People for the Ethical Treatment of Animals
Rebuttal to Federation of American Societies for Experimental Biology's
Reforming Animal Research Regulations

February 8, 2018

Executive Summary

In December 2016, the 114th U.S. Congress enacted the 21st Century Cures Act with the laudable goal of accelerating the discovery, development and delivery of treatments for disease. Section 2034 of the 21st Century Cures Act directs leadership of the National Institutes of Health (NIH), U.S. Department of Agriculture (USDA), and the Food and Drug Administration (FDA) to "complete a review of applicable regulations and policies for the care and use of laboratory animals and make revisions, as appropriate, to reduce administrative burden on investigators while maintaining the integrity and credibility of research findings and protection of research animals."

A vocal minority from the animal experimentation community—led by the Federation of American Societies for Experimentation Biology (FASEB) and the lobbying group, National Association for Biomedical Research (NABR), which has long taken exception to federal oversight of the use of animals in experimentation—has compiled recommendations that would effectively gut current protections for animals in laboratories. If implemented, these recommendations, summarized in FASEB's report, "Reforming Animal Research Regulations" ("the FASEB Report") would nullify the protections enacted by Congress over the past 33 years; violate the will and trust of the American public; and fail to uphold the provision in 21st Century Cures Act that requires "maintaining … protection of research animals."

The FASEB Report is the product of an April 17, 2017, workshop, which involved some three dozen participants who either actively engage in animal experimentation, represent institutions with large animal experimentation programs, or actively promote or lobby for the use of animals in research. Given these participants' lack of credibility with regard to animal welfare, and the history of abuses that took place at their institutions (detailed in this report), we recommend that this and any future reports on this topic that argue that animals are given too much consideration be viewed with the appropriate skepticism and disregarded.

Of the nearly two dozen recommendations listed in the FASEB Report that would undermine animal welfare and place regulatory oversight in the hands of animal experimenters, the following would have particularly catastrophic implications for animal welfare:

- The FASEB Report recommends "harmonizing" federal animal welfare requirements "to conform to the least burdensome standard." However, in order to maintain protection of animals, the regulations, guidelines, and policies governing the use of animals in experimentation should conform to the highest possible standard.
- The FASEB Report recommends reducing the frequency of inspections by both the U.S. Department of Agriculture (USDA) and also facility oversight committees, called Institutional Animal Care Use Committees (IACUCs). However, federal reports show that these inspections are crucial to catching serious violations of animal welfare regulations and guidelines.

- The FASEB Report recommends that the USDA consider an institution's certification through the private, third party organization, Association for the Assessment and Accreditation of Laboratory Animal Care (AAALAC) International as a factor in reducing the inspection frequency. However, a peer-reviewed 2015 study revealed that laboratories accredited by AAALAC were cited for violations of AWA regulations more frequently than unaccredited facilities. The responsibility of overseeing the use of animals in experiments should not be handed over to private, industry-friendly organizations who operate without transparency.
- The FASEB Report recommends that some proposed experiments on animals would only have to be reviewed by a single individual or as an administrative matter, rather than by the full IACUC. This would undermine the critical role played by IACUCs in providing institutional oversight of animal use.
- The FASEB Report recommends less transparency and public accountability. This would shield federally-funded experimenters from the scrutiny of the public whose tax dollars bankroll the experiments.
- The FASEB Report recommends permitting the approval of multiple major survival operative procedures on a single animal. However, this would impair the animal's physical and psychological well-being.
- The FASEB Report recommends weakening requirements for experimenters to search for alternatives to the use of animals in experiments and for methods that minimize the pain and distress suffered by animals. This is lazy, cruel and poor scientific method.

Violations of federal regulations and guidelines are rampant in U.S. laboratories, and animals are suffering as a result. A culture of noncompliance in which fines are considered the "normal cost of conducting business rather than a deterrent for violating the law" has taken root, leaving animals vulnerable to the most egregious of abuses. Furthermore, over the last two decades, we have seen a "gradual erosion of public confidence in researchers and the research process [which] has resulted in questioning, from the public and Congress, about … how animal subjects are being treated" (Dempsey 2001).

Considering that 95 percent of drugs which were developed using animals fail in human studies (National Center for Advancing Translational Sciences 2017), resources must shift toward human-relevant, animal free research methods. If we are serious about reducing administrative burden, more stringent requirements should be placed at the points where projects are funded and protocols approved—to ensure that money is only disbursed and projects only greenlighted when there is confidence that something useful will come from the work. By shifting away from projects involving animals and increasing investments in human-relevant projects, we can successfully comply with the directive of the CURES Act to maintain the integrity of research findings while also protecting animals.

We have summarized our concerns in this analysis, and also provide practical recommendations that would reduce administrative burden while also "maintaining the integrity and credibility of research findings and protection of research animals."

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A. Congressional Directive to Reassess Current Animal Welfare Laws and Recommendations of Animal Experimenters

In an effort to make public funding and oversight of biomedical research more effective and efficient, the 21st Century Cures Act (CURES Act) directs leadership at the National Institutes of Health (NIH), United States Department of Agriculture (USDA), and Food and Drug Administration (FDA) "to reduce administrative burden … while maintaining the integrity … of research findings and protection of … animals" (114th Congress 2016).

In response to this directive, a consortium of groups—the Federation of American Societies for Experimental Biology (FASEB), the Association of American Medical Colleges (AAMC), the Council on Governmental Relations (COGR), and the National Association for Biomedical Research (NABR)—convened a one-day workshop. These groups recommend that animal laboratories should largely be allowed to monitor themselves so it not surprising that the three dozen participants at the workshop either actively engage in animal research, represent institutions with large animal research programs, or actively promote or lobby for the use of animals in research. (NABR is a trade group that, among other activities, advises animal experimenters how to avoid Freedom of Information Act (FOIA) requirements.) The discussions from this workshop formed the basis of a recent report, titled, "Reforming Animal Research Regulations: Workshop Recommendations to Reduce Regulatory Burden," referred to in this analysis as the "FASEB Report" (FASEB, AAMC, COGR, NABR 2017). It proposes recommendations that would reduce transparency and accountability, while also eliminating current minimal protections for animals by reducing the frequency of Institutional Animal Care and Use Committee (IACUC) inspections from semiannual to annual; eliminating the current requirement for annual USDA inspections of laboratories; and diluting IACUCs' protocol review requirements. Perhaps a reflection of the vested interests of the authors, the report contends that the real victims of animal experiments are the experimenters themselves, and argue that "excessive" precautions to protect animals undermine their work.

The authors claim that "[r]esearchers take their commitment to the humane care and use of research animals very seriously, but there are numerous conflicting, outdated, or ineffective regulations that do not improve animal welfare." The notion that these individuals take seriously their responsibility to protect animals is demonstrably false, as outlined later in this analysis. The implication from the FASEB Report that improving animal welfare is a motivation for their reform efforts is also contradicted by the evidence presented here. The CURES Act specifically states that federal oversight of animal welfare should not be weakened; the FASEB Report was clearly written to justify doing exactly that.

B. The Proposed Changes in the FASEB Report Have Catastrophic Implications for Animal Welfare

While the FASEB Report lists almost two dozen recommendations that would undermine animal welfare and place regulatory oversight in the hands of animal experimenters, here we will list and describe those recommendations that are most at odds with the goals of the CURES Act and would have the most severe consequences for the welfare of animals used in experiments.

We will also provide examples that document animal experimenters' disregard for current federal laws and that make clear the intentions of the FASEB Report authors: not to reduce regulatory burden, but to

give animal experimenters absolute authority over their use of animals and to obstruct the transparency of taxpayer-funded animal experiments. We will preferentially offer examples that have occurred at the institutions with which the FASEB Report authors are affiliated and involve the animal use programs that many of these individuals are charged with supervising, though we are able to provide additional examples upon request.

1. *FASEB Report Recommendation: Harmonize existing federal requirements for those species currently covered by USDA and those covered by the PHS Policy to conform to the least burdensome standard while maintaining animal welfare.*
   This recommendation should not be implemented. In order to ensure that the welfare of animals is not compromised, harmonization of existing federal requirements stipulated by the Animal Welfare Act (AWA) and Public Health Service (PHS) Policy should occur at the highest standards of care and not the lowest.

   At present, the AWA excludes "birds, rats of the genus *Rattus*, and mice of the genus *Mus*, bred for use in research; horses not used for research purposes; and other farm animals" from the definition of "animal," meaning there is no federal law with legally-enforceable standards governing the use of these species or protecting them from harm. These species make up an astounding 95 percent of all animals used in laboratories. Although multiple efforts—including a 2000 lawsuit settlement—have been undertaken by animal protection groups to extend the protection of the AWA to the excluded species, these attempts have failed, as animal experimenters have argued that providing protections for these species would be too burdensome (American Psychological Association 2002, FASEB 2000). The grave consequences of this exclusion—advocated for by the very groups that now seek further gutting of protections—are evident in the findings of several surveys that document that vast numbers of mice and rats experience unrelieved pain and distress in laboratories. In particular, a 2009 survey found that post-procedural analgesics are provided to mice and rats undergoing surgical procedures only 20 percent of the time (Stokes, Flecknell and Richardson 2009), while anesthetic agents with analgesic properties are administered only 34 percent of the time. A 2005 paper estimated that 50 to 60 percent of mice and rats used in painful experiments receive no pain relief (Richardson and Flecknell 2005).

   In contrast to the coverage of the AWA, the PHS Policy includes *all* vertebrate species; it defines animal as "any live, vertebrate animal used or intended for use in research, research training, experimentation, or biological testing or for related purposes." By conforming to the "least burdensome standard," as recommended in the FASEB report, any mistreatment experienced by the 11-26 million animals excluded from the AWA (Speaking of Research 2017) would never be monitored or reported, and would have no consequence or scrutiny.

   For example, it is only because PHS Policy includes these species and requires violations of their care and use to be reported to the NIH Office of Laboratory Animal Welfare (OLAW) that there was any record of the following events:

   a. At the University of Alabama Birmingham, the institution with which FASEB Report author J. Crawford Downs is affiliated, at least 58 mice and 14 rats suffered inhumane deaths at the hands of incompetent staff over a two-year period:
      i. Twenty-six mice suffocated, 19 after an airflow valve was left closed by a technician and the other 7 after being left in an air-locked isolator overnight (NIH OLAW 2013, NIH OLAW 2014).

ii. Eleven mice drowned after their cages flooded (NIH OLAW 2014).
iii. Twenty-one mice died following an irradiation experiment because they weren't being closely monitored by the experimenter or any staff (NIH OLAW 2014).
iv. Fourteen rats died after being overdosed with a drug that was improperly prepared (NIH OLAW 2014).

b. At Johns Hopkins University, the institution at which FASEB Report author Nancy Ator is the IACUC Chair, OLAW correspondence revealed that staff attempted to freeze mice and rats who were still alive (NIH OLAW 2008, NIH OLAW 2010).

2. FASEB Report Recommendations to Reduce Inspection Quality and Quantity:
   a. *FASEB Report: Congress should amend §2143(b)(3) of the Animal Welfare Act (AWA) and §495(b)(3) of the Health Research Extension Act (HREA) to require only annual inspection by the IACUC.*
   b. *FASEB Report: Revise §2.31(c)(3) of [the Animal Welfare Regulations] to state: "The IACUC may, at its discretion, determine the best means of conducting an evaluation of the institution's programs and facilities that includes all members wishing to participate in the process. The IACUC may invite ad hoc consultants to assist in conducting the evaluation. However, the IACUC remains responsible for the evaluation and report."*
   c. *FASEB Report: Congress should amend §2146 of the AWA to remove the requirement for annual USDA inspection of research facilities and allow for an inspection frequency based on compliance history, as part of the agency's Risk Based Inspection System process. USDA should consider including AAALAC International accreditation as a factor in their risk assessment.*
   d. *FASEB Report: Revise §2.31(d)(5) of the AWA Regulations (AWR) as follows: 'The IACUC shall conduct continuing reviews of activities covered by this subchapter at appropriate intervals as determined by the IACUC, including a review as required in §2.31(d)(1-4) at least* once every three years." *This would make review frequency consistent with the PHS Policy.*

These recommendations should not be implemented. Currently, IACUCs are required by the AWA to conduct semiannual inspections. In documents received via FOIA requests, correspondence between OLAW and institutions detailing noncompliance with PHS policy as outlined in *The Guide for the Care and Use of Laboratory Animals* makes clear that some of the reported incidents – such as failure to provide analgesia or serious deviations from IACUC-approved experimental protocols – are observed during an IACUC inspection. Therefore, keeping a twice-a-year inspection schedule is an important layer in the current oversight system.

In addition, the growing number of IACUCs implementing post-approval monitoring procedures, a means by which to detect whether or not experimenters deviate from approved protocols, indicates that there is a need for vigilant ongoing monitoring (Dale 2008).

The use of ad-hoc or third party organizations, such as the private, industry-controlled Association for Assessment and Accreditation of Laboratory Animal Care (AAALAC) International, to either conduct evaluations and investigations or inform USDA inspection frequency of facilities using animals would have a serious negative impact on animal welfare. Animal laboratories maintain accreditation with AAALAC through the payment of an annual fee and a prearranged and announced site visit once every three years. A peer-reviewed 2015 study revealed that laboratories accredited by AAALAC were cited for violations of AWA regulations

in USDA inspection reports *more frequently* than unaccredited facilities, and had more violations related to improper veterinary care, personnel qualifications, and animal husbandry (Goodman, Chandna and Borch 2015). Furthermore, as AAALAC is a non-governmental body, its inspection records are not retrievable through public records requests, nor are they published online. The responsibility of overseeing these minimum protections afforded to animals used in experiments should not be handed over to private, industry-friendly organizations that operate without transparency.

Recent violations from AAALAC-accredited facilities, as documented in USDA inspection reports currently available from the USDA's (limited) online database, include leaving injured animals to die without veterinary attention; failing to provide anesthesia and analgesia to animals in compliance with the protocol approved by the Institutional Animal Care and Use Committee; and failing to provide for the psychological well-being of nonhuman primates. At AAALAC-accredited facilities, animals have starved and dehydrated to death and have suffered unimaginable pain and distress when their cages were run through high temperature, mechanical cage washers – with the animals locked inside. Simply stated, AAALAC-accreditation does not guarantee compliance with the most *basic* regulations, and accreditation should not be used as a justification for reducing either the frequency of USDA inspections or the care with which they are conducted.

3. *FASEB Report Recommendation: NIH and USDA should establish a risk-based process for review of animal research protocols similar to that for human subjects research under 45 CFR 46; §46.110. Through issuance of a Notice in the Federal Register similar to the NIH Notice issued in 2014 regarding Significant Changes (NOT-OD-14-126), USDA and the NIH Office of Laboratory Animal Welfare (OLAW) could amend the protocol review requirement to define types of studies involving low-risk, noninvasive, or minimally invasive procedures. These studies could then be deemed exempt from full IACUC consideration or eligible for administrative or single member (expedited) review, without concurrence by the full IACUC.*

   This recommendation should not be implemented. IACUCs already have difficulties reporting appropriate pain categories for invasive and painful experiments to the USDA, categories which are defined in Appendix B and have been in place for decades. Weakening this by excluding pain and distress from consideration will undoubtedly increase animal suffering and is contrary to the goals of protocol review. Further, USDA inspectors often fail to cite facilities for these failures. In its 2014 audit of the oversight of research facilities, the USDA Office of the Inspector General (OIG) found the following:

   > *45 percent of the research facilities in our sample (13 of 29) misreported the animals used in research. The facilities either reported animals in the wrong pain category or could not provide us with documentation to reconcile their annual report. Despite these errors, VMOs [Veterinary Medical Officers] did not cite any of our sampled facilities for misreporting animals. Further, they cited less than 6 percent of facilities nationwide for the same violations over our 3-year scope period.*
   >
   > *Even when VMOs do find inaccuracies in the reports, they may not cite the facilities. During one of our visits, for example, a research facility in Texas reported most of its non-human primates in the "with pain, with drugs" category without any regard to actual pain categories involved in the experiments. Although the facility admitted to the*

VMO that its annual report was completed incorrectly, the VMO did not cite the facility for submitting an inaccurate annual report and did not require the facility to submit a corrected one. (USDA OIG 2014)

In addition to inaccuracy in *reporting* pain categories, IACUCs and investigators appear to have difficulty *assigning* appropriate pain categories to particular experiments. For example, the NIH classified investigator Stephen Suomi's maternal deprivation experiments on baby monkeys as Category C (see Appendix C), meaning they involved no pain or distress, despite the investigator's own research showing that such treatment resulted in severe anxiety, aggression, depression, diarrhea, hair loss, and other physical and mental illnesses, as well as the monkeys' engagement in self-destructive behavior such as biting themselves and pulling out their own hair (Suomi 1997, Dettmer, et al. 2012, Barr, et al. 2003). Suomi's research involved experiments such as the following, which to any reasonable person would appear distressing:

- Infant monkeys were caged with their mothers, who were chemically sedated, had their nipples taped over, and were placed in a car seat. The terrified babies screamed and cried, climbing onto and frantically shaking their unresponsive mothers. In at least one case, experimenters can be heard laughing while a mother tries to remain awake to comfort her distraught child. In some trials, the experimenters even released an electronic snake into the cage with the baby monkeys, who innately fear the reptiles (PETA 2015).
- Newborn infants were restrained inside tiny mesh cages and placed in "startle chambers." The experimenters then deliberately scared the babies with loud noises, causing them to cry out and try futilely to hide or escape (PETA 2015).

With this recommendation, the FASEB Report authors are also proposing that the approval or rejection of experiments involving animals be given after a review by a single individual at that institution. In fact, this is already possible with Designated Member Review (DMR). Under the current law, all members of an IACUC receive, on a monthly basis, a list of all proposed protocols with a brief summary as to what each project entails. Under DMR, "[i]f full Committee review is not requested, at least one member of the IACUC, designated by the chairman and qualified to conduct the review, shall review those activities, and shall have the authority to approve, require modifications in (to secure approval), or request full Committee review of any of those activities" (9 C.F.R. §2.31(d)(2) 2004). What the FASEB Report authors are recommending is further flexibility on the part of the IACUC not to place certain pre-determined experiments on the monthly list of proposed protocols viewed by all IACUC members. With research involving humans, Institutional Review Boards (IRBs) have a similar function which serves to expedite research that involves little to no risk to human subjects (45 CFR 46; §46.110 n.d.). However, this expedited IRB approval process cannot be used for any project that includes vulnerable populations, including individuals unable to give informed consent (children, prisoners, etc.). Experiments involving vulnerable populations must proceed through the normal, rigorous review process. Since animals cannot give informed consent, thus are a vulnerable population, the use of this IRB standard would be inappropriate.

4. FASEB Recommendations to Thwart Transparency:

a. FASEB Report: OLAW specifies that the grant number be included in noncompliance reports, but this is not required in PHS Policy (IV.F.3). Grant numbers should not be

required on noncompliance reports in order to protect investigators and study teams from harassment by parties seeking to disrupt animal research.

b. *FASEB Report: OLAW should not consider IACUC-approved alternative strategies from 'should' statements in the Guide as departures or deviations nor should they be required to be included in the semiannual report to the Institutional Official. This would be consistent with OMB's Agency Good Guidance Practices Bulletin and would significantly reduce administrative burden without compromising animal welfare.*

These recommendations should not be implemented. As OLAW does not publicize the reports detailing the above violations, the only way that taxpayers and stakeholders in the care and use of animals can learn about the treatment of mice, rats, birds, reptiles, and other non-AWA-covered species is through Freedom of Information Act (FOIA) requests. The FASEB Report's suggestion that grant numbers and certain violations need not be included in OLAW documents is a clear attempt to thwart transparency and shield federally-funded experimenters from the scrutiny of the public whose tax dollars bankroll the experiments.

Despite OLAW's documenting of the mistreatment of mice, rats, birds, fish, and other species, as noted earlier, there is already little to no repercussion for violating PHS Policy. OLAW's procedures for an "investigation" into possible policy violations involves simply writing to the institution and asking them to answer a series of questions. Only in very rare instances will OLAW conduct a site visit to a facility to investigate violations.

In a recent testimony, a whistleblower reported that at The Jackson Laboratory (JAX), one of the world's largest breeders of mice used in experimentation, employees used their fingers to tear off ends of mice's tails for genetic identification, even though this procedure is imprecise, can compromise the results of testing by introducing human DNA, and creates a "crush" injury that can become infected and is characterized by extensive bruising and bleeding. In addition, malfunctions in watering systems soaked mice's cages and sometimes drowned them, and mice were euthanized in cages that contained twice the number of mice allowed in one cage, compounding their suffering. After a PETA complaint, NIH OLAW substantiated the whistleblower's claims through their written investigation (NIH OLAW 2017), which adds to JAX's long history of PHS Policy violations (See Appendix D). JAX, which took in more than $75 million in NIH funding in fiscal year 2017, has suffered no meaningful repercussions for its mistreatment of mice.

At the University of Washington, the institution at which FASEB Report author Sally Thompson-Iritani is the Director of Animal Welfare, OLAW reported that mice died of dehydration when they were either not provided with water bottles or the bottles were turned in the wrong direction (NIH OLAW 2017), but no penalty was issued.

At Harvard Medical School, OLAW documented numerous violations of PHS Policy (NIH OLAW 2015), including those listed below, however no NIH grant repayment was demanded for money wasted due to these errors. Harvard still maintains its PHS Assurance and took in over $258 million in NIH funding in fiscal year 2017 alone.

a. Three experimenters failed to use pain relief, even though they had stated how it would be used in their own protocols.
b. Mice had tumors that had become larger than that which was permitted in the approved protocol. Several weeks' worth of documentation of monitoring of animals undergoing tumor studies was absent. This happened repeatedly.

c. Twenty-four mice died of radiation overdose due to improper equipment settings.
d. A mouse had been placed in the corner of a laboratory and forgotten. The mouse was not found dead until *two months* later.
e. Mice in a diabetes experiment unexpectedly died or became moribund. The mice were not being adequately monitored and some cages had no food.
f. Mice who had undergone orthopedic surgery were found to be lame and exhibiting post-operative problems. There were no records of post-operative care or monitoring, the staffer responsible had not been adequately trained, expired drugs were used, post-operative care was not provided as described in the approved protocol, controlled drug documentation was incomplete, and the surgery had not been performed aseptically.
g. A monkey's leg was broken during manual capture. This was a repeat incident.
h. Two-hundred zebrafish died after the aquaculture life support system was inadvertently shut off twice for two-hour intervals during a planned electrical shut down to install an emergency generator.

5. *FASEB Report Recommendation: Revise USDA Animal Care Policy #14 to reflect the language in the AWA §2143 and AWR §2.31(d)(1)(x) (A-C), allowing approval of multiple survival operative procedures at the discretion of the IACUC and as justified for scientific and animal welfare reasons. This will enhance the community's efforts to reduce the number of animals involved in research.*

   This recommendation should not be implemented. Currently, USDA Animal Care Policy #14 states, "No animal is to be used in more than one major survival operative procedure except in cases of scientific necessity, veterinary care or other special circumstances as determined by APHIS" (USDA APHIS 2017), and the AWA and AWR do not require approval from APHIS for multiple major operative procedures. The notion that *less* oversight of experimenters who may wish to conduct repeated, invasive, potentially painful operations on animals would not affect animal welfare is plainly false.

   At the University of Washington, the institution at which FASEB Report author Sally Thompson-Iritani is the Director of Animal Welfare, the IACUC approved an experimenter to perform multiple invasive operative procedures on nonhuman primates, including skull implants, arm implants, and vertebral implants, despite the fact that these procedures were not adequately described in the protocol application. As a result, "three animals used on this protocol had significant health issues following the above surgical procedures. All three animals were euthanized due to the severity of the health issues attributed to the IACUC approved activities" (USDA APHIS 2015). This was not the first time the University of Washington was cited for this same noncompliance. In 2006, a nonhuman primate died from complications related to two craniotomies and multiple eye coil surgeries; the extent of these procedures had not been approved by the IACUC (USDA APHIS 2006). The year prior, the University of Washington IACUC had approved 45 protocols in which experimenters conducted multiple invasive procedures on animals (USDA APHIS 2005).

   This and other examples demonstrate that experimenters and IACUCs alone are not sufficiently equipped to determine the safety of multiple operative procedures on animals, which cause pain and distress and can be deadly. Increased oversight and/or an explicit ban on multiple operative procedures is necessary to ensure animal welfare.

6. *FASEB Report Recommendation: Amend the language in USDA Animal Care Policy #12 with respect to literature searches to be consistent with AWR §2.31(d)(1)(ii), which charges the IACUC to determine "that the principal investigator has considered alternatives to procedures that may cause more than momentary or slight pain or distress to the animals, and has provided a written narrative description of the methods and sources…"*

   This recommendation should not be implemented. As written, the AWA only requires experimenters to search for alternatives to painful procedures; there is no mandate for experimenters to implement any alternatives they may find. USDA Animal Care Policy #12 defines what should be included in the narrative of a database search for alternatives and states that the IACUC can "withhold approval of the study proposal if the Committee is not satisfied with the procedures the PI plans to use in his study" (USDA APHIS 2017). AWR §2.31(d)(1)(ii) should be amended to include all of the parameters for a search and the corresponding documentation detailed in Policy #12. The following examples demonstrate the need to strengthen this mandate.

   At the University of Maryland School of Medicine, the institution with which FASEB Report author Richard Eckert is the Associate Director of Basic Science Research, five protocols that were reviewed by USDA APHIS stated that searches conducted had returned, "No alternatives, Refinements, Replacements, or Reduction methods," however the USDA official determined that the search terms used were "restrictive or inappropriate for the painful procedures" involved (USDA APHIS 2016). Two animals had complications that resulted from one of these procedures, after which the facility's Attending Veterinarian identified refinements, demonstrating, "that there was a potential for a proper literature search to have identified refinements that would have prevented potentially painful or distressful conditions in these study animals" (USDA APHIS 2016). The USDA official was also able to locate "20 relevant article abstracts for one potentially painful procedure" related to another protocol, for which the investigators and the IACUC had identified no alternatives (USDA APHIS 2016).

   At the Icahn School of Medicine at Mount Sinai, the institution at which FASEB Report author Reginald Miller is the Senior Research Integrity Officer, experimenters were performing thoracotomies on dogs, opening their chests with an incision in the chest wall between the ribs. In this case, the IACUC had failed to verify that the experimenter had even used the term for this painful procedure in the search for alternatives (USDA APHIS 2017).

   At the University of California Davis, the institution with which FASEB Report author Scott Simon is affiliated, the IACUC approved a procedure to conduct abdominal surgery on sheep to determine pregnancy status. When questioned by the USDA inspector as to why less invasive methods were not used, the facility representative stated that an ultrasound would be too cost prohibitive (USDA APHIS 2014).

C. The Authors Are Responsible for Failing Oversight at Their Own Institutions

As noted earlier, many of the authors of the FASEB Report represent and are involved in animal use oversight at institutions that the USDA has repeatedly cited for gross abuses and outright negligence and that have repeatedly failed to comply with federal laws and guidelines. Given these individuals' lack of credibility with regard to animal welfare, and the history of abuses that took place at their

institutions, we recommend that this and any future reports on this topic that argue that animals are given too much consideration be viewed with the appropriate skepticism and disregarded.

Weakening oversight as recommended in the FASEB report will mean that serious violations, such those listed below, would go unnoticed. This section touches on just a handful of the egregious violations committed by the very institutions that employ these individuals. For brevity, violations mentioned previously in this analysis are not included in this section.

To be clear, every situation mentioned references a USDA or NIH finding that the entity and experimenters violated the Animal Welfare Act or PHS Policy, and animals suffered as a result. In many cases FASEB report authors are complicit, as they were tasked with overseeing research compliance with laws and guidelines. In some cases these individuals are members or leaders of their employer's IACUC. FASEB Report author J. Crawford Down's institution, the University of Alabama Birmingham School of Medicine, has been cited for at least 24 recent[1] violations, including one incident where a pig died during transport because fans in the truck were not working (NIH OLAW 2013) and another where a ferret was found dead in his enclosure after becoming stuck between the wall and the caging apparatus in an attempt to escape (USDA APHIS 2015).

1. FASEB Report author James Tomasek's institution, the University of Oklahoma Health Sciences Center, of which Tomasek is the Vice President of Research, has been cited for at least 23 recent violations, including one incident where six guinea pigs bled to death after a jugular vein catheterization procedure, when the catheter caps came off while the animals were not being monitored (USDA APHIS 2015). Tomasek's institution was also cited repeatedly for failing to provide pain relief to dogs, rabbits, and baboons who were involved in painful procedures (USDA APHIS 2013, USDA APHIS 2015).
2. FASEB Report author Ara Tahmassian's institution, Harvard University, of which he is the Chief Research Compliance Officer, has been cited for at least 21 recent violations, including an incident where a primate was found dead at the bottom of a cage which had been just run through an industrial, scalding hot, high-pressure washer (USDA APHIS 2010).
3. FASEB Report author Mar Sanchez's institution, Emory University, has been cited for at least 19 recent violations, several of which involved the deaths of nonhuman primates:
    a. An infant rhesus monkey died after becoming entangled in a frayed fire hose which was given as an enrichment device (NIH OLAW 2011).
    b. A seven-month-old macaque was found dead outside her enclosure (USDA APHIS 2015).
    c. Due to the error of three staff members, a juvenile rhesus macaque was returned to the incorrect compound and was later found wounded, lethargic, and hypothermic. The young macaque died (USDA APHIS 2012).
    d. Gauze sponges were left in the abdomens of two primates, one of whom became very sick and was euthanized (USDA APHIS 2016, USDA APHIS 2017).
    e. A rubber band was not removed from a monkey after a tattooing procedure, resulting in respiratory and neurological distress and the monkey's euthanasia (USDA APHIS 2015).
4. FASEB Report author Scott Simon's institution, University of California Davis, has been cited for at least 17 recent violations, including multiple incidents which led to death:
    a. A lamb died after being improperly housed with a larger animal who crushed the young lamb to death (USDA APHIS 2015).

[1] Recent is defined as having occurred or been cited for within the last ten years.

b. An improperly anesthetized rabbit died when a valve was accidently left in the closed position (USDA APHIS 2016).
c. Two incompatible primates were injured when staff failed to secure and lock a divider door that separated them. One primate recovered from injuries but the other was euthanized. This was a repeat offense (USDA APHIS 2016).
d. A transport enclosure was insufficient, leading to a macaque escaping, being tranquilized, and later euthanized due to internal bleeding from the ordeal (USDA APHIS 2016).
e. A macaque monkey died after being trapped in the squeeze mechanism of a cage (USDA APHIS 2013).

5. FASEB Report author Nancy Ator's institution, Johns Hopkins University, at which she serves as the IACUC Chair, has been cited for at least 15 recent violations, including the following fatal incidents:
    a. A rabbit died after being left in a cage that was sent through an autoclave, which typically reaches temperatures of 250°F, for disinfection prior to regular cage washing (USDA APHIS 2015).
    b. A young macaque monkey was found dead in the outdoor portion of her enclosure after her head became trapped in a ball used for enrichment (USDA APHIS 2017).
    c. Two monkeys were found asphyxiated, having been strangled by chains in their cage that were not properly configured (USDA APHIS 2015).
    d. Two squirrel monkeys died of dehydration when no one noticed that their water dispenser wasn't working (NIH OLAW 2007).
6. FASEB Report author Sally Thompson-Iritani's institution, the University of Washington, has been cited for at least 15 recent violations, several of which involved death. At one inspection, USDA officials made note that a lab technician had written that his, "lab is becoming increasingly frustrated with the treatment of animals at our facility," noting lack of food and water, "disappearance" of animals, and losses of entire litters of mice (University of Washington 2016).
    a. Two macaques, one-month and six-months old, suffered fatal injuries from being attacked by adult males. A nine-month old female was attacked by an adult male through mesh contact and had to be euthanized a few weeks later. The USDA said that measures should have been put in place after the first of the three attacks to prevent future ones (USDA APHIS 2014).
    b. An eight-year-old pigtail macaque died of dehydration when the water line to the cage was not properly connected (USDA APHIS 2017).
    c. A primate died while under anesthesia related to an experimental MRI procedure; no anesthetic monitoring was recorded during procedure (USDA APHIS 2017).
    d. A rabbit died during a surgical procedures after being given excessive anesthetic (USDA APHIS 2014).
    e. A rabbit had a fractured pelvis resulting in paralysis and euthanasia (USDA APHIS 2014).
7. FASEB Report author Stacy Pritt's institution, the University of Southwestern Medical Center, at which Pritt serves as the IACUC Director, has had at least four recent violations, including one incident where an animal had complications during a procedure and was left moribund overnight with no observation or follow-up by a veterinarian and another where six rabbits were under anesthesia with only one person monitoring all six animals (USDA APHIS 2008).
8. FASEB Report author Richard Eckert's institution, the University of Maryland School of Medicine, has been cited for at least 4 violations, including failing to provide primates with

sufficient space and enrichment, which is required as a means to improve their mental well-being (USDA APHIS 2015).

9. FASEB Report author Reginald Miller's institution, the Icahn School of Medicine at Mount Sinai, at which Miller serves as the Senior Research Integrity Officer and Dean for Research Operations & Infrastructure, has been recently cited for at least four violations, such as the use of outdated drugs, including an anesthetic.
10. FASEB Report author Jeffrey Henegar's institution, the University of Missouri-Columbia, at which he serves as the Director of Animal Care and Quality Assurance, has been cited for at least three recent violations, including the following:
    a. After staff failed to properly latch the animals' cages, three adult male dachshunds were able to enter an adjoining run and kill a newly weaned puppy (USDA APHIS 2016).
    b. Two boars singly housed in adjacent pens were found in one pen (the pen wall was knocked down) and had been fighting. One boar was found dead, likely due to exhaustion/cardiac arrest (USDA APHIS 2016).
    c. A pig had blood oozing from a hoof and was limping and walking stiffly, but the facility had not documented the pig/s condition or any injury (USDA APHIS 2017).
11. FASEB Report author Kevin Kregel's institution, the University of Iowa, has been cited for at least 3 recent violations, including the improper use of anesthesia which caused complications in a pig, causing the animal to be euthanized (USDA APHIS 2015).
12. FASEB Report author Cindy Buckmaster's institution, Baylor College of Medicine, has been cited for at least two recent violations, including one incident where a newborn piglet who was having trouble nursing was not given supplemental feeding and subsequently starved to death (USDA APHIS 2017) and another where a surgeon did not follow protocol and left rabbits with gaping surgical wounds. The next day one of the rabbits had to be euthanized (USDA APHIS 2016).
13. Michigan State University, the institution at which FASEB Report authors Molly Green, F. Claire Hankenson, and Joseph Haywood serve as the IACUC Advisor, Attending Veterinarian, and Assistant Vice President for Regulatory Affairs, respectively, has been cited for at least two recent violations. In one instance, 66 mink died from heat stress when the facility failed to provide the animals from protection from inclement weather (USDA APHIS 2007). In another, a three-month-old puppy was found dead in a floor drain (USDA APHIS 2007).

D. Reduce Regulatory Burden and Enhance Scientific Discovery by Eliminating Tests on Animals

The NIH, FDA, and USDA must reexamine their priorities and make a conscious effort to move away from experiments on animals toward human-relevant research.

Forty-seven percent of all research grants funded by NIH involve animal experimentation (Pankevich, et al. 2012), despite growing evidence that animal experiments are wasteful and also impede medical progress. As stated in a 2014 review by Bath and Yale scientists, "Several studies have shown that even the most promising findings from animal research often fail in human trials and are rarely adopted into clinical practice. For example, one study found that fewer than 10% of highly promising basic science discoveries enter routine clinical use within 20 years" (Pound and Bracken 2014).

A 2015 analysis concluded that between 50 and 89 percent of all preclinical research findings could not be reproduced, which, at the most conservative U.S. estimate, results in approximately $28 billion per year spent on experimentation that is misleading (Freedman, Cockburn and Simcoe 2015). NIH

Director Francis Collins and Principal Deputy Director Lawrence Tabak have admitted, "Preclinical research, especially work that uses animal models, seems to be the area that is currently most susceptible to reproducibility issues" (Collins and Tabak 2014). The 95 percent failure rate of new drugs (National Center for Advancing Translational Sciences 2017) is in large part a result of an approval process that relies on animal experiments.

We have identified a number of strategic priorities and appended further information regarding areas of biomedical research where there are opportunities for the immediate and near-future replacement of animal use. Multiple systematic reviews have documented the overwhelming failure of specific areas of animal use to benefit human health, including neurodegenerative diseases, neuropsychiatric disorders, cardiovascular disease/stroke, cancer, diabetes/obesity, inflammation and immune responses, HIV/AIDS research, addiction studies, trauma research, and medical training. As such, animal experiments in these research areas should be ended as soon as possible and replaced with more effective and efficient non-animal research methods. At request, we are happy to provide further elaboration and recommendations on these areas.

Forward-thinking scientists are developing and implementing methods for studying and treating diseases and testing products that do not entail the use of animals and are relevant to human health. Researchers have developed human cell-derived models, "organs-on-chips," *in silico* (computer) models, and other methodologies that can replicate human physiology, diseases, and drug responses more accurately than experiments on animals. Studies have repeatedly shown that these new methodologies are better at modeling human diseases than crude experiments on animals. Indeed, NIH in its most recent five-year strategic plan announced that it would reduce and replace animal experiments, stating, "Petri dish and animal models often fail to provide good ways to mimic disease or predict how drugs will work in humans, resulting in much wasted time and money while patients wait for therapies. To address that challenge, NIH, DARPA, and FDA are collaborating to develop 3D platforms engineered to support living human tissues and cells, called tissue chips or organs-on-chips. An integrated body-on-a-chip is the ultimate goal" (National Institutes of Health 2015). The NIH, USDA, and FDA must now take the next step and end the funding of crude experiments that have failed to provide effective treatments and cures.

In addition, agencies such as the FDA and Environmental Protection Agency (EPA), which require certain animal experiments to be conducted for regulatory purposes, should immediately require the use of validated non-animal methods to replace animal tests, for all cases where those validated methods exist.

1. Failure of Animal Research to Yield Human Therapies

   The simplest way to reduce regulatory burden and improve the efficiency of biomedical research would be to eliminate or reduce the use of animals in experiments intended to enhance the understanding, prevention, and treatment of human health and disease. A great deal of scholarly research shows that animal experiments are flawed and divert both economic and intellectual resources from methodologies better suited to curing human disease. There are many factors at play in the failure of animal experimentation to predict human outcomes reliably, including reporting and publication bias, poor study design, and inadequate sample size. But most significantly, intrinsic biological and genetic differences between species contribute significantly to problems in extrapolating results from nonhuman animals to humans.

According to the 2014 review paper in *The BMJ*, "[s]everal studies have shown that even the most promising findings from animal research often fail in human trials and are rarely adopted into clinical practice. . . if research conducted on animals continues to be unable to reasonably predict what can be expected in humans, the public's continuing endorsement and funding of preclinical animal research seems misplaced" (Pound and Bracken 2014). In a recent report based on over 100 in-depth interviews with senior executives of drug discovery companies, a key problem identified in the drug discovery process was reliance on inadequate models for human diseases. The interviewers heard from sector representatives that "the preclinical research process was patient free, and relied on animal models of disease and toxicology that were a poor approximation of humans" and that "emerging technologies that can 'humanise' the drug discovery process" are in high demand (BioIndustry Association, Medicines Discovery Catapult 2018).

These difficulties are compounded by the confinement and unnatural conditions of laboratory life that thwart animals' ability to engage in natural behaviors. This deprivation contributes to their stress and alters their physiology and neurobiology causing them to exhibit various psychopathologies. Importantly, the fact that animals in laboratories have altered physiologies and neurobiologies means that they will not be good "models" for their counterparts in the wild. A mouse in a laboratory will not respond to a drug in the same way as a mouse in a field would. One then has to ask, how does this biologically distinct mouse reliably represent the biology of human beings? Furthermore, artificial disease created in the laboratory is not the same as naturally occurring conditions in humans in the real world—further confounding the value of any data gleaned from such approximations of the actual disease.

2. Systematic Reviews

Systematic reviews of all animal research areas are the first step in eliminating the most wasteful and useless animal experiments.

The move internationally is clearly away from animal-based experiments. In 2012, the Dutch Parliament adopted a motion to ensure that systematic reviews of experiments involving animals be conducted before such experiments receive government funding, such as is done with human clinical studies (Hooijmans and Ritskes-Hoitinga 2013). Dutch scientists C. R. Hooijmans and M. Ritskes-Hoitinga offer the following advice: "Systematic reviews of animal studies should be conducted routinely. Funding agencies should subsidize systematic reviews, not simply for transparency, but also to avoid waste of financial resources and unnecessary duplication of animal studies" (Hooijmans and Ritskes-Hoitinga 2013).

The value of systematic reviews is highlighted by the Institute of Medicine's (IOM's) landmark 2011 report, which used a systematic review to examine the scientific validity of experiments on chimpanzees. The conclusion of this report was that "most current biomedical research use of chimpanzees is not necessary" (Altevogt, et al. 2011). This conclusion was echoed in a 2013 NIH report on chimpanzee use in laboratories (NIH 2013). It is worth noting that at the time that the IOM and NIH reports were undertaken, chimpanzees were being used in painful and invasive experiments—which had been approved by review boards, funding bodies, and animal care committees. The inescapable message of the IOM and NIH reports is that oversight bodies, including IACUCs, need additional guidance in the way of rigorous regulatory standards to ensure that animals are not used in unnecessary or repetitive experiments.

In a landmark forward move, the Dutch government recently announced its plan to phase out animal experimentation in the Netherlands by 2025 and to focus its efforts on new and rapidly evolving non-animal technologies for biomedical research. In this endeavor, the Dutch government consulted with PETA scientists before making their decision do phase out animal experiments. PETA scientists stand ready to offer our assistance in implementing a program of systematic review, or in whatever capacity might be required. The PETA International Science Consortium is actively involved in the development, validation, global implementation, and harmonization of non-animal test methods. PETA's scientists work behind the scenes with many Fortune 100 corporations and regulatory agencies, providing advice and technical support in a range of fields. Given the breadth and depth of our expertise, we believe that we can make a valuable contribution to developing and implementing a strategic plan for the future of biomedical research and regulatory testing.

3. Technology and Job Growth

By mandating a move away from animal experimentation and toward more advanced scientific methods, the U.S. has the opportunity to expand job growth rapidly in science and technology and to reduce healthcare costs for Americans. According to a recent report by Grand View Research, Inc., "[t]he global in-vitro [non-animal] toxicology testing market is expected to reach USD 44.7 billion by 2022 growing at an estimated CAGR [Compound Annual Growth Rate] of 10.5% from 2015 to 2022 …. This expected rise in demand can be ascribed to novel and promising technologies in analytical laboratories" (GlobeNewswire 2016). New technologies will streamline drug development, making the process safer, cheaper, and more effective. Developing these technologies allows for the creation of interdisciplinary research teams that will be fundamental in creating the "human disease models of tomorrow" (hMDT Institute 2016).

With greater investment in exciting and innovative non-animal methods and bold policy initiatives, more promising cures and treatments for humans can be developed. This will serve a multi-tiered purpose of improving human health, reducing regulatory burden, and eliminating the suffering of millions of animals.

D. Additional Recommendations

The following adjustments to the current oversight system will reduce the time and effort expended by animal experimenters to comply with animal welfare regulations, guidelines, and policies:

1. Mandating Ethical Diversity for IACUCs

The burden experienced by experimenters serving on IACUCs could be reduced by requiring a more balanced representation from community members and individuals who represent animal welfare interests. Such balance is already mandated in other countries. For example, in Sweden, oversight committees must have an equal number of scientists and community members—and one-third of the community members must be animal welfare representatives (Schuppli and Fraser 2007). In Germany, one-third of the committees must be animal welfare representatives (Schuppli and Fraser 2007). Germany, Denmark, and Switzerland all mandate appointments onto the oversight committees of individuals from animal welfare organizations (Dresser, 1999). In Australia, one-third of the committee must be composed of community and animal welfare representatives (Dresser 1999). In addition to freeing up some investigators from having to serve

on IACUCs, this would ensure greater ethical diversity on the committees and greater public confidence in oversight of animal laboratories (Hansen, Institution animal care and use committees need greater ethical diversity 2013).

In the United States, however, as noted earlier in this report, evidence indicates that IACUCs are not meeting their mandate, in part because IACUC members are heavily biased toward approving the experiments of their peers, even when the proposals under review are inadequate. In their seminal study of IACUC protocol reviews, Plous and Herzog found that in-house IACUCs—where the voting members presumably knew the investigators whose protocols were being assessed—overwhelmingly approved proposed protocols (98 percent), while blinded IACUCs, whose members did not know the investigators, found the same protocols to be deficient (61 percent) (Plous and Herzog 2001). Other studies have found similar staggering IACUC approval rates, in one case as high as 99.8 percent (Houde, Dumas and Lerous 2003, Forsman 1993).

While minimal IACUC membership requirements are stipulated by PHS Policy and the AWA, neither establishes a limit on the number of animal users or an animal-user to non-animal-user ratio. As a result, IACUCs are often disproportionally comprised of people who use animals—a recent study concluded that, on average, 77.6 percent of the committee membership at top U.S. institutions is comprised of individuals directly engaged in animal experimentations (Hansen, Goodman and Chandna, Analysis of animal research ethics committee membership at American institutions 2012)—which likely contributes to the approval bias discussed earlier. This balance may also undermine public confidence in the objectivity of the animal research review process and contribute to deficiencies in IACUC oversight that have been documented and that may result in unnecessary animal use and suffering.

2. Required Training for IACUC Members on IACUC Functions, the 3Rs, and Alternatives Searches

As noted earlier, multiple audit reports filed by the USDA OIG have outlined the chronic failures of IACUCs to carry out their mandate. Individuals who serve on IACUCs are in dire need of meaningful, comprehensive instruction—and the federally-sponsored IACUC 101/201 program, the predominant program in place to provide training to IACUC members, has failed to address the concerns that have repeatedly been outlined in the OIG's audits. Further, IACUC 101/201 has thus far failed to provide any meaningful guidance to IACUC members on even the basic 3 R's foundation of animal use—replace, reduce, refine.

At a minimum, IACUC members should be trained to be competent in the following key areas to ensure compliance with existing regulations. This will help guide the committees' work so they can confidently and efficiently carry out their responsibilities.

1. Careful review of painful procedures: IACUCs are required to ensure that animals under their purview are provided with "medical care … by a qualified veterinarian" (Section 2.31(d)(1)(vii) of the AWRs); to ensure they are put out of their misery when they are suffering "severe or chronic pain or distress that cannot be relieved" (Section 2.31(d)(1)(v) of the AWRs); and to ensure that "procedures that may cause more than momentary or slight pain or distress" to them will be "performed with appropriate sedatives, analgesics or anesthetics" (Section 2.31(d)(1)(iv)(A) of the AWRs). We recommend that IACUCs

implement consideration of "harm scales" into their evaluations of proposed projects, wherein experiments using animals are "ranked according to the degree of harm inflicted on the animals. These harms include pain, distress, adverse mental states and other compromises to an animal's welfare. Examples of distress and harm include: anxiety or fear; nausea; fatigue; inability to walk; an induced pathological condition such as an infectious disease; functional disability such as loss of a limb; maternal, social, and other deprivations; induction of an abnormal mental state; and a lingering, or even painless, death." The entire lifetime experience of the animals used in a project should be rigorously catalogued and balanced against a realistic expectation of benefits.

With the adoption of a harm scales, the use of procedures categorized as causing moderate to severe distress or severe pain would need to be eliminated or at least strongly justified scientifically. If distress is protracted, or death or morbidity is the endpoint, the IACUC should secure detailed information from the experimenter on the specific criteria that will be used for intervening, terminating the study, or euthanizing an animal.

2. We recommend that unnecessary or repetitive experiments not be conducted. Sections 2.31 (e)(1)-(5) of the AWRs specify that when an IACUC reviews a protocol, it must ensure that the proposal contains a "rationale for involving animals, and for the appropriateness of the species and numbers of animals to be used … [and a] description of procedures designed to assure that discomfort and pain to animals will be limited to that which is unavoidable for the conduct of scientifically valuable research, including provision for the use of analgesic, anesthetic, and tranquilizing drugs where indicated and appropriate to minimize discomfort and pain to animals." In essence, this set of regulations mandates that IACUCs must replace the use of animals with non-animal models and reduce the number of animals used. Dr. Stephen Schiffer, former director of the Division of Comparative Medicine at Georgetown University, noted: "External funding reviews should be viewed as additional assurance, rather than the only assurance, that the research has value. … Since humane animal use implies morally appropriate animal use, IACUCs must determine that the procedures before them are expertly planned and necessary. **It is inhumane to use animals for bad science**" (*emphasis in original*) (Podolsky and Lukas 1999).

   In response to concerns raised by Congressional representatives on the use of infant monkeys in maternal deprivation and psychopathology experiments at a National Institutes of Health laboratory in Poolesville, Md., in which the representatives requested a thorough scientific and ethical review of the experiments, NIH Director, Dr. Francis Collins, wrote: "The [National Institute of Child Health and Human Development] is also revising its peer review process to address research animal welfare issues at the time of scientific review, thus making better use of the knowledge and experience of the outside reviewers that are brought in to assess scientific merit of the NICHD intramural research program. Specifically, the NICHD will now ask these scientific reviewers also to comment directly on the appropriateness of chosen animal models, animal numbers, and species appropriateness." This change in oversight protocols signals an acknowledgement that previous practices were not adequate to ensure that animals were not used in unnecessary experiments.

   PETA has offered to sponsor training for IACUC members, focused on non-animal research methods, but federal agencies have, heretofore, declined PETA's offers. Such training could

help to eliminate the approval of protocols that are not relevant to human or animal health, the advancement of knowledge, or the good of society.

E. Conclusion

If we are serious about reducing administrative burden, more stringent requirements should be placed at the points where projects are funded and protocols approved—to ensure that money is only disbursed and projects only greenlighted when there is confidence that something useful will come from the work. By shifting away from projects involving animals and increasing investments in human-relevant projects, we can successfully comply with the directive of the CURES Act to maintain the integrity of research findings while also protecting animals.

Animal laboratories do not have a right to use animals in experiments that are sometimes painful, often distressful, and ultimately lethal; such use is a *privilege* extended to the facilities through a *social contract* that demands that a certain modicum of protection is extended to the animals. The failure of research institutions to adhere to federal regulations and guidelines—amply demonstrated by institutions represented in the workshop that culminated in the FASEB Report—is a betrayal of the public's expectations and trust related to animal experimentation and of the animals themselves.

The prevailing perspective on oversight is that "a trust relationship [must exist between animal research facilities and] oversight bodies" (Klein and Bayne 2007) to engender a culture of care. Contrary to the expectation of this belief, violations of federal regulations and guidelines are rampant in U.S. laboratories, and animals are suffering as a result. A culture of noncompliance in which fines are considered the "normal cost of conducting business rather than a deterrent for violating the law" has taken root, leaving animals vulnerable to the most egregious of abuses. Furthermore, we have seen a "gradual erosion of public confidence in researchers and the research process [which] has resulted in questioning, from the public and Congress, about … how animal subjects are being treated" (Dempsey 2001).

While federal regulations and guidelines represent minimal standards of care, the failure of the USDA and OLAW to ensure that these smallest provisions are extended to animals in laboratories has, in essence, enabled research facilities to continue their dysfunctional behavior, flouting federal law and mistreating animals. The situation demands a paradigm shift away from the current scenario in which federal agencies dole out an unending stream of "Get Out of Jail Free" cards to facilities that self-report serious violations to one in which laboratories take meaningful responsibilities for deficiencies in animal care. Any actions taken to lessen oversight will exacerbate these problems.

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Appendix A

Background on the Oversight of the Use of Animals in Laboratories and Public Expectations Related to This Oversight

In 1985, in response to growing public concerns about the welfare of animals in laboratories stemming from exposés of abuse at several high-profile federally-funded research facilities, members of Congress from both sides of the aisle worked together to strengthen protections for animals in laboratories (Holden 1986). The results of this collaboration were the 1985 amendments to the Animal Welfare Act (AWA), also known as the Improved Standards for Laboratory Animals Act, and the Health Research Extension Act of 1985 (HREA).

Both of these laws mandated the creation of Institutional Animal Care and Use Committees (IACUCs) to oversee animal use and ensure compliance with federal regulations and guidelines. Intended to be the cornerstone of humane treatment of animals in laboratories, IACUCs are tasked with reviewing animal experimentation protocols and approving, rejecting, or requiring changes to the proposals. These bodies are also responsible for ensuring that experimenters search for alternatives to the use of animals, consider alternatives to painful procedures, and avoid or minimize discomfort, distress, and pain to animals. IACUCs must also evaluate the institution's animal care and use program and conduct semiannual inspections.

The United States Department of Agriculture (USDA) Animal and Plant Health Plant Inspection Service (APHIS) is the agency responsible for enforcing the AWA and its implementing regulations, including regulations that stipulate the responsibilities of IACUCs. Moreover, the USDA is required by Congress to inspect research facilities a minimum of once annually. However, multiple audits by the USDA's Office of the Inspector General (OIG) have documented ongoing failures in the USDA's oversight and enforcement and in the institutional oversight provided by IACUCs. A 1995 OIG report "found that the activities of the IACUCs did not always meet the standards of the [Animal Welfare Act]. Some IACUCs did not ensure that unnecessary or repetitive experiments would not be performed on laboratory animals. In addition, the audit found numerous problems with protocols and reporting" (USDA OIG 2005). In September 2005, the USDA OIG published a scathing audit report describing a climate in which laboratories view fines for AWA violations as a "cost of conducting business" (USDA OIG 2005). The report notes that at almost one-third of facilities, IACUCs failed to ensure that experimenters considered alternatives to painful procedures. The report cites this failure on the part of IACUCs as being the *most frequent* AWA violation. The report further documents the failure of IACUCs to ensure that animals receive adequate veterinary care and that unnecessary or repetitive experiments are not performed on animals. In December 2014, an audit released by the USDA OIG reiterated these concerns, reporting that IACUCs "were not judiciously or adequately trained in reviewing and approving protocols" and "did not make monitoring activities a priority," among other deficiencies. The report documented that "nearly half of all research facilities continued to be cited by the [USDA's Veterinary Medical Officers] for inadequate protocol reviews and monitoring." (OIG's summary can be found in Appendix B) (USDA OIG 2014).

The HREA provides the legislative mandate for the Public Health Service (PHS) Policy on Humane Care and Use of Laboratory Animals (Policy), which in turn requires that institutions that enjoy support from PHS "establish and maintain proper measures to ensure the appropriate care and use of all animals

involved in research, research training, and biological testing activities." NIH's Office of Laboratory Animal Welfare (OLAW) is responsible for ensuring that institutions covered by the PHS Policy are in compliance with the Policy and are following the guidelines set forth in *The Guide for the Care and Use of Laboratory Animals*—but this layer of oversight is carried out primarily through a system of self-reporting. OLAW rarely inspects facilities, but relies instead on PHS-funded institutions to promptly report any activities involving animals where serious or continuing violations of federal animal welfare guidelines occurred. However, even when animal experimentation facilities report serious inadequacies in animal care, OLAW cannot cite or fine the laboratories, but the Director of NIH may "suspend or revoke such grant or contract under such conditions as the Director determines appropriate" (U.S. Department of Health and Human Services, NIH OLAW 2015). Nevertheless, the agency admits that it is rare for failures to comply with federal animal welfare guidelines to affect the disbursement of federal monies (NIH OLAW 2005). Informal reviews of self-reports by facilities have revealed chronic *patterns* of noncompliance, likely stemming from the fact that there is no need for a noncompliant facility to seriously reform its practices when there are generally no meaningful repercussions suffered by the facility for its violations.

While public outrage over documented abuse of animals in laboratories in the 1980s ignited the push for reforms in animal welfare legislation, public concern regarding this issue is greater than ever. Recent polling by the Pew Research Center has found that 50 percent of U.S. adults oppose the use of animals in experiments for any reason (Pew Research Center 2015) and other surveys suggest that the support of the shrinking group that continues to accept animal experimentation is contingent on the existence and enforcement of stringent regulations aimed at protecting animals (Ormandy, Schuppli and Weary 2013, Ipsos MORI 2016).

Appendix B

Summary of Findings From the Office of the Inspector General 2014 Audit of the Animal and Plant Health Inspection Service's Oversight of Research Facilities, Audit Report 33601-0001-41

OIG audited APHIS to determine if the agency provided adequate oversight of research facilities and effectively enforced the Animal Welfare Act.

Since fiscal year (FY) 2001, APHIS' Animal Care (AC) unit conducted at least 500 inspections at 107 research facilities that had not used, handled, or transported any regulated animals for more than 2 years. As a result, AC did not make the best use of its limited resources, which could have been assigned to inspect other more problematic facilities, including breeders, dealers, and exhibitors. Further, the Investigative and Enforcement Services (IES) unit worked with AC and other APHIS programs to reduce a 2,000-case agency wide backlog. However, AC did not follow its own criteria in closing at least 59 cases that involved grave (e.g., animal deaths) or repeat welfare violations.

IES issued penalties that were reduced by an average of 86 percent from Animal Welfare Act's (AWA) authorized maximum penalty per violation. Consequently, 26 of the 30 violators in our sample received penalties in 2012 totaling at least $272,298 less than what they would have received using the worksheet in effect during our 2010 audit. We also found that IES under-assessed penalties by $33,001 in four cases we reviewed by granting good faith reductions without merit or using a smaller number of violations than the actual number.

Finally, some of APHIS' veterinary medical officers (VMOs) and some Institutional Animal Care and Use Committees (IACUCs)—the oversight committees at research facilities responsible for ensuring compliance with AWA—are not always adequately monitoring experimental procedures on animals. As a result, AC has reduced assurance that protocols are properly completed, approved, and adhered to and that animals are always receiving basic humane care and treatment. We found no issues related to AC's mission critical information system. APHIS concurred with all of our recommendations" (USDA OIG 2014).

Appendix C

United States Department of Agriculture Pain Categories

9 C.F.R. 2.36(b)

Category B	Category C	Category D	Category E
Animals being bred, conditioned, or held for use in teaching, testing, experiments, research, or surgery but not yet used for such purposes.	Animals upon which teaching, research, experiments, or tests were conducted involving no pain, distress, or use of pain-relieving drugs. Routine procedures (e.g., injections, tattooing, blood sampling) should be reported with this group.	Animals upon which experiments, teaching, research, surgery, or tests were conducted involving accompanying pain or distress to the animals and for which appropriate anesthetic, analgesic, or tranquilizing drugs were used	Animals upon which teaching, experiments, research, surgery, or tests were conducted involving accompanying pain or distress to the animals and for which the use of appropriate anesthetic, analgesic, or tranquilizing drugs would have adversely affected the procedures, results, or interpretation of the teaching, research, experiments, surgery, or tests.

Appendix D

The Jackson Laboratory: A History of Serious and Repeat Violations of Federal Animal Welfare Guidelines

Federal documents, dating from November 2006 to December 2016, obtained by PETA from the National Institutes of Health's Office of Laboratory Animal Welfare (OLAW) reveal numerous incidents in which mice at The Jackson Laboratory (Jackson) endured pain and distress because of worker incompetence and neglect. On multiple occasions, mice died of dehydration when employees failed to notice empty water bottles. Others suffocated when they were left in airtight jars or transport cages wrapped in plastic then forgotten. A mouse who was being restrained while blood was drawn died from mishandling. On many occasions, live mice were discovered inside bags or freezers intended for dead animals because workers had failed to ensure that they were dead after they had been gassed. And numerous times, experimenters deviated from approved protocols, potentially subjecting the mice to even more pain and distress.

- **December 2016 (Sacramento, California):** Mice in several rooms suffocated to death when the power failed and ventilation to their cages was compromised.
- **May 2016 (Sacramento, California):** After a fluctuation in room pressure caused water bottles to leak into animals' cages, 40 mice had to be euthanized because of their resulting poor condition.
- **April 2016 (Bar Harbor, Maine):** An undisclosed number of mice being transported in 190 shipping boxes died because of a temperature malfunction in a delivery truck. The cause of the malfunction wasn't determined.
- **February 2016 (Bar Harbor, Maine):** Seven mice were found dead and an additional undisclosed number of mice were euthanized after Jackson personnel failed to provide them with sufficient food and water.
- **September 2015 (Bar Harbor, Maine):** An undisclosed number of mice died and additional ones were euthanized after a sprinkler head sprayed water on several racks containing 640 cages of mice for approximately five minutes before it was turned off.
- **July 2015 (Sacramento, California):** A Jackson experimenter began conducting experiments on mice without approval from the facility's oversight body.
- **May 2015 (Sacramento, California):** An undisclosed number of mice were found dead in their cages after Jackson personnel failed to euthanize them as stipulated in the approved protocol.
- **February 2015 (Bar Harbor, Maine):** Nine anesthetized mice died after they were placed on a heating source prior to surgery. The equipment malfunctioned, causing them to die from heat stress.
- **December 2014 (Bar Harbor, Maine):** Several live mice were found in a carcass-disposal bag after Jackson personnel failed to verify death following a euthanasia procedure.
- **October 2014 (Sacramento, California):** An undisclosed number of mice were observed to have tumors that had become ulcerated after Jackson personnel failed to euthanize them as stipulated in the approved protocol.
- **March 2014 (Bar Harbor, Maine):** In two separate incidents, an undisclosed number of mouse pups died after Jackson personnel failed to provide them with sufficient food and water following weaning.
- **January 2014 (Bar Harbor, Maine):** Mice who were being transported were left unattended for several hours in a cage that was double-bagged in plastic. By the time they were discovered, several had died, and the survivors had to be euthanized.

- **November 2013 (Sacramento, California):** Mice died because they did not have a water bottle. Workers had failed to notice its absence during daily checks. Jackson didn't report the number of mice who had died, and federal authorities didn't request the information.
- **November 2013 (Sacramento, California):** An undisclosed number of mice baked to death when the electrical system malfunctioned and personnel ignored the malfunction alarm. In his report to federal authorities, Jackson's executive vice president downplayed the mice's suffering, writing, "[A] small percentage of the population of mice in several animal rooms at The Jackson Laboratory's Sacramento campus succumbed due to a buildup of heat and carbon dioxide." As Jackson's Sacramento facility holds an approximate "daily inventory" of 216,000 mice, a "small percentage" could still be a large number of mice, whose agonizing deaths likely involved extreme respiratory distress, nausea, weakness, and multiple-organ failure. Federal authorities did not request a clarification on the number.
- **March 2013 (Sacramento, California):** A Jackson experimenter deviated from the protocol that had been approved by the facility's oversight body for a study, using mice who were 2 to 3 weeks older than the ages that had been approved. Such deviations can potentially increase the animals' pain and discomfort.
- **January 2013 (Sacramento, California):** A mouse died of dehydration when workers failed to notice that the water bottle in the cage was empty.
- **January 2013 (Sacramento, California):** A mouse died as a result of being improperly restrained while having blood drawn from a cheek.
- **October 2012 (Bar Harbor, Maine):** Eight 4-day-old live mice were left in a tub overnight in a laboratory in which they were scheduled to be killed and then necropsied. The individual responsible for the necropsy had forgotten about them. As a result, three died and five had to be euthanized.
- **August 2012 (Sacramento, California):** Two incidents occurred in which experiments on mice were carried out without first securing approval from the laboratory's oversight body, which may have jeopardized their well-being since the oversight body is responsible for ensuring that animals' pain and discomfort are minimized.
- **August 2012 (Sacramento, California):** Because of a shipping error, two mice were left in their cage without food or water. When they were discovered, one was dead and the other had become dehydrated.
- **July 2012 (Bar Harbor, Maine):** A live mouse was found inside a "cull bag" (a bag intended for dead mice).
- **March 2012 (Bar Harbor, Maine):** Twenty-four live mice who were 3 days old or younger were discovered inside a cull bag, which also contained two dead mother mice with live fetuses.
- **March 2010 (Bar Harbor, Maine):** Two 10-day-old live mice were found inside a bag of dead mice who had been gassed with carbon dioxide.
- **October 2009 (Sacramento, California):** Fifteen live mice were discovered inside a carcass bin in a freezer—they had been there for three days. The incident was the result of a failed attempt at carbon dioxide gassing. Bags containing carcasses of dead mice had been chewed through and the carcasses cannibalized.
- **April 2009 (Bar Harbor, Maine):** A total of 366 mice were found dead in their cages after an HVAC disruption resulted in a complete loss of ventilation to the individually ventilated cages in the room. Their deaths were a result of a buildup of heat and carbon dioxide and the depletion of oxygen in their cages.
- **March 2009 (Bar Harbor, Maine):** A live mouse was discovered inside a bag of dead mice who had been gassed with carbon dioxide.

- **December 2008 (Bar Harbor, Maine):** Three mice suffocated when they were left in airtight jars overnight. An additional mouse in the jar had to be euthanized.
- **June 2008 (Bar Harbor, Maine):** A licensed veterinary technologist at Jackson reported a litany of animal welfare concerns to OLAW. In her reports, which included internal documents and e-mails sent to senior Jackson officials, she described instances of many moribund mice—unable to move, "showing significant signs of debilitation," unable to reach food and water, and close to death. Some of them, genetically modified for use in ALS studies, had become paralyzed and very sick, exhibiting a "hunched" appearance, "cold to the touch, not moving, acutely dehydrated, emaciated, [and with] sunken eyes." According to the documents, an animal health technician had reported concerns related to the ALS mice "at least 20 times over the years," but nothing was done to alleviate their suffering. The veterinary technologist contacted OLAW when her attempts to have the issues resolved internally were unsuccessful. OLAW corresponded with Jackson officials, and they assured the office that they had updated their policies and forms. In December 2008, OLAW wrote the following to Jackson:

OLAW appreciates the efforts by you and The Jackson Laboratory [Institutional Animal Care and Use Committee] to investigate the original allegations and to provide the requested information. OLAW believes that the implementation of these policies and updated forms will mitigate concerns relating to endpoints and clinical intervention. We thank you again for your attention to this matter and find no cause for further action by this office.

- **April 2008 (Sacramento, California):** Eighty mice suffocated when they were left in airtight jars overnight.
- **April 2008 (Bar Harbor, Maine):** Several live mice were found in a bag that also contained dead ones.
- **March 2008 (Bar Harbor, Maine):** Two live mice were found in a cooler intended for dead animals.
- **December 2007 (Bar Harbor, Maine):** Eight mice died of starvation and dehydration when they were left in a cage and forgotten. They had been there without food or water for seven days before their bodies were discovered.
- **November 2006 (Sacramento, California):** When a Jackson experimenter carried out experiments on mice without approval from the facility's oversight body, nine mice sustained injuries to their eyes and had to be euthanized.