THE HUMANE SOCIETY OF THE UNITED STATES

May 4, 2021

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-2020-N-1647 Science Advisory Board to the National Center for Toxicological Research Advisory Committee

On behalf of the Humane Society of the United States (HSUS), Humane Society Legislative Fund (HSLF), and our members and supporters, we appreciate the opportunity to provide comments on Docket No. FDA-2020-N-1647; "Science Advisory Board to the National Center for Toxicological Research Advisory Committee". The Humane Society family of organizations strive to propel transformational change for animals 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 how creation of the FDA Roadmap for Predictive Toxicology,[1] progressive efforts in validating non-animal methods to reduce certain dog testing,[2] and its support and engagement with the creation and future development of the microphysiological 'organ-chip' systems[3] are contributing toward a reduction in animal use in the U.S., and this commitment is further evidenced through the creation of the Alternatives Methods Working Group[4]. We urge the FDA to maintain this impetus, to encourage further development and uptake of NAMs throughout the full remit of the research projects undertaken at the National Center for Toxicology Research (NCTR), 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.

With the upcoming public advisory committee meeting of the Science Advisory Board (SAB) to the National Center for Toxicological Research (NCTR), in which we anticipate hearing more about the contribution of NCTR scientists to enhancing FDA's predictive capability, we offer the following comments. Here we focus on existing NCTR science activities that could be more widely promoted, including through adoption by other Centers, and we make suggestions for how the SAB may be able to offer support or guidance in order to further these more promising initiatives. We note that the general function of the SAB committee is "to provide advice and recommendations to

[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/about-science-research-fda/advancing-alternative-methods-fda.

1255 23rd St. NW, Suite 450, Washington, DC 20037
P 202-452-1100 F 202-778-6132 humanesociety.org

the Agency on research being conducted at the National Center for Toxicological Research (NCTR)."[5] We offer suggestions as to how these research directions could be refined to enhance NCTR efforts, allowing more effective and efficient decision making and facilitating the development of a research program that embraces new technologies to allow truly innovative research.

Promoting wider use of innovative, human relevant technologies under development at NCTR and beyond.
We are encouraged to note, from the 2019 Annual Report of the NCTR[6], that the center undertakes a huge body of work and is vital in identifying evolving scientific areas and driving research in these specific fields. We note that there are several initiatives focused on the use of advanced, human relevant techniques, including application of microphysiological systems (MPS), use of cultured human cells for genotoxicity testing, predictive human physiologically based pharmacokinetic (PBPK) modelling, the use of *in vitro* models of the human microbiome and mouse testis and innovative computational modelling for predicting drug toxicities. The use and development of such non-animal approaches are to be encouraged and facilitated and we would appreciate this being rolled out more widely across all areas of research within the NCTR. The Science Advisory Board (SAB) could play a vital role in reviewing and identifying the potential impact of these projects in other areas and could use their role to facilitate wider dissemination of these technologies and protocols across NCTR and its work with the Centers, to allow sharing of best practices and ensure that advances applied for one project or research area are advocated more widely wherever possible. Ultimately, we encourage the NCTR to follow the inspirational example of the US Environmental Protection Agency, with its recent declaration to end reliance on studies on mammals by 2035[7] and we would urge the NCTR to commit to a defined timeline to phaseout animal testing within its research activities.

Focus on funding, developing and applying data from NAMs.
As noted in the FDA's Roadmap for Predictive Toxicology, exciting breakthroughs in science have led to new tools and methods for predictive toxicology testing. Many of these methods use human-mimetic systems and are proving more human-predictive, less time consuming, and more cost-effective than the animal-dependent test systems currently employed. It is apparent that more effective application of existing NAMs, the creation of novel NAMs and demonstration of their applicability could fall within the remit of NCTR research, and that the SAB may be able to offer their expert inputs and discuss forward-thinking approaches. This would be most relevant for those specific research areas within NCTR where animals are currently preferred (eg cardiotoxicity testing, neurotoxicity, inhalation toxicity) but where NAMs are being applied very effectively outside of NCTR[8,9,10.]

The SAB should encourage continued promotion of MPS use and development. The Human Microphysiological Systems: Organs-on-Chips for Drug Safety and Efficacy Testing Program initiated between the National Center for Advancing Translational Sciences (NCATS), the Defense Advanced Research Projects Agency (DARPA), and the FDA,

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[5] https://www.govinfo.gov/content/pkg/FR-2021-04-05/html/2021-06930.htm
[6] https://www.fda.gov/media/142492/download
[7] https://www.epa.gov/newsreleases/administrator-wheeler-signs-memo-reduce-animal-testing-awards-425-million-advance
[8] Savoji H et al. (2019) Cardiovascular disease models: A game changing paradigm in drug discovery and screening. Biomaterials. Apr;198:3-26. doi: 10.1016/j.biomaterials.2018.09.036.
[9] Bal-Price A., Pistollato F. (2019) Application of Non-Animal Methods to More Effective Neurotoxicity Testing for Regulatory Purposes. In: Aschner M., Costa L. (eds) Cell Culture Techniques. Neuromethods, vol 145. Humana, New York, NY. https://doi.org/10.1007/978-1-4939-9228-7_15
[10] Clippinger AJ et al., (2018) Pathway-based predictive approaches for non-animal assessment of acute inhalation toxicity. Toxicol In Vitro. Oct;52:131-145. doi: 10.1016/j.tiv.2018.06.009.

has been a resounding success in the rapid development and commercialization of several organ-on-a-chip systems that are currently in different phases of implementation. The use of dynamic, physiologically accurate MPS is proving revolutionary for drug discovery and disease modeling. The National Institutes of Health has confirmed their commitment to the development of organs-on-chips with over 72 million dollars devoted to the advancement of these human-based systems.[11] Organ-on-a-chip models of every human organ either exist already or are under development, with many at very advanced stages, including platforms that mimic the complexity of human immune responses.[12]

With 90% of drugs failing to make it to market[13] due to either adverse toxic events not predicted in animal models or lack of efficacy, the development and regulatory acceptance of human-relevant organ chip technology will be revolutionary in the drug discovery process and will ultimately lead to a notable decrease in unnecessary animal testing. In addition, advances in chip technology will enable drugs to come to market more quickly and at less cost than the current drug discovery process. Research at the NCTR should help facilitate the continued development and, importantly, regulatory acceptance of chip technology to reduce and eventually replace animal testing in the drug discovery and approval process. As a step toward building confidence in human chip data and in order to demonstrate the potential of animal chips for replacing live animals used for preclinical testing, we encourage the development of animal chips and their application in cross species comparisons of toxicity profiles. Data from animal chips could be directly compared to data from in vivo animal studies - showing the predictive capacity of chips, both within and across species. This information could not only create a more immediate opportunity to reduce in vivo animal use in veterinary drug evaluations, but also, by enabling estimation of concordance between animal chips and animal in vivo data, could reveal likely correlation(s) between human chip data and human in vivo responses, allowing for a broader replacement of animal use across all FDA centers. NCTR is ideally situated to facilitate this process.

Promoting training and education in NAMs.

We appreciate that wider application of non-animal, human relevant approaches requires effective education and training and that a competent workforce is more globally competitive, confident and able. NCTR—in partnership with the researchers from FDA centers, other government agencies, academia, and industry with which it works so closely—is in the ideal position to provide innovative technology, methods development, vital scientific training, and technical expertise. NCTR has the capacity to be a world leader in the development and application of NAMs in toxicity testing. We urge the NCTR to take note of ongoing initiatives aiming to address this and encourage the SAB to embrace and support this. For example, the European Commission has created a freely-available inventory of training courses and other educational resources that facilitate NAMs development and enable effective implementation of the 3Rs[14]. Various other efforts are underway to create freely available materials for education and training in the use of NAMs and we encourage the NCTR to make use of these and strongly suggest that the SAB advise on the prioritization of requirements for training in NAMs.

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[11] https://ncats.nih.gov/tissuechip/projects/modeling

[12] Oleaga, C., et al. (2018). Investigation of the effect of hepatic metabolism on off-target cardiotoxicity in a multi-organ human-on-a-chip system. Biomaterials 182: 176-190; Edington et al. (2018) Interconnected Microphysiological Systems for Quantitative Biology and Pharmacology Studies. Sci Rep. 2018 Mar 14;8(1):4530. doi: 10.1038/s41598-018-22749-0; Sharifi, F., et al. (2019). A Foreign Body Response-on-a-Chip Platform. Adv Healthc Mater: e1801425.

[13] https://ncats.nih.gov/tissuechip/about

[14] https://data.jrc.ec.europa.eu/dataset/d0569abb-b5ab-4b9e-9e16-d70cea7a89f9

Translating publications into policy.
We note that the NCTR measures its impact through number of peer-reviewed publications and subscriptions to online newsletters and these are very useful metrics to quantify external engagement with its outputs. However, we would like to see the SAB work with the NCTR to consider how and where the innovative, non-animal methodologies under development might be incorporated more formally into guidance. For example, the 2019 Annual report notes that NCTR scientists have used human neural stem cells to demonstrate the neuroprotective effects of xenon in anesthesia – data which could be used to support the FDA's regulatory role in pediatric anesthesia. Converting data into guidance, by promoting and requiring the use of these human cell-based assays in safety testing regimes, would create real impact for the work of NCTR and contribute to the FDA's mandate to apply the 3Rs of reducing, refining and replacing animal use both internally and in terms of animals used by industries to gain regulatory approval by the agency.

We are also aware that the NCTR is extremely active in the area of inhalation toxicity testing, in support of the FDA regulation of tobacco products. For this research area, we suggest that a more consolidated approach that avoids the use of animal models is more likely to generate the requisite benefits. Focusing efforts on the *in vitro* methodologies, including those underway at NCTR, and also encompassing other recent innovations[15], could lead to more human relevant testing strategies for tobacco products and other nicotine-containing devices. The SAB could advise on how best to develop a testing strategy within NCTR that could be incorporated into regulatory requirements for tobacco products. FDA could then disseminate these new, updated requirements through its Alternative Methods Working Group[16] platform and through direct communication with relevant stakeholders, to ensure that needless and ineffective inhalation toxicity testing for tobacco products/nicotine products using animals no longer occurs and that submission of data from animal studies is prevented as soon as the FDA accepts data obtained using NAMs.

In addition, NCTR research has applied transcriptomic analysis of HepaRG cells to distinguish the genotoxic and carcinogenic potential of candidate chemicals for human liver[17], and has developed a high throughput assay to detect carcinogenic biomarkers[18]. These are just two examples of important research that could be developed into regulatory-accepted assays to reduce animal use. We recommend that the ground-breaking, human relevant research carried out at NCTR is converted into policy wherever possible, through updated or amended FDA guidance documents that include recommendations for data generated with the non-animal methodologies for toxicity testing as full replacement for animal use.

Broadening the SAB to bridge toxicology and biomedical research.
Finally, the SAB itself is made up of "authorities knowledgeable in the fields of toxicological research"[19] and whilst we applaud the use of eminent experts, we feel that the direction of some of the NCTR research may also warrant inclusion of expertise outside of traditional toxicology. We suggest that there is input from experts in, for example, the use of methods more usually associated with biomedical research, such as sophisticated, advanced, human

[15] https://www.thepsci.eu/inhalation-webinars/
[16] https://www.fda.gov/science-research/about-science-research-fda/advancing-alternative-methods-fda
[17] Tryndyak, V., Kindrat, I., Dreval, K., Churchwell, M.I., Beland, F.A., Pogribny, I.P., Effect of aflatoxin B1, benzo[a]pyrene, and methapyrilene on transcriptomic and epigenetic alterations in human liver HepaRG cells, Food and Chemical Toxicology (2018), doi: 10.1016/j.fct.2018.08.034.
18 McKinzie, P.B, Bishop. M.E. A Streamlined and High-Throughput Error-Corrected Next-Generation Sequencing Method for Low Variant Allele Frequency Quantitation. Toxicological Sciences (2019), 1-19.
[19] https://www.fda.gov/advisory-committees/committees-and-meeting-materials/toxicological-research-science-advisory-board-national-center-toxicological-research

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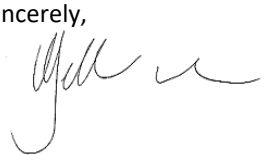
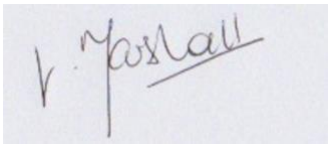
relevant approaches including but not limited to 3D bioprinting, MPS, and human induced pluripotent stem cells. It is not clear to us whether this is already happening, but we see great value in permitting, and in fact encouraging, cross-fertilization between toxicology and biomedical research fields.

We thank you for the opportunity to comment and look forward to seeing more innovative, progressive non-animal approaches emerging from NCTR and being applied for toxicology risk assessments and safety testing across the FDA Centers more broadly.

Sincerely,





Gillian Lyons
Senior Regulatory Specialist, Federal Affairs
Humane Society Legislative Fund

Lindsay Marshall, PhD
Biomedical Science Adviser, Animal Research Issues
The Humane Society of the United States