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Sent by Electronic Mail June 18, 2020

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Alex Azar, Secretary
Health and Human Services
Secretary@HHS.gov
200 Independence Avenue S.W.
Washington, D.C., 20201

Re: **Petition to Include Cephalopods as "Animals" Deserving of Humane Treatment under the Public Health Service Policy on Humane Care and Use of Laboratory Animals**

Dear Director Collins and Secretary Azar:

With this letter and the attached Petition, we are requesting that you take immediate action to amend the Public Health Service Policy on Humane Care and Use of Laboratory Animals to include cephalopods—i.e., octopus, squid, and cuttlefish—within the definition of "animal," so that these animals will receive the minimum protection for "humane" handling and care required by that Policy. This Petition is submitted on behalf of the New England Anti-Vivisection Society, American Anti-Vivisection Society, Physicians Committee for Responsible Medicine, Humane Society of the United States, and Humane Society Legislative Fund, as well as the following cephalopod experts: Jennifer Jacquet, PhD; Becca Franks, PhD; Judit Pungor, PhD; Jennifer Mather, PhD; Peter Godfrey-Smith, PhD; Heather Browning; and Walter Veit.

As explained in the Petition, the requested action is needed because cephalopods are increasingly being used in laboratory research across the country, funded by taxpayer revenue, and yet, because they are currently not considered "animals" under the Public Health Service Policy, these incredibly intelligent animals are being denied basic humane treatment. As also explained, the requested action would bring the United States in line with several other countries and governmental entities that already accord these species such humane treatment when used in government-funded research, including the United Kingdom, Canada, New Zealand, Australia, Switzerland, Norway, and the European Union.

As further explained in the Petition, Congress clearly stated that updating the standards to reflect advancements in scientific knowledge is a necessary part of the Secretary of Health and Human Service's duties under the Health Research Extension Act of 1985, Public Law 99-158. *See, e.g.,* H.R. Rep. No. 99-158, at 40 (1985) ("This ongoing process recognizes that such sensitivity cannot be captured in any set of rules, *that standards of care will change in the future as science advances, and that the value of medical research requires such judgments to be professionally and scientifically sound*.") (emphasis added). In recent years, there has been much research demonstrating that cephalopods are sensitive, intelligent creatures who, like other animals uses in biomedical research, deserve to be treated humanely. Accordingly, it is time to update the Public Health Service Policy on Humane Care and Use of Laboratory Animals to reflect this scientific fact.

All of the scientific journals, articles, and other materials cited in support of the Petition will be included in an Appendix that we will submit separately within the next few days.

The Petitioners and Clinic stand ready and willing to assist you in implementing the requested action, including by helping the Public Health Service devise the appropriate standards that should apply to the care and handling of each species of cephalopods.

We look forward to working with you on this important issue.

Sincerely,

Katherine A. Meyer
Director
Animal Law & Policy Clinic

Kate Barnekow
Clinical Fellow
Animal Law & Policy Program

PETITION FOR RULEMAKING
U.S. DEPARTMENT OF HEATH AND HUMAN SERVICES

Submitted by:
New England Anti-Vivisection Society; American Anti-Vivisection Society; The Physicians Committee for Responsible Medicine; The Humane Society of the United States; Humane Society Legislative Fund; Jennifer Jacquet, PhD; Becca Franks, PhD; Judit Pungor, PhD; Jennifer Mather, PhD; Peter Godfrey-Smith, PhD; Lori Marino, PhD; Greg Barord, PhD; Carl Safina, PhD; Heather Browning; and Walter Veit
Petitioners

I. INTRODUCTION[1]

This petition is submitted on behalf of the New England Anti-Vivisection Society (NEAVS), a non-profit organization dedicated to reducing animal suffering, and co-petitioners and is requesting action by the Secretary of Health and Human Services and Director of the National Institutes of Health (NIH). Specifically, the petitioners request NIH to act consistently with Congress' enactment of Section 495 of the Health Research Extension Act of 1985 and amend the Public Health Service (PHS) Policy on Humane Care and Use of Laboratory Animals to include cephalopods within its regulatory scope. This includes changing the definition of "animal" under the PHS Policy to include cephalopods, as well as updating The Guide for the Care and Use of Laboratory Animals (the Guide) to reflect proper care and handling required by these animals.

A cephalopod, any mollusk of the class *Cephalopoda*, is a bilaterally symmetrical marine animal with a set of arms or tentacles extending from a prominent head, such as a squid or octopus. Currently no regulation covers the use of cephalopods in research in the United States. In this respect, the United States is behind many other countries that have made the decision to regulate the use of cephalopods in research. These decisions have been based on substantial evidence that cephalopods are similar to vertebrates in key aspects that justify providing them with similar welfare-oriented protections. Congress clearly stated that updating the standards to reflect advancements in scientific knowledge is a necessary part of the Secretary's duties under the Health Research Extension Act.[2]

[1] Petitioners wish to acknowledge and thank Katherine Khazal, Harvard Law School class of 2021, for her invaluable research and writing on this project.

[2] H.R. Rep. No. 99-158, at 40 (1985) ("This ongoing process recognizes that such sensitivity cannot be captured in any set of rules, that standards of care will change in the future as science advances, and that the value of medical research requires such judgments to be professionally and scientifically sound.").

Cephalopods have been used in research for decades, but use of these species has increased substantially in recent years.[3] NIH-funded institutions are at the forefront of cephalopod research in the US. From 1978 until 2010 the National Resource Center for Cephalopods (NRCC) in Texas dominated such research. Currently, the Marine Biological Laboratory (MBL) in Massachusetts has taken over as NIH's largest supplier, and possibly largest utilizer, of such animals in conducting research. There has also been a mounting number of research papers published concerning cephalopods[4] and a rise in membership of the Cephalopod International Advisory Council (CIAC)—a group of international scientists aimed at fostering cephalopod research and education.[5] But experiments on cephalopods may cause significant pain, distress, and suffering to these animals, such as by depriving them of food or by conducting invasive neuroscience research.[6]

This ability to experience pain and suffering has been one of the primary reasons other countries have made the change to include cephalopods within their animal welfare regulation. When considering if an animal feels pain, scientists consider several factors.[7] Cephalopods have a complex neural system that is "capable of performing functions similar to those performed by the vertebrate brain cortex."[8] Another element scientists consider is physiological and behavioural responses to painful stimulation, such as avoidance or escape behaviour."[9] There is ample evidence that cephalopods show avoidance or escapist behaviour, including trying to escape when anaesthetized by a chemical they find adverse, and learning to avoid objects that produce electric shocks.[10] Additionally, scientists consider whether the animal can "quickly learn to avoid [a] noxious stimulus and demonstrate sustained changes in behaviour that have a protective function to reduce further injury and pain, prevent the injury from recurring, and promote healing

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[3] *See, e.g.*, Nell Greenfieldboyce, *Why Octopuses Might Be the Next Lab Rats*, National Public Radio (June 3, 2019), https://www.npr.org/sections/health-shots/2019/06/03/727653152/why-octopuses-might-be-the-next-lab-rats (reporting that scientists are increasingly "explor[ing cephalopods'] sophisticated brains and unusual behaviours" and that approximately 3,000 cephalopods are currently being housed at the Woods Hole Marine Biology Laboratory in Massachusetts.").

[4] Paige Helmer, *Defying Classification: Cephalopods in Research*, PhDish (Jan. 30, 2019), http://www.phdish.com/blog/defying-classification-cephalopods-in-research ("Recently, the field of cephalopod research has spread in new directions. Since 2006, every category of aquaculture, behaviour, climate change, cognition, genetics, neuroscience, and welfare had at least 10 papers published, and the largest category, behaviour, saw over 450 papers published.").

[5] Ben Guarino, *Inside the Grand and Sometimes Slimy Plan to Turn Octopuses Into Lab Animals*, Wash. Post (March 2, 2019), https://www.washingtonpost.com/national/health-science/inside-the-grand-and-sometimes-slimy-plan-to-turn-octopuses-into-lab-animals/2019/03/01/c6ce3fe0-3930-11e9-b786-d6abcbcd212a_story.html?noredirect=on&utm_term=.fd933f1c4dd6 ("Erica A.G. Vidal, a marine scientist at the Federal University of Parana in Brazil and a former president of the research organization the Cephalopod International Advisory Council . . . estimated the community increased by about 30 percent between 2012 and 2018.").

[6] *See, e.g.*, Antonio V. Sykes et al., *The Digestive Tract of Cephalopods: A Neglected Topic of Relevance to Animal Welfare in the Laboratory Aquaculture*, 8 Front. Physiol. 1, 11 (2017); Graziano Fiorito et al., *Guidelines for the Care and Welfare of Cephalopods in Research: A Consensus Based on an Initiative by CephRes, FELASA and the Boyd Group*, 49 Laboratory Animals 1 (2015).

[7] Giorgia della Rocca et al., *Pain and Suffering in Invertebrates: An Insight on Cephalopods*, 10 Am. J. Animal & Veterinary Sci. 77, 78 (2015).

[8] *Id*. at 79.

[9] *Id*. at 80.

[10] N.A. Moltschaniwskyj et al., *Ethical and Welfare Considerations When Using Cephalopods as Experimental Animals*, 17 Rev. Fish Biol. & Fisheries 455, 457 (2007).

and recovery."[11] Cephalopods rely heavily on learning throughout their life, and they show a high degree of intelligence.[12] With every indication that cephalopods experience pain, they are deserving of humane treatment and protections to minimize discomfort.

The need for standards to minimize the pain of cephalopods is reason enough to include them within the protections of the PHS Policy. However, regulation also helps ensure accurate scientific results. Cephalopods are complex creatures with sensitive skin and bodily systems. Stress, physical harm, and toxins can not only cause pain to the animal, but can also produce inaccurate research results since variables such as digestive tract parasites, toxins from food or water, and stress from human interactions can impact outcomes.

As Congress stated when enacting the Health Research Extension Act of 1985, "[r]ather than interfering with the administration of research activities, these requirements will insure that research activities conform to professional and humane standards of conduct."[13] They will also "protect the scientific freedom and integrity" of the United States' research efforts.[14] Therefore, whether concerned about cephalopods themselves or research integrity, it is clear that the inclusion of cephalopods in the PHS Policy is both necessary and appropriate.

[11] Lynne Sneddon et al., *Defining and Assessing Animal Pain,* 97 Animal Behaviour 201, 202 (2014).
[12] Peter Godfrey-Smith, *The Mind of an Octopus*, Scientific American (Jan. 1, 2017), https://www.scientificamerican.com/article/the-mind-of-an-octopus/?redirect=1.
[13] 131 Cong. Rec. S00000-02, 1985 WL 721365, 7 (1985).
[14] *Id*. at 14.

II. DESCRIPTION OF PETITIONERS

The **New England Anti-Vivisection Society** (NEAVS) is a non-profit 501(c)(3) organization dedicated to reducing animal suffering. Since its inception in 1895, NEAVS has been working toward ending the use of animals in research, testing, and science education, and replacing these methods with more humane and predictive non-animal alternatives. NEAVS accomplishes these objectives through outreach, research, education, collaboration, and advocating for legislative policy changes.

The **American Anti-Vivisection Society** (AAVS) is the oldest non-profit 501(c)(3) animal advocacy and educational organization in the United States dedicated to ending experimentation on animals in science, including research, testing, and education. Focused on the objectives of strong animal protective legislation, public awareness, and humane education, AAVS has spent much of its history promoting and seeking alternatives to the use of animals in science and society. AAVS also has a Sanctuary Fund through which it protects former lab animals by finding them new, humane homes in animal sanctuaries. Since the 1980s, AAVS has also worked to fund, promote, and reward those scientists who use non-animal methods through direct grants for alternatives-driven research.

The **Physicians Committee for Responsible Medicine** (The Physicians Committee) is a nonprofit 501(c)(3) organization that advocates for preventive medicine, conducts clinical research, and works toward higher ethical standards in research. For more than thirty-five years, the Physicians Committee has improved public safety and public health by working tirelessly for alternatives to the use of animals in medical education and research and advocating for more effective scientific methods. Its staff of physicians, dietitians, and scientists works with policymakers, industry, the medical community, the media, and the public to create a better future for people and animals.

The **Humane Society of the United States** (HSUS) is a non-profit animal protection organization founded in 1954 and headquartered in Washington, D.C. Together with its affiliates, HSUS has regional offices and direct animal care facilities located throughout the country and international offices throughout the world. HSUS actively works (through public education, investigation, litigation, legislation, and advocacy) to combat animal abuse and exploitation and to promote the protection and welfare of all animals, including animals used in research, testing, and training.

The **Humane Society Legislative Fund** (HSLF) is a social welfare organization incorporated under section 501(c)(4) of the Internal Revenue Code and formed in 2004 as a separate lobbying affiliate of the Humane Society of the United States. HSLF works to pass animal protection laws at the state and federal levels. HSLF works to ensure that animals have a voice before lawmakers by advocating for measures to eliminate animal cruelty and suffering and by educating the public on animal protection issues. Among other issues, HSLF advocates against unnecessary and inhumane practices used in animal research.

Jennifer Jacquet, PhD is part of the Department of Environmental Studies at New York University (NYU), which administers a minor and master's degree in Animal Studies. She is also Deputy Director of the Center for Environmental and Animal Protection at NYU. Along with

Becca Franks, Peter Godfrey-Smith, and Walter Sanchez-Suarez, she wrote the "The Case Against Octopus Farming" published in *Issues in Science and Technology* in 2019.

Becca Franks, PhD is a Visiting Assistant Professor at the Department of Environmental Studies at New York University. She has over a decade of research experience working on laboratory animal welfare. In that time, she has published over 30 peer-reviewed empirical papers and review articles on animal welfare science, including one article evaluating the scientific literature on octopus. Through this literature search, she and her co-authors demonstrated that farming octopus would inevitably involve severe welfare risks and direct harms.

Judit Pungor, PhD is a Postdoctoral Scholar in Biology at the University of Oregon. She is a neuroscience researcher who focuses on the investigation of cephalopod nervous system organization. She also assisted in the composition of the EU directives regarding cephalopod use in research.

Jennifer Mather, PhD is a Professor in the Department of Psychology at the University of Lethbridge in Canada. She is a member of the committee that recommended to the Canadian Council of Animal Care that cephalopods be afforded protection and care in research and has published extensively on the cognition and intelligence of cephalopods. She co-edited the book *Cephalopod Cognition* (2014) and has written about cephalopod care issues in the journals International Laboratory Animal Research, Journal of Applied Animal Welfare Science, and Diseases of Aquatic Organisms. She is also a co-editor of and contributing author to the book *Invertebrate Welfare* (2019).

Peter Godfrey-Smith, PhD is a Professor of History and Philosophy of Science in the School of History and Philosophy of Science at the University of Sydney. He wrote the book *Other Minds* (2016), which focuses on the unique place cephalopods have in the history of animals and the evolution of the mind. He has also studied high-density octopus sites in Australia, empirical work that is uncovering surprising forms of complex behavior in wild octopuses.

Lori Marino, PhD is the Executive Director of the Kimmela Center for Animal Advocacy. The Kimmela Center is committed to applying scientifically-based arguments to animal advocacy efforts and endorses strong empirical arguments on behalf of better protections for cephalopods used in research.

Gregory J. Barord, PhD is a Conservation Biologist at Save the Nautilus, a conservation-based organization focused on the awareness, education, research, and conservation of nautiluses and is the Marine Biology Instructor at Central Campus Regional Academy. Barord is also a scientific advisor on the Aquatic Invertebrate Taxon Advisory group and has authored several publications on the husbandry and care of cephalopods, ensuring the most current information is available to the community to promote the best animal welfare practices.

Carl Safina, PhD is the Endowed Chair for Nature and Humanity at Stony Brook University and founder of The Safina Center. Safina is an ecologist specializing in marine ecology and fisheries. He has also written two books on animal cognition and emotional capacities and culture in free living animals. The Safina Center is a is a 501(c)(3) nonprofit dedicated to advancing the case for life on Earth by fusing scientific understanding, emotional connection, and a moral call to action.

Heather Browning is a PhD Candidate in Philosophy at the Australian National University, Australia's leading research university. Her PhD research is on the measurement of animal welfare. She is also a zookeeper and animal welfare officer, with an interest in improving the welfare of captive animals, and she has published on the welfare considerations for octopuses.

Walter Veit is a PhD Candidate in History and Philosophy of Science under the supervision of Peter Godfrey-Smith and Paul Griffiths at the University of Sydney. His work focuses on the evolutionary origins of pain and pathology detection, studying animals across the evolutionary tree including cephalopods. He is also collaborating with Heather Browning to improve animal welfare science and thus animal welfare.

III. REQUESTED ACTION

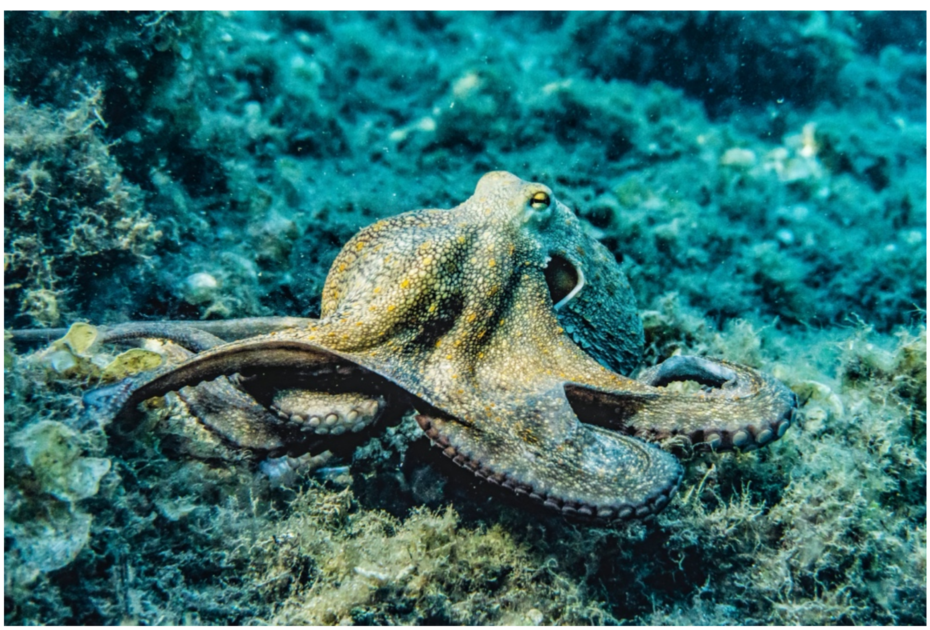
Pursuant to the Administrative Procedure Act, 5 U.S.C. § 553(e), this petition respectfully requests that the Secretary take action consistent with Congress' enactment of the Health Research Extension Act of 1985 § 495 and amend the Public Health Service (PHS) Policy on Humane Care and Use of Laboratory Animals to include cephalopods within its regulatory scope. This encompasses providing cephalopods all the federally mandated protection provided by the Heath Research Extension Act of 1985, implemented through the PHS policy, including "***the appropriate use of tranquilisers, analgesics, anesthetics, paralytics and euthanasia" and "appropriate pre-surgical and post-surgical veterinary medical and nursing care***."[15]

To include cephalopods under the PHS Policy, NIH must amend its current definition of "animal" as follows:

> *any live, vertebrate animal as well as higher-functioning invertebrates, including cephalopods, used or intended for use in research, research training, experimentation, or biological testing or for related purposes.*

This definition should also be used in The Guide for the Care and Use of Laboratory Animals (the Guide), which National Institutes of Health (NIH)-supported organizations are required to follow.

To implement the requested action, the Guide should also be updated to reflect the proper care and handling required by cephalopods. This includes pain management, proper housing, and required nutrition for each species of cephalopod. This information is readily available in many research studies, discussed *infra,* and will ensure that any researcher using or intending to use cephalopods will properly care for these animals.



[15] Health Research Extension Act of 1985, Pub. L. No. 99-158, § 495, 99 Stat 820 (1985).

IV. LEGAL BACKGROUND

In 1985, in response to a widely publicized animal cruelty case and other incidents, Congress, as part of the Health Research Extension Act,[16] gave the Department of Health and Human Services (HHS)—NIH's parent agency—authority to establish guidelines for the proper treatment of animals used in research in NIH-funded laboratories.[17]

The Public Service Health Act provides that the Secretary of HHS "shall establish guidelines for . . . [t]he proper care of animals to be used in biomedical and behavioral research" and that such guidelines "shall require . . . the appropriate use of tranquilizers, analgesics, anesthetics . . . and euthanasia," as well as "appropriate pre-surgical and post-surgical veterinary medical and nursing care."[18] The statute also provides that the guidelines "shall require [an Institutional Animal Care and Use Committee [IACUC]] at each entity which conducts biomedical and behavioral research with [federal funds] . . . to assure compliance with the guidelines."[19] It further requires that if the Director of NIH determines that "the conditions of animal care, treatment, or use in an entity which is receiving a grant, contract, or cooperative agreement involving research on animals [under the Act] do not meet [the] applicable guidelines . . . ," and no action has been taken to correct such conditions, the Director of NIH "shall suspend or revoke such grant or contract under such conditions as the Director determines appropriate."[20]

Pursuant to the Health Research Extension Act, the Public Health Service (PHS)—an entity within HHS that oversees NIH—has issued a "Policy on Humane Care and Use of Laboratory Animals" (the Policy) that is administered by the Office of Laboratory Animal Welfare. The Policy "is applicable to all PHS-conducted or supported activities involving animals," including research by institutions awarded federal funding for such research.[21] The Policy provides that "[n]o activity involving animals may be conducted or supported by the PHS until the institution conducting the activity has provided a written Assurance . . . setting forth compliance with the Policy," and demonstrating the adequacy of the institution's "program for the care and use of animals."[22] It further states that "[w]ithout an applicable PHS-approved Assurance, no PHS-conducted or supported activity involving animals at the institution will be permitted to continue."[23]

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[16] Pub. L. No. 99-158 (Nov. 20, 1985).
[17] *See* Pub. Health Service Act, 42 U.S.C. §§ 201 *et seq.*; Reid G. Adler, *Controlling the Applications of Biotechnology: A Critical Analysis of the Proposed Moratorium on Animal Patenting*, 1 Harv. J. Law & Tec. 36–37 and n.233 (1988) (explaining that this provision was enacted in response to a criminal case brought against a federally funded researcher for his cruel treatment of monkeys in research conducted at NIH's Institute of Behavioral Research in Silver Spring, Maryland); *Int'l Primate Prot. League v. Inst. for Behavioral Research,* 799 F.2d 934, 935-936 (4th Cir. 1986) (recounting history of the case and that it was brought to light by one of the founders of PETA); *see also, e.g.*, The Use of Animals in Medical Research and Testing: Hearings Before the Subcomm. on Science, Research and Technology of the Comm. on Science and Technology, 97 Cong. 24 (1981) (statement of Rep. Ted Weiss) (observing that PETA's exposé of the Silver Spring research facility "shocked and horrified Americans as the hellish tale unraveled in the nation's newspapers," and that the animal abuse at that particular facility was "only the tip of the iceberg of the mistreatment of animals in scientific endeavors").
[18] 42 U.S.C. § 289d(a).
[19] *Id.* § 289d(b).
[20] *Id.* § 289d(d).
[21] Public Health Service Policy on Humane Care and Use of Laboratory Animals, NIH No. 15-8013, § II (2015).
[22] *Id.* § IV(A).
[23] *Id.*

The Guide for the Care and Use of Laboratory Animals (the Guide) is a detailed National Research Council publication, divided into five sections. The Guide is to be used "as a foundation for the development of a comprehensive animal care and use program, recognizing that the concept and application of performance standards, in accordance with goals, outcomes, and considerations defined in the Guide, is essential to this process."[24] The sections are as follows: Key Concepts; Animal Care and Use Program; Environment, Housing, and Management; Veterinary Care; and Physical Plant.[25] The Guide takes into account the U.S. Government Principles for Utilization and Care of Vertebrate Animals Used in Testing, Research, and Training and endorses such principles as consideration of alternatives to reduce or replace the use of animals; avoidance or minimization of discomfort, distress, and pain; use of appropriate sedation, analgesia, and anesthesia; establishment of humane endpoints; and provision of adequate veterinary care and appropriate animal transportation and husbandry.[26]

The NIH Office of Laboratory Animal Welfare provides guidance on the Vertebrate Animals Section, which is required for all NIH applications proposing vertebrate animal use, based on the PHS Policy on Humane Care and Use of Laboratory Animals and federal requirements.[27] Vertebrate Animals Section guidance is provided to assist applicants and reviewers in preparing and reviewing proposals containing vertebrate animal use.[28] If live vertebrate animals are to be used, applicants must address the following criteria: description of procedures, justifications, minimization of pain and distress, and method of euthanasia.[29] Because cephalopods are not vertebrates, these criteria are not required to be addressed by proposals containing cephalopod use and are therefore not considered during funding decisions. In addition, parent institutions of granted applications containing cephalopod use are neither required to obtain an Animal Welfare Assurance nor to approve an IACUC protocol associated with the proposed research.[30]

The Guide covers myriad topics—including water quality, noise control, and anesthesia use—that are well-researched and documented with regard to cephalopods.[31] Indeed, although cephalopods are not currently covered by the Guide, some of this research regarding cephalopods is referenced within it.[32]

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[24] National Research Council, *Guide for the Care and Use of Laboratory Animals* xiii, (8th ed. 2011) (italics removed).
[25] *Id*.
[26] *Id*. at 12.
[27] NIH Office of Animal Welfare, *Vertebrate Animals Section* (last updated May 9, 2018), https://olaw.nih.gov/guidance/vertebrate-animal-section.htm.
[28] *Id.*
[29] *Id.*
[30] *Id.*
[31] *See, e.g.,* Daniel J. Oestmann et al., *Special Considerations for Keeping Cephalopods in Laboratory Facilities*, 36 J. Am. Assoc. Lab. Animal Sci. 89, 92 (1997); Graziano Fiorito et al., *Guidelines for the Care and Welfare of Cephalopods in Research: A Consensus Based on an Initiative by CephRes, FELASA and the Boyd Group*, 49 Laboratory Animals 1 (2015).
[32] *See* National Research Council, *Guide for the Care and Use of Laboratory Animals* xiii, 179 (8th ed. 2011) (references: Berry DJ et al., *Information for Reptiles, Amphibians, Fish and Cephalopods Used in Biomedical Research* (1992); Boyle PR, *The Care and Management of Cephalopods in the Laboratory* (1991).).

Although the Health Research Extension Act of 1985 provides no definition for "animal," the current PHS Policy defines this critical term to mean: "any live, *vertebrate* animal used or intended for use in research, research training, experimentation, or biological testing or for related purposes"[33]—the definition that is repeated in the Guide.[34] The legislative history of the Act, however, does not limit its scope to any "vertebrate" animal.[35] In fact, Congress made clear its intention for the statute—and subsequent implementations thereof—was to broadly cover *any* "animal" used in federally-funded research. As explained by the House Conference Report:

> For the past twenty-years, institutions receiving NIH grants and contracts have been required to meet NIH guidelines regarding the treatment of laboratory animals. These guidelines are presently based on the 'Guide for the Care and Use of Laboratory Animals' developed by the Institute of Laboratory Resources of the National Research Council.
>
> It is important to provide statutory authority and recognition for these requirements.[36]

The Guide, however, did not always have a definitional limit on the word "animal" the way that it does today.[37] Prior to Congress' enactment of the Health Research Extension Act, and indeed for three weeks after the above-cited House Report insisting on "statutory authority" for the then-current requirements was published, the term "animal" was not limited to only vertebrates. It was

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[33] Public Health Service Policy on Humane Care and Use of Laboratory Animals, NIH No. 15-8013, § III(A) (2015) (emphasis added).
[34] National Research Council, *Guide for the Care and Use of Laboratory Animals* 2, (8th ed. 2011).
[35] H.R. Rep. No. 99-158 (1985); H.R. Conf. Rep. No. 99-309 (1985).
[36] H.R. Rep. No. 99-158, at 40 (1985).
[37] Health Research Extension Act of 1985, Pub. L. No. 99-158, §495, 99 Stat 820 (1985); National Research Council, *Guide for the Care and Use of Laboratory Animals* (1978).

only later that the National Research Council inserted a definition it had never included before: that the term "animal" now meant only "any warm-blooded vertebrate animals used in research, testing, and education."[38] Thus, when Congress stated in 1985 that it was "important to provide statutory authority" for the guidelines in the Guide for the Care and Use of Laboratory Animals, it was stating its intent to provide statutory authority for protections for *all* animals used in research—not only vertebrates. This view is further bolstered by other Congressional statements clearly indicating that "the proper care and treatment of animals *used in laboratory research*" was of utmost concern when passing this bill.[39] In fact, Congress went so far as to state in the House Report that "the development of non-animal research methods deserves the focused attention of the National Institute of Health," indicating a concern for *all* animal species.[40]

By failing to regulate the use of cephalopods in research, the United States is lagging behind many other countries. As early as 1986, the United Kingdom included *Octopus vulgaris* as a protected species for scientific research.[41] And Canada began regulating the use of cephalopods in research in 1991, followed by New Zealand in 1999, Australia in 2004, and the European Union in 2010.[42] Switzerland and Norway also cover cephalopods under their animal welfare legislation.[43]

Although each country uses slightly different considerations when deciding which species to include within the scope of animal research regulations, the most important criterion appears to be universally accepted—i.e., the species' ability to experience pain. As explained by the Official Journal of the European Union when the EU changed its Directive to include cephalopods:

> [New] scientific knowledge [is] available in respect of factors influencing animal welfare as well as *the capacity of animals to sense and express pain, suffering, distress and lasting harm*. It is therefore necessary to improve the welfare of animals used in scientific procedures by raising the minimum standards for their protection in line with the latest scientific developments.[44]

Congress expressed similar reasoning when in enacting the Health Research Extension Act. It emphasized that "[t]his ongoing process recognizes that such sensitivity cannot be captured in any set of rules, that standards of care will *change in the future as science advances*, and that the value of medical research requires such judgments to be professionally and scientifically sound."[45] Indeed, pursuant to this proclamation, the Guide has been updated numerous times since its inception.[46] Therefore, revising the definition of "animal" to include cephalopods would reflect

[38] National Research Council, *Guide for the Care and Use of Laboratory Animals* (1985); H.R. Rep. No. 99-158 (1985); NIH Guide for Grants and Contracts 14:8 (1985).
[39] H.R. Rep. No. 99-158, at 40 (1985) (emphasis added).
[40] *Id*. at 43.
[41] Ellen P. Neff, *Considering the Cephalopod*, LabAnimal (Dec. 12, 2018), https://www.nature.com/articles/s41684-018-0199-0?WT.feed_name=subjects_developmental-biology.
[42] *Id*.
[43] The Lush Prize, *A Global View of Animal Experiments* (2014), https://www.lushprize.org/wp-content/uploads/Global_View_of-Animal_Experiments_2014.pdf.
[44] 2010 O.J. (L 276) (33) (emphasis added).
[45] H.R. Rep. No. 99-158, at 40 (1985) (emphasis added).
[46] *See, e.g.*, J. Derrell Clark et al., *The 1996 Guide for the Care and Use of Laboratory Animals*, 38 ILAR J. 41 (1997) ("The *Guide for the Care and Use of Laboratory Animals* (the *Guide)* was first published in 1963 under the

Congress' intention that NIH update its regulations and guidelines to take into account new scientific information about the biological needs of animals used in federally-funded research.

In fact, there is now evidence that cephalopods are similar to mammals in key aspects. Therefore, NIH should amend the definition of "animal" to include these species among those entitled to protection under the Animal Care Policy. Indeed, if vertebrates are regulated by the PHS Policy because they are intelligent animals that can experience pain, it follows that cephalopods—which are also intelligent animals who experience pain—must also be afforded protection under the Policy.

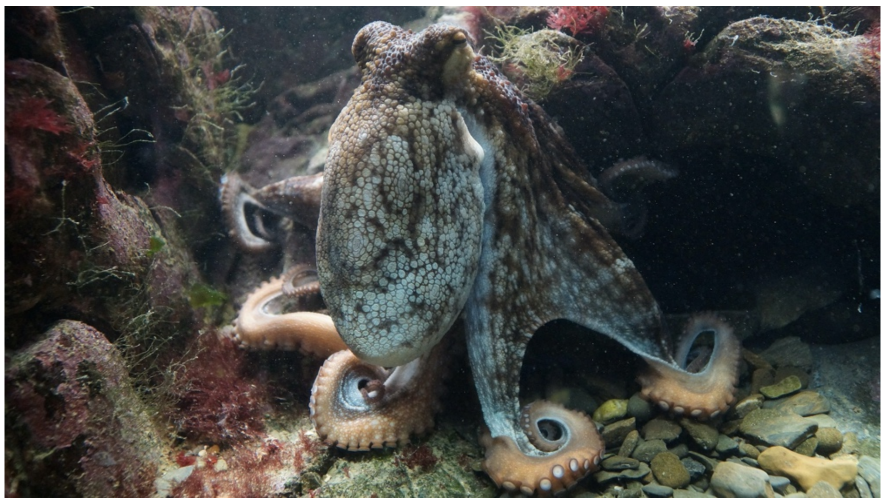
As explained by Congress when it enacted the underlying statute, "[r]ather than interfering with the administration of research activities, these requirements will insure that research activities conform to professional and humane standards of conduct."[47]

title *Guide for Laboratory Animal Facilities and Care* and was revised in 1965, 1968, 1972, 1978, and 1985"); National Research Council, *Guide for the Care and Use of Laboratory Animals* (1996); National Research Council, *Guide for the Care and Use of Laboratory Animals* (2011).

[47] 131 Cong. Rec. S00000-02, 1985 WL 721365, 7 (1985); *see also id.* at 14 (explaining that "the preponderance of provisions of [the statute] protect the scientific freedom and integrity of our research effort.")

V. FACTUAL BACKGROUND

Cephalopods have been used in research for decades, with their use increasing substantially in recent years.[48] In the early 1900s cephalopods were used in experiments surrounding the understanding of the neuron, including the research that led physiologists Alan Hodgkin and Andrew Huxley to be awarded the Nobel Prize in Physiology or Medicine in 1963.[49] Throughout the 1900s cephalopods continued to be used in experiments, often to study their nervous system and learning abilities.[50] Today cephalopods are used for a variety of experiments, including the study of genetics, cognition, and robotics.[51]



The United States has been front and center when it comes to cephalopod experimentation, with NIH funding many of the largest utilizers and suppliers. From 1978 to 2010 the National Resource Center for Cephalopods (NRCC) in Texas dominated such research. In 2002 it was providing upwards of 40% of the cephalopods utilized in NIH-supported research,[52] and by 2008 it was providing over 50%.[53] By the time the Center closed in 2010, it had created generations of cephalopods.[54] NRCC explained its growing cephalopod population as due to "the rapid increase in publications using cephalopods in this century—and exponential increase in the last decade."[55]

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[48] *See, e.g.*, Nell Greenfieldboyce, *Why Octopuses Might Be the Next Lab Rats*, National Public Radio (June 3, 2019), https://www.npr.org/sections/health-shots/2019/06/03/727653152/why-octopuses-might-be-the-next-lab-rats.
[49] Ellen P. Neff, *Considering the Cephalopod*, Lab Animal (Dec. 12, 2018), https://www.nature.com/articles/s41684-018-0199-0?WT.feed_name=subjects_developmental-biology.
[50] Caitlin E. O'Brien, et al*., The Current State of Cephalopod Science and Perspectives on the Most Critical Challenges Ahead from Three Early-Career Researchers*, 9 Frontiers in Physiology 700, 702 (2018).
[51] *Id*.
[52] Phillip Lee Grant, *National Resource Center for Cephalopods*, Granttome (2002), http://grantome.com/grant/NIH/P40-RR001024-26.
[53] Jai Dwivedi, *National Resource Center for Cephalopods*, Granttome (2008), http://grantome.com/grant/NIH/P40-RR001024-32S4.
[54] Daniel J. Oestmann et al., *Special Considerations for Keeping Cephalopods in Laboratory Facilities*, 36 J. Am. Assoc. Lab. Animal Sci. 89 (1997) ("[Seven] generations of European cuttlefish and [six] generations of Pacific long-finned squid had been cultured.").
[55] Phillip Lee Grant, *National Resource Center for Cephalopods*, Granttome (2002), http://grantome.com/grant/NIH/P40-RR001024-26.

The Marine Biological Laboratory (MBL) at Woods Hole, Massachusetts has now taken over as NIH's largest supplier, and possibly largest utilizer of cephalopods in its own federally funded research. Indeed, the MBL has become one of the world's most recognized cephalopod laboratories. "It's the only place on the planet that you can go where…a number of these species [are being cultured] through every life stage, through successive generations."[56] Around 3000 cephalopods can currently be found at the MBL.[57]

The federal Animal Welfare Act, which governs some animal species used in research, defines "animal" as limited to "warm-blooded animal[s]" and, accordingly, does not include cephalopods within its protection.[58] Because cephalopods are not currently covered under any federally regulated scheme, it is extremely difficult to obtain an accurate number of their use in American research. This fact, in and of itself, is a significant concern. Originally introduced over sixty years ago, a concept known as the "3 Rs" (replacing, reducing, and refining) has become a widely accepted principle for the implementation of humane animal research and testing.[59] But without an accurate count of the number of animals used in experimentation, it is impossible to track or measure success of the implementation of these principles. Further, there is some speculation that the lack of regulation may be one of the very reasons cephalopods are increasingly being used in research—i.e. to avoid the cost entailed in meeting NIH requirements that apply to vertebrates.[60] If true, this suggests an active attempt to avoid implementation of the "three Rs" by intentionally using animals not counted or regulated under any federal scheme. Data from the EU supports this

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[56] Nell Greenfieldboyce, *Why Octopuses Might Be the Next Lab Rats*, National Public Radio (June 3, 2019), https://www.npr.org/sections/health-shots/2019/06/03/727653152/why-octopuses-might-be-the-next-lab-rats.
[57] *Id*.
[58] 7 U.S.C. § 2131 *et seq*.
[59] Catherine A. Schuppli et al., *Expanding the Three Rs to Meet New Challenges in Humane Animal Experimentation*, 32 Alternatives to Laboratory Animals 525 (2004).
[60] Ben Guarino, *Inside the Grand and Sometimes Slimy Plan to Turn Octopuses Into Lab Animals*, Wash. Post (March 2, 2019), https://www.washingtonpost.com/national/health-science/inside-the-grand-and-sometimes-slimy-plan-to-turn-octopuses-into-lab-animals/2019/03/01/c6ce3fe0-3930-11e9-b786-d6abcbcd212a_story.html?noredirect=on&utm_term=.fd933f1c4dd6 ("'I've heard, on the ground, that some people are also drawn to using them specifically because there is no regulation,' said Joanna Makowska, a scientific adviser to the Animal Welfare Institute, a Washington, D.C.-based organization that advocates for the three Rs.")

proposition. In the years following the 2013 implementation of EU Directive 2010/63/EU to include cephalopods among protected animals used for scientific purposes, the number of cephalopods used in EU research has declined significantly each year (Figure 1).[61]

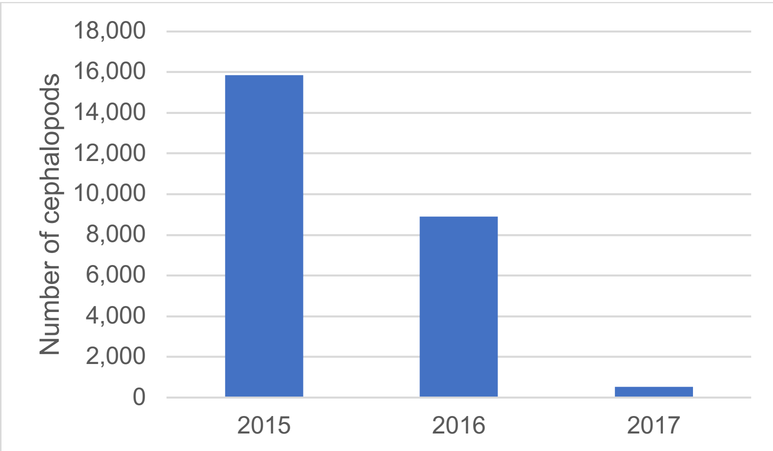

Figure 1. Cephalopod use in the EU over time.

There is demonstrable evidence of the scope and urgency of this problem in the United States. First, it is estimated that the United States uses more animals in research than any other country.[62] This is even more concerning when taking into account the increase in animal use in the U.S. research over the years; one study suggests that from 1997 to 2012 there was a 70% increase in animal use at institutions receiving NIH funding.[63] While most of this increase is believed to be due to increased use of mice, there is significant data suggesting cephalopod use has also risen over the years,[64] including statements about the MBL and its mission, gathered through interviews with MBL personnel and visits to the MBL laboratory:

> ● "Move over mice and fruit flies, the Marine Biological Laboratory in Woods Hole, Massachusetts, is busy developing the next great model organism for science."[65]
>
> ● "Grasse [Manager at MBL] developed the soda bottle incubator to automate the task, freeing the parents up to produce the next batch of eggs. This is one of several low-tech innovations the team has implemented towards mass producing cephalopods as lab animals."[66]

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[61] European Commission, *2019 Report on the Statistics on the Use of Animals for Scientific Purposes in the Member States of the European Union in 2015-2017* (2020), https://op.europa.eu/en/publication-detail/-/publication/04a890d4-47ff-11ea-b81b-01aa75ed71a1/language-en (page 6, Table 3: Numbers of animals used for the first time by species).
[62] The Lush Prize, *A Global View of Animal Experiments* (2014), https://www.lushprize.org/wp-content/uploads/Global_View_of-Animal_Experiments_2014.pdf.
[63] Justin Goodman et al., *Trends in Animal Use at US Research Facilities,* 41 J. Med. Ethics 567 (2015).
[64] *Id*.
[65] Mico Tatalovic, *The Newest Lab Rat Has Eight Arms*, Hakai Magazine (June 3, 2019), https://www.hakaimagazine.com/features/the-newest-lab-rat-has-eight-arms/.
[66] *Id*.

- “Scores of students and scientists arrive [at the MBL] for training and research each summer, creating a palpable vibe of excitement about unraveling nature’s mysteries. The researchers knew that any model organism they developed here would likely be quickly embraced by visiting scientists who would take the new ideas and techniques back to their home labs.”[67]

- “The MBL cephalopod team’s ultimate goal is to have a ready supply of their chosen species at various life stages, so it can respond immediately to requests from scientists around the world.”[68]

- “And efforts like those at the MBL to improve husbandry and develop better tools and approaches for working with the animals are intended to spread the adoption of cephalopods in other interested labs. ‘What we’ve been trying to do here at MBL is work with some of the more hearty, more ‘user-friendly’ species,’ says Grasse. ‘We really want it to be more accessible to a wide variety of studies and scientists.’”[69]

- “The [MBL] lab houses roughly 2,000 to 3,000 cephalopods—likely the largest collection of cephalopods of any research laboratory. But it might not be that way for long, if Grasse and MBL have their way. They hope that one day, these creatures will be as ubiquitous in labs as mice or fruit flies.”[70]

In fact, MBL’s own website states that “at the MBL scientists are embarking on a ground-breaking new effort to culture cephalopods in the laboratory with the goal of creating a new genetic model system.”[71]

67 *Id*.
68 *Id*.
69 Ellen P. Neff, *Considering the Cephalopod*, Lab Animal (Dec. 12, 2018), https://www.nature.com/articles/s41684-018-0199-0?WT.feed_name=subjects_developmental-biology.
70 Luke Groskin, *Cephalopod Inc.*, Science Friday (June 15, 2018), https://www.sciencefriday.com/videos/cephalopod-inc/.
71 Research Facilities and Services, Marine Biological Laboratory (August 3, 2019), https://www.mbl.edu/services/research-svcs/.

On a broader scale, the increase of cephalopod use in research is demonstrated through an increasing number of research papers published about cephalopods (Figure 2), the creation of the Cephalopod International Advisory Council (CIAC) Conference, and a 30% rise in membership of the CIAC from 2012 to 2018.[72]

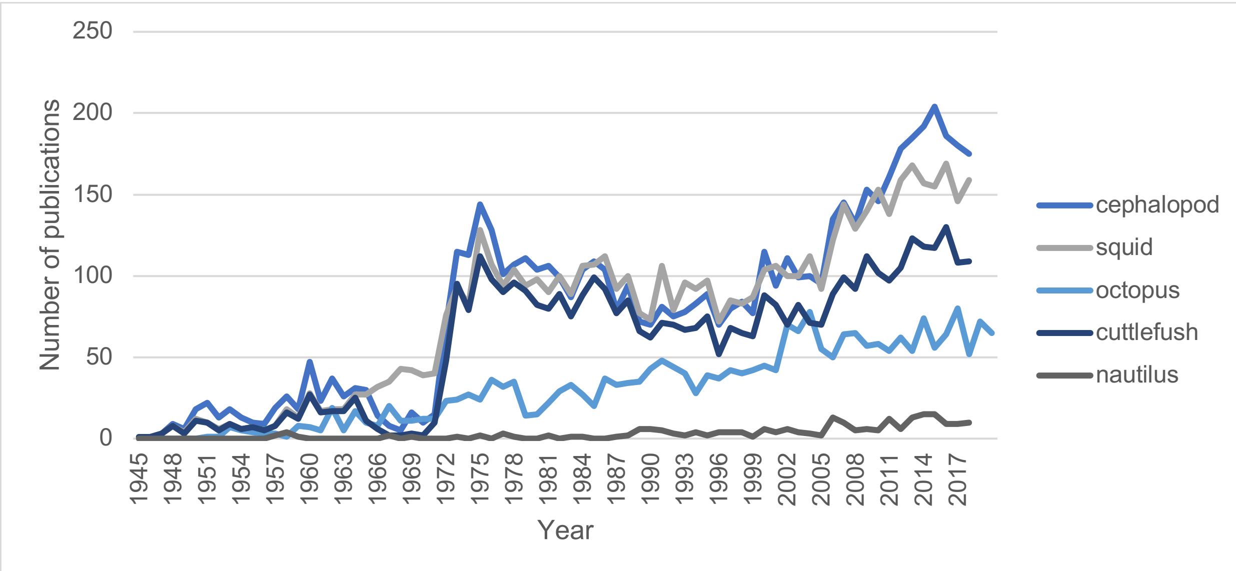

Figure 2. Cephalopod publication trends in PubMed over time.[73]

As an NIH-funded laboratory with an NIH-funded summer cephalopod program,[74] the MBL and other facilities using these animals in research should be required to ensure that the use of these animals is justified, that alternative systems or models are considered, that steps are taken to minimize pain and distress, and that the animals are well cared for.[75] Although the MBL claims to have strict welfare policies in place, it has "yet to establish any animal treatment guidelines to follow for the labs that request eggs or animals."[76] This means that the purchasing institution decides what protocols to use, with many institutions not requiring the same level of care for cephalopods that is used for vertebrate animals.[77] In a survey of 147 IACUC websites, 114 (77.6%)

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[72] Paige Helmer, *Defying Classification: Cephalopods in Research*, PhDish (Jan. 30, 2019), http://www.phdish.com/blog/defying-classification-cephalopods-in-research ("Recently, the field of cephalopod research has spread in new directions. Since 2006, every category of aquaculture, behaviour, climate change, cognition, genetics, neuroscience, and welfare had at least 10 papers published, and the largest category, behaviour, saw over 450 papers published."); Ben Guarino, *Inside the Grand and Sometimes Slimy Plan to Turn Octopuses Into Lab Animals*, Wash. Post (March 2, 2019), https://www.washingtonpost.com/national/health-science/inside-the-grand-and-sometimes-slimy-plan-to-turn-octopuses-into-lab-animals/2019/03/01/c6ce3fe0-3930-11e9-b786-d6abcbcd212a_story.html?noredirect=on&utm_term=.fd933f1c4dd6.

[73] NIH, *PubMed* (February 21, 2020), https://www.ncbi.nlm.nih.gov/pubmed. Search terms: ([animal category]) AND "Animals"[MeSH Terms].

[74] NIH, *Project Information* (2019), https://projectreporter.nih.gov/project_info_description.cfm?aid=9489868&icde=46175447.

[75] National Research Council, *Guide for the Care and Use of Laboratory Animals* xiii, (8th ed. 2011) at 12.

[76] Paige Helmer, *Defying Classification: Cephalopods in Research*, PhDish (Jan. 30, 2019), http://www.phdish.com/blog/defying-classification-cephalopods-in-research.

[77] *Id*. ("[The] decision to review protocols on invertebrate research is up to the discretion of the IACUC at the particular institution to decide if and how invertebrate protocols will be evaluated. Some institutions may require a

explicitly state that their treatment guidelines cover vertebrates only and just 15 (10.2%) state that they cover vertebrates and either invertebrates, cephalopods, or cephalopods and other species (Figure 3). Furthermore, despite many journals requiring animal ethics statements for research involving live vertebrates and higher invertebrates, publications often lack such statements and omit the conditions under which cephalopods are maintained.[78] Hence there is no way of knowing how these animals are used or cared for.

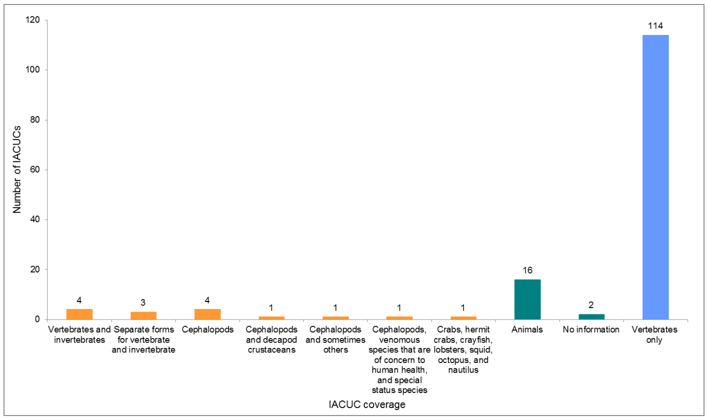

Figure 3. Survey of cephalopod coverage on IACUC websites.[79]

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similar level of review for cephalopods as for vertebrate animals, while others may choose not to review any invertebrate protocols at all. Columbia University, for example, falls somewhere in the middle."); Ben Guarino, *Inside the Grand and Sometimes Slimy Plan to Turn Octopuses Into Lab Animals*, Wash. Post (March 2, 2019), https://www.washingtonpost.com/national/health-science/inside-the-grand-and-sometimes-slimy-plan-to-turn-octopuses-into-lab-animals/2019/03/01/c6ce3fe0-3930-11e9-b786-d6abcbcd212a_story.html?noredirect=on&utm_term=.fd933f1c4dd6 ("At the Johns Hopkins School of Medicine, cephalopods are treated under protocols developed for mice.").

[78] Graziano Fiorito et al., *Cephalopods in Neuroscience* 14 Invertebrate Neuroscience 13, 17 (2014) ("[O]nly in the 40% of papers published in the 2010 (n=65; source WoK: ISI Web of Knowledge), mention the conditions in which cephalopods are maintained. However, only half of those (13 out of 26 papers) provide details on tank and lighting."). For examples of studies lacking ethics statements from journals requiring one for higher invertebrates, *see*: Chhavi Mathur, et al., *Demonstration of ion channel synthesis by isolated squid giant axon provides functional evidence for localized axonal membrane protein translation* 8 Scientific Reports (2018); Annaclaudia Montanino, et al., *Mechanical Characterization of Squid Giant Axon Membrane Sheath and Influence of the Collagenous Endoneurium on its Properties* 9 Scientific Reports (2019); Diana H. Li*, et al., Hypoxia Tolerance of Giant Axon-Mediated Escape Jetting in California Market Squid (Doryteuthis opalescens)* 222 Journal of Experimental Biology (2019); Kristen M. Koenig, et al., *Eye Development and Photoreceptor Differentiation in the Cephalopod Doryteuthis pealeii* 143 Development (2016). Journal policies: Scientific Reports, *Editorial and Publishing Policies* (February 21, 2020), https://www.nature.com/srep/journal-policies/editorial-policies; Journal of Experimental Biology, *Journal Policies* (February 21, 2020), https://jeb.biologists.org/content/journal-policies#exsubjects; Development, *Journal Policies* (February 21, 2020), https://dev.biologists.org/content/journal-policies#exsubjects.

[79] We surveyed IACUC coverage of invertebrates and cephalopods by searching "IACUC invertebrate" in Google and examining the IACUC websites of the top-50 NIH-funded institutions and institutions listed on The American Association for Laboratory Animal Science IACUCs webpage. Website copy may differ from actual policy. For example, we know from personal correspondence that the Wayne State University IACUC has begun reviewing cephalopod protocols as of this year, but this information is not yet reflected on its website. This list represents only a fraction of the at least 1,000 institutions with a PHS Approved Animal Welfare Assurance in the United States.

VI. REASONS TO GRANT THE REQUESTED ACTION

A. CEPHALOPODS HAVE LARGE BRAINS WITH COMPLEX NEUROLOGICAL STRUCTURES SIMILAR TO MANY VERTEBRATES

It is easy to understand why cephalopods are the first invertebrates to be integrated into many countries' animal laws: they have many similarities to vertebrates. One such similarity is the number of neurons in their bodies. The octopus has about 500 million neurons, the largest nervous system of any invertebrate, and in the same range as a number of vertebrate animals who are afforded protection, including amphibians and reptiles.[80] Additionally, many cephalopods, such as octopuses, have brain sizes relative to their overall size in a similar range to that of vertebrates; this is one indicator that an animal has a high degree of brain power or intelligence.[81] This intelligence is shown throughout their lifespan as they acquire different skills.

Despite their relatively short lifespan of only three months to two years, cephalopods "rely heavily on learning" throughout the different stages of their lives.[82] Though these changes do not mimic those of mammals, they show many similarities. Unlike humans and many mammals that are social creatures, most cephalopods are alone for much of their life, including as soon as they are born.[83] Because of this, "they have environment-dependent rather than social-dependent learning."[84] In the juvenile period, cephalopod learning largely centers around the effective gathering of food. A researcher "found that by the age of one month cuttlefish could learn to stop [attacking mysids that were confined to test-tubes and thus inaccessible]…Thus the restricted preprogrammed and

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[80] Peter Godfrey-Smith, *The Mind of an Octopus*, Scientific American (Jan. 1, 2017), https://www.scientificamerican.com/article/the-mind-of-an-octopus/?redirect=1.
[81] *Id*.
[82] Jennifer A. Mather, *Behaviour Development: A Cephalopod Perspective*, 19 Int. J. Comp. Psychol. 98 (2006).
[83] *Id*. at 98–99.
[84] *Id*., referencing N.K. Humphrey, *The Social Function of Intellect*, in GROWING PAINS IN ETHOLOGY 303 (P. P. Bateson, & R. A. Hinde eds., 1976).

automatic behaviour found at birth was modifiable by one month of age."[85] Later research established that, in contrast, newly-hatched cuttlefish did not yet have a fully developed vertical brain lobe, which would be required to make these more complex visual decisions.[86] The vertical lobe has since been linked to the short term memory of these animals, and it is very similar to the human hippocampus.[87]

Cephalopod memory, similar to that of mammals, strengthens as the animals age:

> After training to withhold tentacle strikes, cuttlefish from 8 days onward were significantly less likely to strike 5 min after training and this difference was not affected by age up to 90 days (of a 22-month lifespan). In contrast, retention at 60 min delay was not significant until 30 days, and it was significantly better than that at 60 days. In other words, short-term memory was present a week after birth but long-term memory took weeks more to develop.[88]

This characteristic of distinct long-term and short-term memory represents a psychological continuity between cephalopods and vertebrates, including humans.[89] Similarly, cephalopod memory, like that of humans, is impacted by the animal's environment. When a number of cuttlefish were equally divided between an impoverished environment and an enriched environment, those in the enriched environment "grew significantly more," and,"[a]t one month the cuttlefish reared in enriched conditions showed signs of long term memory and their performance was better than that of the impoverished group even at 3 months."[90] These results demonstrate that laboratory conditions impact the lives and cognition processes of the animals.

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[85] *Id*. at 100, referencing M.J. Wells, *Early Learning in Sepia,* 8 Zoological Society of London (1962).
[86] *Id*. referencing J.B. Messenger, *Learning in the Cuttlefish, Sepia*, 21 Animal Behaviour 801 (1973).
[87] *Id*.; Joseph Zabel, *Legislators Need to Develop a Backbone for Animals that Lack One: Including Cephalopods in the Animal Welfare Act*, 10 J. Animal & Environmental L. 1, 5 (2019).
[88] Jennifer A. Mather, *Behaviour Development: A Cephalopod Perspective*, 19 Intl. J. of Comparative Psychol. 98, 101 (2006), referring to L. Dickel et al., *Time Differences in the Emergence of Short and Long-Term Memory During Post-Embryonic Development in the Cuttlefish Sepia*, 44 Behavioural Processes (1998).
[89] Peter Godfrey-Smith, *The Mind of an Octopus*, Scientific American (Jan. 1, 2017), https://www.scientificamerican.com/article/the-mind-of-an-octopus/.
[90] Jennifer A. Mather, *Behaviour Development: A Cephalopod Perspective*, 19 Intl. J. of Comparative Psychol. 98 (2006), referencing R. Gandelman, *The Psychology of Behavioural Development*, Oxford University Press (1992).

This has been an effect that has been widely studied in mammals and other vertebrates, and is sufficient reason, by itself, to require the proper care of cephalopods.

As cephalopods age, much of their learning centers around "coping with predator pressures and finding and consuming prey."[91] One such way octopuses do this is by changing their appearance.[92] Unlike other animals, octopuses do not simply camouflage into the background. Rather, their changes in appearance involve "choice of behaviour, assessment of results and repeated choice until the octopus is caught or escapes, quite a different matter from simply appearing like the background."[93]

Cephalopods have demonstrated their intelligence and capability of learning in other situations as well:

> Once octopuses have solved a novel problem, they retain long-term memory of the solution. One study found that octopuses retained knowledge of how to open a screw-top jar for at least five months. They are also capable of mastering complex aquascapes, conducting extensive foraging trips, and using visual landmarks to navigate.[94]

Squids and octopuses have also been shown to be able to tell individual humans apart[95] and may even be able to learn by watching another individual perform a task: "something invertebrate[s] had never been known to do before."[96]

This ability to learn means octopuses and other cephalopods are "highly exploratory" in laboratory habitats—exploration being a "critical component" of learning.[97]

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[91] *Id*. at 102.
[92] *Id*.
[93] *Id*., referencing R.T. Hanlon et al., *Crypsis, Conspicuousness, Mimicry and Polyphenism as Antipredator Defences of Foraging Octopuses on Indo-Pacific Coral Reefs, with A Method of Quantifying Crypsis from Video Tapes*, 66 Bio. J. of the Linnean Soc. (1999).
[94] Jennifer Jacquet et al., *The Case Against Octopus Farming*, 35 Issues in Sci. & Tech (2009).
[95] Peter Godfrey-Smith, *The Mind of an Octopus*, Scientific American (Jan. 1, 2017), https://www.scientificamerican.com/article/the-mind-of-a-octopus/ ("Neuroscientist Shelley Adamo of Dalhousie University in Nova Scotia also had one cuttlefish that reliably squirted streams of water at all new visitors to the lab but not at people who were often around. In 2010 the late biologist Roland C. Anderson and his colleagues at the Seattle Aquarium tested recognition in giant Pacific octopuses in an experiment that involved a 'nice' keeper who regularly fed eight animals and a 'mean' keeper who touched them with a bristly stick. After two weeks, all the octopuses behaved differently toward the two keepers, confirming that they can distinguish among individual people, even when they wear identical uniforms.").
[96] Doug Stewart, *Armed But Not Dangerous* (Feb. 1, 1997), https://www.nwf.org/en/Magazines/National-Wildlife/1997/Armed-But-Not-Dangerous ("A pair of researchers in Naples, Italy, Graziano Fiorito and Petro Scotto, used conventional means—food as a carrot, mild electric shock as the stick—to train a group of captive common octopuses to grab a red ball instead of a white one. The scientists then let untrained animals watch from adjoining tanks as their experienced confreres reached for red balls over and over. Thereafter, Fiorito and Scotto reported most of the watchers, when offered a choice, pounced on red balls. In fact, they learned to do so more quickly than had the original group.").
[97] Jennifer A. Mather, *Behaviour Development: A Cephalopod Perspective*, 19 Intl. J. of Comparative Psychol. 98, 105 (2006), quoting M.J. West-Eberhard, *Developmental Plasticity and Evolution*, Oxford Univ. Press (2003).

Octopuses also have a well-established ability to escape their laboratory tanks—sometimes causing their own death.[98] This underscores the need for laboratories to understand these complex creatures and ensure that they are properly handled and cared for.

As cephalopods enter into their elderly phase, much like humans they begin to have more difficulty learning tasks and retaining taught behaviours.[99] This behaviour is linked to axon degeneration in the cephalopod brain and has often been studied in an attempt to learn about the "degeneration of the hippocampus in Alzheimer's disease in humans."[100]

B. CEPHALOPODS EXPERIENCE PAIN AND SUFFERING

As mentioned above, an animal's ability to experience pain is often the reason to include them within the coverage of animal welfare regulation. Unfortunately, because "[i]t was long thought that the cerebral cortex was necessary for the pain experience, the absence of such a structure in invertebrates has fostered the belief that for these species it is impossible to feel pain."[101] This, however, has been disproven, and scientists now consider other factors to determine whether an animal experiences pain. The first factor is whether the animal has nociception—"the capacity to respond to potentially damaging stimuli"—which is "a basic sensory ability."[102] Second, scientists look for evidence that an animal has an "unpleasant sensory and emotional experience associated with actual or potential tissue damage."[103] Scientists also consider whether the animal learns alternative behavior by examining whether they "quickly learn to avoid the noxious stimulus and demonstrate sustained changes in behaviour that have a protective function to reduce further injury and pain, prevent the injury from recurring, and promote healing and recovery."[104]

Applying these three elements to cephalopods, there is every reason to believe that cephalopods experience pain and suffering. Accordingly, research using such animals should be regulated in the same manner as research using vertebrates.

In terms of the first element—as discussed in the previous section—cephalopods have complex neural systems. "The presence of free nerve endings in the skin suggests that perception of pain is possible."[105] Their nervous system is "able to process a huge amount of sensory information" and functions similar to the cerebral cortex in vertebrates.[106] In fact, cephalopods "share some features of the neurochemical systems that are involved in pain perception in vertebrates. In particular,

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[98] *Id*., referring to J.B. Wood & R.C. Anderson, *Interspecific Evaluation of Octopus Escape Behaviour*, 7 J. of Applied Animal Welfare Sci. (2004).
[99] *Id*. at 110.
[100] *Id*., referencing J.W. Santrock et al., *Life-span Development*, McGraw-Hill Ryerson (2003).
[101] Giorgia della Rocca et al., *Pain and Suffering in Invertebrates: An Insight on Cephalopods*, Am. J. Animal and Veterinary Sci. 77, 78 (2015).
[102] Lynne Sneddon et al., *Defining and Assessing Animal Pain,* 97 Animal Behaviour 201, 201 (2014).
[103] *Id*. at 202.
[104] *Id*.
[105] N.A. Moltschaniwskyj et al., *Ethical and Welfare Considerations When Using Cephalopods As Experimental Animals*, Rev. Fish Biol. & Fisheries 455, 457 (2007).
[106] Giorgia della Rocca et al., *Pain and Suffering in Invertebrates: An Insight on Cephalopods*, Am. J. Animal and Veterinary Sci. 77, 79 (2015).

opioid molecules have been found in these animals and they appear to function in similar ways as in vertebrates."[107] This indicates that, with regard to their sheer physical structure, cephalopods can feel pain.

When considering the second element, there is ample evidence that cephalopods engage in escapist or avoidance behaviour—i.e. they:

- Have been known to show signs of pain when subjected to electric shocks.[108]
- Have learnt to discriminate between objects based on being shocked.[109]
- Have tried to avoid being stung by sea anemones by moving away, moving slowly with one arm extended, and blowing jets of water at the anemone."[110]
- Have attempted to vigorously escape and violently eject ink when they are anaesthetized using urethane, which they find aversive.[111]
- Have demonstrated sensitization of an injured area, such as wrapping an arm around an injured one.[112]

These are only a sample of the many findings that have demonstrated cephalopods' ability to experience pain and discomfort. Nevertheless, we should not underestimate the vast number of anecdotes by divers, researchers, and zookeepers in their interactions with cephalopods that are highly suggestive of complex mental lives with pleasure and pain.[113]

Finally, as discussed extensively in the prior section, cephalopods demonstrate the third element: there is myriad evidence to suggest cephalopods can learn, discriminate, and respond to new situations.

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[107] G.B. Stefano et al., *The Blueprint for Stress Can Be Found in Invertebrates*, 23 Neuroendocrinology Letters 85, 93 (2002).
[108] M.J. Wells, OCTOPUS: PHYSIOLOGY AND BEHAVIOUR OF AN ADVANCED INVERTEBRATE 183 (Chapman and Hall, 1978).
[109] Roger T. Hanlon & John B. Messenger, CEPHALOPOD BEHAVIOUR (Cambridge University Press, 2018).
[110] Jennifer A. Mather, *Cephalopod Consciousness: Behavioural Evidence*, 17 Consciousness and Cognition 37, 41 (2008).
[111] J.B. Messenger et al., *Magnesium Chloride as an Aesthetic for Cephalopods*, 82 Comp. Biochemistry & Physiology 203, 203 (1985).
[112] Joseph Zabel, *Legislators Need to Develop a Backbone for Animals that Lack One: Including Cephalopods in the Animal Welfare Act*, 10 J. Animal & Environmental L. 1, 11 (2019).
[113] Heather Browning, *Anecdotes Can Be Evidence Too*, 16 Animal Sentience 1 (2017).

Therefore, there is every reason to believe cephalopods can feel pain. Indeed, these three attributes led the European Food and Safety Authority to state that cephalopods "***fall into the same category of animals as those that are at present protected***" and therefore should be protected as well since "[the] scientific evidence clearly indicates that [cephalopods are a group of animals that] are able to experience pain and distress, or the evidence, either directly or by analogy with animals in the same taxonomic group(s), are able to experiment pain and distress."[114]

Because there is no regulation of cephalopods, researchers are not required to justify their use of the animal or even to mitigate their pain. This lack of oversight has led to cephalopods being involved in many studies that can be considered inhumane. For example, there have been numerous studies on the effects of food deprivation and food-intake interventions in cephalopods.[115] This kind of treatment has been linked to deterioration in cephalopods, rapidly progressing them into their final life cycle phase, senescence, where they are likely to experience a higher degree of suffering, including cataracts, skin lesions, and increased uncoordinated locomotor activity.[116] Because of their impressively complex brains, cephalopods are also widely used in neuroscience experiments, which "are often invasive and may cause pain, suffering, distress and lasting harm."[117] Experiments involving testing drug effects on cephalopods have been heavily criticized. One experiment, studying the effects of MDMA by bathing octopus gills in the drug's liquid form, was criticized by People for the Ethical Treatment of Animals as being "indefensible, curiosity-driven nonsense."[118] Furthermore, breeding attempts in the lab have led to the deaths of cephalopods well before adulthood.[119]

There has also been reporting of cephalopods in inhumane environmental conditions. In one study cephalopods were reportedly "being housed in completely bare 12"x12"x12" plexiglass boxes, without any shelter, little room to move and under constant lightning."[120]

Thus, there is no question that requiring humane handling and conditions for cephalopods is clearly justified.

C. CEPHALOPODS ARE UNIQUE CREATURES THAT REQUIRE SPECIAL HANDLING

Cephalopods are complex animals that require specific conditions and treatment in order to thrive. "To appreciate the health maintenance requirements of cephalopods, it is necessary to understand

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[114] 2005 O.J. (292) 3, 20 (emphasis added).
[115] Antonio V. Sykes et al., *The Digestive Tract of Cephalopods: A Neglected Topic of Relevance to Animal Welfare in the Laboratory Aquaculture*, 8 Front. Physiol. 1, 11 (2017).
[116] *Id.*
[117] Graziano Fiorito et al., *Cephalopods in Neuroscience*, 14 Invertebrate Neuroscience 13, 18 (2014).
[118] Ben Guarino, *Inside the Grand and Sometimes Slimy Plan to Turn Octopuses into Lab Animals*, Wash. Post (March 2, 2019), https://www.washingtonpost.com/national/health-science/inside-the-grand-and-sometimes-slimy-plan-to-turn-octopuses-into-lab-animals/2019/03/01/c6ce3fe0-3930-11e9-b786-d6abcbcd212a_story.html?noredirect=on&utm_term=.fd933f1c4dd6.
[119] *Id.*
[120] Joseph Zabel, *Legislators Need to Develop a Backbone for Animals that Lack One: Including Cephalopods in the Animal Welfare Act*, 10 J. Animal & Envtl. L. 1, 5 (2019).

their biology and life history."[121] During every step of the research process, the necessary steps must be taken to protect cephalopods from unnecessary stress and harm. These best practices are well-recorded and available to be incorporated into the PHS Policy process and the Guide.[122] Though the information below is far from complete, it provides an idea of the number of considerations that must be taken into account, and why it is so imperative to do so. Even more information has been made available in the wake of the EU's 2010 Directive including cephalopods among the animals deserving of welfare protection in laboratory research.[123] However, given that "cephalopod biology is unique, misinformation persists about how to properly treat them."[124]

I. Habitat and Feeding

Cephalopods, particularly squids and cuttlefish, grow exponentially during the first third of their life cycles.[125] Because they only live for about a year, this means that if they are brought into the laboratory before adulthood, they can grow in spurts of 6 and 12% of their body weight per day.[126] Therefore, laboratories must ensure that tanks are large enough to support this growth.[127] Additionally, tank material is of utmost concern:

> To avoid injury to the cephalopods, fiberglass or polyethylene [should be used] …with small observation windows… [so that the] animals will not be startled by activity in the facility. Glass aquarium tanks should be avoided for housing squids and cuttlefishes because of the sensitivity of the animals to human activity. Holding tanks should be in low traffic areas with dim lighting.[128]

Copper must be avoided in materials used in these structures, because it is highly toxic to cephalopods.[129] If copper has been used in the system in the past, even if it has been cleaned, there may still be residual copper that can harm the animals, because "it is extremely difficult to eliminate residual copper."[130]

Cephalopods almost exclusively eat protein.[131] Therefore, particularly as they grow, it is imperative that they get enough food, which can be up to 80 to 100% of their body weight per day.[132] "Plans must be made so that adequate food supplies are readily available prior to arrival of

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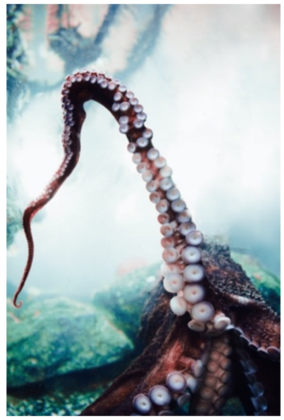
[121] Daniel J. Oestmann et al., *Special Considerations for Keeping Cephalopods in Laboratory Facilities*, 36 J. Am. Assoc. Lab. Animal Sci. 89, 89 (1997).
[122] *See, e.g.*, Association of Zoos & Aquariums, Giant Pacific Octopus (Enteroctopus dofleini) Care Manual (2014).
[123] *See, e.g*., Graziano Fiorito et al., *Cephalopods in Neuroscience* 14 Invertebrate Neuroscience 13 (2014)
[124] Joseph Zabel, *Legislators Need to Develop a Backbone for Animals that Lack One: Including Cephalopods in the Animal Welfare Act*, 10 J. Animal & Environmental L. 1, 3 (2019).
[125] Daniel J. Oestmann, Joseph Scimeca, John Forsythe, Roger Hanlon & Phillip Lee, *Special Considerations for Keeping Cephalopods in Laboratory Facilities*, 36 J. Am. Assoc. Laboratory Animal Sci. 89, 89 (1997).
[126] *Id.*
[127] *Id*. at 89–90.
[128] *Id*. at 90.
[129] *Id*.
[130] *Id*.
[131] *Id*.
[132] *Id*.

the animals."[133] It is also important to note that stress and pain can have a long-term effect on the animals' digestive tract: "[b]oth noxious and non-noxious but stressful external stimuli may also have both acute and chronic effects on the digestive tract via up or down regulation of genes in critical control locations such as gastric ganglion."[134]



II. Water Quality

Cephalopods require more stringent water conditions than most fish.[135] "Cephalopods are sensitive to rapid changes in pH, salinity, low-dissolved oxygen concentrations, and nitrogenous waste."[136] Due to their protein diet they produce a large amount of ammonia which must be cleared from the tank.[137] In order to do this, "it is essential that water filtration is processed" in a precise order:[138]

> first, water leaves the animal holding tanks and then passes through a foam fractionator (protein skimmer), which strips dissolved organic compounds including ink. The water then passes through a mechanical filter, removing particles down to 100 µm. It then passes through high-grade activated carbon, through a biological filter where ammonia is broken down to less-toxic forms by nitrifying bacteria…and lastly through an ultraviolet (UV) sterilizer before returning to the animal holding tank.[139]

Even with this system in place, ammonia and nitrite levels in the water should be monitored vigorously, as cephalopods are very sensitive to this type of waste.[140] If too much nitrogen and ammonia build up, it can cause bacterial infection in the animal, more aggressive behavior, and reduced oxygen intake.[141]

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133 *Id*. 90–91.
134 Antonio V. Sykes, Eduardo Almansa, Gavan M. Cooke, Giovanna Ponte & Paul L.R. Andrews, *The Digestive Tract of Cephalopods: A Neglected Topic of Relevance to Animal Welfare in the Laboratory Aquaculture*, 8 Front. Physiol. 1, 5 (2017).
135 Daniel J. Oestmann, Joseph Scimeca, John Forsythe, Roger Hanlon & Phillip Lee, *Special Considerations for Keeping Cephalopods in Laboratory Facilities*, 36 J. Am. Assoc. Laboratory Animal Sci. 89, 91 (1997).
136 *Id*.
137 *Id*. at 89.
138 *Id*. at 90.
139 *Id*.
140 *Id*. at 91.
141 *Id*.

III. Life-Long Health Monitoring and Treatment

Cephalopods are physically sensitive creatures and must be handled carefully. "Their thin, microvillar epidermis is easily traumatized during confinement or handling; minor skin lesions and abrasions can lead to opportunistic bacterial infections and death."[142] Further, it is not always easy to tell if a cephalopod is ill or injured:

> Specific animals may have discrete external lesions; however, the underlying dermal chromatophores and iridocytes can make injured skin appear normal. Ulcers on the distal tip of the mantle from handling or collision with tank walls may erode through the epidermis and dermis, exposing the mantle muscle…Epithelial loss readily progresses to secondary bacterial infections, because the surface bacterial population of captive cephalopods can be up to 100 times greater than that of wild cephalopods.[143]

Tank crowding, which can cause aggressive behaviour in the animal, can also cause damage to the animal's mantle.[144] Significant harm including edema, hemocyte infiltration, and necrosis of mantle muscle can also be caused through the implantation of identification tags.[145] When cephalopods are harmed or ill, and ameliorative steps are not taken immediately, this can quickly result in exceptional trauma for the animal and/or death.[146]

Stress is another factor that can cause considerable pain and discomfort throughout a cephalopod's lifespan. Stress can be caused by handling of the animal, noise, toxins, or diseases. To ensure the minimization of stress, there must be "careful consideration of the experimental design and

[142] *Id*.
[143] *Id*.
[144] *Id*.
[145] *Id*.
[146] *Id*.

procedures, housing conditions, and handling."[147] For example, lifting cephalopods completely from the water environment causes them significant distress.[148] A "5-minute exposure to air produced a significant increase in plasma noradrenaline lasting up to 30 min and in reactive oxygen species lasting 2h."[149] Special considerations must also be taken when cephalopods are being brought into a laboratory; the steps taken directly after transport are imperative to maintaining their health and keeping their stress to a minimum.[150] Stress can lead cephalopods' health to degenerate much more quickly than normal, causing them to enter the last phase of their life cycle before the usual time.[151]

Moreover, improper handling of cephalopods can lead to inaccurate research results since variables such as digestive tract parasites, toxins from food or water, and stress from human interactions can all adversely impact findings.[152]

Equally important, there is now ample enough scientific knowledge regarding methods to alleviate pain in cephalopods. For example, magnesium chloride and ethanol both work to cut off pain signals for the animal[153] and lidocaine and magnesium chloride can function as local anesthetic agents.[154] But it is crucial for researchers to understand how these chemicals interact with cephalopod biology—i.e., once magnesium chloride has been administered, there is a 15-minute window where the animal appears anesthetized but can still feel.[155] Meanwhile other drugs used to anesthetize cephalopods, such as ether and MS-222, have been shown to be ineffective.[156]

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[147] N.A. Moltschaniwskyj et al., *Ethical and Welfare Considerations When Using Cephalopods As Experimental Animals*, Rev. Fish Biol. & Fisheries 455, 466 (2007).
[148] *Id*.
[149] Graziano Fiorito et al., *Cephalopods in Neuroscience*, 14 Invertebrate Neuroscience 13, 20 (2014).
[150] N.A. Moltschaniwskyj et al., *Ethical and Welfare Considerations When Using Cephalopods As Experimental Animals*, Rev. Fish Biol. & Fisheries 455, 467 ("On arrival, shipping containers should be opened in dim lighting so that the animals, which have acclimated to darkness during transport, will not be started. The high metabolic rate of cephalopods results in high ammonia concentration during transport that should be corrected as soon as possible during acclimation. This is accomplished by slowly removing transport water from the shipping container and replacing it with tank water.").
[151] *Id*.
[152] Antonio V. Sykes, Eduardo Almansa, Gavan M. Cooke, Giovanna Ponte & Paul L.R. Andrews, *The Digestive Tract of Cephalopods: A Neglected Topic of Relevance to Animal Welfare in the Laboratory Aquaculture*, 8 Front. Physiol. 1, 5 (2017).
[153] Danna Staaf, *How to Put an Octopus to Sleep—and Make Cephalopod Research More Humane*, Science (Apr. 4, 2018), https://www.sciencemag.org/news/2018/04/how-put-octopus-sleep-and-make-cephalopod-research-more-humane.
[154] Hanna M. Butler-Struben et al., *In Vivo Recording of Neural and Behavioral Correlates of Anesthesia Induction, Reversal, and Euthanasia in Cephalopod Molluscs*, 9 Frontiers in Psych. 109 (2018).
[155] Danna Staaf, *How to Put an Octopus to Sleep—and Make Cephalopod Research More Humane*, Science (Apr. 4, 2018), https://www.sciencemag.org/news/2018/04/how-put-octopus-sleep-and-make-cephalopod-research-more-humane.
[156] *Id.*

VII. CONCLUSION

Considering the overwhelming evidence demonstrating that cephalopods are intelligent, complex creatures that experience pain, and thereby require proper handling, Petitioners urge NIH to amend the definition of “animal” in the PHS Policy to include cephalopods within its scope. The legislative history, as well as the scientific and qualitative data, clearly supports this requested change. By including cephalopods within the scope of the PHS Policy to gain NIH Assurance, any NIH-supported facility wishing to use cephalopods would have to create a safe and humane environment for these animals, that meets specified guidelines.[157]

Accordingly, and without delay, the NIH should amend the PHS Policy definition of “animal” and begin regulating the use of cephalopods in NIH-supported research. As one neuroscientist at MBL candidly observed when predicting that the United States would likely follow Europe’s lead in extending protections to cephalopods, “no one likes all the paperwork, and stuff like that . . . But if you are trying to justify it biologically, I think that [cephalopods] probably should be [protected].’”[158]

Petitioners stand ready to assist you in this regard and to provide you with any additional information you may need to grant this Petition.

[157] *See* Public Health Service Policy on Humane Care and Use of Laboratory Animals, NIH No. 15-8013, § IV(B)(2) (2015) (“inspect at least once every six months all of the institution’s animal facilities (including satellite facilities) using the *Guide* as a basis for evaluation.”).

[158] Ben Guarino, *Inside the Grand and Sometimes Slimy Plan to Turn Octopuses into Lab Animals*, Wash. Post (March 2, 2019), https://www.washingtonpost.com/national/health-science/inside-the-grand-and-sometimes-slimy-plan-to-turn-octopuses-into-lab-animals/2019/03/01/c6ce3fe0-3930-11e9-b786-d6abcbcd212a_story.html?noredirect=on&utm_term=.fd933f1c4dd6.