Cruelty Free INTERNATIONAL

5 September 2023

Nicole Kleinstreuer, PhD
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Submitted via email: amber.daniel@inotivco.com

RE: Comments on "Validation, Qualification, and Regulatory Acceptance of New Approach Methodologies; A Report of the Interagency Coordinating Committee on the Validation of Alternative Methods (ICCVAM) Validation Workgroup; 2023"

Dear Dr. Kleinstreuer,

Cruelty Free International appreciates the opportunity to submit comments on the ICCVAM draft guidance document on the "Validation, Qualification, and Regulatory Acceptance of New Approach Methodologies".

While we appreciate and commend ICCVAM's efforts in drafting this guidance document, we believe that a few improvements could be made to clarify and strengthen some of its key recommendations. Please see below for our specific comments on the draft text.

Line	Comment
168	We are concerned that there is some confusion and inconsistency surrounding the definition of NAMs. Since one of the main purposes of NAMs is to replace the use of animals, it is important that the definition is clarified in this guidance document to include only non-animal methods and/or approaches. Suggested change in bold: In the context of this document, the term NAM refers to any technology, methodology, approach, or combination thereof that can be used to provide information on chemical hazard and risk assessment and supports **the replacement of animal use.**
215	Please consider that the performance of an alternative method may be compared with the performance of an existing method for a single substance, or across many (potentially even thousands) of substances – greater overall protection may be afforded by certain non-animal methods thanks to their ability to cover many substances rapidly and comprehensively. Suggested change in bold: Specifically, 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 **for individual substances** as the reviewer would make based on existing methods **or will allow for regulatory decisions across many substances that would otherwise not be possible.**

302 & 311	Please ensure that this text will allow for those NAMs which may have been developed using a so-called data-driven approach, as opposed to following a hypothesis-driven design. The GARDTMskin method is one such example (as per OECD test guideline 442E: https://www.oecd-ilibrary.org/docserver/9789264264359-en.pdf?expires=1693928704&id=id&accname=guest&checksum=04D2C243FC6E98457A82E5E05F169942 and supporting document: https://one.oecd.org/document/env/cbc/mono(2022)13/en/pdf); the development of this method involved the evaluation of a "discovery dataset" whereupon it was subsequently identified that the GARDskin assay monitors mechanistic events associated with key event (KE) 3 of the OECD AOP, but also that some events may also be associated with other KEs. Please consider deleting the following text: The 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. So as not to encourage an overly stringent view of the range of chemical substances contained within an applicability domain.
323	The biological and mechanistic relevance of NAMs for eye and skin irritation has been demonstrated to support regulatory applications. Therefore, both eye irritation and skin irritation should be added to Table 3.
374	Reference chemicals are not themselves curated (rather, reference chemicals may be carefully selected based on curated data sets). Suggested change: delete "curated".
467	Suggested change in bold: […] NAMs may be able to provide these mechanistic insights). **Moreover, the data obtained from animal tests may be so clearly unreliable that it is obvious that no meaningful comparison with NAM data can be made (for example, the highly variable Draize test data for category 2 eye irritants).** There are also circumstances in which the animal model may be measuring […]
467	Since comprehensive coverage of complex biology may not be necessary for regulatory decision making, please consider rewording the following text: There are also circumstances in which the animal model may be measuring complex biology **which is relevant to the COU but which is not adequately covered by the NAM in question.** This wording is clearer, and leaves open the possibility that sufficiently comprehensive coverage could be achieved with e.g., a battery of NAMs, an IATA, a defined approach etc.
489	Since it is typically only assumed that data from animal studies are relevant to the species of interest, we suggest deleting "and relevant" or amending to "and **assumed** relevant results".
509	Please also consider that a NAM could afford greater levels of protection due to speed and therefore greater and more rapid coverage of chemicals.

	Suggested change in bold: Ideally, the method will be more predictive, **and/or will allow for more rapid and comprehensive generation of relevant data across many chemicals where data may otherwise be scarce or absent**, thereby engendering confidence among regulators and stakeholder communities.
904	Suggested change in bold: "There is often high confidence in existing approaches with which there is substantial experience. **However, many of these approaches have not** undergone formal validation and **their validity has been assumed.**
Appendix C	Sections 1, 2, 3 and 4 seem to relate to chemical analytical methods more generally, rather than specifically to NAMs – could it be made clear that these sections are included as generic recommendations for completeness (although this is not a comprehensive description of the care that should be taken with respect to chemical analysis; for example, what about the role of analytical confirmation of nominal test item concentrations when dissolved/suspended in test media?)
1812	This sentence is unclear: "If 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 […]" What is meant by "class of chemicals"? A group of chemicals as defined by physical properties, such as physical state (solid, liquid, gas), or ability to form a solution or suspension, viscosity etc. makes sense. However, defining a group of chemicals according to very broad chemical properties (e.g. organic, organometallic, metallic) may not always mean that an applicability domain has been appropriately defined (leading to unreasonable assumptions as to what substances are out of the domain), whereas defining classes of chemicals according to the presence of certain organic functional groups (OFGs) is an overly granular approach that is likely to encourage an unnecessarily stringent interpretation of what is, and is not, within the applicability domain. It is not reasonable, or necessary, to cover every possible OFG in the reference chemicals set.
1824	Suggested change in bold: "At least one positive control **(ideally as identified for the species of interest, see Section 3.2.2 Reference Data**) should be part of the assay development".

Thank you for the consideration of our comments. We look forward to the publication of the final guidance document.

Sincerely,

Laura Alvarez

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