Presentation Abstracts and Background Materials

SCIENTIFIC ADVISORY COMMITTEE ON ALTERNATIVE TOXICOLOGICAL METHODS

Session Ia: Five Years Into ICCVAM Strategic Roadmap: Full Replacement of the Acute Tox 6-Pack
Thursday, September 21, 2023

Roadmap Implementation Plans: Update on Each of the 6-Pack Endpoints, How Close are We to Replacement?

Presenter: Dr. Dave Allen, Inotiv

The 2018 ICCVAM publication, “A Strategic Roadmap for Establishing New Approaches to Evaluate the Safety of Chemicals and Medical Products in the United States” provides a conceptual framework promoting better communication between agencies and test method developers and more flexibility in how confidence is established. ICCVAM developed detailed implementation plans to address roadmap goals, tailored to specific toxicological endpoints of concern. This talk will provide an overview of ICCVAM and NICEATM’s progress in developing, evaluating, and implementing alternatives to animal testing, with specific emphasis on efforts to replace the “six-pack” of acute toxicity tests, which includes acute systemic toxicity by the oral, dermal, and inhalation routes; skin and eye irritation; and skin sensitization. The current status of available alternatives and remaining challenges to complete replacement of animal use for these endpoints will be discussed.

Background

- Karmaus et al. Evaluation of variability across rat acute oral systemic toxicity studies. https://doi.org/10.1093/toxsci/kfac042.
- Strickland et al. Application of defined approaches to assess skin sensitization potency of isothiazolinone compounds. https://doi.org/10.1089/aivt.2022.0014.
- Strickland et al. Application of defined approaches for skin sensitization to agrochemical products. https://doi.org/10.3389/ftox.2022.852856.
- Clippinger et al. Human-relevant approaches to assess eye corrosion/irritation potential of agrochemical formulations. https://doi.org/10.1080/15569527.2021.1910291.
- Hamm et al. Performance of the GHS Mixtures Equation for predicting acute oral toxicity. https://doi.org/10.1016/j.yrtph.2021.105007.
- Mansouri et al. CATMoS: Collaborative Acute Toxicity Modeling Suite. https://doi.org/10.1289/ehp8495.
- Rooney et al. Analysis of variability in the rabbit skin irritation assay. https://doi.org/10.1016/j.yrtph.2021.104920.
- EPA. Guidance for Waiving Acute Dermal Toxicity Tests for Pesticide Technical Chemicals & Supporting Retrospective Analysis. EPA 705-G-2020-3722 (Docket ID: EPA-HQ-OPP-2016-0093). https://www.epa.gov/sites/default/files/2021-01/documents/guidance-for-waiving-acute-dermal-toxicity.pdf.

Modernizing the Acute Toxicity 'Six-Pack' for U.S. EPA's Office of Chemical Safety and Pollution Prevention

Presenter: Dr. Monique Perron, U.S. Environmental Protection Agency

The U.S. Environmental Protection Agency's Office of Chemical Safety and Pollution Prevention (OCSPP) is prioritizing efforts to reduce and replace vertebrate animal testing with established alternative methods that increase rigor in the agency's assessments and remain fully protective of human health and the environment. OCSPP has been collaborating with federal partners and stakeholders to develop and implement new approach methods (NAMs) for the acute toxicity "six-pack" to reduce and replace the traditional animal testing methods prescribed for the "six-pack". This includes continued participation in national and international activities to develop and gain acceptance for defined approaches for skin sensitization, including the Organisation for Economic Co-operation and Development (OECD). A defined approach for testing antimicrobial cleaning products for eye irritation potential was also developed for the Office of Pesticides Program (OPP). There is ongoing work to utilize several OECD *in vitro* test guidelines to develop additional defined approaches and frameworks that can be used to evaluate eye irritation potential of pesticide formulations and new chemical substances under the Toxic Substances Control Act (TSCA) taking into consideration biological understanding, the human relevance of available assays, physicochemical properties of test substances, and/or other relevant irritation data. Similar efforts are underway to determine the applicability of multiple *in vitro* and *ex vivo* tests to identify skin irritation hazard. For acute oral, a recent analysis of the Global Harmonized System for Classification and Labeling (GHS) Mixtures Equation demonstrated the utility of the Mixtures Equation for predicting acute oral toxicity hazard categories of pesticide formulations, particularly for those with lower potency. Additionally, continued work with the Collaborative Acute Toxicity Modeling Suite (CATMoS) to predict acute oral toxicity has shown promising results, particularly for non-toxic chemicals.

Background

- OECD. Guideline no. 497: defined approaches on skin sensitization. https://www.oecd-ilibrary.org/environment/guideline-no-497-defined-approaches-on-skin-sensitisation_b92879a4-en.
- EPA. Use of an alternate testing framework for classification of eye irritation potential for EPA pesticide products. https://www.epa.gov/sites/default/files/2015-05/documents/eye_policy2015update.pdf.
- Clippinger et al. Human-relevant approaches to assess eye corrosion/irritation potential of agrochemical formulations. https://doi.org/10.1080/15569527.2021.1910291.
- Hamm et al. Performance of the GHS Mixtures Equation for predicting acute oral toxicity. https://doi.org/10.1016/j.yrtph.2021.105007.
- EPA. Strategic Vision for Adopting New Approach Methodologies (wbpage). https://www.epa.gov/pesticide-science-and-assessing-pesticide-risks/strategic-vision-adopting-new-approach-methodologies.

Beyond the 6-Pack: Strategic Roadmap Future Priorities?

Presenter: Dr. Nicole Kleinstreuer, NTP Interagency Center for Evaluation of Alternative Toxicological Methods (NICEATM)

To conclude projects on the acute toxicity 6-pack, and shift NICEATM and ICCVAM focus and resources towards other priorities and activities, emphasis first needs to be placed on what is required to achieve full 6-pack replacement. This goes well beyond scientific advances and accomplishments, which have largely been realized, and extends to implementation and harmonization strategies to ensure broad recognition of the readiness of NAMs for various regulatory

contexts of use. Public/private partnerships will be key to providing education and training for regulators and regulated industry alike, support data sharing and data generation efforts to extend beyond single chemicals to mixtures applications, and further the development of international guidelines for global acceptance. Looking past acute endpoints to facilitate future planning and resource allocation, agency- and endpoint-specific needs must be well understood to prioritize NAM development and validation and leverage the enormous potential of NAMs in improving environmental health protection across diverse populations.

Session Ib: Five Years Into ICCVAM Strategic Roadmap: Evolution of Validation
Thursday, September 21, 2023

ICCVAM Validation Work Group Report

Presenter: Dr. John Gordon, U.S. Consumer Product Safety Commission

Major points that will be covered:

- Update ICCVAM report on development and validation of alternative methods (i.e., "Validation and Regulatory Acceptance of Toxicological Test Methods" originally published in 1997).
- This process includes but is not limited to:
    - Developing and evaluating flexible practices that consider context of use to build confidence in new methods.
    - Seeking to align validation approaches such that international harmonization can be supported.
    - Pointing to other well-established validation documents for more context-specific information regarding validation (e.g., GIVIMP, OECD GD34, GD69 on QSAR Validation, FDA Guidance for Industry).
    - Evaluating guidance document(s) outlining best practices.
    - Examining best practices for quality and quality systems development.
- "Living document" that will be updated as needed.
- Will serve as a resource for U.S. federal agencies and stakeholders seeking to establish confidence in new approaches that address the 3Rs.
- We may, depending on timing, be able to discuss the public comments received, although this point is tentative and will only occur if we have the public comments in before SACATM and in time for agency clearance.

Background

- ICCVAM Validation Workgroup. Validaton, Qualification, and Regulatory Acceptance of New Approach Methodologies (draft). https://ntp.niehs.nih.gov/sites/default/files/2023-08/VWG%20Report%20Draft_for%20public%20comment_08Aug2023.pdf.
- Comments received on the Validation Workgroup Document. https://ntp.niehs.nih.gov/go/ICCVAM-submit.

International Harmonization and Global Considerations: Organizational and Financial Aspects of Validation Studies

Presenter: Dr. Anne Gourmelon, Organisation for Economic Cooperation and Development

OECD Member countries established the system of Mutual Acceptance of Data (MAD), composed of two pillars to ensure trustable data are generated and can be re-used beyond borders to satisfy diverse regulatory needs. The Test Guidelines and the Good Laboratory Practice combined together ensure MAD. In that context, member countries and industry support validated methods as the basis to develop Test Guidelines. With the ethical pressure to test chemicals without using animals, progress in science, knowledge and techniques, it is feasible to develop Test Guidelines that make use of modern technologies with limited to no animal usage.

In December 2022, the OECD Working Party of the National Coordinators of the Test Guidelines Programme held a workshop on how to adapt the Programme for the uptake of emerging science and technologies. Six main themes were addressed, including incentivizing participation in validation studies. With the rapid development of technologies and the need to maintain relevant high quality, robust and reproducible methods, there is interest in understanding where efficiencies might be gained in the processes of method validation.

Various work streams are pursued to modernize validation processes and gain efficiency. One of these is the update of Guidance Document 34 on the Validation and International Acceptance of Test Methods for Hazard Assessment. Another workstream is the understanding of stakeholders' interests in validation, including the operational and financial considerations. The landscape of key players (e.g. test developers, validation platforms and bodies, funding bodies, testing service providers, etc.) is evolving and there might be opportunities to make better use of limited resources and gain time in the operational aspects, without losing quality and trustability of outputs.

The Working Party of the National Coordinators of the Test Guidelines Programme will launch a stakeholders' survey in Q3 2023 to collect input on operational and financial considerations around validation processes. Survey responses will be analysed by a steering group to prepare the programme of a stakeholders' workshop in December 2023.

My presentation will provide further details on this workstream, the survey questions, and possibly a preliminary overview of responses collected and an outline of the stakeholders'workshop and objective.

Background

- OECD. Report on the WNT Workshop: How to Prepare the Test Guidelines Programme for Emerging Technologies. https://one.oecd.org/document/ENV/CBC/MONO(2023)14/en/pdf.

International Harmonization and Global Considerations: Update on GD 34 and ICATM Position

Presenter: Dr. Valerie Zuang, European Commission, Joint Research Centre

The International Cooperation on Alternative Test Methods (ICATM) organised a workshop on "Validation towards internationally recognised standards for regulatory application" on 23-24 October 2018.

At that workshop, the ICATM partners discussed various aspects concerning the principles and process of validation of alternative methods and approaches and the lessons learned from past validation studies. It also reflected on how to evolve validation practice to increase efficiency, encourage more innovation and flexibility in study design and accommodate scientific progress.

An action that resulted from the workshop was to start to check, on a voluntary basis, if and what parts of OECD GD 34 on the validation and international acceptance of new or updated test methods for hazard could be updated.

Four years later, the European Commission's (EC) Joint Research Centre submitted a new project proposal to the OECD with concrete proposals for updating GD 34. The US and the NL joined the EC as co-leads.

On 26 September 2023, during a satellite meeting of the 12th World Congress on Alternatives and Animal Use in the Life Sciences, the ICATM partners met again to develop a collective ICATM position on the key elements necessary for the validation and establishment of confidence in new approach methodologies that should be included in an updated OECD GD 34. The comments that had been provided by ICATM partners during the workshop on validation in 2018, as well as the project proposal on revising GD 34 submitted to the OECD in 2022, served as starting points for the agenda and the associated discussions. The main points discussed were the following:

- Defined Approaches/IATA considerations and how to approach their validation.
- Technical validation and acceptance of mechanistic methods.

- Assessment of relevance (e.g., appropriate benchmark for comparison/performance assessment) and fitness for purpose.
- Any practical considerations.

My presentation will provide information on the status of the OECD project on the update of GD 34, as well as focus on the outcome of the ICATM discussion at the ICATM satellite meeting of WC12.

Background

- OECD. Publications on Testing and Assessment. https://www.oecd.org/chemicalsafety/testing/series-testing-assessment-publications-number.htm.