Science Advancement & Outreach
A DIVISION OF PETA

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Request for Information on the Helping to End Addiction Long-term® Initiative

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We are writing on behalf of Science Advancement and Outreach (SAO) regarding the Request for Information (RFI) on the Helping to End Addiction Long-term (HEAL) Initiative. SAO is a division of People for the Ethical Treatment of Animals—PETA entities have more than 9 million members and supporters globally.

Recognizing the failure of animal-based research results translating into human-relevant knowledge, PETA supports the HEAL's Initiative's and the National Institute on Drug Abuse's (NIDA's) intention to place a concrete focus on data science, prevention, access to care, health equity, stigma reduction, and incorporating lived experiences with opioid use disorder (OUD). These initiatives, which can improve and make better use of existing systems, will have the most immediate and direct impact on reducing and treating OUD.

In these comments, we focus our recommendations on areas of basic, translational, and preclinical biomedical research in which the HEAL Initiative can make substantial progress toward improving the lives of individuals with OUD. **Our key recommendation for the HEAL Initiative is to conduct and fund research using only human biology-based systems and not those that use other species.**

We also take this opportunity to share our Research Modernization Deal, a strategy for advancing biomedical research in the U.S. through non-animal methods, applicable across various research domains. This plan can be accessed at https://www.peta.org/wp-content/uploads/2023/01/peta-research-modernization-deal.pdf. We are happy to meet and discuss with your team any questions related to this response or the topics covered in the Research Modernization Deal.

Rationale

Fundamental aspects of nonhuman animals make them inappropriate for the study of human opioid use disorder. The use of and addiction to drugs of abuse in humans is a vastly complex

experience, including social and environmental factors, as well as language, and has been impossible to mimic using animals in a laboratory setting.[1] It has been argued that attempts to model human disorders such as addiction in nonhuman animals, especially rodents, are "overambitious" and that the "'validity' of such models is often limited to superficial similarities, referred to as 'face validity' that reflect quite different underlying phenomena and biological processes from the clinical situation."[2] The former National Institute of Mental Health director reasoned that "it is difficult to argue that [drug self-administration by rodents] truly models compulsion, when the alternative to self-administration is solitude in a shoebox cage."[3]

Serious flaws in experimental design of addiction experiments greatly skew interpretation of their results. In the human experience with drugs, the user chooses to consume the addictive substance. They choose it over other substances or activities that they may find rewarding. Animals in laboratories are typically not given this option. Even in animals with very heavy previous drug use, only about 10% would continue to give themselves a drug when they had the option to make another rewarding choice.[4] In a review on the "validation crisis" in animal models of drug addiction, French neuroscientist and addiction researcher Serge Ahmed asserts that the lack of choice offered to animals in these experiments elicits "serious doubt" about "the interpretation of drug use in experimental animals."[5]

Others in the field have echoed this concern. Field and Kersbergen from the University of Sheffield wrote: "Animal models of addiction have a poor track record for the identification and development of addiction treatments that have clinical benefit in humans, and their contribution has consistently been misrepresented and oversold. More fundamentally, **animal models have misled us about the very nature of addiction in humans**"[6] [emphasis added]. Field and Kersbergen discuss how the U.S. opioid crisis has seen its rise primarily due to "de-industrialization, economic decline and urban decay alongside massive increases in the availability of prescription opioids" and that these truths bring futility to attempts to "map addiction to brain function independently of the relations between subjective symptoms and the broader environmental context," adding that, "this may account for the poor predictive validity and explanatory power of animal models of psychiatric disorders, including addiction."[7]

In addition, these experiments are incredibly harmful to animals. Experimenters often force animals to unknowingly ingest substances dissolved in water, inject them with opioids or other drugs, or force animals to inhale them. For many self-administration protocols, invasive surgery is required to catheterize an animal's veins before the protocol. All animals used in these experiments are killed at the end of the study.

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[1] Tzschentke TM. Where do we stand in the field of anti-abuse drug discovery? *Expert Opin Drug Dis*. 2014;9(11):1255-1258.
[2] Stephens DN, Crombag HS, Duka T. The challenge of studying parallel behaviors in humans and animal models. *Curr Top Behav Neurosci*. 2013;13:611-45.
[3] Hyman SE, Malenka RC. Addiction and the brain: The neurobiology of compulsion and its persistence. *Nat Rev Neurosci*. 2001;2(10):695-703.
[4] Ahmed SH. Validation crisis in animal models of drug addiction: Beyond non-disordered drug use toward drug addiction. *Neurosci Biobehav Rev*. 2010;35(2):172-184.
[5] *Ibid*.
[6] Field M, Kersbergen I. Are animal models of addiction useful?. *Addiction*. 2020;115(1):6-12.
[7] *Ibid*.

For these reasons, the HEAL Initiative must immediately end funding for experiments on animals.

Gap areas in the current or past HEAL research portfolio

Several HEAL research programs have relied or continue to rely on the use of animals, particularly in the "Preclinical and Translational Research in Pain Management" program. Research on human pain must be conducted in the ways that are most relevant to human physiology and neurobiology. Therefore, all new research funded by HEAL research programs should rely solely on human biology-based, non-animal methodologies. For example, researchers at Queen's University Belfast used *in vitro* and *in vivo* human neuronal models to study a molecular basis for the modulation of nociception in human peripheral nerves.[8] Biotechnology companies like AxoSim, NETRI, and others have developed human neuronal *in vitro* models that can be used by HEAL grantees in their research.

The "Translational Research to Advance Testing of Novel Drugs and Human Cell-Based Screening Platforms to Treat Pain and Opioid Use Disorder" program for the use of microphysiological systems in understanding how the human nervous system responds to painful stimuli and the human mechanisms that underlie acute and chronic pain, addiction, opioid use disorder, and overdose should be continued or built upon.

Opportunities to strengthen, expand, and diversify the SUD and pain research workforce and enhance research capacity to incorporate diverse approaches and contributions to the HEAL Initiative

To ensure the global competitiveness of the U.S.' substance use disorder and pain research workforce, new infrastructure and professional training should focus on non-animal, human-relevant research to best prepare teams for the future of science. As the fields of animal-free research and testing continue to expand, increased education and hands-on training will accelerate the transition to these methods. Students and early-career scientists, especially, must be provided with opportunities to develop the skills necessary to contribute to this research field. Established researchers and regulators using animal-based methods should be provided with retraining opportunities and encouraged to forge multidisciplinary collaborations to evolve their skills and establish new and innovative ways of asking research questions and methods for answering them that don't use animals. Building a trained team with the proper resources is important to address OUD with science-based interventions that have a real chance of benefiting human health

[8] McMillan H, Lundy FT, Dunne OM, et al. Endogenous Mas-related G-protein-coupled receptor X1 activates and sensitizes TRPA1 in a human model of peripheral nerves. *FASEB J*. 2021;35(5):e21492.