Presentation Abstracts and Background Materials

SCIENTIFIC ADVISORY COMMITTEE ON ALTERNATIVE TOXICOLOGICAL METHODS

Introduction
Wednesday, November 4, 2026

From Innovation to Public Health Impact: ORIVA's Strategy for Advancing Human-Based Science

Presenter: Dr. Warren Casey, National Institutes of Health (NIH)

The NIH Office of Research Innovation, Validation, and Application (ORIVA) provides a timely opportunity to make human-based science a durable part of the biomedical and public health enterprise. By coordinating NIH-wide efforts to develop, validate, increase access to, and promote adoption of approaches such as organoids, tissue chips, computational models, and real-world human data, ORIVA can help ensure that methods are selected based on their fitness for purpose, human relevance, reproducibility, and translational value. This presentation will outline ORIVA's role as a hub for NIH-wide and cross-agency coordination and regulatory translation; its relationship to the ongoing alternative-methods work of (D)NICEATM and ICCVAM; and the practical infrastructure needed to move promising methods from development to credible, routine use. Particular emphasis will be placed on validation frameworks, workforce training, stakeholder partnerships, and evidence pathways that build regulatory confidence, advance public health protection, and reduce reliance on animal studies where scientifically appropriate.

Background

- Press release, "NIH to prioritize human-based research technologies": NIH, April 29, 2025. https://www.nih.gov/news-events/news-releases/nih-prioritize-human-based-research-technologies
- Press release, "NIH makes major investments to advance human-based research infrastructure and technologies": NIH, September 21, 2026. https://www.nih.gov/news-events/news-releases/nih-makes-major-investments-advance-human-based-research-infrastructure-technologies
- Website: Office of Research Innovation, Validation, and Application (ORIVA). https://dpcpsi.nih.gov/oriva
- Website: ICCVAM 2024-2025 Biennial Progress Report. https://ntp.niehs.nih.gov/iccvamreport/2025

Session I: International Harmonization Around Validation
Wednesday, November 4, 2026

OECD GD34: Guidance Document on the Validation and International Acceptance of New or Updated Test Methods for Hazard Assessment

Presenter: Dr. João Barroso, European Commission Joint Research Centre

This presentation will provide a concise overview of the ongoing revision of the Organisation for Economic Cooperation and Development's "Guidance Document on the Validation and International Acceptance of New or Updated Test Methods for Hazard Assessment" (OECD GD34) and the motivations behind the update. Topics will include readiness criteria, revised validation concepts, training and transferability expectations, updated approaches to reproducibility assessment, and new considerations for defined approaches. The talk will demonstrate how the revised guidance reflects the evolving landscape of new approach methodology (NAM) development and regulatory implementation.

Background

- OECD. 2005. Guidance Document on the Validation and International Acceptance of New or Updated Test Methods for Hazard Assessment. OECD Series on Testing and Assessment Number 34. Paris: Organisation for Economic Co-operation and Development. https://www.oecd-ilibrary.org/environment/guidance-document-on-the-validation-and-international-acceptance-of-new-or-updated-test-methods-for-hazard-assessment_e1f1244b-en.
- ICCVAM. 2024. Validation, Qualification, and Regulatory Acceptance of New Approach Methodologies. Research Triangle Park (NC): National Institute of Environmental Health Sciences. https://doi.org/10.22427/NICEATM-2.

Enhancing the Regulatory Value of In Vitro Mechanistic Data Through Internationally Harmonized Reporting Templates

Presenter: Dr. Ingrid Langezaal, European Commission Joint Research Centre

Internationally approved templates for the reporting of mechanistic information facilitate the exchange of data between organizations and their re-use for various purposes.

In 2020, OECD Harmonised Template 201 for the reporting of “intermediate effects / mechanistic information” (OHT 201) was updated to include in vitro method elements as described in OECD’s good in vitro method practices. Furthermore, the description of the biological effect measured by the method was aligned with the way it is done for adverse outcome pathways by allocating a “process,” an “object,” and an “action.” In 2024, the U.S. Environmental Protection Agency (EPA; Michelle Angrish) proposed to develop OECD harmonized templates specifically for the reporting of research data, to implement the recommendations from the OECD guidance document on the generation, use and reporting of research data for regulatory assessments. EPA, together with the European Commission Joint Research Centre are developing OECD harmonized templates for the reporting of in vivo and mechanistic (ex vivo, in vitro, in chemico, in silico) research data.

During the presentation an update will be given about the current uses and further developments of the reporting templates relevant for intermediate effects / mechanistic information.

Background

- Webpage: OECD Harmonised Template 201: Intermediate Effects. https://www.oecd.org/en/topics/assessment-of-chemicals/harmonised-templates-intermediate-effects.html
- Carnesecchi E, Langezaal I, Browne P, Batista-Leite S, Campia I, Coecke S, Dagallier B, Deceuninck P, Dorne JLCM, Tarazona JV, Le Goff F, Leinala E, Morath S, Munn S, Richardson J, Paini A, Wittwehr C. 2025. OECD harmonised template 201: Structuring and reporting mechanistic information to foster the integration of new approach methodologies for hazard and risk assessment of chemicals. Reg Toxicol Phamacol 142:105426. https://doi.org/10.1016/j.yrtph.2023.105426.
- OECD. 2025. Guidance Document on the Generation, Reporting and Use of Research Data for Regulatory Assessments, OECD Series on Testing and Assessment, No. 417, OECD Publishing, Paris. https://doi.org/10.1787/8d49ec1d-en.

New Estimates for In Vivo Test Guideline Data Replicability for Deciding on Acceptability of Nonanimal Methods-based Approaches

Presenter: Dr. Martin Paparella, Innsbruck Medical University

The replicability of in vivo test guideline (TG) data is often uncertain due to their historically limited validation. This situation is changing due to the increasing availability of freely accessible databases which include metadata for data

quality pruning. Reviews for knowledge about the replicability of TG-like data were recently published for human toxicology [1-4] and ecotoxicology [5]. Useful replicability estimates include data from all in vivo TG-conforming protocol variants. These may provide benchmarks for (eco)toxicological data replicability which is currently accepted by regulators.

Where quantitative estimates for in vivo TG data replicability are available, they may now be used to set benchmarks for (a) NAMs data replicability and (b) NAMs based protection levels which shall be similar or better compared to in vivo TG-based approaches. This principle, to avoid overfitting, is well recognized for quantitative structure–activity relationship (QSAR) model development, but practically not comprehensively applied, neither for QSARs nor for experimental NAMs, due to limited availability of estimates for reference TG-data replicability.

Quantitative replicability estimates are uncertain as such. They depend on metadata availability, use of the latter for specific quality filters and the resulting amount of data for specified protocols which are usually evolving over time. Several uncertainties in replicability estimates usually cannot be resolved and need qualitative consideration for deciding on acceptability of any NAM based approach.

The presentation will summarize knowledge about in vivo TGs replicability based on recent publications [1-5] and indicate uncertainties in such replicability estimates with a focus on genotoxicity and acute fish toxicity TGs. The potential use of this quantitative and qualitative knowledge for deciding on the acceptability of NAM based approaches will be indicated.

Citations

1. Karmaus AL, Kreutz AL, Oyetade O, Friedman KP, Paparella M, Reinke EN, Allen D, Hogberg HT, Kleinstreuer NC. 2026. Perspectives on variability of in vivo toxicology studies: considerations for next-generation toxicology. Front Toxicol. https://doi.org/10.3389/ftox.2026.1778353.
2. Raitano G, Pronk TE, Battistelli CL, Bossa C, Hatzi V, Nikolopoulou D, Chaideftou E, Tcheremenskaia O, Adam-Guillermin C, Audebert M, Mertens B, Paparella M. 2026. Variability and uncertainty of data from genotoxicity test guidelines: what we know and why it matters. Arch Toxicol 100:1713-1734. https://doi.org/10.1007/s00204-025-04277-9.
3. Paparella M, Bennekou SH, Bal-Price A. 2020. An analysis of the limitations and uncertainties of in vivo developmental neurotoxicity testing and assessment to identify the potential for alternative approaches. Reprod Toxicol 96:327-336. https://doi.org/10.1016/j.reprotox.2020.08.002.
4. Paparella M, Colacci A, Jacobs MN. 2017. Uncertainties of testing methods: What do we (want to) know about carcinogenicity? ALTEX 34(2):235-252. https://doi.org/10.14573/altex.1608281.
5. Schur C, Paparella M, Fassbender C, Stoddart G, Baity Jesi M, Schirmer K. 2025. Daphnids can safeguard the use of alternative bioassays to the acute fish toxicity test: A focus on neurotoxicity. Environ Toxicol Chem 44(9):2635-2647. https://doi.org/10.1093/etojnl/vgaf014.

Overview of Validation Studies Being Supported by NICEATM

Presenter: Dr. Helena Hoegberg, Acting Director NICEATM, on Detail to ORIVA, DPCPSI, NIH OD

NICEATM's move to the NIH Office of Research Innovation, Validation, and Application (ORIVA) has strengthened our coordination of method validation and qualification. To assess whether nominated methods are ready for validation, NICEATM has developed a method readiness questionnaire covering various relevant factors, such as context of use, biological relevance, technical characterization, and performance. Challenges in providing readiness information have highlighted the need for greater support during the transition from method development to validation.

The electrophilic allergen screening assay (EASA), which addresses hapten formation (Key Event 1) in skin sensitization, completed a NICEATM coordinated validation study of 20 chemicals. Results suggested that EASA may be a useful non-animal method for identifying skin sensitizers. EASA was added to the 2024 OECD workplan for inclusion in Test Guideline 442C. Following expert review, additional testing was required and is underway with NICEATM support.

NICEATM/ICCVAM is supporting validation of a reconstructed human respiratory epithelium (RHRE) method led by the PETA Science Consortium International. Related projects include comparing signaling pathways of chemicals tested with both GARDskin and GARDair to evaluate differences between dermal and respiratory sensitization.

In 2025, NICEATM coordinated the transfer of a human thyroid microtissue assay from EPA to three laboratories, with additional testing now underway. Its three-dimensional, primary-cell format introduces donor variability and material limitations that require a flexible approach to validation.

Background

- Reinke EN, Petersen EJ, Gordon JD, Uhl R, Adams VH, Rua D, Johnson VJ, Burleson GR, Strickland J, Gutierrez R, Sprankle CS, LaPratt T, Lehmann DM, Germolec DR, Kleinstreuer NC. 2026. Validation of the Electrophilic Allergen Screening Assay for Detection of Key Event 1 of the Skin Sensitization Adverse Outcome Pathway. Toxics 14(6):511. https://doi.org/10.3390/toxics14060511.
- Deisenroth C, Foley B, Rogers E, Kühnlenz J, Chen W, Feshuk M, Bianchi E, McKenna J, Hill BN, Larocca J, LeCluyse EL, Kleinstreuer N, Thomas RS, Hogberg HT. 2025. Interlaboratory validation of the human thyroid microtissue assay. Toxicol Sci 209(2):kfaf166. https://doi.org/10.1093/toxsci/kfaf166.

SACATM Discussion

Lead Discussants: Dr. Antonio Baines, North Carolina Central University; Dr. Kristini Miles, Miles Consulting, LLC

Discussion Questions

- NICEATM's current validation/qualification efforts focus on developmental neurotoxicity, thyroid disruption, and respiratory/dermal sensitization endpoints. What other endpoints lacking adequately validated NAMs could be prioritized?
- When analyzing the predictive capacity of a method, how can we address challenges such as a lack of reference data or high variability inherent to the animal models?
- As models become more complex, each additional element becomes a potential source of variability. Discuss elements that have potential for contributing to model variability (e.g., genetic variation among cell donors). How can we account for the variability introduced by these elements?
- What challenges do you envision in the broad implementation of standardized data templates like OHT 201 for reporting validation studies? How do you suggest these be addressed?