unrelieved pain or distress, or the death of an animal. Adverse events are a risk of conducting research, and effective risk management practices are needed to prevent and mitigate such risks. Although the probability of a serious adverse event at a research facility may be low, its effect can be great, involving not only animal welfare but also research data and the institution's reputation. This article surveys adverse events that might occur or that have actually occurred at facilities regulated by APHIS, to provide useful data for those institutions desiring to make plans to help prevent or mitigate such events. To ensure animal, personnel, and institutional wellbeing, every facility must carefully consider its risk of exposure to adverse events and their sequelae, to be prepared to prevent or mitigate such events in the future.

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