THE HUMANE SOCIETY OF THE UNITED STATES

HUMANE SOCIETY LEGISLATIVE FUND

March 28, 2023.
Dr Donna Mendrick,
National Center for Toxicological Research, Food and Drug Administration
10903 New Hampshire Ave., Bldg. 32, Rm. 2208,
Silver Spring, MD 20993-0002

Dear Dr Mendrick,

Re: Docket No. FDA-2023-N-0217 Science Advisory Board to the National Center for Toxicological Research Advisory Committee

On behalf of the Humane Society of the United States (HSUS), the Humane Society Legislative Fund (HSLF), and our members and supporters, we appreciate the opportunity to provide comments on Docket No. FDA-2023-N-0217; "Science Advisory Board to the National Center for Toxicological Research Advisory Committee; Notice of Meeting." The Humane Society family of organizations are together the world's largest animal protection organization, driving transformational change in the United States and around the globe through the use of science, advocacy, and education. We advocate for global harmonization of the best available science and appreciate the important role that the Food and Drug Administration (FDA) plays toward achieving that objective.

We thank the FDA for its leadership on advancing new approach methodologies (NAMs). We are encouraged to see creation of the FDA Roadmap for Predictive Toxicology,[1] progressive efforts in validating non-animal methods to reduce dog testing,[2] and its support and engagement with the creation and future development of the microphysiological 'organ-chip' systems[3] and we look forward to the time when these efforts will lead to a meaningful reduction in animal use. We urge the National Center for Toxicological Research (NCTR) to encourage further development and uptake of NAMs to improve the efficiency, speed, and cost reduction of the essential toxicology research vital to the FDA Centers, while maintaining a strong commitment to public safety, and the Science Advisory Board (SAB) can play a vital role in supporting NCTR to achieve this.

We understand that the general function of the SAB is to "provide advice and recommendations to the Agency on research being conducted at the National Center for Toxicological Research." We would like to offer the following comments for the attention of the SAB as it considers the programs of work at NCTR.

We were encouraged to see the updates presented in the 2021: Advancing Regulatory Science at FDA: Focus Areas of Regulatory Science[4] where FDA discusses its commitment to novel technologies and the application of the 3Rs (Replace, Reduce, and Refine use of animals in research and testing). The 2021 annual report[5] also demonstrates the diverse research areas covered by NCTR as a whole and indicates the use of non-animal models across many research programs. However, there also appears to be potential conflict, or at least a failure to commit to non-animal approaches in some areas. For example, we note that in the inhalation toxicology research program, there are several projects using nose-only exposure of rats as the

[1] https://www.fda.gov/media/109634/download
[2] https://www.fda.gov/news-events/press-announcements/statement-fda-commissioner-scott-gottlieb-md-efforts-reduce-animal-testing-through-study-aimed
[3] https://ncats.nih.gov/tissuechip/projects/modeling
[4] https://www.fda.gov/science-research/advancing-regulatory-science/focus-areas-regulatory-science
[5] https://www.fda.gov/media/158513/download

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investigative "tool." Nose-only exposure remans the preferred method for inhalational toxicity testing in Organisation of Economic Cooperation and Development [OECD] test guidelines[6] in order to allow mutual acceptance of data across OECD countries. However, where research is **not** carried out to fulfil regulatory requirements, we urge the NCTR to adopt alternative, non-animal methods instead and suggest that the SAB offer advice on where this is possible, perhaps referring to the National Toxicology Program's work on alternative methods for inhalation toxicity testing[7]. Nose-only exposure poses significant animal welfare implications, with a risk of injury or even mortality and the repeated restraint necessary for prolonged exposures (up to 90 days), can lead to sustained, increased stress in the animals.[8] A recent parliamentary inquiry into the use of animals in New South Wales, Australia considered this issue and came to the conclusion that nose-only exposure should be phased out.[9] We urge the SAB to take a similar line with NCTR projects that are currently reliant on this distressing and stressful methodology and request that at the very least, the SAB recommend that more stringent approval requirements are needed for projects employing nose-only exposures. We do not see that reducing, or even stopping, nose-only exposure would have a detrimental impact on NCTR's research progress. It seems that NCTR already includes extensive expertise in the development and use of alternative methods for inhalation toxicity testing, with several projects using the air-liquid interface (ALI) cell-based culture method to produce highly differentiated, and therefore more physiologically accurate, models of airways.[10]

The continued use of outdated animal methods alongside the more innovative human relevant tools is a recurring theme across NCTR research. We firmly believe that, instead of conducting **new** animal studies alongside non-animal NAMs, NCTR should be using human data wherever possible and existing animal data where human data are not available. We are concerned that some of these animal and non-animal projects are unintentionally duplicative and that would waste time, research expertise, money and animal lives. Given that the SAB is charged with providing advice and recommendations on NCTR research, we think it appropriate that the SAB acts to ensure that there is no repetition of projects in this fashion. We suggest that a living database of NCTR projects is established if it is not yet available, mapping all NCTR projects, categorizing them according to aim and animal use and classifying them with regard to their application of NAMs and advancement of 3Rs. The database would serve not only as a living repository of NCTR work but would also map progress toward replacement and could therefore inform NCTR's metrics. Initially, this database could incorporate all NCTR research projects and be accessible to all NCTR researchers (and the SAB members) but ultimately, it could include other databases of non-animal methodologies[11,12] to encourage engagement with, and knowledge of, these tools, and to enable further replacement of animals across NCTR research. We would be interested to hear the SAB's thoughts on the potential utility of such a database, whether this would be a useful tool for its activities in assessing NCTR research, and therefore if it would support development of this and, further, whether creation of the database would be appropriate as an activity for the FDA's Alternative Methods Working Group.

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[6] Organisation for Economic and Cooperative Development. "Guidance Document on Inhalation Toxicity Studies, Series on Testing and Assessment No. 39. " (2018).
[7] Clippinger, A. J., D. Allen, A. M. Jarabek, M. Corvaro, M. Gaca, S. Gehen, J. A. Hotchkiss, et al. "Alternative Approaches for Acute Inhalation Toxicity Testing to Address Global Regulatory and Non-Regulatory Data Requirements: An International Workshop Report." Toxicol In Vitro 48 (Dec 22 2018): 53-70.
[8] van Eijl, S., R. van Oorschot, B. Olivier, F. P. Nijkamp, and N. Bloksma. "Stress and Hypothermia in Mice in a Nose-Only Cigarette Smoke Exposure System." Inhal Toxicol 18, no. 11 (Oct 2006): 911-8.
[9] Report No. 59. Use of Primates and Other Animals in Medical Research in New South Wales. (2022).
[10] https://www.fda.gov/media/158513/download
[11] https://www.nat-database.org
[12] https://www.re-place.be/database

We were encouraged to see that, at the Society of Toxicology 62nd Annual Meeting and ToxExpo in Nashville this month, NCTR scientists were involved in over fifty poster presentations and more than half of these appear to use alternatives to animals.[13] It seems that NCTR research is strong in its use of machine learning and other computational techniques and the Tox-GAN and Animal-GAN initiatives are impressive examples. Additionally, we note the use of human induced pluripotent stem cells across many areas of research, including neurotoxicity and reproductive toxicity and applaud NCTR for developing these human-relevant tools. With their overarching vision of the direction of travel of NCTR research, the SAB are ideally placed to offer suggestions as to where these methods may be taken up across other research areas within NCTR to further reduce reliance on animal models. It appears that there are areas where this is already occurring (for example with the use of *in vitro* models for inhalation toxicity testing at the Center for Tobacco Products and for genetic and molecular toxicity through the Centers for Drug Evaluation and Research, Biologics Evaluation and Research and Devices and Radiological Health). We urge the SAB to consider areas where crosstalk between FDA centers or even individual researchers would be profitable in terms of advancing the overall mission of NCTR to "develop innovative tools and approaches that support FDA's public health mission"[14] and to share these through its interaction with NCTR. Ideally, we would like to see SAB help NCTR develop a roadmap with timelines for transition away from reliance on animals that could cement NCTR's vision, implementing the innovative, human relevant and more predictive tools across all NCTR research areas and which could be used as a valuable metric. At the least, we envisage a role for the SAB in advising the NCTR where the non-animal approaches could be more effectively weaved throughout the disparate research programs to ensure minimal animal use.

In terms of metrics against which to measure progress, we were encouraged to see that NCTR is maintaining its publication record, with over 130 papers per year. We suggest that the SAB help to categorise these papers to map the number of papers in which non-animal methods are implemented, in order to determine progress in terms of using fewer animal-based techniques and more alternative, non-animal technologies. With the vast experience present on the SAB, we suggest that it could also offer additional input on other measures of research "success" for NCTR to consider, including citation counts or even mapping H indices of key researchers at NCTR. One of the roles of NCTR is to develop "novel translational research approaches"[15] and so it seems appropriate that this is included as a metric of success for the NCTR. We request that the SAB advises on the most effective or appropriate way to measure this- whether this would be through translational analysis with tools such as the National Institutes of Health's iCite,[16] or assessing wider uptake of the tools developed through, for example quantifying the number of qualified methods, making use of FDA's Innovative Science and Technology Approaches for New Drugs (ISTAND)[17] program.

Finally, following the promising news of Congress' $5 million appropriation to Reduce Animal Testing Through Alternative Methods in Fiscal Year 2023, which fully funded President Biden's budget request, we are urging the FDA to spend the allocated funding judiciously to advance the move away from animal testing in a measurable and impactful way as soon as possible. NCTR plays a critical role in this, in terms of reducing its animal use and also in developing the innovative non-animal methods required for regulatory decision-making. The SAB could play a role in directing NCTR activities to support this request through its review of

[13] https://ntp.niehs.nih.gov/ntp/pressctr/ntp_news/2023/sot_nctr_508.pdf
[14] https://www.fda.gov/about-fda/office-chief-scientist/national-center-toxicological-research
[15] https://www.fda.gov/about-fda/office-chief-scientist/national-center-toxicological-research
[16] https://icite.od.nih.gov
[17] https://www.fda.gov/drugs/drug-development-tool-ddt-qualification-programs/innovative-science-and-technology-approaches-new-drugs-istand-pilot-program

NCTR activities - ensuring that projects and proposals which further animal replacement through development and implementation of non-animal approaches are given precedence. There is an admirable breadth of activity in these non-animal tools across NCTR already and with SAB guidance, the NCTR could lead the way within FDA activities to provide toxicology research which advances alternative approaches with increased translational potential whilst protecting public health.

Thank you again for the opportunity to comment. We look forward to seeing how the SAB can help to accelerate progress toward the ultimate replacement of animals and integrate and further implement the innovative, human relevant tools across FDA research activities and programs.

Sincerely,

[redacted]

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