Interagency Coordinating Committee on the Validation of Alternative Methods

Presentation Abstracts and Background Materials

SCIENTIFIC ADVISORY COMMITTEE ON ALTERNATIVE TOXICOLOGICAL METHODS

Session III: Integrated Approaches to Testing and Assessment (IATA) Case Studies
Thursday, November 5, 2026

OECD IATA Frameworks Program

Presenter: Dr. Patience Browne, Organization for Economic Co-operation and Development (OECD)

The OECD IATA Case Studies project was started in 2014 to provide examples of how NAMs could be used in combination to address a regulatory question and increase uptake in OECD Test Guidelines. A decade of reviewing and finalizing approximately 40 case studies focused on various endpoints considerably advanced the collective understanding of the opportunities and challenges of IATAs applied to regulatory contexts. The review process led to the development and update of guidance and best practices related topics, such as how to: use AOPs to build IATAs, assess the scientific validity of types of NAMs, report NAM data and models, physiologically based kinetic modelling, and improve data gap filling. In addition, the collection of multiple case studies addressing a common endpoint (e.g. developmental neurotoxicity, endocrine disruption, systemic toxicity) provided an opportunity to distill lessons learned from the collective review of the group. Despite the advances and experiences gained, the reuse, adaptation, and implementation of IATAs remained limited.

To increase the potential of IATAs to be reused, updated, modified or fixed (i.e. as defined approaches (DAs)), the IATA Framework was proposed in 2024. The IATA Framework concept was intended to be an evolutionary step, introducing a modular and standardized structure that enables approaches to be more easily reviewed, adapted, updated, and ultimately fixed as DAs when appropriate. The specific modules included in the IATA Framework are determined by the problem formulation, and the workflow can be reused and easily modified, adding/subtracting new modules to address a new problem formulation, along with a revised data interpretation procedure. After gaining some experience using the new IATA Framework Template, additional documents were drafted to support IATA authors and reviewers. The IATA Framework Guidance is mapped to each section of the Framework Template and instructs authors on the types of information and level of detail to include in each section. Similarly, the IATA Assessment Framework, modelled after the QSAR Assessment Framework (OECD, 2024), is also mapped to the Framework Template. The IATA Assessment Framework guides reviewers with elements to assess for each section of the Framework Template and criteria to evaluate if each element is met. Thus, the IATA Assessment Framework is a systematic approach for determining if the IATA is suitable for application to the [new] regulatory context and determining sources of uncertainty and confidence.

The intention of the new IATA Framework is to increase the standardization and transparency of all aspects of IATA development and review, clearly document where expert judgement is used, facilitate iterative refinement and fixing the flexible elements of IATAs, creating a path between IATAs and DAs. Only DAs that are validated following procedures agreed by the OECD Test Guidelines Programme and included in OECD Test Guidelines are covered by the Mutual Acceptance of Data. However, there is a possibility of developing IATAs or non-guideline DAs that are not validated following OECD processes, but nonetheless have gone through expert peer-review, thorough consideration of the fitness for use in regulatory decision making, and are associated with high confidence.

Background

- OECD. 2024. (Q)SAR Assessment Framework: Guidance for the regulatory assessment of (Quantitative) Structure Activity Relationship models and predictions, Second Edition, OECD Series on Testing and Assessment, No. 405, OECD Publishing, Paris. https://doi.org/10.1787/bbdac345-en.

Systemic Toxicity IATA Case Studies Project

Presenter: Ms. Kristie Sullivan, Institute for in Vitro Sciences (IIVS)

Assessment of systemic toxicity has historically employed the use of repeat dose animal tests to derive a point of departure (PoD) for further consideration in quantitative risk assessment to inform potential risk management activities. However, the advent of new approach methodology (NAM)-based frameworks introduced human-relevant, exposure-based and mechanism-informed approaches to chemical risk assessment, moving beyond strictly hypothesis-driven models. These frameworks allow data from diverse assays to inform potential biological activity without requiring a predefined mode of action. An integrated approach that encompasses a suite of fit for purpose in silico and in vitro information sources could be used to derive a NAM-based PoD value that is protective of potential in vivo systemic effects. Such PoD values may serve as an alternative to a repeated dose animal study, such as a 28-day or 90-day study under certain decision contexts.

Incorporating exposure predictions into this framework allows for the calculation of bioactivity:exposure ratios (BERs), providing a decision support tool that parallels the current in vivo paradigm of using margin of safety/exposure (MoS/MoE) coupled with relevant uncertainty factors to determine risk. Several published examples of NAM-based approaches for PoD estimation suggest that different assays and toxicokinetic methods for estimation can be employed to obtain a human-health protective and relevant PoD and BER.

During the construction of this IATA, over 30 NAM approaches for PoD and BER estimation were reviewed, and common elements identified for the development of a NAM-based PoD. The common elements have been described as individual modules. The incorporation of exposure predictions enhances the relevance and interpretability of these methods by linking bioactivity to estimated internal doses thereby supporting a more comprehensive assessment of systemic toxicity. A generalized framework for applying such an approach is accompanied by a table of potential information sources to be used within an IATA and two case studies demonstrating the application of the IATA.

Background

- Paul Friedman K, Thomas RS, Wambaugh JF, Harrill JA, Judson RS, Shafer TJ, Williams AJ, Lee JYJ, Loo LH, Gagné M, Long AS, Barton-Maclaren TS, Whelan M, Bouhifd M, Rasenberg M, Simanainen U, Sobanski T. 2025. Integration of new approach methods for the assessment of data-poor chemicals. Toxicol Sci 205(1):74-105. https://doi.org/10.1093/toxsci/kfaf019.
- Baltazar MT, Cable S, Cubberley R, Hewitt NJ, Houghton J, Kukic P, Li H, Malcomber S, Nicol B, Pendlington R, Punt A, Reynolds J, Scott S, Spriggs S, Dent MP. 2025. Making safety decisions for a sunscreen active ingredient using next-generation risk assessment: Benzophenone-4 case study. ALTEX 42(3):511-530. https://doi.org/10.14573/altex.2501201.

Development of an IATA Framework for Respiratory Sensitization Under the OECD Hazard Assessment Programme

Presenter: Dr. Ashley Peppriel, U.S Environmental Protection Agency (EPA)

Respiratory sensitization is an allergic reaction that manifests through the respiratory tract. In humans, the clinical manifestation of sensitization of the respiratory tract and subsequent re-exposure leads to asthma, allergic rhinitis, rhino-conjunctivitis, and sinusitis. It has been estimated that 15-25% of all asthma cases have been associated with occupational onset, underscoring the importance of this hazard to regulatory stakeholders. Despite this, there are currently no regulatory-accepted test methods or approaches for hazard identification, classification, or quantitative risk assessment for chemical respiratory sensitizers. However, substantial progress in non-animal models and increased understanding of the adverse outcome pathway for respiratory sensitization has facilitated the development of IATA that the Organisation for Economic Co-operation and Development (OECD) is currently considering. This presentation will provide an overview of the recent and ongoing work from the OECD Working Party on Hazard Assessment (WPHA) towards the development of an IATA Framework for Respiratory Sensitisation. The ultimate goal of the WPHA group is to progress the regulatory acceptance of approaches for assessing respiratory sensitization by developing an IATA framework (as well as defined approaches) for respiratory sensitization under the Hazard Assessment Programme starting with methods described in the detailed review paper on respiratory sensitization. Subgoals will be described during the presentation.

Background

- OECD. 2026. Detailed Review Paper on Respiratory Sensitization. https://www.oecd.org/en/publications/detailed-review-paper-on-respiratory-sensitisation_b5258246-en.html

Progressing Towards a Defined Approach for Developmental Neurotoxicity

Presenters: Dr. Anna Kreutz and Dr. Mary Jacketti, General Dynamic Information Technology (GDIT)

Over the past several decades, the developmental neurotoxicity in vitro battery (DNT-IVB) was developed to facilitate increased testing for DNT in a faster, cheaper and more human-relevant approach that offers mechanistic insights. While the OECD endorsed the document “Initial Recommendations on Evaluation of Data from the Developmental Neurotoxicity (DNT) In-Vitro Testing Battery” in 2023, regulatory implementation of these assays has remained limited to a handful of weight of evidence case examples. To increase regulatory uptake, data from the DNT-IVB have been incorporated into IATA, weight-of-evidence evaluations, and regulatory decision-making across different problem formulations. Currently, DNT is one of the regulatory endpoints included in the OECD IATA framework project that aims to facilitate progress from flexible IATAs towards a structured, rule-based defined approach (DA) for DNT. Several challenges remain in developing a DA for DNT, including few substances with robust human and/or animal DNT data available for benchmarking, incomplete biological and mechanistic coverage of the current DNT-IVB,and a limited number of DNT adverse outcome pathways that can support building confidence in the data. Moreover, the feasibility of running the entire 17 assay battery, and how to translate data from the DNT-IVB into human relevant doses pose additional hurdles for regulatory application.

We have supported efforts to address each of these challenges. Some of our recent work includes development of an in vitro to in vivo extrapolation approach tailored towards specific DNT considerations that may support development of a DNT DA through integration of exposure information. To evaluate whether the number of assays in the current DNT-IVB can be reduced to enable a more feasible testing approach, we are now also developing a deep neural network (DNN) framework to identify the most informative assays within the battery. As a proof-of-concept, we are focusing on neurite outgrowth (NOG), represented by five assays that constitute the largest assay group targeting a specific biological process within the DNT-IVB. NOG assay data were extracted from the EPA ToxCast database and curated using

standardized chemical identifiers. Assay overlap and chemical diversity were characterized using predicted functional use categories, ClassyFire classifications, and 213 RDKit molecular descriptors. The curated dataset contained 351 unique chemicals, with individual assay coverage ranging from 71 to 306 chemicals. Pairwise overlap ranged from 42 to 253 chemicals, while only 31 chemicals were tested across all five assays. To leverage these partially observed data, the DNN integrates chemical descriptors with available assay responses in a multi-task framework to reconstruct complete assay profiles from partial measurements. Conventional machine learning models were developed as performance benchmarks. By reconstructing complete NOG profiles, this framework will identify a tiered, reduced set of assays that preserves predictive performance while minimizing experimental burden. Through these efforts we aim to help progress DNT testing towards a DA for regulatory application.

Background

- Kreutz A, Chang X, Lawless M, Proença S, Schaller S, Kleinstreuer N, Hogberg HT. 2026. Comparison of physiologically based pharmacokinetic modeling platforms for developmental neurotoxicity in vitro to in vivo extrapolation. Toxicol Sci 209(2):kfaf147. https://doi.org/10.1093/toxsci/kfaf147.
- OECD. 2025. Workshop Proceedings on Critical Innovations in Pesticides Safety Testing and Chemical Risk Assessment for Developmental Neurotoxicity (DNT). OECD Series on Testing and Assessment, No 412, OECD Environment, Health and Safety, Paris, https://one.oecd.org/oPicial-document/ENV/CBC/MONO(2025)10/en.
- Sachana M, Hogberg HT, Mangas I. 2026. From concept to regulation: OECD's role in the development of the DNT in vitro battery. Front Toxicol 8:1774469. https://doi.org/10.3389/ftox.2026.1774469.

Additional References

- Blum J, Masjosthusmann S, Bartmann K, Bendt F, Dolde X, Dönmez A, Förster N, Holzer AK, Hübenthal U, Keßel HE, Kilic S, Klose J, Pahl M, Stürzl LC, Mangas I, Terron A, Crofton KM, Scholze M, Mosig A, Leist M, Fritsche E. 2023. Establishment of a human cell-based in vitro battery to assess developmental neurotoxicity hazard of chemicals. Chemosphere 311(Pt 2):137035. https://doi.org/10.1016/j.chemosphere.2022.137035.
- Dobreniecki S, Mendez E, Lowit A, Freudenrich TM, Wallace K, Carpenter A, Wetmore BA, Kreutz A, Korol-Bexell E, Friedman KP, Shafer TJ. 2022. Integration of toxicodynamic and toxicokinetic new approach methods into a weight-of-evidence analysis for pesticide developmental neurotoxicity assessment: A case-study with DL- and L-glufosinate. Regul Toxicol Pharmacol 131:105167. https://doi.org/10.1016/j.yrtph.2022.105167.
- Hall LA, Hsieh JH, Marvel SW, Behl M, Fritsche E, Koch K, Kreutz A, Leist M, Muriana A, Shafer TJ, Stanko JP, Sills RC, Hogberg HT, McPherson CA. 2026. Prioritizing chemicals for developmental neurotoxicity by integrating data from a new approach methods (NAMs) battery covering key cellular events in neurodevelopment. Neurotoxicology 115:103485. https://doi.org/10.1016/j.neuro.2026.103485.
- Kreutz A, Oyetade OB, Chang X, Hsieh JH, Behl M, Allen DG, Kleinstreuer NC, Hogberg HT. 2024. Integrated approach for testing and assessment for developmental neurotoxicity (DNT) to prioritize aromatic organophosphorus flame retardants. Toxics 12(6):437. https://doi.org/10.3390/toxics12060437.
- OECD. 2023. Initial Recommendations on Evaluation of Data from the Developmental Neurotoxicity (DNT) In-Vitro Testing Battery. OECD Series on Testing and Assessment, No. 377, OECD Publishing, Paris, https://doi.org/10.1787/91964ef3-en.

SACATM Discussion

Lead Discussants: Dr. Patricia Silveyra, Indiana University Bloomington; Dr. Corie Ellison, Procter and Gamble; Dr. Nathan Price, Buck Institute for Research on Aging

Discussion Questions

- IATAs lay the groundwork for development of DAs. How would you propose overcoming the following shortcomings to build confidence in both IATAs and the eventual DAs that are developed: complex AOP networks, lack of an AOP, lack of reference data, incomplete assay coverage of key events within an AOP?

- For the DNT IVB and data integration effort using a computational model like a generative adversarial network (GAN), is this a reasonable approach when applied to multiple assays? What pitfalls might you envision from this approach?
- What other endpoints could be considered to support the development of IATAs and DAs?