

September 13, 2023

Dr. Milene Brownlow
Designated Federal Officer for SACATM
Office of Policy, Review, and Outreach
Division of Translational Toxicology, NIEHS
P.O. Box 12233, K2-03, Research Triangle Park, NC 27709

Dear Dr. Brownlow,

These comments are submitted on behalf of People for the Ethical Treatment of Animals (PETA) in response to the National Institutes of Health's August 2, 2023 Federal Register Notice "Scientific Advisory Committee on Alternative Toxicological Methods; Notice of Public Meeting; Request for Public Input" (88 FR 50884).

Session Ia: 5 years into ICCVAM Strategic Roadmap: Full Replacement of the Acute Tox 6-pack

We commend the Interagency Coordinating Committee on the Validation of Alternative Methods (ICCVAM) and National Toxicology Program Interagency Center for the Evaluation of Alternative Toxicological Methods (NICEATM) for their work to develop and implement reliable and relevant non-animal approaches for assessing acute toxicity. Given the ever-increasing availability of robust non-animal test methods for acute toxicity, we encourage ICCVAM member agencies to adopt policies clarifying the acceptance of these methods. For example, the use of *in vitro* reconstructed human tissue models for assessing skin irritation potential of device extracts has been extensively validated, is included in an International Organization for Standardization (ISO) standard, and is accepted by the European Union member states, Australia, Japan, and China.^{1,2,3,4} The U.S. Food and Drug Administration (FDA) Center for Devices and Radiological Health, however, has yet to integrate this approach into its own guidance on use of the ISO standard.⁵ As another example, the U.S. Environmental Protection Agency (EPA) has published on substantial progress to advance the use of non-animal approaches for health effects including systemic toxicity,^{6,7} dermal absorption,^{8,9} and eye irritation.¹⁰ Final steps need to be taken to formalize the EPA's acceptance of these approaches as policy guidance.

Some ICCVAM member agencies keep lists of representative methods that the agency may consider to meet their data requirements.^{11,12} These lists can be useful to the regulated industry to understand what methods are often accepted and to clarify that additional methods will be considered; i.e., the list is not exhaustive of all methods that could be used, rather, it provides select, representative methods that the agency may consider. However, these lists can

PEOPLE FOR
THE ETHICAL
TREATMENT
OF ANIMALS

Washington, D.C.
1536 16th St. N.W.
Washington, DC 20036
202-483-PETA

Los Angeles
2154 W. Sunset Blvd.
Los Angeles, CA 90026
323-644-PETA

Norfolk
501 Front St.
Norfolk, VA 23510
757-622-PETA

Oakland
554 Grand Ave.
Oakland, CA 94610
510-763-PETA

Info@peta.org
PETA.org

Affiliates:

- PETA Asia
- PETA India
- PETA France
- PETA Australia
- PETA Germany
- PETA Netherlands
- PETA Foundation (U.K.)

become problematic if they are not regularly updated or if there is not a process for nominating methods to add to the list. For example, under TSCA Section 4(h)(2)(C), the EPA is directed to maintain and regularly update such a list. This list was published in June 2018 and updated in December 2019 and February 2021.^{13,14} To remain relevant five years after the publication of the initial list and more than two years since its last update, there is a need for a process for adding methods and an updated list (for example, one that includes the use of the GHS additivity equation and the *in silico* CATMOS model for systemic toxicity predictions).

Several years after the publication of ICCVAM's strategic roadmap, as well as similar individual ICCVAM agency roadmaps,^{15,16,17,18,19} it would be useful to analyze metrics on submissions using animal and non-animal test methods to help evaluate the impact of the roadmaps and subsequent activities and programs. The European Union has increasingly recognized the value of transparency in animal use data.²⁰ With a history of reporting animal numbers, species, and use of animals in Member States, the European Commission's statistical report expanded the scope of animals and uses covered starting in 2015, e.g., the inclusion of all species of Cephalopods and the creation and maintenance of genetically altered animals.²¹ The European Commission notes, "To progress towards the ultimate goal of full replacement, it is crucial to understand where, how and why animals are still required to be used for scientific purposes."²² ICCVAM member agencies should do the same, including reporting (1) the number of animals used per endpoint; (2) the number of *in vitro* tests that are submitted versus the number that are accepted per endpoint; (3) the number of *in vitro* tests that are submitted versus the number of animal tests that are submitted per endpoint; and/or (4) the number of waivers granted versus the number of required studies.

As ICCVAM member agencies look beyond the acute toxicity six-pack, in addition to advancing new methods, they should consider revisiting where non-animal methods are ready and available for implementation but are not fully accepted by agencies or being used by industry. For example, the mouse bioassay (MBA) is commonly used to test for marine biotoxins in shellfish in order to fulfil FDA data needs. More specific and sensitive methods are available—and are required in some countries—but the MBA is still commonly used in the U.S. As another example, millions of animals are likely used to produce antibodies per year, and replacement technologies are well developed and available, yet there has not been a concentrated effort to implement the use of non-animal antibodies.

Session Ib: 5 Years into ICCVAM Strategic Roadmap: Evolution of Validation

We congratulate ICCVAM on the publication of its draft framework for transparently and consistently establishing scientific confidence in test methods. Its swift and transparent adoption by ICCVAM member agencies will allow for the uptake of reliable and relevant scientific tools that will best protect human health and the environment. Our comments on this framework have been submitted and are available [here](#).²³

Session II: The Role of NAMs in Improving Environmental Health Protection

Non-animal methods provide the opportunity to address human population variability and susceptibility that tests on animals cannot. *In vitro* assays and microphysiological systems can be

developed to represent specific populations to assess human health susceptibility and outcomes, and *in silico* models allow us to conduct more comprehensive clinical trials. Similarly, to improve environmental health protection, resources should be directed towards data sharing and the use of 21st century *in vitro* and *in silico* approaches for the timely evaluation of chemicals of concern, such as PFAS.

Thank you for considering our comments.

Sincerely,
(signature redacted)

Amy J. Clippinger, Ph.D.
Managing Director
Regulatory Toxicology Department
AmyJC@peta.org

(phone number redacted)

(signature redacted)

Katherine Groff, M.S.
Senior Scientist
Regulatory Toxicology Department
KatherineG@peta.org

(phone number redacted)

¹ Organisation for Economic Co-operation and Development (OECD). *Test No. 439: In Vitro Skin Irritation: Reconstructed Human Epidermis Test Method, OECD Guidelines for the Testing of Chemicals, Section 4*. OECD; 2021. <https://doi.org/10.1787/9789264242845-en>. Accessed September 12, 2023.

² De Jong WH, Carraway JW, Liu C, et al. The suitability of reconstructed human epidermis models for medical device irritation assessment: a comparison of *in vitro* and *in vivo* testing results. *Toxicol In Vitro*. 2020;69:104995.

³ De Jong WH, Hoffmann S, Lee M, et al. Round robin study to evaluate the reconstructed human epidermis (RhE) model as an *in vitro* skin irritation test for detection of irritant activity in medical device extracts. *Toxicol In Vitro*. 2018;50:439-449.

⁴ ISO. 10993-23: Biological evaluation of medical devices—Part 23: Tests for irritation.

⁵ FDA. *Use of International Standard ISO 10993-1, "Biological evaluation of medical devices - Part 1: Evaluation and testing within a risk management process"*. Available at: <https://www.fda.gov/regulatory-information/search-fda-guidance-documents/use-international-standard-iso-10993-1-biological-evaluation-medical-devices-part-1-evaluation-and>. Published 2023. Accessed September 11, 2023.

⁶ Mansouri K, Karmaus AL, Fitzpatrick J, et al. CATMoS: Collaborative Acute Toxicity Modeling Suite. *Environ Health Perspect*. 2021;129(4):47013.

⁷ Karmaus AL, Mansouri K, To KT, et al. Evaluation of variability across rat acute oral systemic toxicity studies. *Toxicol Sci*. 2022;188(1):34-47.

⁸ Allen DG, Rooney J, Kleinstreuer NC, Lowit AB, Perron M. Retrospective analysis of dermal absorption triple pack data. *ALTEX*. 2021;38(3):463-476.

⁹ van der Zalm AJ, Daniel AB, Raabe HA, et al. Defined approaches to classify agrochemical formulations into EPA hazard categories developed using EpiOcular™ reconstructed human corneal epithelium and bovine corneal opacity and permeability assays. *In Press*.

¹⁰ Clippinger AJ, Raabe HA, Allen DG, et al. [Human-relevant approaches to assess eye corrosion/irritation potential of agrochemical formulations](#). *Cutan Ocul Toxicol*. 2021;40(2):145-167.

¹¹ CPSC. CPSC's policy on animal testing. <https://www.cpsc.gov/FAQ/CPSCs-Policy-on-Animal-Testing>. Accessed September 12, 2023.

¹² EPA. Strategic plan to reduce the use of vertebrate animals in chemical testing. <https://www.epa.gov/assessing-and-managing-chemicals-under-tsca/strategic-plan-reduce-use-vertebrate-animals-chemical>. Accessed September 12, 2023.

-
- ¹³ EPA. List of alternative test methods and strategies (or New Approach Methodologies [NAMs]). https://www.epa.gov/sites/default/files/2021-02/documents/nams_list_second_update_2-4-21_final.pdf. Published 2021. Accessed September 12, 2023.
- ¹⁴ EPA. Alternative test methods and strategies to reduce vertebrate animal testing. <https://www.epa.gov/assessing-and-managing-chemicals-under-tsca/alternative-test-methods-and-strategies-reduce>. Accessed September 12, 2023
- ¹⁵ FDA. *Advancing new alternative methodologies at FDA*. FDA; 2021. <https://www.fda.gov/media/144891/download?attachment>. Accessed September 12, 2023.
- ¹⁶ FDA. *Advancing regulatory science at FDA: A strategic plan*. FDA; 2011. <https://www.fda.gov/science-research/advancing-regulatory-science/strategic-plan-regulatory-science>. Accessed September 12, 2023.
- ¹⁷ FDA. *FDA's predictive toxicology roadmap*. FDA; 2017. <https://www.fda.gov/media/109634/download>. Accessed September 12, 2023.
- ¹⁸ EPA. *New approach methods work plan*. EPA; 2020-2021. <https://www.epa.gov/chemical-research/new-approach-methods-work-plan>. Accessed September 12, 2023.
- ¹⁹ EPA. *Strategic plan to promote the development and implementation of alternative test methods within the TSCA program*. EPA; 2018. https://www.epa.gov/sites/default/files/2018-06/documents/epa_alt_strat_plan_6-20-18_clean_final.pdf. Accessed September 12, 2023.
- ²⁰ European Commission. *Animals in science: EU actions for the protection of animals used for scientific purposes*. https://environment.ec.europa.eu/topics/chemicals/animals-science_en. Accessed September 11, 2023.
- ²¹ European Commission. *Report from the Commission to the European Parliament and the Council: 2019 report on the statistics on the use of animals for scientific purposes in the Member States of the European Union in 2015-2017*. European Commission; 2020. <https://eur-lex.europa.eu/legal-content/EN/TXT/?qid=1581689520921&uri=CLEX:52020DC0016>. Accessed September 11, 2023.
- ²² European Commission. *Statistics and non-technical project summaries: Improving transparency through open access to information on the use of animals for scientific purposes*. https://environment.ec.europa.eu/topics/chemicals/animals-science/statistics-and-non-technical-project-summaries_en. Accessed September 11, 2023.
- ²³ Van der Zalm A and Clippinger AJ. RE: Comments on ICCVAM guidance document, Validation, qualification, and regulatory acceptance of new approach methodologies. August 24, 2023. https://ntp.niehs.nih.gov/sites/default/files/2023-08/VWG_Doc_Comments_PETA_20230824.pdf. Accessed September 12, 2023.