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Submitted to the U.S. House of Representatives Committee on Oversight and Government Reform, Subcommittee on Cybersecurity, Information Technology and Government Innovation for the Hearing "Transgender Lab Rats and Poisoned Puppies: Oversight of Taxpayer Funded Animal Cruelty."

6 February 2025
2:00 PM
2247 Rayburn

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Chairwoman Mace, Ranking Member Brown and Members of the Committee and Subcommittee, thank you for inviting me to submit testimony for today's hearing and for your interest and attention to the development, use and validation of non-animal, human-centric science and its capacity to replace animals in biomedical research.

My name is Paul Locke, and I am a Professor in the Department of Environmental Health and Engineering at the Johns Hopkins Bloomberg School of Public Health in Baltimore, Maryland. I am an attorney licensed to practice before the bars of the state of New York and the District of Columbia, as well as the Southern District Court of New York and the United States Supreme Court. I also hold a doctoral degree in public health with a concentration in environmental health studies. I have been a faculty member for 26 years and a substantial portion of my research and practice has concentrated on the development, deployment and use of non-animal methodologies in research and regulatory decision-making, with an emphasis on the promise that these methods have for both reducing animal use and improving evidence-based decisions. At Johns Hopkins I head an interdisciplinary toxicology policy research group that is dedicated to improving public health. We believe that reducing and ultimately replacing animal models will lead to improvements in health, stronger environmental protection, and new and innovative cures and treatments for diseases like cancer and neurological conditions such as Parkinson's and Alzheimer's disease.

I want to state for the record that the opinions expressed in this testimony are my own and do not necessarily reflect the views or positions of the Johns Hopkins University or the Johns Hopkins Health System.

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Consistent with these purposes, my testimony today will cover three major points. First, the scientific questions facing us increasingly call into question our reliance on non-human animal tests, and demand that we move toward more human centric science, including the use of microphysiological systems and organoids. Second, federal agencies must play a leadership role in the transition to these new human centric models. And third, the development and deployment of these models represent innovation and places where US businesses and science are, and must continue to be, at the cutting edge.

Twenty-first century scientific questions call for innovative scientific methods based on human biology

The scientific and popular literature contains many articles that point out – correctly – that animal models and research based on them have led to many scientific successes, including Nobel Prize winning insights and block buster drug breakthroughs. Animal tests have also been instrumental in keeping unsafe drugs off the market. I am not here to debate these points. But rather than looking back at past accomplishments, I think it makes sense to look ahead at what we need for future successes. In other words, what can and should we be doing to tackle present day and emerging public health problems? How can the United States continue to be the world leader in science? My research into these questions indicates that the complex scientific challenges we now face require that we move away from traditional animal models and embrace new technologies that do not involve animals but instead incorporate human biology. These technologies include small, engineered systems, such as organs-on-a-chip, or three dimensional groups of cells, such as organoids, that allow groups of cells to self-organize in ways that mimic many of the important functions of human organs. I also include artificial intelligence, AI, into this group.

Members of my toxicology policy group and other researchers at Johns Hopkins are actively involved in using two of these methods to try to better understand how to improve health. A recent article in the journal Scientific American highlights this work.

At the Johns Hopkins School of Medicine, Dr. Vasiliki Machairaki is studying Alzheimer's disease. Animal models of Alzheimer's, such rodent models, have been described in the medical literature as having "dubious reliability" for therapeutic uses. To make progress in understanding how to better treat Alzheimer's, Dr. Machairaki uses blood samples of people with Alzheimer's to make stem cells, which she then differentiates into stem cells and ultimately to brain cells and brain organoids. The organoids show signs of Alzheimer's, which allows Dr. Machairaki to test the effectiveness of various pharmaceuticals. This type of personalized model could eventually help determine the best drug for different patients.

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In another Johns Hopkins laboratory, an organoid model is being used to test cardiotoxicity and the risks associated with new chemotherapy drugs, which can potentially damage the heart. These organoids mimic functions of human heart tissue and allow scientists to evaluate a number of parameters like contraction frequency, contractile force and calcium signaling dynamics to assess how various drugs impact cardiac performance.

These are just two examples of where twenty-first century human-centric science can make a difference in public health. While it is important to share information about these developments, the bottom line is that much more needs to be done to nurture and support the growth of these technologies, and to utilize the information they produce, especially at US federal agencies. I will turn to that point now.

Federal agencies and departments must play a leadership role in the transition to these new human centric models.

While there is considerable enthusiasm around the promise of these new methodologies, unless US federal agencies and departments support their development and recognize their promise they will not be able to reach their full potential. Agencies such as the Environmental Protection Agency (EPA), the Food and Drug Administration (FDA) and the National Institutes of Health (NIH) all have important roles to play in unlocking the potential that these technologies have for designing better drugs, protecting the environment and improving health. Based on our research, there are currently major gaps in the regulatory framework needed to support new methodologies and it is imperative that the federal government step forward. The federal approach has been passive and reactive. What we need is for federal agencies and departments to lead efforts to develop, implement, and use these methods.

The EPA has several programs related to non-animal alternatives. Its pesticides office has been very active, even releasing metrics about the cost savings associated with waiving animal tests when it is shown scientifically that they are not needed. According to EPA, it saved approximately $379,000 from 2018 to 2023 by waiving the requirement to conduct certain repeat dosing studies. The 2016 amendments to the Toxic Substances Control Act (TSCA) include several new provisions addressing the use of non-animal alternatives. Among other things, TSCA requires EPA to produce a work plan for alternatives and a list of approved alternatives. The last workplan, released in December 2021, committed the Agency to finalizing two critical deliverables by 2024: a scientific confidence framework to evaluate NAM reliability and reporting templates to standardize data submission. These tools are essential to fulfill TSCA's mandate to phase out animal testing while ensuring chemical safety. EPA has missed this deadline, leaving stakeholders without clarity on how to validate and apply NAMs.

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While these efforts are important, much more needs to be done. As my colleagues and I point out in the attached article from The Environmental Forum, there are over 85,000 chemicals in commerce, and we have adequate toxicological information on about 1000 of them. The only feasible way to assess these chemicals is using non-animal alternative methods, a point supported by studies carried out under the sponsorship of the U.S. National Academy of Sciences, Engineering and Medicine (NASEM).

These methods are not getting the attention they deserve at the FDA. While the FDA has said publicly that it is willing to accept non-animal model toxicity data, it has yet to identify and communicate clear standards for the use of such data. In other words, the agency has not outlined validation criteria. Researchers who use alternatives in product development and in applications for regulatory approval thus have no guarantee about whether their data will be acceptable. FDA can, and often has, responded to those who use alternative methods with a simple statement that the data is insufficient and a demand for animal-based data.

This catch-22 situation persists at FDA, even though the agency put forward a "predictive toxicology roadmap" in 2017 and formed an Alternative Methods Working Group in 2020. These efforts seem largely directed at publishing research papers and holding seminars, without moving the ball down the field when it comes to actually submitting data that can be used for decision-making. For example, FDA established a program in 2020 called "the Innovative Science and Technology Approaches for New Drugs (ISTAND) Pilot Program such as organ-on-a-chip technology. This program is meant to stimulate new technologies for use in drug development and approval. As of 2024 only one organ-on-a-chip has been accepted into this pilot program. This shows a stunning lack of progress.

Congress has recognized the need to push the FDA to do more. In 2022, it passed the FDA Modernization Act, (called FDA Modernization Act 2.0) which was signed into law by President Biden. The Act, which had very strong bipartisan support, removed a requirement to use animals for drug testing and other purposes, and explicitly allows for the use of alternatives to animals. Since the passage of this legislation, FDA has not made progress implementing the law, and as a result the FDA Modernization Act 3.0 has been introduced in the House and Senate, again with strong bipartisan support. The intent of the bill is to require FDA to implement this earlier legislation.

The National Institutes of Health should also play a leadership role but our research indicates that it has not done so. It is not possible to fully assess how the NIH allocates its resources between animal and non-animal models. We have tried, but NIH's publicly available database cannot be used to answer this question. NIH has taken some steps to acknowledge the importance of non-animal approaches based on human biology. A high level group advised the NIH director to made recommendations about innovative "'novel alternative methods' or NAMs, which include computational modeling and predictive

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technologies, cell-free methods and assays and cell-based culture models, [that] hold tremendous promise." This report, issued in December 2023, came up with seven recommendations to catalyze the development of NAMs.

It is hard to tell if NIH has implemented these recommendations in a tangible way. NIH has launched a program called "Complement-ARIE" to "speed the development, standardization, validation, and use of human-based New Approach Methodologies (NAMs)." This program is funded at about $35 to $40 million per year over a 10-year period, with a total funding commitment of about $400 million. Given that NIH's annual budget is about $48 billion, that means less than one-tenth of one percent of NIH's yearly annual budget is supporting this important research. (40M/48B x 100 ≈ .083%). More resources should be dedicated to this work.

In addition, NIH must play a greater role in validating these new methodologies for use in regulatory decision-making. Validation is the process that establishes scientific confidence in a method by determining that the method is fit for its intended use and regulatory purpose. The Interagency Coordinating Committee on the Validation of Alternative Methods (ICCVAM) is housed at NIH's National Institute of Environmental Health Sciences. Established by a federal law in 2000, it is charged with reducing and replacing animal methods, working across federal agencies to review and evaluate alternative test methods and help facilitate validation of these new methods. ICCVAM and the National Toxicology Policy Interagency Center for the Evaluation of Alternative Methods (NICEATM) could and should play a much more prominent role in validating these new methods, providing standards that researchers can follow to demonstrate that new methods are relevant and reliable for use in decision-making. Unfortunately, both ICCCVAM and NICEATM are not funded appropriately to carry out these growing responsibilities and, I believe, need additional legal authorities. Annually they receive about $5 to $6 million, and they do not have the ability to require that agencies use methods that are validated.

In sum, federal agencies, especially FDA and NIH, must rise to be leaders in developing, using and validating these human-centric methods. While they have begun some programs and taken small steps in that direction, much more is needed.

The development and deployment of these innovative models are sparked by U.S. entrepreneurs.

The United States has an enviable record as a leader in scientific research, drug development and public health protection. Many of these new methods are being developed by US companies. For example, the developers, researchers and users of microphysiological systems (MPS), which are one type of alternatives, established a worldwide organization in 2023. That organization hosts a world summit that has attracted

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about 1000 participants who attended the MPS World Summit in 2023 (in Berlin) and 2024 (in Seattle). About 1300 attendees are expected to register for the 2025 World Summit.

Of the 940 registered attendees at the 2024 MPS summit, 540 were from the U.S. Among those were 189 businesses. A recent report puts the value of the global MPS businesses at about $109M in 2023, expected to rise to $706M in 2030. The U.S. share of the global market is about $74M today, expected to rise to $325M by 2030. According to this report, the global key companies of include Emulate, Mimetas, InSphero, TissUse, CN Bio, Hesperos, Valo Health (TARA Biosystems), TNO, AxoSim and Newcells Biotech, which collectively hold a 51% market share. Five of these companies are located in the U.S.

The US must continue to lead the way in MPS and related technologies, such as computational modeling, so that that we are setting the global standards in these fields, rather than following other nations. Regulatory agencies worldwide look to the U.S. for leadership and if the US leads in alternatives methods development and validation, its standards will shape international regulations, assist in high-tech job creation, and strengthen US economic growth.

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To summarize, scientific advancements have created multiple opportunities for us to develop and deploy more human centric techniques in toxicology and biomedical research and therefore call into question our current reliance on animal testing. Championing these non-animal methods is a win-win situation. It will allow us to not only to reduce the number of animals used, but also produce data that is more relevant to human health.

Federal agencies and departments must play a central role in this transition, and they have already begun to do so. However, to realize the full potential that the transition holds, agencies and departments must do more, including dedicating additional resources and leading in efforts to validate new, innovative technologies.

There is also an economic incentive for us to act. American entrepreneurs are situated to scale up these technologies once the institutional structure is set. These markets are expanding rapidly, and several American companies' investments in these emerging scientific business opportunities has positioned them for success in this marketspace once the regulatory environment is opened up for them. With federal agencies taking the lead to guide our regulatory decision making, we can improve the outlook for these and other companies in the near and long term.

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In closing, I urge the subcommittee to work with federal agencies to further develop the criteria for validation and acceptance of these new technologies within each department and in a coordinated way across multiple agencies. If we can advance our regulations, departments and agencies to embrace these new technologies, we will reduce the number of animals in research, better inform decision-making on human health impacts and advance American entrepreneurial science which is poised to take advantage of this opportunity.

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