Organisation for Economic Co-operation and Development

ENV/CBC/MONO(2025)23

Unclassified

English - Or. English

9 January 2026

ENVIRONMENT DIRECTORATE

CHEMICALS AND BIOTECHNOLOGY COMMITTEE

Report on Considerations from Case Studies on Integrated Approaches for Testing and Assessment (IATA): Tenth Review Cycle (2024)

Series on Testing and Assessment No. 423

JT03579182

Please cite this publication as:

OECD (2025), *Report on Considerations from Case Studies on Integrated Approaches for Testing and Assessment (IATA): Tenth Review Cycle (2024)*, Series on Testing and Assessment No. 423, OECD Environment, Health and Safety, Paris, https://one.oecd.org/document/ENV/CBC/MONO(2025)23/en/pdf.

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This publication was developed in the IOMC context. The contents do not necessarily reflect the views or stated policies of individual IOMC Participating Organizations.

The Inter-Organisation Programme for the Sound Management of Chemicals (IOMC) was established in 1995 following recommendations made by the 1992 UN Conference on Environment and Development to strengthen co-operation and increase international co-ordination in the field of chemical safety. The Participating Organisations are FAO, ILO, UNDP, UNEP, UNIDO, UNITAR, WHO, World Bank, Basel, Rotterdam and Stockholm Conventions and OECD. The purpose of the IOMC is to promote co-ordination of the policies and activities pursued by the Participating Organisations, jointly or separately, to achieve the sound management of chemicals in relation to human health and the environment.

Foreword

Using New Approach Methods (NAMs) for assessing the safety of chemicals has increased globally as these methods have been demonstrated to be less expensive, more reproducible, more relevant for predicting effects on target species (i.e., humans), and reduce the number of animals used in toxicity testing. In addition, NAMs can address mechanistic endpoints that were not testable or not known to be involved in toxicity pathways when older tests were developed. These methods are generally faster and higher throughput, representing a substantial increase in efficiency and modernization of toxicity testing.

The Organisation for Economic Co-operation and Development (OECD) Member Countries, in partnership with stakeholders, has developed guidance documents and tools for the use of NAMs which include *in silico*, *in chemico*, and *in vitro* methods, as well as *in vivo* methods that support the "3Rs" principles to reduce, refine, and replace animal tests. To relate NAMs to *in vivo* guidelines tests that historically were used for chemical risk assessment, the OECD also developed guidance on developing Adverse Outcome Pathways (AOPs) that can support mechanism-based NAMs that predict adverse effects observed in animals and populations. However, the biological coverage of NAMs is often limited, and therefore, may not be one-for-one replacements for *in vivo* test data, particularly for complex endpoints. Thus, there is a need to develop NAM-based approaches that rely on more than one method to expand the chemical and biological domain of applicability.

Integrated Approaches for Testing and Assessment (IATAs) are frameworks for using methods in combination for assessing the safety of chemicals. IATAs begin with problem formulation and document the information sources, data integration procedure, and any expert decisions. IATAs may be developed using AOPs, though this is not a requirement. There is a need to demonstrate the practical applicability of these methods/tools for various aspects of regulatory decision-making by showing how IATAs can be used across jurisdictions.

The objective of the IATA Case Study Project (CSP) is to share experiences using NAMs by developing CSs, which illustrate examples of chemical assessments that are designed to address regulatory decision contexts. The CSs are reviewed on an annual cycle and discussed with experts who provide input on the technical and implementation aspects.

This document reports the learnings and lessons from reviewing two CSs submitted in the 2024 tenth review cycle of the IATA CSP. The topics discussed in this document include each case study's strongest aspects and uncertainties. In addition, from the collective review of all IATA CSs submitted to date, the IATA CSP and the WPHA have discussed the new IATA framework template to increase the reuse and application of existing CSs or approaches used in the CSs.

These CSs illustrate examples of using NAMs and their publication as OECD monographs does not indicate acceptance of these methodologies for regulatory purposes across OECD countries. In addition, these CSs should not be interpreted as an official regulatory decision made by the authoring Member Countries.

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Abbreviations

AOP	Adverse Outcome Pathway
BMD	Benchmark dose
CLP	Classification, Labelling and Packaging
CoCAP	Cooperative Chemicals Assessment Programme
CS	Case Study
CSP	Case Study Project
DA	Defined Approach
DAL	Defined approach liquid
DASF	Defined approach surfactants
DASS	Defined Approaches on Skin Sensitisation
DIP	Data interpretation procedure
ECHA	European Chemicals Agency
EFSA	European Food Safety Authority
ERC2	Ecological Risk Classification Approach for organic substances, version 2
GHS	Globally Harmonized System of Classification and Labelling of Chemicals
G2P-SCAN	Genes-to-Pathways Species Conservation Analysis
HRAC	Herbicide Resistance Action Committee
IATA	Integrated Approaches for Testing and Assessment
ITS	Integrated Testing Strategy
LoE	Lines of Evidence
MIE	Molecular initiating events
MoA	Mode of Action
MoE	Margin of exposure
MoIE	Margin of internal exposure
NAM	New Approach Method
NM	Nanomaterial
OECD	Organisation for Economic Co-operation and Development
PARC	Partnership for the Assessment of Risks from Chemicals
PBK	Physiologically Based Kinetic. PBK is synonymous of physiology-based pharmacokinetic (PBPK), physiologically-based biokinetic (PBBK) and physiologically-based toxicokinetic (PBTK).
pMoA	Pesticide mode of action
PoD	Point of departure
PoP	Persistent organic pollutants
QAF	(Q)SAR Assessment Framework
QSAR	Quantitative Structure Activity Relationship
ReCAAP	Rethinking chronic toxicity and carcinogenicity assessment for agrochemicals project
RhCE	Reconstructed human Cornea-like Epithelium
(Q)SAR	(Quantitative) Structure-Activity Relationship
SeqAPASS	Sequence Alignment to Predict Across Species Susceptibility
SOE	Strength of Evidence

TG	Test Guideline
TSCA	Toxic Substances Control Act
UN	United Nations
US EPA	U.S. Environmental Protection Agency
UVCB	Substances of Unknown or Variable composition, Complex reaction products or Biological materials
WHO	World Health Organization
WoE	Weight of Evidence

1 Introduction

The use of New Approach Methods (NAMs) is expanding globally as biotechnology has increased the availability of reliable and relevant methods as alternatives to animal tests and chemical regulations reduce or prohibit the use of animals for chemical safety testing. To support this shift, the Organisation for Economic and Cooperative Development (OECD), in collaboration with stakeholders, has developed guidance on using various NAMs as stand-alone approaches and as a part of Integrated Approaches for Testing and Assessment (IATA). The OECD also developed guidance on the Adverse Outcome Pathways (AOPs) concept that supports the development of predictive NAMs, which also may be used to guide the development of IATAs. There is a need to investigate the practical applicability of these approaches for various aspects of regulatory decision-making using case studies (CSs) in OECD Member Countries.

The objectives of the Cooperative Chemicals Assessment Programme (CoCAP)[1] were revised in 2014 to provide a forum for sharing experiences developing and applying IATAs. The IATA Case Studies Project[2] (IATA CSP) was launched in 2015 as a follow-up activity focused on scientific exchange on the application of novel approaches for assessing chemical safety. The project's objective is to increase experiences using IATAs by developing CSs, which constitute examples of approaches that are fit for regulatory use. The outcome of these shared experiences helps to create a common understanding of using NAMs, identify considerations, and provide guidance for using IATA approaches that stem from these CSs.

CSs are submitted and reviewed annually by experts from Member Countries and other stakeholders. The results of the reviews are discussed in an annual meeting of the IATA CSP Team. The discussion includes the strongest aspects, uncertainties, areas for further guidance, and possible uses of each CS in a regulatory context. Following each review cycle, approved studies are published, along with a Considerations document capturing the learnings and lessons stemming from CSs in the annual cycle, and of all CSs reviewed to date. The past nine review cycles of the project (2015-2024) included 37 CSs and nine Consideration documents, which have all been published on the OECD website[2]. These CSs are illustrative examples, and their publication as OECD monographs in the OECD Series on Testing and Assessment does not indicate the approaches described in the IATAs are accepted for regulatory purposes across OECD Member Countries. In addition, these CSs should not be interpreted as official regulatory decisions made by the authoring Member Countries.

Three CSs were submitted and reviewed in the tenth review cycle (2024). Following initial feedback on one of the case studies (CS 2024-01), the authors determined that resources were not available to address the comments from the reviewers and the Case Study was withdrawn from the current review cycle. This document briefly summarises the two CS finalized in the tenth review cycle, along with the learnings and lessons.

[1] OECD, Cooperative Chemicals Assessment Programme (CoCAP). See ENV/JM/HA(2010)10.

[2] OECD, IATA Case Studies Project. https://www.oecd.org/en/topics/sub-issues/assessment-of-chemicals/integrated-approaches-to-testing-and-assessment.html

2 Learnings and Lessons

2.1. Learnings from the Tenth Review Cycle

This section describes the learnings gained through the review of the two CSs submitted in the 2024 tenth review cycle (Table B.1). Four topics, described in the subsections below, were selected as learnings from this review cycle during the expert discussion that took place at the tenth OECD IATA CSP meeting on 19 November 2024.

2.1.1. How to tailor the IATA to other geographies/jurisdictions (CS 2024-2)

The Ecological Risk Classification Approach for organic substances, version 2 (ERC2) was developed to address prioritization needs and used in the Canadian regulatory context under the Canadian Environmental Protection Act, 1999. One of the key features that should be highlighted in CS 2024-2 is the flexibility of the workflow to accommodate specific regulatory contexts.

While the scoring and weighting in CS 2024-2 reflects the Canadian context, the intent is that these thresholds can be adjusted to a jurisdictional need. The rules-based approach of workflows in the Ecological Risk Classification for organic substances, version 2 (ERC2) is flexible, where decision rules can be altered to accommodate a specific regulatory context. For example, the confidence scoring rules for specific data elements of an ERC2 descriptor can be changed to give different weighting to the data elements (e.g., in silico data) such that the maximum confidence score for the descriptor aligns with a jurisdictional position on the relevance and sufficiency of the data for the descriptor. Likewise, the numerical thresholds used by Canada to assign categorical hazard, exposure or risk outcomes (e.g., ‘low’, ‘moderate’ or ‘high’) can also be altered depending on context and level of acceptable uncertainty. These considerations can also be applied to confidence and severity workflows. Greater detail on rationales for scoring rules can be found in the ERC2 Science Approach document (ECCC 2022), cited and linked in the ERC2 IATA report.

While the specific risk-based Canadian prioritization system may not be directly applicable to other OECD jurisdictions, the hazard workflows and the general concepts of data integration, weighting, confidence, and severity scoring may still be applicable. To foster discussions on how to make use of the wealth of information included in IATAs and move forward, it is important to explore the practical applicability of these methods and tools for various aspects of regulatory decision-making. Building on case studies and assessment experiences across jurisdictions can help create a common understanding and generate valuable considerations.

2.1.2. How data streams are combined; how additional data could be added (CS2024-2, CS2024-3)

The integration of diverse data streams and the ability to incorporate new data are central to the flexibility and adaptability of IATA frameworks. Case studies in CS2024-2 and CS2024-3 illustrate how these principles are applied in practice, showcasing both technical implementation and strategic considerations.

In CS2024-2, due to the flexibility of ERC, users can add new parameter(s) as additional data metrics for a descriptor in both the hazard and exposure profiles. For each iteration of ERC2 (e.g., as noted for v2.3 in the IATA ERC2 case study report), new models and data can be added or removed—for example, to avoid duplication across endpoints. Proprietary models are often among the most powerful in silico tools available for a given property or endpoint; however, their inclusion may limit publication options. Public versions may need to exclude proprietary models and data. The OECD and ECHA have planned to include ERC2 hazard profile workflows in future version 4.9 of the QSAR Toolbox as a profiler, which will enable automation and integration of data streams available in the Toolbox. At ECCC, efforts to combine and automate data streams for individual descriptors and profiles are ongoing using the open-source Konstanz Information Miner software (KNIME).

In CS2024-3, the authors provided a complete and detailed guide in ANNEX II to walk through each step of the combined approaches (Page 15: Guide to the Combined Use of NAMs: SeqAPASS and G2P-SCAN), along with input and output files for each component of the protocol and workflow (ANNEX II README.doc and ANNEX II Data.xlsx). The team intends to develop further case studies to demonstrate how additional data can be incorporated through new case studies (New ANNEX II) and additional tools (New ANNEX I). Our intent as the IATA team is to continue demonstrating how additional data can be effectively integrated to enhance predictions of chemical susceptibility across species. While adding new data is a complex task—dependent on the nature and quality of the data—we aim to build upon this foundational IATA proposal and show how other approaches and data streams can be incorporated.

These case studies demonstrate that IATA frameworks are not static but are designed to evolve with scientific advancements and regulatory needs. They enable the integration of new data and tools by ensuring that the rationale, source, and impact of the data are clearly recorded. They also provide detailed descriptions of how data from different models and sources are compiled, as well as the outputs of the tool (e.g., example chemicals), thereby supporting more robust, transparent, and context-specific decision-making across jurisdictions.

2.1.3. How to deal with contradictory results [btw SeqAPASS and G2P-SCAN] (CS2024-3).

CS2024-3 describes how to use complementary bioinformatics tools to evaluate the conservation of biology across species and how to address potentially contradictory results.

The SeqAPASS tool and G2P-SCAN are more complementary than comparative, as they evaluate different aspects of biological conservation. G2P-SCAN focuses on extrapolation from humans to six specified model species—rat (Rattus norvegicus), mouse (Mus musculus), zebrafish (Danio rerio), fruit fly (Drosophila melanogaster), nematode (Caenorhabditis elegans), and budding yeast (Saccharomyces cerevisiae)—across biological pathways. In contrast, SeqAPASS enables extrapolation from any species to all other species with available protein sequence information, based on known chemical–protein interactions. The only area where contradictory results might arise is in the detection of ortholog candidates, as the two tools use different algorithms for ortholog identification. Moreover, orthologs are used differently: SeqAPASS uses functional similarity to determine binary susceptibility calls (“yes” or “no”) for each species, while G2P-SCAN evaluates pathway-level conservation across a fixed set of species. Any discrepancies in ortholog detection are unlikely to significantly affect the overall interpretation. In fact,

agreement between the tools on ortholog identification for the six G2P-SCAN species can reinforce confidence in the results. SeqAPASS, which evaluates hundreds or thousands of species, is not meaningfully impacted by a lack of consensus for this smaller subset.

While both tools aim to support cross-species extrapolation of chemical susceptibility, they operate at different biological scales and use distinct methodologies. As a result, some divergence in outputs may occur. However, this case study highlights the importance of understanding the methodological differences and intended applications of each tool when interpreting results. Rather than undermining confidence, such divergence can be seen as an opportunity to strengthen the overall weight of evidence through complementary perspectives.

2.1.4. Inclusion of 'tiers' to determine if enough information is available to make decisions (CS2024-3).

The concept of incorporating 'tiers' within the IATA framework allows for a structured evaluation of whether sufficient information is available to support decision-making, depending on the intended regulatory application and the strength of evidence provided by each approach.

In CS2024-3, each approach described in ANNEX I provides information that can be applied to decision making, however, combining approaches adds pathway breadth and species depth. The idea is to bring together the approaches to strengthen confidence for biological conservation that can be used to predict chemical susceptibility and add multiple lines of evidence for making predictions.

This tiered perspective ensures that the integration of multiple tools not only enhances scientific robustness but also provides a flexible, scalable framework for applying IATA in diverse regulatory contexts.

2.2. Topics identified for further guidance development from IATA CSs reviewed

Since 2021, the OECD IATA CSP and the WPHA have discussed how to apply lessons learned from previous case studies (CSs). The main goals were to build on past experience to improve confidence and usability, and to reuse elements from earlier CSs. To support this, the Secretariat developed the IATA Framework Template (Annex D), which promotes the reuse of existing case studies and approaches, helping to save time and resources in developing and reviewing new CSs. CS2024-3 is the second case study to use this template, following CS2023-1.

The IATA CSP further discussed the template during the 10th OECD IATA CSP meeting on 19 November 2024. The updated template is currently under review and is expected to be published in 2025. The IATA Framework Template (IFT) outlines a process for combining multiple information sources, including NAMs, and also serves as a bridge between traditional IATAs and Defined Approaches (DAs). It is designed to be flexible and easy to reuse—for example, to assess additional chemicals, incorporate new data, or address different regulatory questions. This approach moves away from a "one-and-done" model and reduces the effort needed to update or reuse existing IATAs. While the IFT aims to be globally applicable and scientifically robust, the specific problem formulation may vary depending on the regulatory context (e.g., GHS classification or exposure-based risk assessment).

During the 10th OECD IATA CSP meeting on 19 November 2024, the OECD IATA CSP members also discussed and emphasized the importance of the weight of evidence and uncertainties as additional key topics for the further guidance development, other than those identified in CS2024-2 and CS 2024-3. Uncertainties are inherent at every stage of IATA and can arise from any elements of IATA including data quality, methodological choices and integration process. These uncertainties must be clearly characterized, documented, and communicated to ensure the credibility and transparency of the assessment. The weight of evidence as a systematic approach considers all available information to

support regulatory decisions and helps manage uncertainty by integrating diverse data sources and highlighting where evidence is strong or weak, guiding how much weight to assign to each data stream. Member of the CSP also noted that the summary of how different regulatory authorities conducted weight of evidence in CS 2023-3 was a helpful addition and could be added to the table of topic for additional guidance and further elaborated (see Table 2.1).

Over the ten review cycles, the considerations documents have identified priorities for further guidance. There is not an intention to address all these topics in OECD Guidance Documents, but rather, to note that a potential need was identified. In addition, activities have been undertaken to address some of these topics (e.g. Guidance Document on Characterization, Validation and Reporting of PBK models for Regulatory Purposes (OECD, 2021b)). In 2023, the IATA CSP team and the WPHA were asked to consider which topics were high/medium/low priories, and which may be addressed in other document under development or recently completed. In addition, the specific items identified in the case study review have been reorganized into general topics.

The IATA CSP group suggested, during their 10th meeting in November 2024, some reorganization of topics and to consider this a "living document" that could be revised, as well as act as a driving force for developing new guidance. The OECD Secretariat is considering how this could be done. The results are summarized in Table 2.1.

Table 2.1. Additional topics for the development of further guidance

Areas for the development of further guidance	STATUS (H/ML)*
SCIENTIFIC RATIONALE	
Building hypotheses based on MoA/AOP	H Some subtopics may be addressed in other activities
BIOLOGICAL COVERAGE/DOMAIN OF IATA	
Understanding the adequacy of the level of biological coverage when combinations of non-animal methods are used	H; but not clear if this can be generalized beyond case-by-case
How to define applicability domain when multiple data streams are combined	H
Coverage of key events (KEs) in AOP based testing strategy	L May be too soon for general guidance Some experience gained from IATA Framework examples
How to include data on/predictors for metabolism when building IATAs according to the defined purpose. Assessment of metabolism *in vitro* with varying degrees of uncertainty	L/M/H
Tips on using non-endorsed AOPs regarding documentation/uncertainty/terminology	L No good quality control for non-endorsed AOPs, would be difficult to develop guidance
Guidance / Guideline on *in vitro* (comparative) biotransformation	M/H
DATA INTEGRATION	
How to integrate NAM data e.g. integrating multiple data streams, combining *in vitro* and computational information sources, linking to mechanistic relevance, deriving integrated conclusions, how to define applicability domain	H Leverage work from DASS and case studies
Guidance on how to develop ITS and data interpretation procedures (DIP)	M Might be too soon for general guidance
Combining approaches/methodologies for predicting bioaccumulation	L Addressed in recent IATA Case study; also ongoing work on Bioaccumulation elsewhere
Integrating (Q)SAR predictions, including when to use consensus modelling or not	L* Recent revision to QAF address this
Comparative weight of evidence across authorities	Recent addition to topics, following example from CS 2023-3 Table 5.

Areas for the development of further guidance	STATUS (H/ML)*
DATA INTERPRETATION	
Decision logic for low/no toxicity predictions	L/M
The application, interpretation and limitations of the Bayesian Network analysis in the quantitative assessment of the WoE	L/H May be addressed in SARA-ICE DASS model in TGP
How to describe the rationale for justification of the benchmark dose (BMD) and PoD used	M
UNCERTAINTY	
Uncertainty Analysis and harmonized uncertainty assessment	H
How uncertainties impact on overall conclusion	M/H
How to define acceptable uncertainty	H (especially for NEG outcomes) Addressed to some degree in OECD GD on WoE
Uncertainty framework (Overall uncertainty in the assessment resulting from the combined uncertainties of the different IATA components and data types)	H
GROUPING AND READ-ACROSS	
Hypothesis for category formation that includes the use of omics data	L* Partially addressed in updated Guidance on Grouping of Chemicals and project on CG-ARM
Definition of analogue/category boundaries	L* Partially addressed in updated Guidance on Grouping of Chemicals
Describing scope and context for read-across	L* Partially addressed in updated Guidance on Grouping of Chemicals
What is needed to address biological read-across	L* Partially addressed in updated Guidance on Grouping of Chemicals
Defining boundaries based on- phys/chem properties, toxicokinetic, toxicodynamic, bioavailability and metabolism, or nanomaterials-specific parameters.	L* Partially addressed in updated Guidance on Grouping of Chemicals
Justification of data gap filling	L* Partially addressed in updated Guidance on Grouping of Chemicals
Guidance for when *in vitro* data could be further generated to support read-across	L* Partially addressed in updated Guidance on Grouping of Chemicals
Reporting of uncertainty of read-across (e.g. Ranking of uncertainty vs descriptive analysis/ quantitative vs qualitative analysis)	L* Partially addressed in updated Guidance on Grouping of Chemicals *
PBK/HTTK/IVIVE	
The extrapolation from the *in vitro* POD via such as IVIVE and HTTK modelling.	H May be addressed in upcoming PBK Guidance
Guidance for evaluating the reliability/robustness of data including toxicokinetic/ toxicodynamic (TK/TD) data • Similarity of metabolic pathways • Whether differences in the structure of target chemicals would have any significant impact on the metabolic pathway When should information on metabolites be included?	L Addressed in GD 331; may be further extrapolated in upcoming PBK Guidance
Guidance for use of HTS and HTTK assays	M/H
EXPOSURE	
Exposure route, including guidance on route to route extrapolation	M/H Also consider the uncertainty component
Rationale for the choice of an acceptable *in vitro*-based MoIE	L/H May be difficult to generalize across regulatory sectors/frameworks/jurisdictions
Guidance for reporting from exposure simulation models (e.g. environmental concentrations)	L

Areas for the development of further guidance	STATUS (H/ML)*
BENCHMARKING/CONFIDENCE BUILDING	
Establishing a list of chemicals (comprising data rich chemicals with various MoAs) to be used as standards for NAM validation	L/M/H Could be by method-by-method, in collaboration with research projects (e.g. PARC); consider existing databases (e.g. DASS, ICE)
Tools or approaches for building confidence when available reference chemicals are limited (e.g. absence of 'moderate' reference chemicals; absence of reference data for new endpoint, etc.)	H
REPORTING	
Considerations for justifying focus of an IATA (e.g. choosing 'major' effect vs 'minor' effect); providing explanation why a certain effect is considered the most relevant (toxicological response observed at a lower dose), while others are minor (occurring at a higher dose)	L: Partially addressed in updated Guidance on Grouping of Chemicals * H: Not only relevant to read-across (H)
Guidance for describing NAM data in the context of IATA case studies	L* Addressed by IATA Framework and various reporting formats (e.g. omics)?
Reporting interpretation, also linked to specific NAMs	L* Addressed by IATA Framework and various reporting formats (e.g. omics)?
Reporting of (Q)SAR prediction results	L Addressed by QAF
Guidance on use or reporting new approach methods (chem-informatics tools, HTS, HTTK assays; docking/modeling approaches)	M/H
APPLICATION AND REGULATORY USE	
The application of machine learning and AI approaches in a regulatory setting.	M Limited experience in IATA CSP; other groups working in this area
The justification of the selection and use of a specific DA	L Done on a case-by-case basis
Guidance on developing prioritisation scheme based on IATA	L Done on a case-by-case basis
GUIDANCE FOR SPECIFICT TYPES OF NAMs	
Guidance for evaluating ToxCast data	L: Guidance available from ToxCast/US
Guidance for use and reporting of results of HTS and HTTK assays	M/H Reporting addressed in OHT 201, GD 211, etc.?
OTHER	
UVCBs, multi-constituents coverage (composition coverage, methodology and other)	M/H
Level of detail needed in case studies according to the defined purpose	L Done on a case-by-case basis
Guidance on the interpretation of NM-related data	L

H/M/L: high/medium/low ranking by IATA Case Studies Project Team and WPHA in 2023 survey.

*Pending guidance to be reviewed to determine if the topic is adequately addressed.

3 Conclusion

Two CSs were reviewed in the tenth review cycle of the project in 2024. Four consideration topics from the tenth review cycle are discussed in this document.

- How to tailor the IATA to other geographies/jurisdictions (CS 2024-2)
- How data streams are combined; how additional data could be added (CS2024-2, CS2024-3)
- How to deal with contradictory results [btw SeqAPASS and G2P-SCAN] (CS2024-3).
- Inclusion of 'tiers' to determine if enough information is available to make decisions (CS2024-3)

In recent years, the IATA CSP and the WPHA discussed the reuse of IATA CSs. The IATA framework template was developed and used for CS2023-1 and CS 2024-3. Furthermore, the framework template has been made refined to enhance clarity and focus on specific assessment methods and specific endpoints.

In summary, the considerations obtained from the two CSs in the tenth review cycle have provided new knowledge on prioritization of chemicals and the application of combined bioinformatics approaches for cross species extrapolation. These topics have added new insights to existing OECD documents. The findings and insights provide important considerations for the use of NAMs in the context of IATAs.

The CSs reviewed in all review cycles are summarised on the OECD website[3].

[3] OECD, IATA Case Studies Project. https://www.oecd.org/en/topics/sub-issues/assessment-of-chemicals/integrated-approaches-to-testing-and-assessment.html

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Annex A. Questions for authors and reviewers of CSs included in the tenth review cycle.

Seven countries/stakeholders (Australia, Canada, Germany, Japan, the Netherlands, ECHA (The European Chemicals Agency) and OECD) participated to review in the tenth review cycle. The authors used templates to document the CSs on the OECD website[4]. The template for the CSs on read-across was based on the reporting format in the OECD Guidance on Grouping of Chemicals (OECD, 2014a) and an example using read-across in a weight of evidence approach (OECD, 2014b). The general template for IATA CSs was developed to fit CSs with multiple components, such as adverse outcome pathways (AOPs), Mode of Action (MoA), Defined Approaches (DAs), Workflows, and Grouping /Read-Across. The Physiologically Based Kinetic (PBK) template was based on Table 3.1 of the OECD guidance document on the characterisation, validation and reporting of PBK models for regulatory purposes (OECD, 2021b). The templates are continuously updated based on the case study reviews.

Questions were developed to guide the review of CSs and to get feedback from case study authors. The questions for authors and reviewers are also updated based on experiences gained in each review cycle. The questions in the tenth review cycle are indicated below (Table A.1).

[4] OECD, IATA Case Studies Project. https://www.oecd.org/en/topics/sub-issues/assessment-of-chemicals/integrated-approaches-to-testing-and-assessment.html

Table A.1. Guided reviewer questions for tenth (2024) IATA Case Study review cycle

Part I: Guided Questions for Review of CSs	
	Is the purpose of the case study clear?
	Are the justifications presented in the different sections sound? If not, suggest how to improve it.
	Does the case study report template work well? Please indicate if there are topics not covered by the template
Part II: Guided Questions for Review and Consideration Document	
	What are the strongest aspects of the case study?
	What are the dominant and most relevant areas of uncertainty and how do you think they could be reduced? Could their reduction lead to a different conclusion of the case study?
	Are there specific topic areas in the case study that could benefit from the development of further guidance for application or interpretation?
Part III: Guided Questions for Potential Regulatory Acceptance	
	Endpoint/ Scope
	Country/ Agency of reviewer
	Regulatory Need for Chemical/Sector
	Specific Data Requirements for This Endpoint
	Applicable for Reviewer
	If no, are there useful aspects of the case study?
	Is there additional information that would make the IATA applicable?
Part IV: Questions on logistics	
	Are there tools in the case study that you would like the author to demonstrate?
	How long and how many people does it take to review this case study?
	Other comments

The reviewers' comments and the revised CSs were discussed at the tenth meeting of the IATA CSP (19 November 2024), in order to finalise the CSs and summarise the learnings and lessons.

Annex B. Summary of results of the review of CSs included in the tenth review cycle

The two CSs in the tenth review cycle are summarised in Table B.1.

Table B.1. CSs Reviewed in the Tenth Review Cycle (2024)

No.	Title	Endpoint	Purpose of CS	References
2024-2	Case Study on Prioritization of chemicals using the Integrated Approaches for Testing and Assessment (IATA)-based Ecological Risk Classification (ERC) approach, Version 2	Ecotoxicity	To help prioritise substances for further regulatory action including assessment, identify substances with the highest potential to cause adverse effects and those of low concern, and to identify data gaps.	OECD, 2025b
2024-3	Case Studies for the Integrated Approaches for Testing and Assessment in the Application of Combined Bioinformatics Approaches for Cross Species Extrapolation of Toxicity Knowledge to inform Chemical Safety	Cross Species Extrapolation	To combine available bioinformatics tools and databases strategically to address challenges in extrapolating toxicity knowledge across species, creating results that can be used in regulatory decision-making [Schumann et al., 2024].	OECD, 2025c

Annex Section B.1 summarises answers regarding a potential regulatory use of the two CSs from reviewers (Australia, Canada, Germany, Japan, the Netherlands, and the United States). Annex Sections B.2 to B.5 summarise the review results of the two CSs.

B.1 Potential regulatory application of two CSs in 2024 review cycle

Table B.2 and Table B.3 show review results regarding the potential regulatory application replied to by reviewers (Australia, Canada, Germany, the Netherlands, ECHA (The European Chemicals Agency) and OECD).

Table B.2. Potential regulatory application of CS 2024-2

CS 2023-2: Case Study on Prioritization of chemicals using the Integrated Approaches for Testing and Assessment (IATA)-based Ecological Risk Classification (ERC) approach, Version 2

8.1 ENDPOINT/ SCOPE of reviewer's organisation	8.2 COUNTRY/ AGENCY OF REVIEWER	8.3 REGULATORY NEED FOR CHEMICAL/ SECTOR	8.4 ARE THERE ENDPOINT-SPECIFIC DATA REQUIREMENTS FOR The Case study ENDPOINT? IF SO, IS THIS A BARRIER TO USING THIS IATA IN REGULATORY ASSESSMENT?	8.5 APPLICABLE FOR REVIEWER?	8.6 IF NO, ARE THERE USEFUL ASPECTS OF THE CASE STUDY?	8.7 IS THERE ADDITIONAL INFORMATION THAT WOULD MAKE THE IATA APPLICABLE?
Scope: Risk characterisation (environment focussed) **Chemical sector: Industrial chemicals**	Australia/ Department of Climate Change, Energy, the Environment and Water Regulatory sector: Government (environment focussed)	risk assessment of industrial chemicals (environment focussed), scheduling of industrial chemicals (risk management regulatory action)	Not directly. The case study is presented as a prioritisation tool. Various flags can be used in Australia to prioritise chemicals for assessments.	ERC2 may not be used for prioritisation purposes in Australia in its current form because of differences in the weight given to some models and data sources. ERC2 relies heavily on modelled data, for example in the exposure assessment, whereas prioritisation in Australia puts more weight on information on use patterns and emissions. The ERC2 approach is nevertheless innovative and reflective of a long history of leadership by Canada in large scale prioritisation of a national inventory of industrial chemicals. The tool may not be as useful in its current form for risk assessment in Australia as some aspects of risk characterisation in ERC2 are different from requirements in Australia (for example, ERC2 uses the same thresholds for acute EC50 and chronic NOEC, while different thresholds are used in Australia).	Yes, the prioritisation approach is risk-based and considers information from an extensive list of models and databases. It could inform refinements for prioritisation of industrial chemicals for environmental risk assessment in Australia, with further information on how to adapt parameters, scoring systems, etc.	Potentially. The provision of additional guidance as stated above, and demonstration/public availability of the tools mentioned below, would help us re-assess the applicability of the IATA to regulatory needs in Australia.

Table B.3. Potential regulatory application of CS 2024-3

CS 2024-3: Case Studies for the Integrated Approaches for Testing and Assessment in the Application of Combined Bioinformatics Approaches for Cross Species Extrapolation of Toxicity Knowledge to inform Chemical Safety

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Human health: acute toxicity, corrosion/irritation, sensitisation, repeat dose toxicity, genotoxicity, carcinogenicity, reproductive and development toxicity, neurotoxicity, neurodevelopmental toxicity, immunotoxicity, and endocrine effects **Environment: Effects on atmosphere, effects on aquatic life, effects on sediment dwelling life, and endocrine effects/activity** **Scope: Hazard identification, characterisation, and POD** **Chemical sector: Industrial chemicals including chemicals used in cosmetics**	Australia, Australian Industrial Chemicals Introduction Scheme (AICIS) Regulatory sector: Regulatory sector: Industrial chemicals sector. AICIS is a risk proportionate scheme regulating the introduction (manufacture and import) of industrial chemicals in Australia. It conducts risk assessments for chemicals categorised using guidelines published by AICIS as being medium to high risk, which are termed Assessments. Evaluations are proportionate risk assessments of industrial chemicals	MOA, NOAEL, to enable risk assessment. Based on the risks identified make recommendations for safe use. GHS classification	No. Relevant data are considered in AICIS risk assessments, however AOPs and extrapolation across species are not routinely considered in these assessments. There are specific data requirements for chemicals introduced under the Assessed category. For chemicals undergoing an Evaluation there are no specific data requirements and all available and relevant data are considered.	Yes There are potential applications for chemical prioritisation or to provide supplementary information to support risk assessment work.		

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	that are being introduced or used in Australia, or matters related to these chemicals.					
human health hazard and risk assessment **Scope: hazard ID, hazard characterisation, risk assessment** **Chemical sector: pesticide / biocide**	German Federal Institute for Risk Assessment Regulatory sector: consumer health protection	MoA,, CLP/GHS, PoD/TRVs/HBGVs	Not yet, but the use of NAMs has been promoted by ECHA and EFSA to support EU chemicals assessment as additional information in a WoE approach (e.g. endocrine disruption MoA) for human health and the environment.	Partially We consider that the case study is not applicable in the regulatory context in its current form.	The case study has potential as an IATA method, however further validation of the method is needed before it could be applied in a regulatory manner.	Further data validation is needed to strengthen the IATA. Pesticides and their metabolites as examples would help the applicability to our assessments, but we acknowledge that their chemical structure is usually complex and/or their MIE or defined molecular target is mostly unknown. Therefore, they are considered out of the applicability domain for the use of bioinformatics approaches in this IATA.
Risk to aquatic and terrestrial species in the Environment. **Scope: Chemical risk assessment, Hazard characterization, SVHC identification, Prioritisation** Chemical sector: pesticides, Biocides, Industrial chemicals, Pharmaceuticals	Umweltbundesamt (German Environmental Agency) Regulatory sector: Government	GHS categorization, Risk assessment, Authorization, Restriction	Yes It might be used in a Weight of Evidence context.	If used in a weight of evidence approach it can be used without a big effort. It seems to be scientifically sound. However, without a guide how to apply this framework we cannot directly use it.	Not beyond the concept.	A guidance document how to use the approach or training by the project members might make it applicable.
ECCC: **Endpoint: ecological risk assessment endpoints both acute and chronic, but with a one-health or one-toxicology objective**	ECCC: Endpoint: Scope: prioritization, ecological risk assessment	ECCC: Regulatory need: -NOEL and MOA analysis in prioritization activities and risk	Yes/No No, there are no requirements. However, it could be applicable as part of the weight of evidence	ECCC: Yes/No: Yes, the approaches outlined could potentially be used as a line of evidence in the hazard characterization in ecological risk	ECCC: n/a HC: n/a	ECCC: Training webinars on the tools and further guidance on data generation, interpretation and consideration of uncertainties

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Scope: Prioritization Chemical sector: Federal government; Industrial Chemical risk assessments under the *Canadian Environmental Protection Act, 1999* (CEPA) **HC:** **Endpoint: NOAEL, EC50, LC50** **Scope: Hazard Characterization, POD** **Chemical sector: New substances under the Canadian Environmental Protection Act (CEPA)** **and** **Endpoint: Human health risk assessment endpoints both acute and toxic – requires a POD** **Scope: Prioritization, hazard ID, hazard characterization, POD** **Chemical sector: Existing substances under the CEPA**	Chemical sector: Federal government (Environment and Climate Change Canada) HC: Country: Canada Agency: Health Canada Regulatory Sector: Government HC: Headings on form had to be changed to match question	assessments - Chemical hazard data (MoA, effects end points) and exposure data for chemicals for the purpose of risk evaluation HC: Regulatory need: NOAEL (POD), BMD, EC50, LC50	for hazard characterization in the ecological risk assessment context as it becomes more standardized and adapted in terms of ease of generating data and interpretation. The key barrier is lack of or limited training and knowledge on the use for these tools and data. HC: No	assessment under CEPA. Technical guidance and training would have to be available first. If no……. (Please respond to 8-6 as well) HC: Yes - Toxicity data submitted is for limited species (aquatic and freshwater). Extrapolation to other species would be valuable information to address data gaps. Yes – could potentially be used for rodent data to demonstrate susceptibility in humans		HC: A basic user guidance on a step by step process to use, integrate and interpret the information from the various sources. Training webinars and SOPs

B.2 Review Results for CS2024-2: Case Study on Prioritization of chemicals using the Integrated Approaches for Testing and Assessment (IATA)-based Ecological Risk Classification (ERC) approach, Version 2

The strongest aspects of the case study were identified as follows:

- The prioritization tool, Ecological Risk Classification (ERC) approach, Version 2 enables high-throughput of chemicals in a risk-based approach, considering environmental hazards and exposure.
- The tool integrates various defined approaches including both modelled and experimental data sources, using a confidence scoring system within a consensus and weight-of-evidence approach.
- Hazard assessments are mechanism-based, with models analyzing the ways chemicals exert their toxicity.

The main uncertainties identified for the case study were as follows:

- While the uncertainty of the models is given some weight through confidence scoring and consensus approaches, some in vivo effects are not supported by in silico data and may be the result of an unknown mechanism.
- An alteration of the scoring system may result in different risk characterizations.
- A lack of information on use volumes, end uses and emission patterns for the assessed chemicals in the exposure assessment.
- The possibility of somewhat arbitrary when combining data streams by categorizing measured data and new data sources.

Based on the experience reviewing this case study, the following areas were identified for potential guidance development:

- How the data from different sources were extracted and integrated in ERC2 in practice.
- How to define some parameters and adapt them to other regulatory needs.
- How to include end use and release reduction factors considerations in the exposure assessment.
- How to consider the differences between new experiment data and prediction data and integrate new experiment data into well-established prediction model, if needed.

Overviews of the case study are as follows.

The purpose of the case study is to demonstrate the principles, core science and workflow organic chemicals based on an IATA, called the Ecological Risk Classification Approach for organic substances, version 2 (ERC2), which is developed to address prioritization needs and used in the Canadian regulatory context under the Canadian Environmental Protection Act, 1999.

The intent of ERC2 is to provide a conceptual workflow to classify hazard, exposure and risk outcomes as ‘low’, ‘moderate’ or ‘high’, to indicate level of concern and to facilitate regulatory decision making. ERC2 gathers multiple lines of evidence, including new approach methodologies (NAMs) such as in silico, in chemico, and in vitro data. It also incorporates individually or combines logic rules for the key elements of classification, confidence and severity Moreover, the weight-based approach of ERC2's workflows are flexible, allowing logic rules to be altered to accommodate a specific regulatory context. For example, the

confidence scores and severity score assigned to specific data elements of an ERC2 descriptor, and the numerical thresholds used by Canada to assign categorical hazard, exposure and/or risk outcomes (e.g., 'low', 'moderate' or 'high') can also be altered depending on context and level of acceptable uncertainty by a member country.

In this case study, a group of 15 organic flame retardants (OFRs) with diverse hazard and exposure profiles and 9 non-specific acting chemicals with little or no concern for hazard or exposure classification, available in ERC2 inventory (published as part of the 2022 ERC2 Science Approach document), are used to illustrate the functionality of ERC2 and to demonstrate important aspects of the ERC2 approach. An example of a single substance is presented throughout the report to help with explanations of methodology.

Further information on the case study can be found in (OECD, 2024b).

B.3 Review Results for CS2024-3: Case Studies for the Integrated Approaches for Testing and Assessment in the Application of Combined Bioinformatics Approaches for Cross Species Extrapolation of Toxicity Knowledge to inform Chemical Safety

The strongest aspects of the case study were identified as follows:

- Demonstrating the utility and challenges of the combined complementary bioinformatics methodologies, which is largely demonstrated and publicly available, to help support predictions of chemical toxicity and biological pathway conservation across species with existing biological information.
- Showing how decisions were made on the evidence, with clear delineation of applicability domains, a generalized workflow diagram, and transparency and scientific justification/publications. This enables regulators to challenge the implementation of this approach, which requires considerable expert judgement and extensive user experience over time to gain confidence and familiarity.

The main uncertainties identified for the case study were as follows:

- Understanding the mechanism by which a chemical exerts biological effects is challenging. Different conclusions could be reached depending on the regulatory context and level of acceptable uncertainty.
- The extent of the understanding of a chemical's biological action and which pathways identified by the method are linked to actual AOP data affect conclusions and interpretations.
- Determining the molecular initiating event and other key events in the AOP for any given substance includes uncertainties. Because SeqAPASS does not take into account ADME differences between species, leading to differences in susceptibility. Additionally, there is limited protein/ amino acid sequencing done for any given species
- User error can occur because this IATA goes beyond a simple read-across level of IATA and has some hidden complexities when using the suggested bioinformatics tools.

Based on the experience reviewing this case study, the following areas were identified for potential guidance development:

- Guidance for non-experts in omics

Overviews of the case study are as follows.

This IATA demonstrated the application of two complimentary bioinformatics approaches, Genes-to-Pathways Species Conservation Analysis (G2P-SCAN) and the Sequence Alignment to Predict Across Species Susceptibility (SeqAPASS) tool. It provides a framework for future integration of additional approaches that address toxicokinetic and (additional) toxicodynamic factors influencing species susceptibility, along with three case studies.

These two tool can be combined for the purpose of extrapolating toxicity knowledge across species and evaluating conserved biological pathways across species, through comparisons of relevant molecular and functional data gleaned from adverse outcome pathways (AOPs) to mapped biological pathways. While SeqAPASS allows for the in depth evaluation of the conservation of proteins and further chemical-protein interactions across the diversity of species providing multiple lines of evidence customized to the degree of knowledge that exists for a chemical-protein interaction (sequence and structure), G2P-SCAN can complement SeqAPASS by allowing for a bi-dimensional analysis which looks at the conservation of entire pathways where the input gene/target has been well-annotated in human, despite being applicable to 6 model species. Each approach has significant utility in-of-itself, as described in ANNEX I for SeqAPASS and G2P-SCAN.

Overall, the combined approach adds both pathway breadth and species depth across potentially hundreds of species. This approach is considered to help identify potentially susceptible species, facilitate the design of intelligent testing strategies which can be targeted at data generation in relevant (the most likely susceptible) species only and aimed at maximizing the use of all the available knowledge in decision making.

Please see (OECD, 2024c) for more information on the case study.