AN INTERNATIONAL ORGANIZATION DEDICATED TO PROTECTING THE RIGHTS OF ALL ANIMALS

PETA

PEOPLE FOR THE ETHICAL TREATMENT OF ANIMALS

Washington
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

Info@peta.org
PETA.org

August 24, 2023

Dr. Nicole Kleinstreuer
Director, NICEATM
Research Triangle Park, NC 27709

Submitted via email to Amber Daniel, amber.daniel@inotivco.com

RE: Comments on ICCVAM guidance document, *Validation, Qualification, and Regulatory Acceptance of New Approach Methodologies*

Dear Dr. Kleinstreuer,

We thank you for the opportunity to submit comments on behalf of People for the Ethical Treatment of Animals (PETA) in response to the publication of the Interagency Coordinating Committee on the Validation of Alternative Methods (ICCVAM) draft guidance document, *Validation, Qualification, and Regulatory Acceptance of New Approach Methodologies*.

We support the key concepts outlined in the document, including the emphasis on biological relevance, a flexible and fit for purpose approach, and the possibility that new testing approaches may provide better information for regulatory decision making than traditional test methods. Below, please find suggestions to further improve the consistency and usefulness of this document.

Broadly applicable

We recommend that the principles described in the document are more broadly applied to the evaluation of any method, including new or existing *in vitro* or *in vivo* methods.

Recommendations:

We recommend the following revision to the title of the document: Validation, Qualification, and Regulatory Acceptance of Methods for Regulatory Use.

We recommend the following revision to the Disclaimer on page 1: This document has been developed as a resource for U.S. federal agencies and stakeholders seeking to establish confidence in existing or new testing approaches.

We recommend the following addition on page 2, after "These resources described a validation model that is flexible in principle, but in practice has demonstrated various limitations such as being lengthy and resource intensive": slowing the rate at which scientific innovations are incorporated into regulatory science. The approach outlined below should enable a more rapid incorporation of robust, modern techniques that can effectively and efficiently protect human health and the environment.

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

We recommend the following addition to page 2: While the text that follows provides specific insight on establishing confidence in new approach methodologies (NAMs) and builds upon the principles outlined in the ICCVAM 2018 Roadmap, the principles described are broadly applicable to the assessment of all methods intended for regulatory use.

Definition of NAMs

The definition of new approach methodologies (NAMs) used in the draft guidance document is not aligned with previous definitions used by ICCVAM[1] and its member agencies[2], and therefore, has the potential to cause further confusion surrounding the term and its use. For scientific, ethical, and logistical reasons, a key purpose of NAMs is to avoid the use of animal tests, and this should be recognized in ICCVAM's definition.

Recommendation: On page 2, we recommend using the definition of NAMs used in the U.S. Environmental Protection Agency NAMs Work Plan[2]: "NAMs are defined as any technology, methodology, approach, or combination that can provide information on chemical hazard and risk assessment to avoid the use of animal testing."

Clarification of general concepts

On page 6, the document states that "there should be evidence to support that the use of an alternative method will lead a regulatory review to the same or more protective decision as the reviewer would make based on existing methods." The phrase "more protective" needs clarification as it may be interpreted that new approaches must provide more conservative data in order to be used for regulatory purposes. As described later on page 6, it is possible that NAMs provide "better quality and more relevant information for regulatory decision-making than the traditional animal test method". We may envision a situation in which the existing animal test significantly over predicts the actual harm chemical exposure could have to human health, and where a more human-relevant NAM – with the potential to be more predictive of human biology – provides data that lead to higher exposure values that are still protective of human health. In this scenario, the NAM should still be applicable for regulatory use.

Recommendation: We suggest the following wording change on page 6: Where possible and appropriate, there should be evidence to support that the use of an alternative method will provide information that is as good as or better than the existing method, and that it will lead a regulatory review to decisions that are protective for human health.

On page 7, different needs for validation at different agencies are highlighted, and this would be a good place to introduce the OECD Mutual Acceptance of Data.

Recommendation: In addition to mentioning Mutual Acceptance of Data on page 44, we recommend adding the following text to page 7: "In order to avoid redundant testing, the OECD Mutual Acceptance of Data clause requires all member countries to accept safety data generated using an OECD test guideline."

On page 7, Table 2 lists manuscripts by ICCVAM workgroups providing details on agency testing needs.

Recommendation: Please include the following reference in a new row for "Skin and Eye Irritation Testing": Choksi NY, Truax J, Layton A, et al. United States regulatory requirements for skin and eye irritation testing. *Cutan Ocul Toxicol*. 2019;38(2):141-155.

Biological relevance

On page 10, the document states that "[t]he absence of an understanding of the biological and mechanistic relevance of a NAM may limit its applicability to boundaries tightly defined by the data used to validate the NAM and make it difficult to extend NAMs to chemical classes outside those used in establishing and validating the NAM." This logic is applicable to all methods.

Recommendation: On page 10, replace 'NAM' with 'method' and clarify that this statement applies to all existing or new methods.

On page 11, Table 3 outlines a number of endpoints that have been biologically and/or mechanistically investigated to demonstrate that new approaches are available to support regulatory applications. We note that eye irritation and skin irritation are missing from this table although the U.S. Environmental Protection Agency (EPA) Office of Pesticide Programs (OPP) recorded using 32 *in vitro* eye irritation methods, and 28 *in vitro* skin irritation methods to support registration of pesticides.[3]

Recommendation: We suggest adding eye irritation[4] and skin irritation[5] to Table 3.

On page 14, under Reference Data, the document states that "A key aspect of demonstrating the scientific validity of a NAM is assessing its performance against existing test methods in use."

Recommendation: To clarify that direct comparison of existing test methods with new approaches is a traditional way to assess validity, and not necessarily the most scientifically robust way, we recommend changing "A key aspect of demonstrating…" to "A traditional way to demonstrate…"

On page 18, the document states "Data from animal studies can be curated and compared to yield reference standard lists with reproducible, robust, and relevant results." However, curated and reproducible data are not necessarily biologically relevant to the species of interest.

Recommendation: Delete "relevant" from the sentence above on page 18.

Evolution of confidence based on experience gained

On page 21, the document highlights the importance of discussions between method developers and regulators prior to validating a NAM.

Recommendation: To provide examples of formal routes of communication between stakeholders/method developers and regulators, please make reference to the U.S Food and Drug Administration's Medical Device Development Tools and the Innovative Science and Technology Approaches for New Drugs programs.

On page 39, the document states that "[t]here is often high confidence in existing approaches with which there is substantial experience. These existing approaches may not have undergone formal validation but repeated successful use of the existing approach along with assumed inherent validity of testing in animals often builds substantial confidence in the approaches." Long standing use of a method does not necessarily indicate reliability, relevance, or the most efficient and effective protection of public health and the environment.

Recommendation: Please replace the phrasing above with the following: Most existing *in vivo* approaches have not undergone formal validation, and validity has been assumed. Understanding the strengths and limitations of an existing *in vivo* method helps to set performance benchmarks for a new approach and evaluate confidence in new and existing approaches.

Applicability domain

On page 73, the document states that "[i]f an assay is not evaluated for a certain class of chemicals, there will be greater uncertainty regarding the assay performance for this class of chemicals both from analytical (e.g., whether there are biases that impact the assay performance) as well as potential concordance (e.g., whether the assay yields similar results as an *in vivo* assay) considerations. Therefore, it may also be valuable to assess the assay concordance across different chemical classes to increase confidence in the applicability of the assay with a broader range of chemicals." This statement is in contrast to the standard applied to most existing animal tests, where they were not formally validated across different chemical classes (or at all), and were instead assumed to be relevant and reliable across chemical classes without mechanistic investigation or a biological understanding of interspecies differences. Concordance assessments against information that is not known to be relevant and reliable has the potential to confound scientific confidence in a new approach and misrepresent the appropriate levels of uncertainty.

> *Recommendation:* Please replace "potential concordance (e.g., whether the assay yields similar results as an in vivo assay) considerations" with "potential relevance considerations". Please also replace the second instance of "concordance" with "performance".

Communication and training to encourage the use of NAMs

Training and communication on NAMs encourages regulators and regulated industries to transition to use them. Page 44 could be improved by demonstrating that agencies intend to fulfil the suggestions outlined in this section.

> *Recommendation:* As an example, the following changes could be made to the first two sentences: Communication from agencies about the acceptability of specific NAMs and training on NAMs facilitate their use. Agencies should communicate publicly when and how a NAM is acceptable, depending on agency-specific rules and policies.

We look forward to the publication of the final guidance document. Thank you for considering these comments, and please contact us if you have any questions.

Sincerely,

Anna van der Zalm, MChem
Scientific Specialist
PETA Regulatory Toxicology Department
AnnaZ@peta.org

Amy J. Clippinger, PhD
Managing Director
PETA Regulatory Toxicology Department
AmyJC@peta.org

References:

1. Interagency Coordinating Committee on the Validation of Alternative Methods. *A Strategic Roadmap for Establishing New Approaches to Evaluate the Safety of Chemicals and Medical Products in the United States*. 2018.
2. U.S. Environmental Protection Agency. *New Approach Methods Work Plan (V2)*. 2021.
3. U.S. Environmental Protection Agency. Strategic Vision for Adopting New Approach Methodologies - Metrics. Published 2021. Accessed August 17, 2023. https://www.epa.gov/pesticide-science-and-assessing-pesticide-risks/strategic-vision-adopting-new-approach-0
4. 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.
5. Organisation for Economic Co-operation and Development. *New Guidance Document on an Integrated Approach on Testing and Assessment for Skin Corrosion and Irritation. Series on Testing and Assessment. No 203*. 2014.