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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 modernisation 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 three CSs submitted in the 2023 ninth 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
BAF	Bioaccumulation factors
BCF	Bioconcentration factor
BMF	Biomagnification factors
CLP	Classification, Labelling and Packaging
CoCAP	Cooperative Chemicals Assessment Programme
CS	Case Study
CSP	Case Study Project
DA	Defined Approach
DASF	Defined approach surfactants
ECHA	European Chemicals Agency
EFSA	European Food Safety Authority
GHS	Globally Harmonized System of Classification and Labelling of Chemicals
HRAC	Herbicide Resistance Action Committee
HTTK	High-Throughput Toxicokinetics
IATA	Integrated Approaches for Testing and Assessment
IVIVE	*in Vitro* to i*n Vivo* Extrapolation
LoE	Lowest Observed Adverse Effect Level
LoE	Lines of Evidence
MIE	Molecular initiating events
MoA	Mode of Action
NAM	New Approach Method
NOAEL	No Observed Adverse Effect Level
OECD	Organisation for Economic Co-operation and Development
PBK	Physiologically Based Kinetic. PBK is synonymous of physiology-based pharmacokinetic (PBPK), physiologically-based biokinetic (PBBK) and physiologically-based toxicokinetic (PBTK).
PBT/vPvB	Persistent, bioaccumulative and toxic and very persistent and very bioaccumulative
pMoA	Pesticide mode of action
PoD	Point of departure
PoP	Persistent organic pollutants
PPO	Protoporphyrinogen Oxidase
ReCAAP	Rethinking chronic toxicity and carcinogenicity assessment for agrochemicals project
RhCE	Reconstructed human Cornea-like Epithelium
(Q)SAR	(Quantitative) Structure-Activity Relationship
SOE	Strength of Evidence
STE	Short Time Exposure
TMF	Trophic magnification factors
TG	Test Guideline
TSCA	Toxic Substances Control Act
UDP-GT	Uridine Diphosphate-Glucuronosyltransferase

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
WNT	Working Group of the National Coordinators of the Test Guidelines Programme
WoE	Weight of Evidence
WPHA	Working Party on Hazard Assessment

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 eight review cycles of the project (2015-2022) included 34 CSs and eight Consideration documents, which have all been published on the OECD website (https://www.oecd.org/chemicalsafety/risk-assessment/iata-integrated-approaches-to-testing-and-assessment.htm). 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 reviewed in the ninth review cycle (2023) (Table A B.1). This document briefly summarises each CS, the learnings and lessons in this (ninth) review cycle.

[1] OECD, Cooperative Chemicals Assessment Programme (CoCAP). https://web-archive.oecd.org/2016-10-19/58206-cocap-cooperative-chemicals-assessment-programme.htm

[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 Ninth Review Cycle

This section describes the learnings gained through the review of the three CSs submitted in the 2023 ninth review cycle. In this review cycle, a CS assessed chronic toxicity and carcinogenicity of agrochemicals with Exemplar Case Studies (OECD, 2024a), a CS was the potential eye hazard of surfactants (OECD, 2024b), and a CS was bioaccumulation (OECD, 2024c) (Table A B.1).

Three topics, described in the subsections below, were selected as learnings from this review cycle during the expert discussion that took place at the ninth OECD IATA CSP meeting on 15 November 2023.

The CSs reviewed in all review cycles are summarized in Annex C.

2.1.1. Analogue selection based on (p)MoA/biological response (CS 2023-1)

This subsection focuses on the (pesticide (p)) MoA when selecting the analogue chemicals for the carcinogenicity. CS 2023-1 utilised read across approach to assess the chronic toxicity and carcinogenicity for agrochemicals (Saflufenacil and Spiropidion).

General considerations for evaluation of analogues include an assessment of the structural similarity and similar physical-chemical properties, biochemical processes, and mode (and/or mechanism) of action, or environmental fate (OECD, 2014a). For read-across assessment on common biological/toxicological factors, three types of similarity are most commonly considered; toxicophores, mechanistic plausibility and relevant endpoints, the most important of which is mechanistic plausibility (Schultz, 2015). The CS authors report using commonality in mode of action to support chemical selection for the analogue inclusion for the read-across assessment (e.g., PPO inhibition mode of action for Saflufenacil, ACCase inhibition mode of action for Spiropidion), as well as a structural similarity assessment to further filter the analogue inclusion.

The CS authors mention that for agrochemicals, the selection of appropriate analogues could be based on chemical class, (p)MoA and/or biological effects.

The authors note that when the target substance belongs to a large chemical class, or to a chemical class with a clearly established (p)MoA, these serve as a helpful starting point for determining inclusion – especially if the read-across is used to propose a biological MoA. In the case of non-agrochemicals, where the chemical class and MoA data are not well developed, structural similarities may be more appropriate in the search for analogues. The authors are reminded to report both uncertainties as well as justification for when structural similarity should be considered over the bioactivity or pesticidal MoA in the selection of analogues. Further information regarding uncertainty and lessons identified in conducting read-across are documented in saflufenacil and spiropidion case studies (Table A A.2. and A B.4., and Annex C.).

The approach for the selection of analogue chemicals in the CS was as follows. In the CS, the selection of analogues was first based on similarity in pMoA, then analogues were further considered for inclusion based on structural and biological similarity. The assessment for biological similarity was based on an

analysis of the toxicological profile and physico-chemical data that are publicly available in risk assessments conducted by the United States Environmental Protection Agency (USEPA). Taken together, these similarity assessments contributed to the reliability assessments for analogue inclusion in the chemical read-across.

Saflufenacil

Saflufenacil (target chemical) belongs to the N-phenylimide class (Herbicide Resistance Action Committee (HRAC), 2019) and is a Protoporphyrinogen oxidase (PPO) inhibitor. PPO inhibitors cause an accumulation of protoporphyrinogen and possibly other precursors in the pathway, and an increased concentration of porphyrins in the blood, which is commonly referred to as porphyria.

The CS authors identified at least 29 herbicide active ingredients as PPO inhibitors (HRAC, 2019). A quantitative metric was used to evaluate the relative chemical similarity of these chemicals to saflufenacil, using the GenRA tool (US EPA GenRA[3], 2021).

Six different analogues were then selected from EPA registered PPO inhibitors based on structural and biological similarities to saflufenacil and based on the availability of data. The analogues are from the N-phenylimide class, the thiadizole class, the oxadiazole class, the triazolinone class and the "other" chemical classification (HRAC, 2020).

The pMoA and toxicological MoA (biological effects) are similar in the target chemical. Since the pMoA and biological effects of the analogues were the same as the target chemical, the structural similarity and physical chemical property data are not the main factors to select the analogues in this CS. Common key toxicological effects included markers of porphyria, anaemia and resulting changes in liver, which support that the analogues have the same MoA as that proposed for saflufenacil.

As a result, six analogues were selected by (p)MoA, chemical class and biological effects.

Spiropidion

Spiropidion belongs to the acetyl CoA carboxylase (ACCase) inhibitors, according to the HRAC and IRAC classification schemes. All the ACCase inhibitor herbicides and insecticides share the inhibition of lipid biosynthesis. 23 herbicides and insecticides have been identified as ACCase inhibitor chemicals and consist of four chemical classes: phenylpyrazolin (DENs), cyclohexanedione (DIMs), tetronic and tetramic acid derivatives (TAs/TADs) and the aryloxyphenoxypropionate (FOPs).

Biological similarity is based on pMoA (the ACCase inhibition). For structural similarity, ToxPrints were gathered for all 23 ACCase inhibitors, and 96 of the 729 defined fingerprints were present in one or more ACCase inhibitor. Principal coordinate analysis was conducted based on the binary distance matrix between each ACCase inhibitor, and a clustering analysis was also conducted. All approaches concluded spiropidion is most similar to TAs/TADs class.

Toxicological data included toxicokinetics, acute, subacute, subchronic, chronic/carcinogenicity, genotoxicity, reproductive and development, hormone perturbation, neurotoxicity, immunotoxicity, and mechanistic studies. Publicly available data exist for 17 out of 23 ACCase inhibitors. The differences between the ACCase chemistries, a comparison of the collective structural, mechanistic, biological activity and the similarity across the toxicity points of departure also support the use of the TAs/TADs chemical family as the analogues.

[3] Generalized Read-Across (GenRA) is an algorithmic approach to permit objective and reproducible read-across predictions of in vivo toxicity and in vitro bioactivity. https://www.epa.gov/comptox-tools/generalized-read-across-genra

The thyroid UDP-GT MoA for the analogues and the target chemical is the only common MoA based on an evaluation of the toxicological data sets for all ACCase chemicals. The data for the target chemical support the liver induced UDP-GT thyroid MoA in rats. The data also demonstrate that this MoA does not quantitatively relate to the human hazard/risk assessment due to difference in response between rats and humans.

The validity of analogues was assessed on the basis of similarity such as structure, physicochemical property, toxicokinetic profile, metabolic profile, toxicophore/structural alerts, mechanistic profile (MIE, AOP) and *in vivo* toxicological responses.

As a result, three TAs/TADs ACCase inhibiting insecticides were identified as the most appropriate analogues based on structural similarity, pMoA, biological effects and toxicological endpoints (NOAEL/LOAELs) from the other ACCase inhibitor herbicides.

2.1.2. The applicability of the DA for eye irritation for different classes of surfactants and/or functional group (CS 2023-2)

CS 2023-2 developed a new rule-based Defined Approach (DA) (the Defined Approach for Surfactants (DASF)) to assess eye irritation for three surfactants (liquid, semi-solid and solid chemicals). The DASF is incorporated as Part IV of TG 467 (Alépée et al., 2023, OECD, 2025a). The DASF is based on a combination of the Reconstructed human Cornea-like Epithelium (RhCE) test methods described in OECD Test Guideline (TG) 492 (OECD 2025d) and a modification of the Short Time Exposure (STE) test method, named the $STE^{0.5}$ for surfactants (, currently part of OECD TG 491 (OECD, 2025c)).

'Surfactant' means any substance and/or mixture, which has surface-active properties and which consists of one or more hydrophilic heads and one or more hydrophobic tails of such a nature and size that it is capable of reducing the surface tension of water (< 45 N/m), and of forming spreading or adsorptive monolayers at the water-air interface, and of forming emulsions and/or microemulsions and/or micelles, and of adsorption at water-solid interfaces (as modified by Regulation (EC) No. 648/2004 on detergents).

Surfactants are classified according to the composition of their head and are divided into four classes: non-ionic (no charge), cationic (+ charge), anionic (- charge), and amphoteric (opposite charge). The target three surfactants represent the different classes (cationic, anionic, and non-ionic) from different families (a quaternary ammonium chemical, a fatty alcohol phosphoric acid ester, and a sorbitan ethoxylated fatty acid ester) and include a mono-, a multi-constituent, and a Substances of Unknown or Variable composition, Complex reaction products or Biological materials (UVCB). One liquid and one solid surfactant were tested neat, while a second solid surfactant was tested diluted in saline at concentrations ranging from 0.1% to 10%.. All results predicted by the DASF were the same as United Nations (UN) Globally Harmonized System of Classification and Labelling of Chemicals (GHS) categories derived from the Draize eye test (Table 1).

Table 1. Comparison between UN GHS category and DASF predictions

Chemical	CASRN	Concentration	UN GHS [a]	Prediction DASF [b]	Substance
Ethylhexyl acid phosphate ester	12645-31-7	Neat	Cat. 1	Cat. 1	multi-constituent anionic
Cetylpyridinium bromide	140-72-7	10%	Cat. 1	Cat. 1	mono-constituent cationic surfactant
		6%	Cat. 1	Cat. 1	
		1%	Cat. 2	Cat. 2	
		0.1%	No Cat.	No Cat.	
Tween 80	9005-65-6	Neat	No Cat.	No Cat.	non-ionic UVCB

[a] Barroso et al, 2017 - DRD Supplementary Material 1

[b] The different variations of the DIP come to the same hazard assessment conclusion with a low uncertainty. Source: Table 6 of OECD 2024b

In addition, the performance of the DASF was evaluated for 31 surfactants with Draize eye test data. The set of surfactants assessed with the DASF includes cationic, anionic, non-ionic and amphoteric surfactants from the four different classes. Each class is represented by mono- and multi-constituent or UVCBs. Several families are represented in the set (e.g. alcohol ethoxylates, alkyl sulfates, sulfosuccinates,). A total 47 tests were performed to assess the predictivity of the DASF, since some chemicals were tested at different dilutions. Table 2, Table 3 and Table 4 presented the 47 tests by chemical class, chemical type, and chemical family, respectively with the GHS category derived from the Draize eye test data. Detailed information on the 47 tests is provided in Table 8 of (OECD, 2024b) for detailed information on the 47 tests.

According to Table 4 of (OECD, 2024b), the DASF met the OECD minimum acceptance criteria, 90.9% of Cat. 1 (N=22), 75.0% of Cat. 2 (N=8), and 76.0% of No Cat. (N=17) were correctly predicted. The number of available reference chemicals for *in vivo* Cat. 2 surfactants (N = 8) is small since, following a request sent for additional data, no additional Cat. 2 surfactants could be identified that met predefined requirements. Although the number of Cat. 2 surfactants is low, all chemicals included in these analyses had a high quality Draize eye test and lacked conflicting results when multiple *in vivo* studies were available.

Table 2. The numbers of reference chemicals divided by chemical class.

	Cat.1	Cat.2	No	Total
Cationic	14	4	2	20
Anionic	4	2	4	10
Amphoteric	1	1	-	2
Nonionic	3	1	11	15

Table 3. The numbers of reference chemicals divided by chemical type.

	Cat.1	Cat.2	No	Total
mono-constituent	15	7	6	28
multi-constituent/ UVCB	7	1	11	19

Table 4. The numbers of reference chemicals divided by chemical family.

	Cat.1	Cat.2	No	Total
Quaternary ammonium compound	11	3	-	14
Alkyl pyridinium	3	1	2	6
Octylphenol, ethoxylated	2	1	1	4
Alkyl sulfates	1	-	2	3
Amino acid surfactant	1	1	1	3
Sorbitan ethoxylated fatty acid ester	-	-	3	3
Alcohol ethoxylate	-	-	2	2
Ammonium salt	1	-	-	1
Sulphosuccinates	1	-		1
Fatty alcohol phosphoric acid esters	1	-	-	1
Steroid	-	1	-	1
Sulphobetaine	-	1	-	1
Nonylphenols, ethoxylated with triethanolamine	1	-	-	1
Alkoxylated fatty acids	-	-	1	1
polymeric quaternary ammonium salt of hydroxyethyl cellulose	-	-	1	1
other	-	-	4	4

Source: (OECD, 2024b)

The limitation of the DASF is the same as OECD TG 491 (OECD, 2025b) and TG 492 (OECD, 2025d). The test item of the STE test methods should dissolve or form a stable suspension in a selected solvent for at least five minutes. This may thus limit the DASF applicability domain. There is no technical limitation known for the RChE methods for the evaluation of surfactants. The DASF is not applicable to non-surfactants. Because the reference set for Cat. 2 contains only surfactants tested in dilution, the reliability of a Cat. 2 predictions for neat surfactants is unknown.

Overall, CS 2023-2 conducted the performance test including different classes of surfactants and/or the functional group and confirmed the applicability of the DASF.

2.1.3. How to make the scoring lines of evidence within WoE fit for purpose (e.g. scenarios for scoring and weighting selection) (CS 2023-3).

CS 2023-3 provides an example of scoring lines of evidence. Through the evaluation of this CS, this subsection summarises the elements of scoring system to be considered. While there are some quantitative and qualitative approaches on scoring system, respectively, as described by Linkov et al. (2009) (e.g. listing evidence, scoring, and indexing), the OECD Weight of Evidence (WoE) document (OECD, 2019d) does not conclude which is the best approach for weighting lines of evidence.

Scoring approaches are highly context-dependent, and therefore there is no single approach that can be applied to all scenarios, whepther regulatory or non-regulatory. In addition, there are advantages and disadvantages of quantitative and qualitative approaches to scoring within a WoE approach, which are outlined in the OECD Guidance on WoE Section 3.5 (OECD 2019d).

It is important to recognise that there are various steps within a WoE approach that involve some sort of scoring or ranking, and the number and range of scoring bins may vary. Within the four main phases of the WoE approach used in CS 2023-3 (Figure 1), there are different types of scoring approaches used. Importantly, the most critical part of any approach is that it is transparent and well supported, whether qualitative or quantitative.

Stage 1: The **relevance** of each line of evidence (LoE) is assigned within the problem formulation step. In OECD (2018j) the termp “relevance” describes whether a procedure is meaningful and useful for a particular purpose (i.e., “fit for purpose”). In this CS, the term relevance thus refers to the appropriateness or degree of correspondence of evidence to the question(s) outlined in the problem formulation.

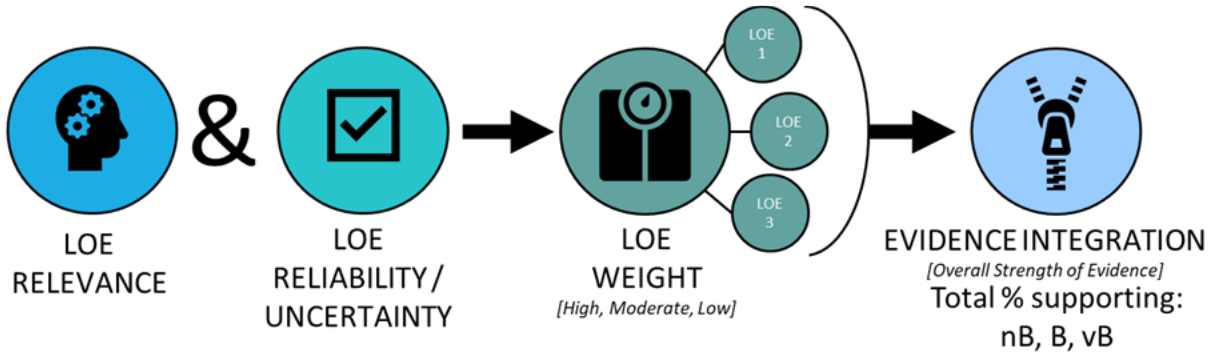
Stage 2: The **reliability / uncertainty** of each LoE is evaluated. All data, whether measured or predicted, are inherently uncertain. Some sources of uncertainty include deviation from standardised protocols (contributing to variability and/or error), insufficient reporting of supporting data to understand how key parameters influence the results or marginalise the reproducibility of the results, experimental or technical errors, or limited statistical significance. The overarching objective for developing and applying data quality assessment methods is to identify uncertainty and guide the selection and application of the best available information providing confidence in the decision. Data reliability assessment methods cannot guarantee that all uncertainty in the data have been identified - uncertainty in the data will remain; however, relevant data quality issues can be identified, considered, and transparently communicated to stakeholders to support the decision. Data quality scoring approaches are necessarily fit for purpose and tailored to the specific data / study types. Ideally data reliability scoring methods are developed from existing OECD TG that are available specific to the generation of the LoE. For example, in CS 2023-3 most of the data reliability criteria and scoring methods are derived directly from OECD TG.

Stage 3: The overall **weight** of each LoE is assigned. In the case of this CS, a qualitative approach was used within this step. In this step, outcomes of the relevance and reliability evaluations are summarised and used to assign a qualitative weight to each LoE used to address the defined problem statement(s). Again, a categorical approach (e.g., low, medium, high) is suggested, noting that this is a judgment-based

(normative) process. The goal of this step is to transparently communicate how weight was assigned to various LoE to address the problem statements. The number of weight categories is also subjective and can be selected according to the context of the problem (e.g., degree of categorical or numerical resolution, such as 3 or 5 or 10 categories). It should be noted that the user may wish to report all LoE including those that may not be directly relevant to the hypothesis so that reviewers can transparently see that they were considered. Determining a categorical or numerical weight outcome in this step is situational. The assigned weight is a function of equal consideration given to relevance and reliability; such that the given weights reflect a combination of these criteria. While guidance and examples are provided in CS 2023-3 and OECD guidance (OECD, 2019d) to judge the level of reliability and relevance for weighing bioaccumulation epvidence, such approaches will also be context dependent and could be developed by individual agencies or groups.

Stage 4: Evidence is **integrated.** The last stage of CS 2023-3 is focused on evidence integration and reporting which includes an evaluation of the strength of the evidence. This step is designed to evaluate the overall strength of evidence (SoE), or consistency, across all the data elements (LoE). This process provides a means to evaluate the extent of variability among the LoE in terms of assessment outcomes and identify possible outliers within a particular dataset. When data are more consistent, confidence is increased and can allow for values of central tendency or a selected percentile be used to represent multiple results (e.g., multiple bioaccumulation model predictions). The overall SoE can be determined by the frequency of specific categorization outcomes based on all LoE and is expressed as a percentage (e.g., in CS2024-4: Bioaccumulation IATA, “Bioaccumulation” categorisation).

Figure 1. Diagrammatic overview of the Bioaccumulation IATA (Figure 6 of CS 2023-3 (OECD 2024c))



The OECD guidance (OECD, 2019d) states that WoE is the process of assigning a weight to assembled lines of evidence based on the combined impact of:

- Reliability
- Relevance

However, absolute rules or criteria for determining the level of reliability and relevance are not provided in (OECD, 2019d). There is cpurrently no agreed scoring system in either the scientific or regulatory communities for bioaccumulation metrics, which is the endpoint of this CS,

The components of the European Chemicals Agency (ECHA), European Food Safety Authority (EFSA) and US EPA WoE assessment are shown in Table 5 as an example of the regulatory definition. The ECHA guidance (2016) adds Adequacy to Reliability and Relevance. Instead of Adequacy, EFSA (2017) uses Consistency, and the U.S. Environmental Protection Agency (US EPA) (2016) uses Strength for ecological

assessment. In addition, the US EPA has published data reliability criteria for ecotoxicity and fate studies under the Toxic Substances Control Act (TSCA) for existing chemicals risk evaluations (US EPA 2021).

Although there are some elements to consider, the detail and definition of each element is not harmonised and will be determined by the assessor to suit the purpose. This CS is an example of WoE scoring for bioaccumulation. In any case, it is important to document the criteria for transparency.

Table 5. Components of WoE assessment of the OECD, ECHA, EFSA and US EPA

	CS 2023-3[*1]	OECD[*2]	ECHA[*3]	EFSA[*4]	US EPA[*5]
Reliability	assessment of data reliability to identify uncertainty and guide the selection and application of the best available information providing confidence in the decision.	the confidence assigned to evidence based on the assessment of data quality, sufficiency (quantity), plausibility and uncertainty	evaluating the inherent quality of a test report or publication relating to preferably standardised methodology and the way the experimental procedure and results are described to give evidence of the clarity and plausibility of the findings. Reliability of data is closely linked to the reliability of the test method used to generate the data.	the extent to which the information comprising a piece or line of evidence is correct.	A property of evidence determined by the degree to which it has quality or other attributes that inspire confidence.
Relevance	the appropriateness or degree of correspondence of evidence to the question(s) outlined in the problem formulation.	the degree of correspondence of scientific or regulatory evidence to the hypothesis	covering the extent to which data and tests are appropriate for a particular hazard identification or risk characterisation.	Relevance: the contribution a piece or line of evidence would make to answer a specified question, if the information comprising the line of evidence was fully reliable.	A property of a piece or type of evidence that expresses the degree of correspondence between the evidence and the assessment endpoint to which it is applied
Other	Strength of Evidence (SoE) : evaluating the extent of variability among the Lines of Evidence (LoE) in terms of Bioaccumulation assessment outcomes and identify possible outliers within a particular dataset and residual uncertainty: uncertainty that is not or cannot be considered in the data evaluation	-	Adequacy: defining the usefulness of data for hazard/risk assessment purposes. Where there is more than one study for each endpoint, the greatest weight is attached to the studies that are the most relevant and reliable. For each endpoint, robust summaries need to be prepared for the key studies.	Consistency: the extent to which the contributions of different pieces or lines of evidence to answering the specified question are compatible.	Stremgth: A property of evidence determined by the degree of differentiation from randomness or from control, background, or reference conditions

[*1]: OECD, 2024c, [*2]: OECD, 2019d, [*3]: ECHA, 2016, [*4]: EFSA, 2017, [*5]: USEPA, 2016

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

Since 2021 the OECD IATA CSP and the WPHA have discussed the use of lessons learned from all case studies. The main opinions were to add experience to previous CSs to increase application and confidence, and to use a part of previous CSs. The Secretariat developed the IATA framework template (3Annex D) to stimulate the reuse and application of existing CSs or approaches used in the CSs, and to conserve resources for CS development and CS review. CS 2023-1 is the first CS to use the IATA framework template. This framework template works well, based on the experience of developing and reviewing the CS, but an assessment method and endpoint specific improvements are suggested. The IATA CSP discussed this IATA framework template at the November 2024 meeting. A new project is under way to further develop an IATA framework template that is specific to an endpoint.

The OECD IATA CSP members also identified the further guidance development at the 9th OECD IATA CSP meeting on 15 November 2023.

- Tools or approaches to increase the confidence in IATA/DA performance when the number of reference chemicals is limited (CS 2023-2)

The IATA CSP discussed approaches to increase confidence when the number of reference chemicals is limited. While there are several statistical approaches that can be used, they are all based on limited underlying data. This is an interesting topic for further discussion and is relevant to the GD 34 updated project in the Test Guidelines Programme. Additional discussion or guidance may be helpful. The team agreed that the case study was a good example of increasing confidence using multiple results in a context of few relevant chemicals. In addition, the case study may be a good example of using cross validation approaches to increase confidence when the number of reference chemicals is limited. The use of a resampling method such as bootstrapping was proposed in the WNT, and it was noted that this would only provide information on the reproducibility of the NAMs but could not account for the limited CAT 2 chemical data. The USA noted that the DA is being used in the USA and if there is no consensus for inclusion in a Test Guideline, it is useful to maintain this as an “opt in” option.

Over the nine 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 Case Studies Project team and the WPHA were asked to consider which topics were high/medium/low priorities, 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 results are summarized in Table 6.

Table 6. 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
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 the 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

Areas for the development of further guidance	STATUS (H/ML)*
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, toxicokinetics, toxicodynamics, 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 toxicokinetics/ 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
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, etcl.)	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

Areas for the development of further guidance	STATUS (H/ML)*
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

Three CSs were reviewed in the ninth review cycle of the project in 2023. Three consideration topics from the ninth review cycle are discussed in this document.

- Analogue selection based on MoA or biological response (CS 2023-1)
- The applicability of the DASF for different classes of surfactants and/or functional group (CS 2023-2)
- How to make the scoring lines of evidence within WoE fit for purpose (e.g. scenarios for scoring and weighting selection) (CS 2023-3).

At the 9th OECD IATA CSP meeting on 15 November 2023, the project members proposed as priority areas for further development of guidance, including:

- Tools or approaches to increase the confidence in IATA/DA performance when the number of reference chemicals is limited (CS 2023-2)

In recent years, the IATA CSP and the WPHA discussed the reuse of IATA CSs. The IATA framework template was developed and used for CS 2023-1. The framework template will be discussed to focus on specific assessment methods and the template will be further developed into and an endpoint specific template as part of the ongoing project.

In summary, the considerations obtained from the three CSs in the ninth review cycle have provided new knowledge on MoA, WoE and DA for eye irritation. 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 in Annex C.

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

Eight countries/stakeholders (Australia, Canada, Germany, Japan, the Netherlands, the United kingdom, the United States, The European Chemicals Agency ECHA) participated to review in the ninth review cycle. The authors used templates to document the CSs (Annex D, Annex F, and Annex G). The template for the CSs on read-across (Annex E) 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 (Annex F) 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 (Annex G) 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 ninth review cycle are indicated below (Table A A.1).

Table A A.1. Guided reviewer questions for ninth (2023) 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
	General (scientific) review results
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 ninth meeting of the IATA CSP (15 November 2023), 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 ninth review cycle

The three CSs in the ninth review cycle are summarised in Table A B.1.

Table A B.1. CSs Reviewed in the Ninth Review Cycle (2023)

No.	Title	Endpoint	Purpose of CS	References
2023-1	Case Study on the Use of Integrated Approaches for Testing and Assessment for Chronic Toxicity and Carcinogenicity of Agrochemicals with Exemplar Case Studies	Chronic toxicity and carcinogenicity	to illustrate a process whereby a scientific WoE-based approach allows the estimation of a Point of departure (POD) for use in risk assessment that is health protective in preventing a chronic event, including carcinogenicity, from exposure to humans.	OECD, 2024a
2023-2	Case Study on the use of Integrated Approaches for Testing and Assessment for "Eye hazard identification" of "surfactants"	Eye damage/irritation	to illustrate the applicability of the DAs for serious eye damage and eye irritation integrated in the TG 467 (OECD, 2025a).	OECD, 2024b
2023-3	Case study on the use of Integrated Approach for Testing and Assessment (IATA) for Bioaccumulation	Bioaccumulation	to guide the collection, generation, evaluation, and weighing of various types of bioaccumulation data including physical-chemical, *in silico*, *in vitro* and *in vivo* data.	OECD, 2024c

Annex Section B.1 summarises answers regarding a potential regulatory use of the three 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 three CSs.

B.1 Potential regulatory application of three CSs in 2023 review cycle

Table A B.2, Table A B.3 and Table A B.4 show review results regarding the potential regulatory application replied to by reviewers (Australia, Canada, Germany Japan, the Netherlands and the United States).

Table A B.2. Potential regulatory application of CS 2023-1

CS 2023-1: Case Study on the Use of Integrated Approaches for Testing and Assessment for Chronic Toxicity and Carcinogenicity of Agrochemicals with Exemplar Case Studies

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?
Endpoint: Human health and environmental hazard and exposure endpoints **Scope: Human health and environmental risk assessment of new substances** **Chemical sector: Responsible for the chemicals within the Canadian market, including substances looking to enter the market**	Canada, Health Canada/ Environment and Climate Change Canada Regulations as defined under the Canadian Environmental Protection Act (CEPA)	MOA, NOAEL/LOAEL, POD, quantitative exposure estimates, quantitative risk assessment for human health and the environment	The woe approach, uncertainty examination, MoA considerations, and read-across approaches are all relevant to the human health and ecological context and generally to the assessment of chemical substances conducted under the *Canadian Environmental Protection Act, 1999*. If this data were available it would be considered and be useful, however there is no data requirement for carcinogenicity studies for existing substances, so a waiver package is not necessary. Concern for carcinogenicity would typically arise from a positive genotoxicity call, which were not the case in these case studies. Read-across is frequently used and this is a very useful tool for data-poor	This approach could be considered applicable to substances such as novel substances. The challenge becomes the amount of information that is available for other substance types. Agrochemicals tend to be data-rich, while other substances (e.g., new/novel substances) do not tend to have the data available to be able to apply this approach in a robust manner. Information, such as a known mode of action, may	There are useful aspects of the case study. Systematic data gap filling using a weight of evidence approach for endpoints that are regulatory requirements is applicable for new substances regulation in Canada.	Guidelines on analogue selection – beyond MoA, thresholds for physical-chemical properties or structural similarities that would cause the chemical to be excluded from the analysis.

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?
			substances.	not be available. The woe approach would be applicable; however, genotoxicity would be examined in a single step with other MoA(s) as part of hazard assessment. Using a WoE approach with read-across data along with consistent MoA across the analogues can be applied in the ecological risk assessment context.		
All endpoints relevant for human health risk assessment/ health assessment of the safety of substances (chemicals, pesticides, biocides) and selected products (consumer products, cosmetics, tobacco products, textiles and food packaging)	German Federal Institute for Risk Assessment Regulatory sector: consumer health protection	-	-	No, since the justifications are not comprehensive and the data basis is not sufficient resulting in a high uncertainty.	All available data and its uncertainties have to be thoroughly discussed and the conclusions have to be scientifically sound which means that major revisions of the case study are needed.	-
Risk assessment and management of chemical substances	National Institute for Public Health and the Environment (RIVM, The	GHS, CLP, risk mitigation, risk assessment, risk management	Yes, classification of substances and mixtures is based on the criteria in GHS and their implementation in national legislation which is in our case CLP. Currently, only a few	No, see answer on previous question.	Yes, it's a good design to expand to other chemicals.	-

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?
	Netherlands) Government		GHS classification criteria include the use of in vitro methods, physical/chemical properties, defined approaches, etc.. The CLP regulation is more open to different types of data that can be used in general. More specific, the classification and labelling for the endpoint carcinogenicity is mostly hazard-based and relies largely on the availability of long-term studies in rodents. It is currently doubtful whether the proposed approach will provide convincing evidence that carcinogenicity can be excluded at high doses levels.			
Endpoint: **Human health: acute toxicity, corrosion/irritation, sensitisation, repeat dose toxicity, genotoxicity, carcinogenicity, reproductive and development toxicity, neurotoxicity, neurodevelopmental toxicity, immunotoxicity, and endocrine effects**	Australia, Australian Industrial Chemicals Introduction Scheme (AICIS) 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	MOA, NOAEL, to enable risk assessment. Based on the risks identified make recommendations for safe use. GHS classification	Yes Carcinogenicity endpoint is to be considered when the chemical is being categorised into one of the various categories Specific data requirements exist for the Assessed category and data on carcinogenicity is not a specific data requirement. For listed chemicals (chemicals on the inventory) there are no specific data requirements and available carcinogenicity data are considered in the evaluation process. As described in the report this approach for industrial chemicals	Yes WoE approaches including the use of validated OECD TG data from analogue chemicals are accepted methodologies for assessments conducted at AICIS. The approach detailed in the case study is applicable for human health hazard and risk assessments if there are sufficient hazard and exposure data.	-	-

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?
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**	guidelines published by AICIS as being medium to high risk.		needs to be further evaluated with use of appropriate case studies	May not be applicable for data poor chemicals.		
Endpoint: **Repeated-dose toxicity, carcinogenicity** **Scope:** **Hazard identification, screening assessment, risk assessment** **Chemical sector: CSCL (Chemical Substances Control Law)**	Japan NIHS	ADI, MOA	In vivo data of the endpoint is required for new substances. However, application of alternative approaches is expected for existing substances or contaminants.	Yes, it may be applicable for hazard identification.	-	International guidance, and examples of actual use in regulatory contexts

Table A B.3. Potential regulatory application of CS 2023-2

CS 2023-2: Case Study on the use of Integrated Approaches for Testing and Assessment for “Eye hazard identification” of “surfactants”

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?
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**	Name: Australia/Australian Industrial Chemicals Introduction Scheme (AICIS) 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.	Regulatory need: Hazard characterisation (MoA, NOAEL) to enable risk assessment. Based on the risks identified make recommendations for safe use. GHS classification.	Yes The eye irritation endpoint may be considered during categorisation of an industrial chemical for introduction. Eye irritation is an end point requiring data for new industrial chemicals introduced into Australia through the Assessed category. For listed chemicals (chemicals on the inventory) there are no specific data requirements and available eye irritation data are considered in the evaluation process. A DA may be used if results from the specific TGs used in the DA are provided to AICIS for assessment. However, the modified STE method used in the DASF is not an OECD test method. Validation of this method would be required for use in the assessment of new chemicals.	Yes The DASF could be incorporated into the hazard and risk assessment of chemicals as part of a WOE approach.	-	-

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Scope: Hazard identification, characterisation, and POD Chemical sector: Industrial chemicals including chemicals used in cosmetics						
Endpoint: Human health and environmental hazard and exposure endpoints **Scope: Human health and ecological risk assessment of new substances, particularly prioritization, hazard identification, and POD derivation.** Chemical sector: Substances in industrial, commercial, and consumer products, and indirect exposure	Canada, Health Canada Canada / Health Canada/ New Substances Assessment and Control Bureau and Existing Substances Risk Assessment Bureau Regulatory sector: Substances new to Canada, as defined under the Canadian Environmental Protection Act (CEPA), as well as existing substances as found on Canada's Domestic Substances List	MoA, NOAEL/LOAEL, POD, quantitative exposure estimates, quantitative risk assessment for human health and the environment	No, there are no specific data requirements for eye irritation/damage testing in the New Substances Notification Regulations (NSNR) of CEPA. The Existing Substance Risk Assessment Bureau doesn't have specific needs; however, our Cosmetic Bureau may have regulations.	Yes, approaches used in this case study can be used in the Health Canada New Substances Program context. Eye irritation data are not required under the New Substances Notification Regulations (NSNR) for chemicals and polymers. Still, these data are received regularly to inform the toxicity, potency, and acceptable use levels of substances in products that may involve inadvertent eye exposure or intentional near-eye exposure. Because the methodology follows a validated OECD-defined approach under OECD TG 467, this approach would be acceptable to the Program, assuming the guideline was correctly followed. The modified STE test may present a minor challenge since it is not an OECD-validated method. So, regulatory acceptance may be difficult as the validation of this method is not apparent. Sufficient justification and documentation may alleviate this. It might be able to be used in the Existing	-	Validation of the modified STE test method would make the entirety of the IATA applicable. Automated workflows are so helpful for prioritization and quickly allow adoption/tailoring. KNIME is an excellent platform for non-coders!

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to substances contained in Canadian Food and Drug Act products (including cosmetics, personal care products, pharmaceuticals, medical devices, food additives, novel foods, veterinary drugs, natural health products)				Substances Risk Assessment Bureau as we try to make use of the most available data in our regulatory assessments.		
Endpoint: hazard characterization for Pesticide/ Biocide Regulation **Scope: hazard characterization, POD** Chemical sector: pesticides, biocides	German Federal Institute for Risk Assessment (BfR) Regulatory sector: Pesticide/ Biocide Regulation	GHS categorization, Risk mitigation measures	Yes: data requirements exist (e.g. Regulation (EC) No 1107/2009, Regulation (EU) No 528/2012) but these are no barrier for the regulatory assessment of single substances.	Yes, but only partly: IATA appreciated for harmonized pesticide/biocide evaluation in the EU. This case study explains the process and shows that it is applicable to surfactants. Nevertheless, acceptance and confidence would increase significantly if the choice of model substances were optimised. So that it would be clear that the case study is applicable to all surfactant classes or which classes should be assessed more closely.	-	-
Endpoint: Eye irritation **Scope: hazard identification**	National In statute of Health Sciences, Japan	GHS categorization	In vitro studies can be substituted with *in vivo* studies, but the validity of DA will be discussed shortly.	No For regulatory acceptance in Japan, Japanese Center for the Validation of Alternative Methods (JaCVAM) would need to evaluate this CS (However, JaCVAM has not evaluated individual CS so far).	Of course, the CS is helpful to enhance the use of TG492 in Japan.	International guidance, and examples of actual use in regulatory contexts will be useful.

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Chemical sector: pesticide and quasi-drug						
Risk assessment and management of chemical substances	National Institute for Public Health and the Environment (RIVM, The Netherlands) Government	GHS, CLP, risk mitigation, risk assessment, risk management	Yes, classification of substances and mixtures is based on the criteria in GHS and their implementation in national legislation which is in our case CLP. Recently, an update version of GHS was published which now also addresses the use of non-animal methods. Based on the new GHS, the CLP regulation should be updated. The current IATA case study is only an inventory on the possibilities on the applicability of the defined approaches.	No, see answer on previous question, the case study is only an inventory.	Yes, but as mentioned it should be performed with a broader set of test chemicals.	Acceptance would be facilitated by updating the CLP regulation based on the 10th revision of GHS.

Table A B.4. Potential regulatory application of CS 2023-3

CS 2023-3: Case Study on the use of Integrated Approach for Testing and Assessment (IATA) for Bioaccumulation

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?
Risk characterisation (environment focussed)	Australia/ Department of Climate Change, Energy, the Environment and	risk assessment of industrial chemicals (environment focussed), scheduling of industrial chemicals (risk management regulatory	Yes *Specific data requirements in Australia:*	Partially. There are useful aspects to the CSs and some of the background theoretical discussions, but the	For an experienced risk assessor the CSs are useful, because the general principles can be used to inspire the	The IATA in its current form is repetitive and overly complex, and not presented in a way that will facilitate adoption into routine

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Industrial chemicals	Water Environment	action)	*Aquatic:* bioaccumulation factors *(BAF) and/or bioconcentration factor (BCF) ≥ 2000, log KOW ≥ 4.2 (if BAF/BCF not available). Terrestrial: log Koa > 6 and log KOW ≥ 2. All: biomagnification factors (BMF) > 1.*	overall procedure described in this IATA does not represents a generally applicable approach and seems to overlook some important lessons about the limitations of the predictive power of physico-chemical properties in bioaccumulation assessments. We have the following bioaccumulation assessment thresholds and assessment procedure: *Aquatic: BAF and/or BCF ≥ 2000, log KOW ≥ 4.2 (if BAF/BCF not available). Terrestrial: log Koa > 6 and log KOW ≥ 2. All: BMF > 1.* We first look to the BCF/BAF values before considering the log KOW. In comparison, the CSs first consider the physical and chemical properties (log KOW) before moving on to other lines of evidence. This limits the use of this IATA and is the reason it cannot be directly applied to our needs.	development of a tailored framework. However, explicit explanation of how to tailor the IATA would be very useful and make the document more generally applicable.	regulatory assessment workflows. There is also an overreliance on the use of one particular set of evaluation tools (BAT/BET) when in most regulatory assessment systems other more familiar and better-established tools such as EPISuite and Catalogic are the primary evaluation platforms. While the choice of BAT/BET to illustrate the concepts and workflows is understood in this context, the IATA itself should be model and platform agnostic and be applicable in regulatory systems that do not use these tools.
Most, if not all, endpoints are considered, highlights include BAF, BCF, and K_{OW}. Scope	Health Canada & Environment and Climate Change Canada Federal regulation:	Point of Departure (POD), NOEC, MoA, NOAEL/LOAEL, quantitative exposure estimates, quantitative risk assessment for human health and the	No, there are no specific data requirements in the New Substances Notification Regulations (Chemicals and Polymers), but	Yes. The BAT tool can evaluate bioaccumulation data and arrive at a consensus-based conclusion for that endpoint. The approaches highlighted in this	N/A	A guidance document or a simplified step-wise outline of the process and considerations may be helpful to intended users of the IATA.

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includes but is not limited to prioritization, hazard ID, hazard characterization, POD, exposure assessments, and risk assessment. The chemical sector covers the Domestic Substances List (DSL) and any new chemicals brought into the Canadian market.	substances new to Canada, as defined under the Canadian Environmental Protection Act, 1999 (CEPA)	environment Persistent, Bioaccumulative and inherently Toxic (PBiT) categorization, pass/fail against the *Persistence and Bioaccumulation Regulations*, ADME profiling, hazard profiling, exposure profiling, predicted no effect concentration derivation	bioaccumulation assessment is undertaken.	case study will benefit the determination of whether a substance is considered to be bioaccumulative. Although Canada already has bioaccumulation thresholds for BCFs, BAFs, and Log K_{ow}s under the *Persistence and Bioaccumulation Regulations*, the implantation of a weight of evidence approach for bioaccumulation will provide the department with greater confidence in its bioaccumulation conclusions for chemicals, including those that are data poor.		
BCF / BMF Scope: hazard assessment, classification Chemical sector: REACH, CLP, Persistent organic pollutant (POP)	FRANCE / Ineris REACH, CLP, POP	Regulatory need: Regarding the regulatory context, the CLP regulation is not mentioned as a framework for bioaccumulation assessment. However, bioaccumulation is not only assessed only for PBT/vPv identification. Under CLP regulation, beyond the new hazard class as PBorMT/vPvBorvM, the bioaccumulation is assessed for aquatic chronic classification purposes. The	No	Yes		

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		threshold used (BCF = 500) is lower than that usually used for the B criteria (BCF = 2000 in REACH regulation for instance). It should be noted that this low threshold is also considered in other context such as the Oslo and Paris (OSPAR) convention. It would be helpful to clarify whether this lower threshold is taken into account for the application of this Integrated Approach for Testing and Assessment (IATA) for Bioaccumulation, or whether the uncertainties associated with the IATA are considered too high to be used in a different context than the B and vB thresholds.				
Risk assessment and management of chemical substances	National Institute for Public Health and the Environment (RIVM, The Netherlands) Government	GHS, CLP, risk mitigation, risk assessment, risk management		Yes, it might be used for future persistent, bioaccumulative and toxic and very persistent and very bioaccumulative (PBT/vPvB) assessment.		Some more guidance would be helpful.
Risk assessment Pesticides	U.S. Environmental Protection Agency (Office of Chemical Safety and	Risk assessment	Yes	No	-	-

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	Pollution Prevention, Office of Pesticide Programs) Regulatory sector: Pesticides					
BCF/BAF/BMF/ trophic magnification factors (TMF) **Hazard characterization, risk characterization** TSCA Existing Chemicals	U.S. Environmental Protection Agency (Office of Chemical Safety and Pollution Prevention, Office of Pesticide Programs, Existing Chemicals Risk Assessment Division) Regulatory sector: Industrial chemicals	Regulatory need: PBT characterization for prioritization and screening, risk assessment	No, there are not specific data requirements and measured data are preferred over modelled data. TSCA evaluations are not binary (bioaccumulative/not bioaccumulative); rather, they are comprehensive in evaluating nuances that might make a chemical potentially bioaccumulative/persistent.	Yes, the case study is helpful and applicable but would not likely be used exclusively for bioaccumulation potential. Rather, it could be used to help standardize terminology and approaches for WoE/quality evaluations of available studies. The guidance relies predominantly on BAT/BET models where there is not a consensus on the use and application. TSCA evaluations tend to focus on empirical data where available.	Not applicable	Some additional details would be helpful as described above in the other comments.
monitoring and evaluation of field-based accumulation *Scope*: Research *Chemical sector*: Government	U.S. Environmental Protection Agency (Office of Research and Development; ORD) Regulatory sector: not applicable	nonregulatory need	No	Yes While I personally do not focus on this specific angle, folks in our office would benefit from this sort of application in both the context of learning as well as the context of research-oriented decision making (which compounds to explore next and why). At ORD's Great Lakes Toxicology and Ecology Division	Not applicable	Further inclusion of novel compounds not included, like PFASs, likely because they are poorly understood in most aspects of research (e.g., fate and transport, biotransformation, mode of assimilation).

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				(GLTED), we focus on research for our stakeholders and US EPA managers alike so in this way, the written tool also gives our managers a rubric to decide what they might prefer we focus on next.		
Safety evaluation of food ingredients, including food additives and food contact substances Risk Assessment *Chemical sector*: Food additives	U.S. Food and Drug Administration (Center for Food Safety and Applied Nutrition) Regulatory sector: food ingredients, including food additives and food contact substances	Establishing uncertainty factors for bioaccumulative chemicals for their risk assessment and assessing the potential for bioaccumulation in the body for data-poor chemicals.	No	Yes A step-wise approach based on physicochemical properties and toxicology is helpful to assess the potential of bioaccumulation, but it is important to consider steady state kinetics, mechanistic data and presence of certain structural moieties to draw definitive conclusions.	Consideration of steady state kinetics and mechanistic data will expand the utility of the approach. The template should also be validated by evaluating a large number of wide range of diverse chemicals with different chemical structures, both data-rich and data-poor, with no as well as varied bioaccumulative properties.	Additional steps for including some suggestions from above would be helpful. A work product of a guidance document and an expert committee white paper or publication would be useful for regulators as well as researchers.
PBT/vPvB assessment REACH / CLP industrial chemicals	ECHA industrial chemicals	identification of data gaps and request of data generation, SVHC identification and classification of PBT and vPvB substances;	Yes – REACH Annexes VII-X (see also ECHA guidance documents on information requirements and chemical safety assessment R.7a,b,c and PBT assessment R.11) There are some differences between the IATA case study and B assessment under	We propose to introduce a disclaimer at the start of the case study as follows: "The case study is an illustrative example, and its publication as an OECD monograph does not translate into direct acceptance of the methodologies for regulatory purposes across OECD countries. In addition, the case study should not be interpreted as an official regulatory decision."	Bringing the discussion on the use of complex information in a weight of evidence to an international level is valuable. We should strive for harmonisation of approaches at a global level for efficiency reasons and scientific progress, and this case study contributes to this process. It shows as well	At the moment we don't see the need for guidance development based on this case. Additional discussion may be considered.

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?
			REACH as described in more details in other sections.	***Note from the Secretariat: The proposed disclaimer is included in the Foreword of all IATA CSs.***	where regulators have different angles to the assessment and points out where there is need for further discussion and development.	

B.2 Review Results for CS 2023-1: Case Study on the Use of Integrated Approaches for Testing and Assessment for Chronic Toxicity and Carcinogenicity of Agrochemicals with Exemplar Case Studies

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

- MoA/AOP (PPO inhibition), and use of read-across data.
- The IATA workflow systematically summarises the data to be collected and the workflow of the assessment.
- The WoE evaluation is comprehensive and logically presented.

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

- The selection of analogues. The structural similarity indexed used for analogues selected were fairly low. Analogues were selected based on MoA and had very low calculated similarity scores or in physical chemical properties. It might be beneficial to include some structural analogues in addition to MoA analogues to strengthen the results.
- Adequate validation is lacking for the assessment methodology. In addition to the approaches followed by the authors, existing chronic toxicity/carcinogenicity data (studies) on saflufenacil should have been considered in order to compare whether the IATA provides reasonable predictions/conclusions.
- Insufficient data analysing the MoA/AOP for saflufenacil and the read-across analogues. the potency for this MoA for the different substances should be analysed to evaluate if saflufenacil is likely more toxic with regard to possible downstream effects. Toxicological assessment (comparison of toxicological profiles of the target and the analogues, including the relevance of tumour development for two of the read-across analogues) needs to be discussed in more detail.
- When considering the omission of the long-term study, the rationale for the additional UF values should be carefully discussed.
- The difference in regulatory decision in the US (approved for use) vs that in the EU (not approved for use)

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

- Guidance on sufficiency of data to support a weight of evidence approach.
- The criteria for selection of analogues should be expanded upon. As the selection is based on MoA, are there thresholds for physical-chemical properties or structural similarities that would cause the chemical to be excluded from the analysis.

Overviews of the case study are as follows.

This case study provided a framework to demonstrate WoE based on read-across for chronic toxicity and carcinogenicity assessment for the registration of agrochemicals without the lifetime rodent bioassays

(OECD TG 451[4]; 452[5]; 453[6]) using two agrochemicals. The framework aims to structure with the process that helps determine when sufficient information is available to identify a health protective endpoint for risk assessment for a non-genotoxic agrochemical without performing the lifetime rodent bioassays. The process for identifying a POD for a risk assessment is shown in Figure 2 of OECD 2023a.

The assessment of this case study is mainly based on a retrospective evaluation of the use pattern(s), exposure scenario(s), pesticidal mode-of-action, physicochemical properties, metabolism, toxicokinetics, toxicological data including mechanistic data, and an evaluation of the reliability and consistency of the toxicological response(s) between the agrochemical of interest and chemical analogues used for read-across assessment.

Further information on the CS can be found in (OECD, 2024a).

B.4 Review Results for CS 2023-2: Case Study on the use of Integrated Approaches for Testing and Assessment for "Eye hazard identification" of "surfactants"

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

- developing a strategy in the form of the DASF to address limitations in categorising surfactants and discriminating between Cat. 1 and Cat. 2 substances.
- addresses a gap by the currently adopted Defined Approaches in OECD TG 467 which is applicable to non-surfactant liquids and solids only.
- selecting varying surfactants (class and family)
- consideration reproducibility.

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

- the small number of chemicals (3) used to demonstrate the applicability of the DASF. In order to increase the number of tested substances and subsequently relevant uncertainties, further tests could be performed for example with pesticides containing surfactants as co-formulants. For these products, a large number of *in vivo* data is available. Moreover, it could be addressed whether the DA is expected to work for surfactant containing mixtures (cf AISE data).

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

- How to increase the confidence using tools or approaches when the number of chemicals is limited.
- How to assess model substances that represent a borderline case in the classification and a direct comparison of the same surfactant classes (tested in the same concentrations)
- better prediction for complex mixtures containing surfactants is needed.

[4] OECD, 2018g

[5] OECD, 2018i

[6] OECD, 2018i

- The applicability for different classes of surfactants and/or functional

Overviews of the case study are as follows.

In CS2022-2 (OECD, 2023b), two DAs were developed for eye hazard identification of non-surfactant liquids, and integrated into OECD TG 467(OECD, 2025a). In this case study, a new DA (DASF) was developed to predict the eye hazard identification for liquid, semi-solid and solid chemicals with surfactant properties to distinguish between the three UN GHS categories.

The DASF (Figure 1 of OECD 2024b) is based on a combination of the Reconstructed human Cornea-like Epithelium (RhCE) test method described in OECD TG 492 (2019a) and a modification of the Short Time Exposure (STE) test method. The target chemicals are three representative surfactants.

The set of reference chemicals used to assess the performance of the DASF consisted of 31 surfactants including cationic, anionic, non-ionic and amphoteric surfactants. The DASF is applicable to neat and diluted surfactants, including, mono- and multi-constituent substances and UVCBs, but not applicable to non-surfactants. The reference chemicals for Cat. 2 contain only surfactants that have been tested in dilution. The reliability of Cat. 2 predictions for pure surfactants is unknown.

The hazard identification conclusion based on predictions from the DASF is the same as the UN GHS categories that were assigned based on *in vivo* Draize eye test studies.

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

B.5 Review Results for CS 2023-3: Case Study on the use of Integrated Approach for Testing and Assessment (IATA) for Bioaccumulation

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

- Inclusion of both data poor and rich chemicals
- The completeness and robustness of the overall write-up
- The systematic step-wise approach using many of the major *in silico* methods and software tools

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

- The scoring for the reliability of the prediction or the (Quantitative) Structure-Activity Relationship ((Q)SAR) in question, i.e., data evaluation templates (DET). These are mainly subjective scores, making it challenge to be accurate and reliable.

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

- How the scoring system can be designed as fit-for-purpose (e.g. scenarios for selecting score and weights)
- How to deal with ionisable substances, as well as surface active substances for bioaccumulation assessment.
- How to address a data poor chemical that is largely outside of the application domain of relevant models
- Limits of extrapolation from physico-chemical properties to bioaccumulation potential (the failure of the standard suite of physico-chemical properties to predict the bioaccumulation potential of perfluoroalkyl acids)

Overviews of the case study are as follows.

The case study aimed to help evaluators collect, generate, evaluate, and integrate multiple lines of evidence (LoE) (e.g. bioconcentration factor (BCF), bioaccumulation factor (BAF), biomagnification factor (BMF) and trophic magnification factor (TMF)) for clear and transparent decision making within defined problem contexts using WoE. Three chemicals representing both data poor and data rich chemicals, were used to illustrate the applicability of the IATA for bioaccumulation assessment. An overview of the approach was shown in Figure 3 (OECD, 2024c)

The data evaluation criteria were developed from the OECD TG for each LoE (e.g., OECD TG 319 A (OECD, 2018k)/B (OECD, 2018)), and a systematic approach was developed to address uncertainty within each individual LoE. For each LoE, the case study provided a transparent process to evaluate whether there is sufficient confidence in the WoE to make a decision.

Three chemicals highlight the flexibility of the context of applicability for the proposed IATA and illustrate the utility of the IATA as a transparent process.

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

Annex C. Summary of the CSs reviewed in all review cycles.

This Annex summarises learnings and lessons from the 37 CSs of the IATA CSP including the 34 CSs from the past seven review cycles. Some CSs include more than one endpoint/approach.

The target endpoints included:

- repeated dose toxicity (9 CSs),
- developmental neurotoxicity (5),
- systemic toxicity (6)
- neurotoxicity (3).
- estrogenicity (3),
- carcinogenicity (2)
- eye irritation (2)
- bioaccumulation (2),
- skin sensitisation (2),
- reproductive toxicity (2)
- genotoxicity & mutagenicity (2),
- developmental toxicity (1)
- ecotoxicity (1)

A variety of assessment approaches have been used in the IATAs reviewed to date with a focus on read-across. Approaches include:

- read-across (21 CSs),
- IATA workflow (16) *including* Developmental Neurotoxicity *(DNT)* (5) defined approach (5)

In addition, CSs reviewed also demonstrated examples of using;

- MoA/AOP approaches (28 CSs),
- describing uncertainty (35),
- application of NAMs (32), and
- deriving low/no toxicity prediction (17)

Table A C.1. Summary of the CSs reviewed in the past nine review cycles

Year-No.	Assessment Approach	Endpoint	Usage classification	Key words provided by Authors	IATA Topics				Reference
					AOP*1	UR*2	NAM*3	L/N*4	
2023-1	Read-across	chronic toxicity and Carcinogenicity	Pesticide	• New Approach Methodology (NAM) • Weight of Evidence (WoE) • Chronic Toxicity / Carcinogenicity • Risk Assessment • Reporting Framework	X	X	X	X	OECD, 2024a
2023-2	Defined Approach	Eye damage/irritation	Cosmetic	• Eye hazard identification, • UN GHS, • surfactants, • Defined approach, • OECD TG 497	X	X	X		OECD, 2024b
2023-3	IATA workflow WoE	Bioaccumulation	Industrial chemical	• Bioaccumulation • Weight of Evidence • Aquatic organisms • Air breathing organisms • Biotransformation		X	X		OECD, 2024c
2022-1	Defined Approach	Skin sensitisation	Cosmetic	• Case study demonstrates application of NGRA framework for an ingredient with inconsistent NAM info. • Inconsistent NAM info does not allow a non-sensitiser exit from framework. • NAM data integration in six DA resulted in inconsistent hazard and potency predictions. • Point of departure (PoD) derived using weight-of-evidence approach. • Margin of exposure (MoE) calculated by dividing PoD by consumer exposure level. • Considering MoE the NGRA conclusion was safe for four DA and unsafe for two DA. • NGRA framework was further refined.	X	X	X	X	OECD, 2023a
2022-2	Defined Approach	Eye damage/irritation	Cosmetic	• Two rule-based Defined Approaches for non-surfactant liquids (DAL) were adopted by TG 467 - for Eye Hazard Identification according to the three UN GHS categories.	X	X	X		OECD, 2023b

Year-No.	Assessment Approach	Endpoint	Usage classification	Key words provided by Authors	IATA Topics				Reference
					AOP*1	UR*2	NAM*3	L/N*4	
				• Four liquid chemicals that cover the different UN GHS categories were selected to illustrate application of both DAL-1 & DAL-2. • The DAL-1 describes the combination of physicochemical properties with the results of two *in vitro* test methods (TG 437 and TG 492). The DAL-2 describes the combination of TG 491 and TG 437 test methods. • The chemicals in any UN GHS categories led to the same conclusion with little uncertainty. • Feasibility and reliability of the TG 467 DAL approaches was demonstrated.					
2021-1	*In vitro* battery (Hazard characterisation)	Developmental neurotoxicity	Pesticide	• I*n vitro* developmental neurotoxicity testing battery (DNT-IVB) • Pyrethroids • *In vivo* developmental neurotoxicity study	X	X	X		OECD, 2022a
2021-2	*In vitro* battery (Hazard characterisation)	Developmental neurotoxicity	Pesticide	• *In vitro* developmental neurotoxicity testing battery (DNT-IVB) • Flufenacet • *In vivo* developmental neurotoxicity study	X	X	X	X	OECD, 2022b
2021-3	*In vitro* battery (Prioritisation)	Developmental neurotoxicity	Industrial chemical	• DNT – developmental neurotoxicity • Prioritisation • Flame retardants • Zebrafish	X	X	X		OECD, 2022c
2021-4	*In vitro* battery (Hazard characterisation)	Developmental neurotoxicity	Pesticide	-	X	X	X		OECD, 2022d
2021-5	*In vitro* battery (Hazard characterisation)	Developmental neurotoxicity	Pesticide	-	X	X	X		OECD, 2022e
2021-6	IATA workflow	Systemic Toxicity and Estrogenicity	Industrial chemical	• Hazard characterization of BPA and alternatives • Transcriptomic points of departure • *In vitro* and *in silico* weight of evidence • Estrogen receptor agonism	X	X	X		OECD, 2022f
2021-7	IATA workflow	Systemic Toxicity and Inhalation toxicity	Pesticide	• Exposure calculation • Computational fluid dynamics • Inhalation toxicity • Three-dimensional lung model • Benchmark dose level and point of departure calculations	X	X	X	X	OECD, 2022g

Year-No.	Assessment Approach	Endpoint	Usage classification	Key words provided by Authors	IATA Topics				Reference
					AOP*1	UR*2	NAM*3	L/N*4	
2021-8	Defined Approach	Skin sensitisation	Cosmetic	• Case study demonstrates application of NGRA framework for an ingredient with consistent NAM info. • Based on existing positive NAM info geraniol hypothesised to be a skin sensitiser. • NAM data integration in five DA resulted in weak or moderate potency predictions. • Point of departures (PoD) derived using weight-of-evidence approach. • Margin of exposure (MoE) calculated by dividing PoD by consumer exposure level. • Considering MoE the NGRA conclusion was safe or borderline safe.	X	X	X	X	OECD, 2022h
2020-1	IATA workflow	Systemic Toxicity	Cosmetic	-	X	X	X	X	OECD, 2021a
2019-1	IATA workflow Read-across	Reproductive toxicity and Systemic Toxicity	Cosmetic	-	X	X	X	X	OECD, 2020a
2019-2	Read-across	Systemic toxicity	Cosmetic	-	X	X	X		OECD, 2020b
2019-3	Read-across	Repeated dose toxicity	Industrial chemical, Pesticide	-	X	X			OECD, 2020c
2019-4	Read-across	Repeated dose toxicity	Industrial chemical	• hepatotoxicity, • p-Alkylphenol, • reactive metabolite	X	X	X		OECD, 2020d
2019-5	Read-across	Repeated dose toxicity	Industrial chemical	-	34, 36, 57, 58, 60, 61	X	X	X	OECD, 2020e
2019-6	Read-across	Developmental toxicity	Industrial chemical	-	275	X	X	X	OECD, 2020f
2019-7	Read-across	Neurotoxicity	Pesticide	-	3	X	X		OECD, 2020g
2019-8	Read-across	Neurotoxicity	Pesticide	-	X	X	X	X	OECD, 2020h

Year-No.	Assessment Approach	Endpoint	Usage classification	Key words provided by Authors	IATA Topics				Reference
					AOP*1	UR*2	NAM*3	L/N*4	
2018-1	Read-across	Reproductive toxicity (Testicular toxicity)	Industrial chemical	• testicular toxicity • metabolic similarity • *in silico* screening, • human relevance	212	X			OECD, 2019b
2018-2	Defined approach	Estrogenicity	Industrial chemical	-	X	X	X	X	OECD, 2019c
2017-1	Read-across	Estrogenicity	Industrial chemical, pesticide	-		X	X	X	OECD, 2018b
2017-2	IATA workflow	Ecotoxicity	Industrial chemical	• Ecological risk • Hazard assessment • Weight of evidence • Chemicals • Profiling	X	X	X	X	OECD, 2018c
2017-3	Read-across	Genotoxicity	Cosmetic	-		X	X		OECD, 2018d
2017-4	Read-across	Repeated dose toxicity	Cosmetic	-		X	X	X	OECD, 2018e
2016-1	Read-across	Repeated dose toxicity	Industrial chemical	• transcriptome analysis • subcategory • similarity hypothesis		X	X		OECD, 2017b
2016-2	Read-across	Neurotoxicity	Pesticide	-	X		X		OECD, 2017c
2016-3	Read-across	Repeated dose toxicity	Industrial chemical	-		X	X	X	OECD, 2017d
2016-4	Read-across	Repeated dose toxicity	Industrial chemical	-		X	X	X	OECD, 2017e
2016-5	IATA workflow	Repeated dose toxicity Systemic Toxicity	Cosmetic	-	34, 38		X		OECD, 2017f
2015-1	Read-across	Mutagenicity	Industrial chemical	-	X	X			OECD, 2016b

Year-No.	Assessment Approach	Endpoint	Usage classification	Key words provided by Authors	IATA Topics				Reference
					AOP*1	UR*2	NAM*3	L/N*4	
2015-2	Read-across	Repeated dose toxicity	Industrial chemical	-		X	X		OECD, 2016c
2015-3	Read-across	Repeated dose toxicity	Industrial chemical	• category approach • common reactive metabolite	X	X			OECD, 2016d
2015-4	Read-across	Bioaccumulation	Industrial chemical	• Biodegradation Products • Chemical Substance Control Law in Japan • reverse-phase HPLC.		X		X	OECD, 2016e

*1: AOP: Use of mode of action/adverse outcome pathways. If the IATA includes an AOP in the AOP Wiki, the AOP Wiki number is listed with the link of the AOP.
*2: UR: Uncertainty reporting
*3: NAM: Use of new approach methodologies
*4: L/N: Low/no toxicity or risk prediction

Annex D. IATA Framework Template*

*Several elements could be expanded/adapted over time; e.g. add new modules, information sources, data interpretation for different regulatory applications, etc.

SECTION	CONTENT	COMMENT
Intro	Background, endpoint(s) addressed, type of work flow/approach	
Purpose	Regulatory context of use(s); can have different DIPs/approaches Subsections for: • Regulatory relevance • Application/regulatory context	
Chemical domain	If there are limitations for any particular reason due to approach (e.g. inhalation tox); technical limitations of information sources (e.g. no metals, assay interference); in silico model applicability domain based on training set data.	
Description of work flow	Imagined to be a diagram, with some text description	
Basis for IATA work flow	AOP, physiology, etc.	Include rationale for relevance; e.g. human biology (e.g. cell/tissue/target type, physiology represented, AOP-mapping, complementarity of info sources), predictive performance, use and exposure scenario, etc.
Modules	Pchem Bioactivity – HH + Ecotox PBK (internal exposure/ extrapolation/metabolism)	Can expand over time (e.g. initial framework may be designed for hazard identification based on bioactivity, later users may adapt for quantitative RA by adding PBK and exposure modules). Every chemical run through the

	Environmental Fate + Transport Bioaccumulation Exposure (external/environnmental exposure)	framework can describe which modules were used in the assessment **(Appendix II**).
Information sources in each module	In vitro, in silico, MPS/3D tissue culture, models, existing data What is required, what can be substituted Could be assays, models, or types of information (e.g. RAx to fill gaps, literature reviews, in which case, see item on data selection/gathering below)	Essentially a list of information sources, which can expand over time to include novel information sources, me too assays, substitutes (e.g. in silico model to replace in vitro assay); links to where detailed descriptions of information sources. **Details to be described elsewhere (Appendix I)**
Data selection/gathering	For existing information, description of how information was identified; search terms, inclusion/exclusion criteria	Relevant to literature searches, use of publicly available databases, etc. High level, and generalisable. Details can be found in the assessment for individual chemicals (**Appendix I**I).
Data Evaluation	Data quality / uncertainty considerations	High level, and generalisable. Details can be found in the assessment for individual chemicals (**Appendix II**).
Data integration and interpretation	How data are combined, weighted, DIPs or where points for expert decisions, rationale for each	High level, and generalisable. Details can be found in the assessment for individual chemicals (**Appendix II**).
Expert judgement + alternative interpretations	Description of what expert judgement is needed at each identified point; Points where there is flexibility and may result in an alternative outcome/interpretation	High level, and generalisable. Details can be found in the assessment for individual chemicals (**Appendix II**).
Description of uncertainties	General, but details probably in individual information sources.	High level, and generalisable. Details can be found in the

	When possible, include descriptions of how the uncertainties are addressed/overcome.	assessment for individual chemicals (**Appendix II**).
Appendix I: Description of individual information sources	Would include description of all information sources associated with the framework. May be several different information sources to provide the same input (e.g. me too assays; different computational models, etc.).	Can be a sort of library that expands over time. Can use existing reporting formats, depending on the information source (e.g. QMRF, OORF) or add as a link to existing descriptions (e.g. scientific literature, OECD or other TG)
Appendix II: Reporting IATA Outcomes	Each example of chemical run through work flow Each new application of the IATA Framework should require a relatively brief Appendix if illustrating same approach for new chemicals. Could expand other parts of the Framework to include new modules, regulatory contexts, data interpretation, specific information sources, etc.), but even for the second case, should be less work that a new stand-alone Case Study.	Needs a general intro describing which modules and information sources used, but then should focus on results

Appendix I: reporting individual information sources*

Name of the information source	*Provide the name of the information source and the acronym (if applicable).*
Relevance of information source; e.g. biological, physiological, or mechanistic basis including AOP coverage	*Describe the chemical and/or biological mechanism addressed by the information source and provide an indication of the plausible linkage of the modelled mechanism to the endpoint being predicted (i.e. mechanistic relevance). In case the information source is addressing a specific (key) event within an existing AOP, described the extent to which the mechanistic basis of the information source relates to the chemical/biological mechanism covered by the (key) event. In case of cell-based or tissue-based test methods, describe how the experimental system (i.e. the cells or tissues) models the target tissue/organ. Biokinetic (ADME/TK) considerations should be described if appropriate.*
Description	*Provide a short description of the information source including the experimental system used and any relevant aspect of the procedure (e.g. time of exposure of the experimental system with the test chemical, number of doses/concentrations tested, number of replicates, concurrent testing of control(s) and vehicle(s), laboratory instruments/techniques used to quantify the response, etc.).*
Response(s) measured	*Specify the response(s) measured by the information source and its measure (e.g. in chemico binding to synthetic peptides, expressed as % peptide depletion).*
Prediction model	*Indicate whether there is a prediction model associated to the information source and its purpose. Briefly describe the prediction model and provide a reference to a paper or document where the prediction model is described (if available).*
Metabolic competence (if applicable)	*Specify whether the information source encompasses any metabolically competent system/step and, to the extent possible, how this relates to the situation in vivo.*
Status of development, standardisation, validation	*Indicate whether the information source is a) an officially adopted (standard) test method (e.g. a test method covered by an OECD Test Guideline); b) a validated but non-standard test method; c) a test method undergoing formal evaluation (e.g. prevalidation, validation, others); d) a non-validated test method widely in use; e) a non-validated test method implemented by a small number of users.*
Technical limitations and limitations with regard to applicability	*Indicate the chemicals and/or chemical categories (e.g. based on physicochemical properties or functional groups) for which the information source is not applicable because of technical limitations (e.g. highly volatile chemicals, poorly water soluble chemicals, solid materials, interference of the chemical with the detection system (e.g. coloured or autofluorescent chemicals interfering with spectrophotometric analysis)). Indicate whether the information source is technically applicable to the testing of multi*

	constituent-substances, UVCBs (substances of unknown or variable composition, complex reaction products or biological material) and mixtures. In addition indicate the chemicals and/or chemical categories for which the information source is technically applicable but has been experimentally shown to yield incorrect and/or unreliable predictions with respect to the reference classifications (e.g. false negative predictions with chemicals requiring enzymatic activation, high false positive rate for alcohols etc.).
Weaknesses and Strengths	*Provide an indication of the strengths and weaknesses of the information source, compared to existing similar non-testing or testing methods, considering among others the following aspects: a) extent of mechanistic information provided and relevance (i.e. measurement of various responses in the same experimental model, limited or good coverage of the mechanisms at the basis of the target endpoint, predictive of responses in humans), b) level of information provided (single point estimate or dose-response information), c) level of performance (e.g. higher or lower reproducibility, predictive capacity etc.) d) extent of domain of applicability, e) number of chemicals with published information, f) costs involved in implementing the procedure g) others.*
Reliability (within and between laboratories) **(if applicable)**	*Describe the level of reliability of the information source (i.e. the agreement among results obtained from testing the same chemicals over time using the same protocol in one or multiple laboratories) and to what extent this has been characterised including the number of chemicals used for the assessment.*
Predictive capacity (if applicable)	*Describe the extent to which the information source predicts the effect of interest (this could either be a specific chemical/biological mechanism or an apical endpoint) by considering all existing evidence (as reported in scientific publications and as determined in validation studies). Express the predictive capacity in terms of sensitivity, specificity and accuracy if applicable or by other goodness-of-fit statistics (e.g. linear correlation analysis). Include the number of chemicals used in this assessment. Consider the reliability and relevance of the reference data for the target of the evaluation if possible.*
Proprietary aspects	*Indicate whether the information source is fully disclosed or contains proprietary elements. For proprietary elements, describe the information that cannot be disclosed or is not publicly available. If the information source contains proprietary elements indicate whether it can still be widely implemented and used and provide a justification.*
Proposed regulatory use	*Indicate the proposed regulatory use of the information source (e.g. stand-alone full replacement method, partial replacement method, screening method, others).*

*If the information requested in this document is available in other sources (e.g. QSAR Model Reporting Format (QMRF), OECD Omics Reporting Format (OORF), OECD or other Test Guidelines, methods described in the scientific literature) the reference can be added, rather than transcribing the information into this format.

Appendix II: reporting IATA Outcomes

Name of Chemical	*Provide the name of the name of chemical assessed, along with identifiers of structure (if applicable).*
Purpose	*Describe the regulatory context of use/problem formulation. Particularly if there is more than one possible context/formulation. Should be linked to the DIP.*
Description of IATA Framework, including all information sources used, and modules included in the specific approach	*Provide a short description of the information source including the experimental system used and any relevant aspect of the procedure (e.g. time of exposure of the experimental system with the test chemical, number of doses/concentrations tested, number of replicates, concurrent testing of control(s) and vehicle(s), laboratory instruments/techniques used to quantify the response, etc.).*
Data review	*For the specific chemical, describe how data were gathered, selected and evaluated (e.g. sources, search terms, inclusion/exclusion, data quality considerations)*
Data Integration and Interpretation	*If the IATA includes more than one data interpretation procedure or prediction model, specify which DIP was used. This should be linked to the specific Regulatory Context of Use/Problem Formulation.*
Expert Judgement	*Include any points where expert judgement was used, along with a rationale for decisions made. For the specific chemical*
Uncertainties in the specific workflow followed	*For the specific path through the workflow (i.e. assays selected, modules, and DIP) discuss possible uncertainties.*
Uncertainties specific to the chemical assessed	*For the specific chemical assessed, discuss uncertainties.*
Outcome of the Assessment	*Summarise the conclusion for the specific chemical.*
Discussion of other interpretations (if applicable)	*Describe possible alternative interpretations (likely based on expert judgement).*

Annex E. Template for IATA CSs on Chemical Grouping (Read-across)

Title: Case Study on the use of Integrated Approaches for Testing and Assessment for “Target Endpoint(s)” of “Target Chemical(s)/Category”

NOTE: The following template should not be viewed as a strict structure, but rather identifies the information that should be included in this type of case study. Depending on the specific case study additional information/ (sub) section(s) may be required or particular subsections may not apply. The order of the (sub) sections of the template can be changed and two or more (sub)sections of the template can be merged, as necessary. The titles of a (sub) section can be changed as necessary. The template will be revised based on experience with use. A case study based on the template is expected to be assessed as stand-alone, thus needs to contain all necessary information and appropriate links for a detailed assessment.

The overview document (OECD, 2020i) helps understanding of IATA, by explaining key concepts and providing basic definitions, and to support easier access to existing resources.

Abstract / Synopsis / Executive summary

This section should provide a brief overview of the case study, including the objectives, concepts, methodologies, outcomes and conclusion in about 300 words. Please refer to Executive Summary in Case Study 2018-1 (OECD, 2019b) and 2018-2 (OECD, 2019c), and Summary in 2017-3 (OECD, 2018d) as examples.

Table of Contents

Abbreviations and acronyms

1. Introduction

This should include a very short summary of the background/problem formulation, purpose, endpoints covered and description of the target chemical(s)/category.

2. Purpose

a. Purpose of use

Specify the purpose of use of the IATA (e.g. regulatory context: hazard identification, hazard characterisation, risk assessment, screening etc.). If the IATA is used for low toxicity prediction, please

define what is meant by 'low toxicity' for the purposes of the particular case study. If in a regulatory context, provide a short but sufficient description of any (e.g. legal) requirements for the IATA approach to be accepted.

b. Target chemical(s)/category definition [See 3.2.3.1 "Chemical identity and composition" of the grouping guidance (OECD, 2014a)]

- For analogue approach, provide the chemical descriptor common identifiers (including CAS number, name and composition including impurities) and chemical structure(s) of the target substance(s).
- For category approach, provide a summary of the common features of the category members; describe the boundaries; allowed variations (e.g. in chemical structures); composition including impurities; and if known, any limitations in the information.

c. Endpoint(s)

- Identify the endpoint(s) for which the analogue/category approach is applied. Endpoint-specific considerations/approaches may be needed if more than one endpoint is addressed by the read-across.

d. Exposure information (if needed)

- Provide the considered exposure for the grouping/read-across, such as route(s) of administration covered by the experimental model (e.g. oral), the population of interest (.e.g. human, ecological), and as relevant, any route to route or *in vivo/in vitro* extrapolations that were applied to inform the grouping/read-across

Tip

- The description of the purpose of use is important for considering the acceptable uncertainty of the case study, which could be linked to the uncertainty assessment. For example, if the conclusion derived by case study is renewable in a framework such as tiered-approach, this needs to be clearly stated (see CSs OECD, 2016b and 2016c).
- As the goal of the OECD IATA CSs project is to discuss CSs which would lead to regulatory application a description of the regulatory relevance is important to contextualise the case and discuss the further development of guidance and how use IATA for regulatory purpose.
- It is recommended to specify the analogues and justification for data gap filling, used for each addressed endpoint, in order to identify for what endpoints is the analogue/category being applied.

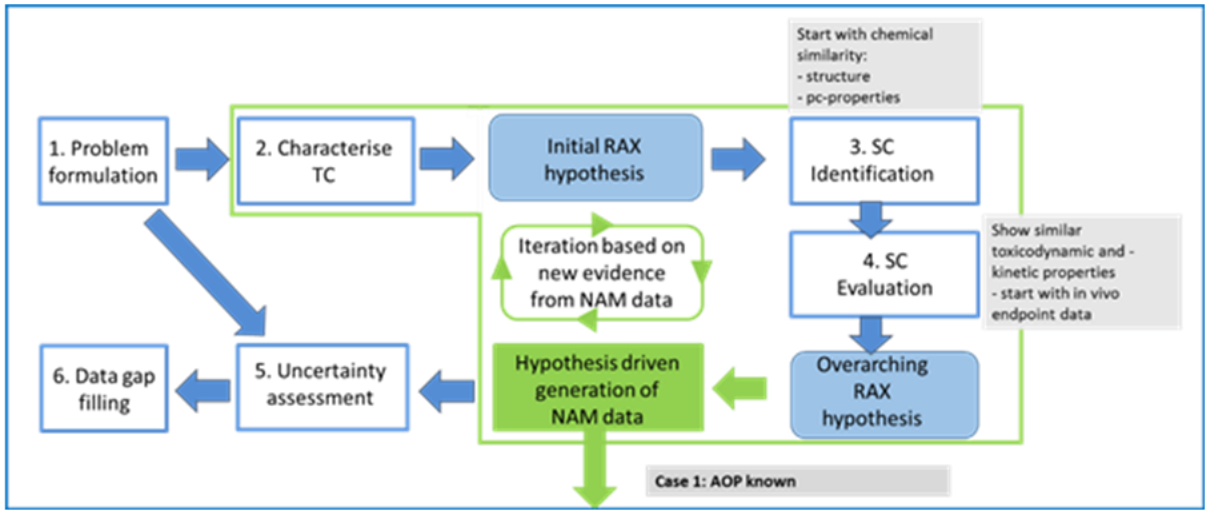
Tip for nanomaterials

- The parameters to be considered for grouping and read-across of nanoforms and their relevance for human health and environmental endpoints are for example surface chemistry, size, shape and surface area, along with physical/chemical properties. (See *"1.2 Target chemicals"* of the case study 2017-3 (OECD, 2018d))
- For the complete list of parameters and more information on grouping of nanomaterials please, see "ECHA (2017a), Guidance on information requirements and chemical safety assessment Appendix R.6-1 for nanomaterials applicable to the Guidance on (Q)SARs and Grouping of Chemicals", Appendix I, Table 2: Key physicochemical parameters to be considered for grouping and read-across of nanoforms and their relevance for human health and environmental endpoints.

3. Hypothesis for the analogue approach/category [See 2.4 “The mechanistic basis of using analogues or chemical categories” and 3.2.1 “Hypothesis and evidence based approaches” of the grouping guidance (OECD, 2014a)]

- If many steps are included in the IATA, include a figure for the workflow of the IATA applied in the case study to make IATA approach clear. Please refer to Figure 1 in Case Study 2019-4 (OECD, 2020d) and Figure 2 under section 4.1 “Testing and assessment strategy” in Case Study 2019-5 (OECD, 2020e).

Figure A E.1. Example of Workflow Figure, which was used in Case Study 2019-5



- For an analogue approach, describe the characteristics that a substance must have to be suitable as a source substance, including a description of the composition of the source substance (e.g. level of purity). Provide the hypothesis for why read-across can be performed between the source and target chemicals [See 4.2.2 “Step 1: Identification of potential analogues” of the grouping guidance (OECD, 2014a)].
- For a category approach, provide the hypothesis for why the category was formed including the relational features of the category. Provide the hypothesis for why read-across can be performed within the category [See 5.2.2 “Step 1: Develop category hypothesis and definition and identify category members” of the grouping guidance (OECD, 2014a)].
- These hypotheses can be argued by a number of elements as follows [See 3.2.3 “Elements for a read-across justification” of the grouping guidance (OECD, 2014a)]. Chemical identity and composition, including level of purity
  - Chemical identity and composition, including level of purity [See 3.2.3.1 “*Chemical identity and composition* of the grouping guidance (OECD, 2014a)]
  - Physical-chemical properties and other molecular description [See 3.2.3.2 “*Physical-chemical properties* of the grouping guidance (OECD, 2014a)]
  - Kinetics: Absorption, distribution, metabolism and excretion [See 3.2.3.3 “*Absorption, distribution, metabolism and excretion* of the grouping guidance (OECD, 2014a)]
  - Mode/Mechanism of action or adverse outcome pathways (MoA/AOP) [See 3.2.3.4 “*Mode/ mechanisms of action or adverse outcome pathways (MoA/AOP)* of the grouping guidance (OECD, 2014a)]

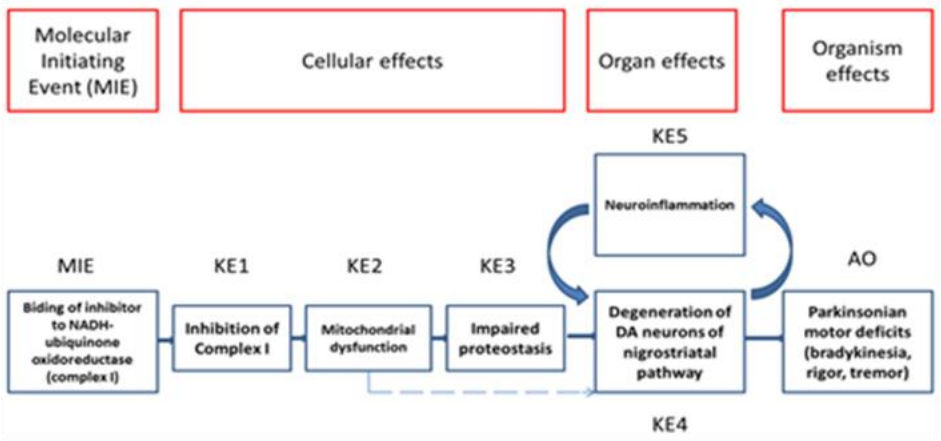
- Chemical / biological interaction [See 3.2.3.5 "*Chemical / biological interaction* of the grouping guidance (OECD, 2014a)]
- Toxicological and epidemiological information, along with information from new approach methodologies (NAMs) [See 3.2.3.6 "*Responses found in in vitro methods* of the grouping guidance (OECD, 2014a)]
- Information obtained from other endpoints/species/routes
- Information on fate in the environment (hydrolysis, biodegradation)
- The route and duration of expected exposure

Ideally, all elements relevant for the assessment should be addressed. In addition, it is recommended to describe how the (combination of) elements support the hypothesis (see for more detail OECD, 2014a).

- Especially, hypothesis of mechanism(s) (AOP/MoA) for how the target chemical induces target endpoint toxicity need to be described in this section. Hypothesis of structural boundaries and limitations for the approach should also be clearly described, including possible impact of structural dissimilarities. The graphical representation of the AOP would be helpful for the reader and key references (See "Graphical Representation of the AOP" at section 1- AOP Description (OECD, 2016g)). If an AOP together with testing of various MIE/KE/AO is used in the case study, a figure demonstrating the alignment of the AOP with the various tests should be included. Please refer to Figure 1 in Case Study 2018-2 (OECD, 2019c), Figure 3 in Case Study 2019-4, Figure 7 in Case Study 2019-5, Figure 2 (A and B) in Case study 2019-7 and Figure 5.1 (A and B) in Case Study 2019-8.

Figure A E.2. Example of AOP figure together with MIE/KE/AO, which was used in Case Study 2019-7

A)



B)

Key event	MIE	KE1	KE2	KE3	KE4	AO
Assay	Receptor Docking studies	Seahorse assay (complex inhibition and whole cell)	Mitochondrial membrane potential assay	Protease activity assay	Viability assays (Resazurin, PI, ATP)	
	Similarity studies			CHOP-GFP expression	Neuronal health (outgrowth and degeneration)	
Key event					KE5	
Assay					No assay available	

The tools in the AOP-KB[7] should be referred to as appropriate (e.g. AOP wiki[8], Effectopedia [9] etc.). Identifying the relevant AOP from AOP wiki is required. Please provide the AOP number, status on AOP-wiki and the link. For AOPs that are not documented, consider the "Users' Handbook supplement to the Guidance Document for developing and accessing Adverse Outcome Pathways" (OECD, 2016g) - although an entire AOP description is not the purpose here. If needed, the entire AOP can be described in Annex.

- Describe how a data gap is intended to be filled for the purpose of read-across (the prediction model used - worst case scenario, regression etc.). Here it could also be justified as to why read-across is sufficient, and why further testing is not needed.

[7] AOP-KB. https://aopkb.oecd.org/

[8] AOP Wiki. https://aopwiki.org/

[9] Effectopedia. https://www.effectopedia.org/

Tip

- Hypothesis needs to be described as a testable format.
- For the hypothesis that metabolite induces target effect, the effects induced by other metabolites other than the toxicant need to be considered (see "(“*2.2 Elements for a read-across hypothesis* of the case study 2015-3" (OECD, 2016d)).

Tip for nanomaterials

- Provide an explanation which parameters are critical for the analogue approach/category hypothesis.
- Hypothesis could be argued using for example the following physicochemical and chemical properties (list is not exhaustive) (see for example “ 2.2 Characterisation of the analogue nanoforms" of 2017-3 (OECD 2018d)):
  - Chemical composition
  - Surface chemistry (including coating chemicals and the coating ratio)
  - Impurity
  - Size (including primary particle diameter)
  - Shape (including surface chemistry)
  - Surface area
  - Solubility
  - Hydrophobicity
  - Zeta potential
  - Dispersibility
  - Dustiness
  - Physical hazard
  - Biological (re)activity
  - Photoreactivity
- For the complete list of parameters and more information on grouping of nanomaterials please, see "ECHA (2017a), Guidance on information requirements and chemical safety assessment Appendix R.6-1 for nanomaterials applicable to the Guidance on (Q)SARs and Grouping of Chemicals", Appendix I, Table 2: Key physicochemical parameters to be considered for grouping and read-across of nanoforms and their relevance for human health and environmental endpoints.

4. Source chemicals/Category members [See 2.3 "Selecting analogues/Creating chemical categories and setting boundaries", 4.2.2 "Step 1: Identification of potential analogues" and 5.2.2 "Step 1: Develop category hypothesis and definition and identify category members" of the grouping guidance (OECD, 2014a)]

a. Identification and selection of source chemicals/category members

- Provide the selection criteria, based on the hypothesis described in section B, that were used to identify the source chemicals/category members.
- Provide the rationale for selection of analogue(s)/category members with respect to the defined purpose and endpoint.
- Provided consideration of a selection bias in the choice of source chemicals when using the analogue or category approach (e.g. data quality and completeness, support for hypothesis etc.).

- Describe the methods used to identify the source chemicals/category members (e.g. inventories and tools used should be provided). Listing search criteria to establish initial pool of candidate analogues is helpful.
- Recommend to use positive and negative reference chemicals if possible, especially in the case of testing that it is done to support the IATA.

b. List of source chemicals/ category members

- Provide the common chemical identifiers (including CAS number, name and composition including impurities) and chemical structure(s) of the source chemicals/category members. (See 3.2.3.1.3 "Examples of categories and structural relationships" of the grouping guidance (OECD, 2014a); example of the chemical identifiers for UVCBs)

Tip

- Not only structural similarity but also impacts of structural differences to the target effect need to be considered when selecting analogues. A clear description of boundaries is also important.

5. Justification of data gap filling

a. Data gathering [See 4.2.3 "Step 2: Data gathering for the analogues" and 5.2.3 "Step 2: Gather data for each category member" of the grouping guidance (OECD, 2014a)]

- Provide a summary of the methods used for gathering the data for target and source chemicals/category members (e.g., selection criteria of the data, data source). More detailed information on the methods can be included in the Annex.

b. Data and methods [See 4.2.4 "Step 3: Evaluation of available data for adequacy", 4.2.5 "Step 4: Construct a matrix of data availability" (analogue approach); 5.2.4 "Step 3: Evaluate available data for adequacy." 5.2.5 "Step 4: Construct a matrix of data availability" (category approach) of the grouping guidance (OECD, 2014a)]. Provide a matrix of data (see data matrix template) with the following:

- If mass unit such as mg/kg-bw is used in the data, it should also be expressed in molar units such as mmol/kg-bw.
- Provide a summary of the essential data. Recommended to include the detailed data in case that the detailed data are used for the justification of the hypothesis. The appropriate degree of detail of the data should be considered in the context of the purpose of case study. Examples of reports of detailed data can be found in past IATA CSs[10]. One of the examples is Case Study 2018-1 (OECD, 2019b). More detailed or supporting information can be included in an Annex.
- If data from non-guideline test methods are included, provide descriptions of the methods or links to sources that summarise the methods. The appropriate degree of detail of the description should be considered in the context of the purpose of the case study. A template for the description is available in the OECD guidance document No. 211 (OECD, 2014c) Examples of description using the template can be found in JRC EURL ECVAM Database service on Alternative Methods to animal

[10] OECD Integrated Approaches to Testing and Assessment (IATA). http://www.oecd.org/chemicalsafety/risk-assessment/iata-integrated-approaches-to-testing-and-assessment.htm#casestudies

experimentation (DB-ALM)[11]and US EPA Toxicity ForeCaster (ToxCast™) Data [12]. More detailed information on the methods can be included in an Annex.

- If (Q)SAR data are included, provide the name, version, owner of the models used for deriving (Q)SAR estimation data. If not described elsewhere, (Q)SAR models should be reported using the QSAR Model Reporting Format (QMRF), and individual predictions, if applicable, should be reported using the QSAR Prediction Reporting Format (QPRF). A QMRF inventory is maintained by JRC that can be utilised as a resource of QMRFs and its reference number can be referred to JRC QSAR Model databases[13]. QPRF(s) and QMRF should be included in an Annex.
- If data derived from defined approaches of IATA are included, provide the descriptions of the defined approaches. A template for the description and case study examples are available in OECD guidance documents 255 and 256 (OECD, 2016h; 2016i). In this section, please describe the individual information sources used and data interpretation procedure applied (See "6. Description of the individual information sources used (see Annex II)" and "7. Data interpretation procedure applied" of the OECD guidance (OECD, 2016h)). Detailed information on the defined approaches can be included in Annex. Please refer to the section "4. Data/Information Gathering" of the case study 2018-2 (OECD, 2019c).
- Provide justification/purpose for each assay/information used. Only necessary information should be provided, avoid giving information not directly useful for your Case Study (do not provide data just because you have it).
- Provide all available suitable information regarding the defined purpose, including the data from the different IATA components (*in silico*, *in vitro* and *in vivo*, if applicable). If possible, the cells of the data matrix should also indicate the available key study results.

c. Justification [See 2.5 "Robustness of a chemical category and of an analogue approach", 2.6 "The interdependence between categories and (Q)SARs.", 4.2.6 "Step 5: Assess the adequacy of the analogue approach and fill the data gap" and 5.2.6 "Step 5: Perform a preliminary evaluation of the category and fill data gaps" of the grouping guidance (OECD, 2014a)]

- Based on the data matrix, summarise how these data support the hypothesis described in section 3.
- Identify similarities/trends in the experimental data of the endpoint(s) for the chemicals in the data matrix and verify their concordance with the hypothesis described in section 3.
- Identify which elements drive the toxicity/endpoint.
- For category approach, describe the set of inclusion and/or exclusion rules that identify the boundaries within which reliable estimations can be made for category members. A broader consideration including mechanistic information, profiling computational methods, screening with non-standard *in vitro* tests should be given. Clearly indicate the boundaries of the category and for which substances the category does not hold i.e. substances outside scope of predictions e.g. by endpoint [See 5.2.4 "Step 3: Evaluate available data for adequacy" of the grouping guidance (OECD, 2014a): example of outlier].

[11] JRC, EURL ECVAM Database service on Alternative Methods to animal experimentation (DB-ALM). https://ecvam-dbalm.jrc.ec.europa.eu/

[12] U.S. EPA, Toxicity ForeCaster (ToxCast™) Data https://www.epa.gov/chemical-research/toxicity-forecaster-toxcasttm-data

[13] JRC, QSAR Model Database. https://qsardb.jrc.ec.europa.eu/qmrf/

The applicability domain of each estimation method including (Q)SAR and alternative methods should be discussed based on the consistency between the estimation data and the experimental data of the source chemical(s)/category members.

Tip

- Reliability of each (Q)SAR prediction result needs to be described in terms of the applicability domain of (Q)SARs. For example, it can be discussed by the coverage of the fragments in the training sets (See the case study 2015-4 (OECD, 2016e)).
- It is recommended that every approach be described separately, e.g., if read-across, (Q)SAR and *in vitro* tests are used, every one of these approaches would need to be described separately before combining in IATA.
- Please explain how satisfying comprehensiveness/coverage of the data gathering is achieved.
- For transparency, the data reporting is an important aspect. For example, if estimation relies on qualitative/semi-quantitative estimation, it is important to explain how these support quantitative estimations where needed for that purpose. Further, to demonstrate coherence of findings and similarity/trend/strength of effects sufficient reporting of the experimental data is needed (e.g., type, degree, and dose levels). If data reveal inconsistencies or similar studies show different concerns this would also benefit from explanation.
- Please, try to ensure maximal use of existing experimental information before considering (Q)SAR predictions.
- Alert-based system work best for predicting an alert and not lack of it, unless there are structure-specific definitions for lack of activity

Tip for nanomaterials (See "5. JUSTIFICATION OF DATA GAP FILLING" of the case study 2017-3 (OECD, 2018d))

- Describe methods used for measuring the endpoints
- It is recommended to describe which methodologies for measurements of the relevant parameters are applied, and to describe what are differences between the methodologies are, if applicable.
- Identify which parameters are relevant to which endpoints, if possible.
- For the complete list of parameters and more information on grouping of nanomaterials, please see ECHA (2017a) "Guidance on information requirements and chemical safety assessment Appendix R.6-1 for nanomaterials applicable to the Guidance on QSARs and Grouping of Chemicals", Appendix I, Table 2: Key physicochemical parameters to be considered for grouping and read-across of nanoforms and their relevance for human health and environmental endpoints.

6. Strategy for and integrated conclusion of data gap filling

a. Uncertainty

- Discuss the uncertainty of each factor for the read- across. For the given purpose, it seems that the consideration of uncertainty may start from the choice of hypothesis (like in Appendix 1). Another consideration includes severity of effect, if it is present. (e.g., Does the number of targets matter? Could all targets meet all sources? How read-across could be addressed (e.g., subgrouping)?)

- Aspects can include uncertainty and confidence associated with all type of the data used in the IATA, including the underlying data used for read-across from the source chemicals (e.g. applicability domain, type and quality) as well as assumptions used to develop the similarity rationale of the analogues/category members and uncertainty.
- The following table provides an example of reporting uncertainty (Please modify as appropriate and also it is recommended to describe what is not addressed.): Examples of modified templates, which were used for past CSs, are shown in Appendix 1, 2,and 3. Appendix 4 lists a series of questions to guide through the assessment of uncertainties. Also, refer to the CSs published in the past[14].
- **The magnitude and impact of the sources of uncertainty should be considered** and to the extent possible, **how the individual sources of uncertainty affect the overall uncertainty in the final outcome of the IATA**. OECD guidance documents on defined approaches of IATA (" Consideration of uncertainties associated with the application of the defined approach" of OECD, 2016h; " Consideration of uncertainties associated with the application of the defined approach" of CASE STUDY I-XII of OECD, 2016i) might be helpful for considering uncertainties related to non-guideline test methods
- If AOP is used, please discuss uncertainty on AOP (e.g., endorsed AOP: the AOP approved and published by OECD vs putative AOP; the AOP not approved by OECD and established based on the known knowledge.)
- For the application of WoE approach, the ECHA WoE template[15] provides a structured template for presenting the WoE approach/ uncertainty (EU-ToxRisk, 2018)
- The EFSA guidance documents (EFSA, 2018a; 2018b) could be considered for uncertainty assessment as a good starting point. In addition, for quantitative hazard assessments, the WHO Guidance on Evaluating and Expressing Uncertainty in Hazard Assessment (WHO, 2018) can provide further support (EU-ToxRisk, 2018)
- In application of WoE, please refer to the OECD WoE guidance document (OECD, 2019d), which provides universal Guiding Principles that should be considered when developing or augmenting systematic approaches to WoE for chemical evaluation and Key Elements to formulating a systematic approach to WoE.

[14] OECD Integrated Approaches to Testing and Assessment (IATA). http://www.oecd.org/chemicalsafety/risk-assessment/iata-integrated-approaches-to-testing-and-assessment.htm#casestudies

[15] ECHA – Template for Weight of Evidence / Uncertainty in Hazard Assessment https://echa.europa.eu/documents/10162//17169198/template_for_weight_of_evidence_en.docx

Factor	Uncertainty (low, medium, high)	Impact of uncertainty on hypothesis	Comment
Hypothesis used for the read-across			
Structural similarity			
Similarity of physico-chemical properties			
Similarity of toxicokinetics data			
Similarity of other supportive data (e.g. data related to key event)			
Number of analogues used for the read-across			
Quality of the endpoint data used for the read-across			
Similarity of the endpoint data (among source chemicals)			
Concordance and weight of evidence of all data used for justifying the hypothesis			
Overall uncertainty of the read-across			

Tip

- When using ranks to indicate uncertainties (e.g., low, medium, high), definitions should be provided.

Tip for nanomaterials

- In addition to the above-mentioned aspects, the following should be considered in the characterisation of uncertainties related to the analogue/category approach for nanomaterials (See "7. UNCERTAINTY ASSESSMENT" of the case study 2017-3 (OECD, 2018d)):
  - Complexity of nanostructures: similarity, category boundaries and members
  - Identity characterisation of the nanomaterials
  - Variability of the measurements, test system relevance for nanomaterials and possible nanospecific artefacts in assays
- For more information on grouping of nanomaterials please, see "ECHA (2017a), Guidance on information requirements and chemical safety assessment Appendix R.6-1 for nanomaterials applicable to the Guidance on QSARs and Grouping of Chemicals"

b. Integrated conclusion

- Provide the strategy used to fill the data gap and integrated conclusion of data gap filling, including description how the data gap is actually filled (e.g., average, most sensitive, similarity weighted, qualitative). In case of category approach, indicate proposed conclusion/value for each data gap. If prediction models were used, please describe the satisfaction with parameters related to the prediction.
- Give discussion of remaining uncertainties and how they might be addressed.
- Finally, provide a short conclusion wrapping up the outcome of the evaluation with linking to the given purpose.

7. References

Annex

- Author can include supplemental or background data in an Annex in order to increase readability of case study if the data supports a particular aspect of the case study. The below table is an example of a summary table for *in vivo* data (Reference of Case Study 2019-4).

References	
Species/strain	
Sex	
Route of admin.	
Exposure period	
Doses	
GLP	
Test substance	
NOAEL	
Result	
Other findings	

- Author can provide a summary of methods and tools used in the case study, that a regulator may be less familiar with, such as an *in vitro* method, *in silico* ((Q)SAR) model or high throughput assay; or provide links to references of these methods for further information in order to increase readability of case study. The description should be sufficient for an expert, which a regulator may consult to get approval and better understanding of the methodology.

Appendix 1. Example of Reporting Template of Uncertainty (1)

The template was prepared based on the following frameworks and was used for the CSs 1&2 in 2015 of the project (OECD, 2016b; 2016c).

- Wu, S., K. Blackburn, J. Amburgey, J. Jaworska and T. Federle (2010) A Framework for Using Structural, Reactivity, Metabolic and Physicochemical Similarity to Evaluate the Suitability of Analogs for SAR-based toxicological assessments. Regulatory Toxicology and Pharmacology. Vol. 56, Issue 1, pp 67-81. https://doi.org/10.1016/j.yrtph.2009.09.006
- Blackburn, K. and S.B. Stuard (2014) A Framework to Facilitate Consistent Characterisation of Read Across Uncertainty. Regulatory Toxicology and Pharmacology. Vol. 68, Issue 3, pp 353-62. https://doi.org/10.1016/j.yrtph.2014.01.004

An overview of the template is shown below. Please refer to the original papers and the CSs above for details.

Part 1: Analogue suitability rating for read-across [a]

Evaluation Criteria [b]	Question [c]	Uncertainty [d]
Structure and reactivity	Do the target & analogue have similar structural features& chemical reactivity?	
Metabolism	Do the target & analogue have similar metabolic pathways?	
Physicochemical Properties	Do the target & analogue have similar phys-chem properties?	

……..		
Overall "suitability rating" [e]		

a This table is based on the decision tree of the framework by Wu et al. (2010)
b Criteria used for evaluating the suitability of analogues.
c Question and answer used for evaluating the criteria.
d Description of the uncertainties in the answer to the question.
e Rank (Suitable, Suitable with interpretation, Not suitable, Suitable with preconditions) derived from the decision tree.

Part 2: Uncertainty associated with the prediction of hazard using read-across [e]

Analogue Data Set Characteristics [f]	Comment [g]
Number of analogues contributing data	
Robustness of analogue data set	
Concordance of effect(s)	
……..	
Overall uncertainty of read-across prediction [h]	

e This table is based on the framework by Blackburn and Stuard (2014).
f Analogue data set characteristics used for evaluating overall uncertainty of read-across prediction.
g Description of the evaluation results of the analogue data set characteristics obtained by answering the questionnaire of the framework.
h Rank of overall uncertainty of read-across prediction derived from the evaluation results of analogue data set characteristics (Low, Low to Moderate, Moderate, High) with the description of the reason.

Appendix 2. Example of Reporting Template of Uncertainty (2)

The template was developed in the following framework and was used for the CSs 3&4 in 2016 of the project (OECD 2017d; 2017e) as well as in case study 4 in 2017 (OECD 2018e).

- Schultz, T.W., P. Amcoff, E. Berggren, F. Gautier, M. Klaric, D.J. Knight, C. Mahony, M. Schwarz, A. White and M.T.D. Cronin (2015), A Strategy for Structuring and Reporting a Read-across Prediction of Toxicity. Vol. 72, Issue 3, pp 586-601. https://doi.org/10.1016/j.yrtph.2015.05.016

An overview of the template is shown below. Please refer to the original paper and the CSs above for details.

Part 1: Parameters and associated uncertainty used to justify category membership

Justification Parameter [a]	Data Uncertainty [b]	Strength of Evidence [c]	Comment [d]
Structural Similarity	Table Cell (Alt+E)		
Phys/Chem Properties			
Metabolic Similarity			
Mechanistic Similarity			
Trends in Effects			
……..			
Overall uncertainty in similarity of category members			

a Similarity parameter used for justifying the category.
b Rank of uncertainty (low, medium, high) associated with underlying data used for analysis
c Rank of consistency (low, medium, high) within the data
d Description of the reason for the assignment of the ranks of the uncertainty and strength of evidence
e Rank of overall uncertainty (low, medium, high) and description of the reason

Part 2: Uncertainty associated with the prediction of hazard and dose-response using read-across

Factor [e]	Uncertainty [f]	Comment [g]
Number of analogues contributing data		
Robustness of analogue data set		
Concordance of effects		
Concordance of potency		
Severity of critical effect ……..		
Overall uncertainty of read-across (low, medium, high)		

e Uncertainty factor associated with the prediction of hazard and dose-response using read-across.
f Rank of uncertainty (low, medium, high)
g Description of the reason for the assignment of the ranks of the uncertainty
h Rank of overall uncertainty (low, medium, high) and description of the reason

Appendix 3. Examples of Reporting uncertainty Following the ECHA Read-Across Assessment Framework (RAAF)[16] (3)

Examples of assessment elements (AEs) for an analogue approach, for all RAAF read-across scenarios and detailed description of the AEs see (ECHA, 2017b).

Assessment Elements for Scenario 1 (analogue approach for read-across based on hypothesis for (bio)transformation to common compound(s))

AE A.1 Common AE: Identity and Characterisation of the source substance
AE A.2 Common AE: Link of structural similarities and differences with the proposed prediction
AE A.3 Common AE: Reliability and adequacy of the source study
AE 1.1 Scenario-specific AE: Formation of common (identical) compound(s)
AE 1.2 Scenario-specific AE: The biological targets for the common compound(s)
AE 1.3 Scenario-specific AE: Exposure of the biological target(s) to the common compound(s)
AE 1.4 Scenario-specific AE: The impact of parent compounds
AE 1.5 Scenario-specific AE: Formation and impact of non-common compounds
AE A.4 Common AE: Bias that influences the prediction

Assessment Elements for Scenario 2 (analogue approach for read-across based on hypothesis that different compounds have the same type of effects)

AE A.1 Common AE: Identity and Characterisation of the source substance
AE A.2 Common AE: Link of structural similarities and differences with the proposed prediction
AE A.3 Common AE: Reliability and adequacy of the source study
AE 2.1 Scenario-specific AE: Compounds the test organism is exposed to
AE 2.2 Scenario-specific AE: Common underlying mechanism, qualitative aspects
AE 2.3 Scenario-specific AE: Common underlying mechanism, quantitative aspects
AE 2.4 Scenario-specific AE: Exposure to other compounds than to those linked to the prediction
AE 2.5 Scenario-specific AE: Occurrence of other effects than covered by the hypothesis and justification
AE A.4 Common AE: Bias that influences the prediction

[16]ECHA, Grouping of substances and read-across

https://echa.europa.eu/support/registration/how-to-avoid-unnecessary-testing-on-animals/grouping-of-substances-and-read-across

Appendix 4. Examples for reporting uncertainty (4)

30 questions relating to 12 types of uncertainty were identified to be addressed in assessing uncertainties of a read-across in the following study:

- Terry W. Schultz, Andrea-Nicole Richarz, Mark T.D. Cronin (2019) Assessing uncertainty in read-across: Questions to evaluate toxicity predictions based on knowledge gained from CSs. Computational Toxicology, Vol. 9, pp. 1-11 https://doi.org/10.1016/j.comtox.2018.10.003

Uncertainty in Read-Across	Uncertainty in Read-Across
The context of, and relevance to, the regulatory use of the read-across prediction as defined by appropriate problem formulation	• Is the regulatory purpose of the read-across prediction clearly defined? • Is the acceptable level or degree of uncertainty for the stated purpose defined? • Is the stated acceptable level or degree of uncertainty appropriate for the stated regulatory purpose?
Type of category/group including the definition of the applicability domain	• Is the read-across approach (e.g., analogue or category) clearly reported? • Are the target and source chemicals clearly identified? • Is the applicability domain of the analogue or category defined? • Do target and source chemicals fit within the defined applicability domain?
The premise or hypothesis of the read-across.	• Is the hypothesis on which the read-across is based clearly stated and presented in sufficient detail to be assessed?
Mechanistic plausibility including completeness of the understanding of the MoA or AOP	• How clearly does the hypothesis state the chemical and biological mechanisms underpinning the toxic effect being read-across? • Is there sufficient experimental information provided to support the proposed chemical and toxicological mechanisms? • How extensively does the experimental information provided support the mechanistic plausibility and / or the AOP or MoA on which the read-across is based?
Similarity in chemistry	• Are the chemical structures (i.e., 2D structure, isomers, SMILES and molecular formula) reported for the derivatives used in the read-across? • Are the dissimilarities in chemical structure reported and are they toxicologically relevant? • Are the relevant molecular and physico-chemical properties (e.g., for molecular size, hydrophobicity, solubility, volatility, degradation etc.) reported for the derivatives used in the read-across? • Are the dissimilarities in molecular and physico-chemical properties reported and are they toxicologically (or pharmacokinetically) relevant?
Toxicodynamic similarity	• Is there sufficient and consistent toxicodynamic information provided to establish similarity in the hazard of the derivatives used in the read-across?
Toxicokinetic similarity	• Is there sufficient ADME information provided to establish toxicokinetic similarity for the derivatives used in the read-across? • Are any dissimilarities in ADME properties (and, as appropriate, metabolism / degradation) toxicologically relevant?
The quality of the apical endpoint data used to fill the data gap	• Is the performance (e.g., reliability, accuracy, precision, repeatability and reproducibility) of the data read-across reported clearly? • Has the quality of the data to be read-across been assessed and are they sufficient to meet the purpose of the exercise i.e., complete and of sufficient quality?
The consistency in the effects and severity of the apical *in vivo* hazard and their concordance with regards to the intermediate and apical effects and potency data	• Is the qualitative expression of the data reported and is it consistent among the source chemicals? • Is the potency of the hazard reported and is it consistent among the source chemicals? • What are the temporal relationships between relevant endpoints? • What are is the dose–response relationships between relevant endpoints?
Strength or robustness of the supporting datasets	• How extensively are the relevant or key events either empirically measured and/or modelled by appropriate *in silico, in chemico* and *in vitro* data? • Is the performance (e.g., reliability, accuracy, precision, repeatability and reproducibility) of the supporting methods adequately reported?
The Weight-of-Evidence (WoE) supporting the prediction	• Is there consistency in the supportive information (e.g., structural alerts) between analogues or within the category? • How many and how large are the dissimilarities in the supporting information (i.e., data gaps)?
Documentation and written evidence provided	• Is the read-across prediction adequately documented? • Does the evidence support the hypothesis that the uncertainty is acceptable for the stated purpose (as per Question 1)?

Data matrix for analogue approach

Data matix, IATA for "indication of title of case study"

Chemical ID									
		Source1	Target	Source2	Source3	Source4	Source5	Outlier1	Outlier2
CAS									
Name									
Structure									
Summary of data gap filling									
		Source1	Target	Source2	Source3	Source4	Source5	Outlier1	Outlier2
Target endpoint1	Experimental result	value, unit, test method (eg. test guide line)		value, unit, test method (eg. test guide line)		value, unit, test method (eg. test guide line)	value, unit, test method (eg. test guide line)	value, unit, test method (eg. test guide line)	value, unit, test method (eg. test guide line)
	Integrated conclusion (eg. read-across)		derived result						
Target endpoint2	Experimental result	value, unit, test method (eg. test guide line)		value, unit, test method (eg. test guide line)		value, unit, test method (eg. test guide line)	value, unit, test method (eg. test guide line)	value, unit, test method (eg. test guide line)	value, unit, test method (eg. test guide line)
	Integrated conclusion (eg. read-across)		derived result						
Molecular profiling related to the analogue approach hypothesis									
Parent chemical	Profiler 1 (name, version)								
	Expert system 1 (name, version)								
Metabolite*	Profiler 1 (name, version)								
	Expert system 1 (name, version)								
Physical-chemical data									
Melting point									
Boiling point									
Density									
logPow (measured value)									
logPow (calculated value)									

…									
Kinetics**									
Absorption									
Distribution									
Metabolism									
Excretion									
Supporting data related to the target endpoint(s)									
		Source1	Target	Source2	Source3	Source4	Source5	Outlier1	Outlier2
In vivo	Toxicogenomics								
	…								
In vitro	Alternative method A								
	…								
In chemico	…								
In silico	(Q)SAR1 (Target endpoint1)								
	(Q)SAR2 (Target endpoint1)								
	(Q)SAR3 (Target endpoint2)								
	(Q)SAR4 (*In vitro* endpoint)								
	…								
Other data	Battery approach								
	Defind approach of IATA								
	…								

* More relevant metabolite such as toxicant

**General outline of relative comparative kinetics

Data matrix for category approach

Data matix, IATA for "indication of title of case study"

Chemical ID									
		Member 1	Member 2	Member 3	Member 4	Member 5	Member 6	Member 7	Member 8
CAS									
Name									
Structure									
Summary of data gap filling									
		Member 1	Member 2	Member 3	Member 4	Member 5	Member 6	Member 7	Member 8
Target endpoint1	Experimental result	value, unit, test method (eg. test guide line)		value, unit, test method (eg. test guide line)		value, unit, test method (eg. test guide line)	value, unit, test method (eg. test guide line)	value, unit, test method (eg. test guide line)	value, unit, test method (eg. test guide line)
	Integrated conclusion (eg. read-across)		derived result		derived result				
Target endpoint2	Experimental result	value, unit, test method (eg. test guide line)		value, unit, test method (eg. test guide line)	value, unit, test method (eg. test guide line)	value, unit, test method (eg. test guide line)		value, unit, test method (eg. test guide line)	value, unit, test method (eg. test guide line)
	Integrated conclusion (eg. read-across)		derived result				derived result		
Molecular profiling related to the category hypothesis									
Parent chemical	Profiler 1 (name, version)								
	Expert system 1 (name, version)								
Metabolite*	Profiler 1 (name, version)								
	Expert system 1 (name, version)								
Physical-chemical data									
Melting point									
Boiling point									
Density									
logPow (measured value)									

logPow (calculated value)									
…									
Kinetics**									
Absorption									
Distribution									
Metabolism									
Excretion									
Supporting data related to the target endpoint(s)									
		Member 1	Member 2	Member 3	Member 4	Member 5	Member 6	Member 7	Member 8
In vivo	Toxicogenomics	result	result	result	result	result	result	result	result
	…								
In vitro	Alternative method A		result	result	result				
	…								
In chemico	…								
In silico	(Q)SAR1 (Target endpoint1)	result	result	result	result	result	result	result	result
	(Q)SAR2 (Target endpoint1)	result	result	result	result	result	result	result	result
	(Q)SAR3 (Target endpoint2)	result	result	result	result	result	result	result	result
	(Q)SAR4 (*In vitro* endpoint)	result	result	result	result	result	result	result	result
	…								
Other data	Battery approach	result	result	result	result	result	result	result	result
	Defind approach of IATA								
	…								

* More relevant metabolite such as toxicant

**General outline of relative comparative kinetics

Annex F. General Template for IATA CSs - Building Blocks

Title: Case Study on the use of Integrated Approaches for Testing and Assessment for “Target Endpoint(s)” of “Target Chemical(s)”

NOTE: The following template should not be viewed as a strict structure but rather identifies the information that should be included in this type of case study. Depending on the specific case study additional information/(sub)section(s) may be required or particular subsections may not apply. The order of the (sub)sections of the template can be changed and two or more (sub)sections of the template can be merged, as necessary. The titles of a (sub)section can be changed as necessary. The template will be revised based on experience with use.

The overview document (OECD, 2020i) helps understanding of IATA, by explaining key concepts and providing basic definitions, and to support easier access to existing resources.

Abstract / Synopsis / Executive summary

This section should provide a brief overview of the case study, including the objectives, concepts, methodologies, outcomes and conclusion in about 300 words. Please refer to Executive Summary in Case Study 2018-1 (OECD, 2019b), 2018-2 (OECD, 2019c) and 2020-1(OECD, 2021a) and Summary in 2017-3 (OECD, 2018d) as examples.

Table of Contents

Abbreviations and acronyms

1. Introduction

This should include a summary of the background/problem formulation, purpose, endpoints covered and description of the target chemical(s)/category, assessment approach

2. Purpose

a. Purpose of use

Indicate the regulatory relevance (i.e. intended application) of the IATA. This may be: a)screening for priority setting in view of further evaluation; b) hazard identification/characterisation; c) risk assessment; d) other (please specify). If more than one purpose is possible, please specify the purpose as d) other. If the IATA is used for low toxicity prediction, please define what is meant by ‘low toxicity’ for the purposes of the particular case study.

If in a regulatory context, provide a short but sufficient description of any (e.g. legal) requirements for the IATA approach to be accepted.

b. Target chemical(s)

Provide the chemical descriptor common identifiers (including CAS number, name and composition including impurities [See 3.2.3.1 "*Chemical identity and composition* of the grouping guidance (OECD, 2014a)]) and chemical structure(s) of the target substance(s). In some CSs, target chemicals may be entire chemical classes, or the IATA illustrated may be generic. Or if there are no specific target chemicals, example chemicals can be used to illustrate the IATA (SEE "1. PURPOSE" or "3. RESULTS OF ERC PRIORITISATION" of the case study 2017-2 (OECD, 2018c) and "1.2. Target Chemical(s)" at the section "A. Purpose" of the case study 2018-2(OECD, 2019c)).

c. Endpoint(s)

Identify the endpoint(s) for which the IATA is applied.

d. Exposure information (if needed)

Provide the considered exposure, such as route of exposure (dermal, oral and inhalation), type of exposure (consumer, occupational and environment), for example, if the case study addresses prioritisation or chemical assessment workflows. The inclusion of this section and its level of detail/quantification will depend on the case study.

If relevant, please describe extrapolation from *in vitro* into *in vivo*.

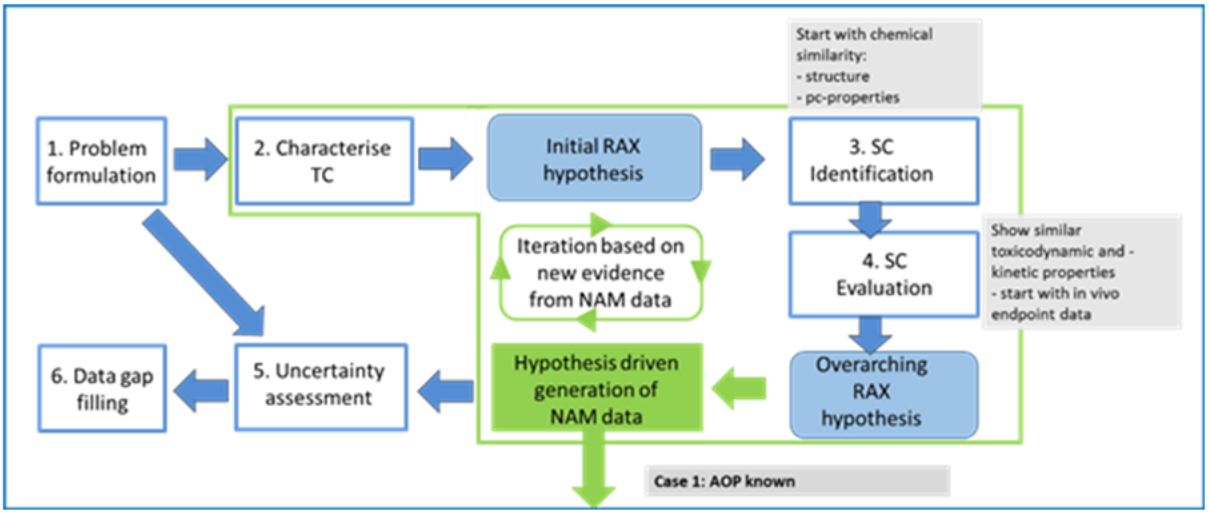
Tip

- The description of the purpose of use is important for considering the acceptable uncertainty of the case study, which could be linked to the uncertainty assessment. For example, if the conclusion derived by case study is renewable in a framework such as tiered-approach, this needs to be clearly stated (see CSs OECD, 2016b and 2016c).
- As the goal of the OECD IATA CSs project is to discuss CSs which would lead to regulatory application a description of the regulatory relevance is important to contextualise the case and discuss the further development of guidance and how to use the IATA for regulatory purpose.

3. Hypothesis for performing IATA

- Provide the hypothesis for performing IATA for the identified purpose
- Describe how the IATA will be performed for the specific purpose.
- If many steps are included in the IATA, include a figure for the workflow of the IATA applied in the case study in order to provide an overview on how the IATA work through. Please refer to Figure 1 in Case Study 2019-4 (OECD, 2020d) and Figure 2 under section 4.1 "Testing and assessment strategy" in Case Study 2019-5. (OECD, 2020e). The below figure used in Case Study 2019-5 is an example.

Figure A F.1. Example of Workflow Figure, which was used in Case Study 2019-5



4. Approaches used (Potential Blocks for Inclusion)

Describe which approaches are applied for assessing the chemicals under the provided hypothesis:

- **AOP/MoA**: Description of potential mechanism(s) for the target chemicals to induce target endpoint toxicity. In particular, the graphical representation of the AOP would be helpful for the reader and key references (See "Graphical Representation of the AOP" at section "1- AOP Description" of "User's Handbook supplement to the Guidance Document for developing and accessing Adverse Outcome Pathways" (OECD, 2016h)). The tools in the AOP-KB [17] should be referred to as appropriate (e.g., AOP wiki[18], Effectopedia[19] etc.).

  Identifying the relevant AOP from AOP wiki is required. Please provide the AOP number, status on AOP-wiki and the link. For AOPs that are not documented, consider the "Section 1-AOP Description" of "Users' Handbook supplement to the Guidance Document for developing and accessing Adverse Outcome Pathways" (OECD, 2016h) - although an entire AOP description is not the purpose here. If needed, the entire AOP can be described in Annex.

  If an AOP together with testing of various MIE/KE/AO is used in the case study, a figure demonstrating the alignment of the AOP with the various tests should be included. Please refer to Figure 1 in Case Study 2018-2 (OECD, 2019c), Figure 3 in Case Study 2019-4 (OECD, 2020d), Figure 7 in Case Study 2019-5 (OECD, 2020e), Figure 2 (A and B) in Case study 2019-7 (OECD, 2020g) and Figure 5.1 (A and B) in Case Study 2019-8 (OECD, 2020h). The below figure is an example of the figure demonstrating the alignment of the AOP with the various tests, which was used in Case Study 2019-7. The figure indicated where the assay is available and not available.

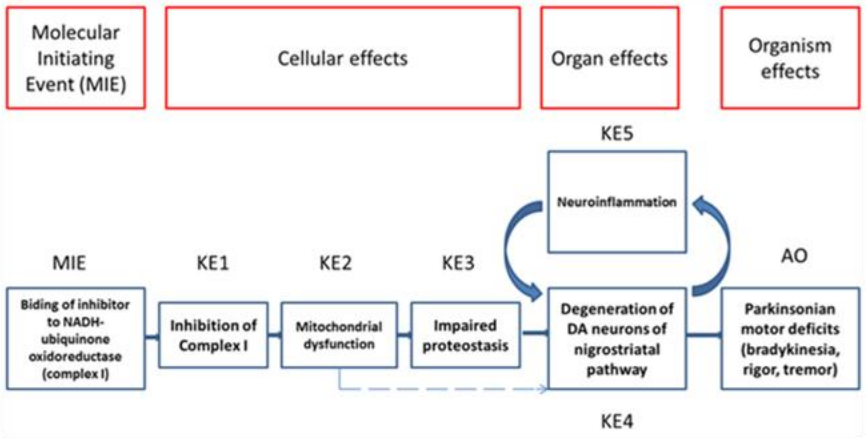
[17] AOP-KB. https://aopkb.oecd.org/

[18] AOP Wiki. https://aopwiki.org/

[19] Effectopedia. https://www.effectopedia.org/

Figure A F.2. Example of AOP figure together with MIE/KE/AO, which was used in Case Study 2019-7

A)



B)

Key event	MIE	KE1	KE2	KE3	KE4	AO
Assay	Receptor Docking studies	Seahorse assay (complex inhibition and whole cell)	Mitochondrial membrane potential assay	Protease activity assay	Viability assays (Resazurin, PI, ATP)	
	Similarity studies			CHOP-GFP expression	Neuronal health (outgrowth and degeneration)	
Key event					KE5	
Assay					No assay available	

- **Defined Approach**: If a defined approach is included, please refer to the ANNEX I: TEMPLATE FOR REPORTING DEFINED APPROACHES TO TESTING AND ASSESSMENT BASED ON MULTIPLE INFORMATION SOURCES" of "Guidance Document on the Reporting of Defined Approaches to be used within Integrated Approaches to Testing and Assessment" (OECD, 2016h). Please copy into this section the "*5. Rationale underlying the construction of the defined approach*" from the above-mentioned template (OECD, 2016h), completed with proper explanations. The elements described in the section "3. Approaches Used" of the case study 2018-2 (OECD, 2019c) can be helpful for development of an IATA using Defined Approach.
- **Workflow**: If an IATA workflow is included, provide a schematic and explanation of the elements of the workflow including input, decision and exit points. If prioritisation is the goal of IATA workflow, provide an explanation of how to classify the hazard and exposure profiling and potential risk classification. Please refer to the section "CHEMICAL SAFETY ASSESSMENT WORKFLOW" of the case study 2016-5 (OECD, 2017f), "3.3 IATA Workflow" of the case study 2017-1 (OECD, 2018b) and the section "2. PRIORITISATION OF CHEMICALS USING AN IATA-BASED ERC APPROACH" of the case study 2017-2 (OECD, 2018c), the section "2. PRIORITISATION OF CHEMICALS USING AN IATA-BASED ERC APPROACH" of the case study 2017-2 (OECD, 2018c) and "2. Hypothesis for performing IATA and Approaches used" of the case study 2020-1(OECD, 2021a).

- **Read-across**: If a read-across is included, use elements of the template for IATA CSs on Read-Across or the grouping guidance (OECD, 2014a). Please refer to "*4. Identification of analogues, suitability assessment and existing data*" of the case study 2016-5 (OECD, 2017f) and "4.1. Analogue chemicals" of the case study 2017-1 (OECD, 2018b).

5. Data/Information gathering

In this section, please describe the test methods or data sources used for gathering data for target chemicals

a. Data/Information

- Provide the methods used for gathering the data for target chemical(s) (e.g. selection criteria of the data, data source).
- Provide the data gathered using appropriate reporting format. The levels details for reporting the data should be considered depending on the purpose of the IATA.
- If data from non-guideline test methods are included, provide descriptions of the methods or links to sources that summarise the methods. The appropriate degree of detail of the description should be considered in the context of the purpose of the case study. More detailed information on the methods can be included in an Annex. A template for the description is available in an OECD guidance document (OECD, 2014c). Examples of description using the template can be found in JRC EURL ECVAM Database service on Alternative Methods to animal experimentation (DB-ALM)[20] and US EPA Toxicity ForeCaster (ToxCast™) Data[21].
- If (Q)SAR data are included, provide the name, version, owner of the models used for deriving (Q)SAR estimation data. If not already described elsewhere (Q)SAR models should be reported using the QSAR Model Reporting Format (QMRF)[22], and individual predictions, if applicable, should be reported using the QSAR Prediction Reporting Format (QPRF)[23]. A QMRF inventory is maintained by JRC that can be utilised as a resource of QMRFs and its reference number can be referred to JRC QSAR Model databases[24]. QPRF(s) and QMRF should be included in Annex.
- If the exposure elements are included, provide the methods used for the data generation (e.g. data source, exposure models/tools.) Please refer to "2. Identification of the use scenario of the case study 2016-5 (OECD, 2017f)" and "*Exposure profiling*" of the case study 2017-2 (OECD, 2018c) If PBK models are included, please refer to OECD guidance (OECD, 2021b) of PBK which provide characterisation, Validation and Reporting of PBK models.
- If a defined approach is included, please refer to the template of "Guidance Document on the Reporting of Defined Approaches to be used within Integrated Approaches to Testing and Assessment" (OECD, 2016h). In this section, please describe the individual information sources used and data interpretation procedure applied (See *"6. Description of the individual information sources used (see Annex II)"* and *"7. Data interpretation procedure applied"* of the OECD guidance (OECD, 2016h). Detailed information on the defined approaches can be included in the Annex. Please refer to the section "4. Data/Information Gathering" of the case study 2018-2 (OECD,

[20] JRC, EURL ECVAM Database service on Alternative Methods to animal experimentation (DB-ALM). https://ecvam-dbalm.jrc.ec.europa.eu/.

[21] U.S. EPA, Toxicity ForeCaster (ToxCast™) Data https://www.epa.gov/chemical-research/toxicity-forecaster-toxcasttm-data

[22] QMRF is available: https://community.oecd.org/docs/DOC-144256

[23] QPRF is available: https://community.oecd.org/docs/DOC-144257

[24] JRC, QSAR Model Database. https://qsardb.jrc.ec.europa.eu/qmrf/

2019c). Please also refer to OECD guideline, “Defined Approaches on Skin Sensitisation” (OECD, 2025e)

- If high throughput or omics data are used then indicate how the data has been applied in the specific case study i.e. to support *in vivo*/*vitro* data or any other reason etc.
- Provide justification/purpose for each assay/information used. Only necessary information should be provided, avoid giving information not directly useful for your Case Study (do not provide data just because you have it).

b. Analogue chemicals.

- If the data of analogue chemicals were used for the IATA, provide the selection criteria that were used to identify the analogue chemicals. This can be based on the hypothesis described in section 3.
- Provide rational for selection of analogue(s) with respect to the defined purpose and endpoint.
- Consider selection bias selecting analogue chemicals in relation to employment of the IATA (e.g. data completeness, support for hypothesis etc.).
- Describe the methods used to identify the analogue chemicals (e.g. inventories and tools used should be provided). Listing search criteria to establish initial pool of candidate analogues is helpful.
- Provide the common chemical identifiers (including CAS number, name and composition including impurities) and chemical structure(s) of the analogue chemicals.
- Recommend to use positive and negative reference chemicals if possible, especially in the case of testing that is done to support the IATA.

6. Application of IATA

a. Summary of data

- Provide a summary of data in a suitable format for the purpose of IATA.
- Reliability of data should be discussed.
- The applicability domain of each estimation method including (Q)SAR and alternative methods should be discussed
- Provide analysis of the available information for suitability regarding the defined purpose. If possible, the available key study results should be indicated.

b. Application of IATA

- Describe how to apply IATA based on the hypothesis and the data gathered.
- Describe the result of IATA.
- Refine the hypothesis used, if necessary.

c. Uncertainty

- Discuss the uncertainty of each element of the IATA. We recommend to use a table to describe the uncertainty of each element. The following table provides an example of reporting uncertainty (Please modify as appropriate and also it is recommended to describe what is not addressed.) Also, you can refer the past CSs which the general template was applied. (Case Study 2017-2 (OECD, 2018c); Case Study 2018-2 (OECD, 2019c))
- Aspects can include uncertainty and confidence associated with the data and assumptions used to develop hypothesis.
- The magnitude and impact of the sources of uncertainty should be considered and to the extent possible, how the individual sources of uncertainty affect the overall uncertainty in the final outcome of the IATA. OECD guidance documents on defined approaches of IATA *(“Consideration of*

uncertainties associated with the application of the defined approach" OECD, 2016h; "*Consideration of uncertainties associated with the application of the defined approach"* of CASE STUDY I-XII of OECD, 2016i) might be helpful for considering uncertainties related to non-guideline test methods. The uncertainty approaches outlined in the template for IATA CSs on Read-Across would be helpful for performing the uncertainty analysis.

- If AOP is used, please discuss uncertainty on AOP (e.g., endorsed AOP: the AOP approved and published by OECD vs putative AOP; the AOP not approved by OECD and established based on the known knowledge.).
- For the application of WoE approach, the ECHA WoE template [25]provides a structured template for presenting the WoE approach/ uncertainty (EU-ToxRisk, 2018).
- The EFSA guidance documents (EFSA, 2018a; 2018b) could be considered for uncertainty assessment as a good starting point. In addition, for quantitative hazard assessments, the WHO Guidance on Evaluating and Expressing Uncertainty in Hazard Assessment (WHO, 2018) can provide further support (EU-ToxRisk 2018).
- In application of WoE, please refer to the OECD WoE guidance document (OECD, 2019d), which provides universal Guiding Principles that should be considered when developing or augmenting systematic approaches to WoE for chemical evaluation and Key Elements to formulating a systematic approach to WoE

Factor	Uncertainty (low, medium, high)	Impact of uncertainty on hypothesis	Comment
Hypothesis			
Used Approach (e.g. AOP/MoA, Defined Approach, workflow, read-across etc.)			
Methods/assays used in the IATA			
Data/information gathered in the IATA			
Quality of the data/information used in the IATA			
Concordance and weight of evidence of all data used for justifying the hypothesis			
Overall uncertainty of the IATA			

Tip

- When using ranks to indicate uncertainties (e.g. low, medium, high), definitions should be provided.

d. Strategy and integrated conclusion

- Describe the strategy used to develop the integrated conclusion.
- Discuss how/if to further address the uncertainties.
- Finally, provide a short conclusion wrapping up the outcome of the evaluation.

[25] ECHA – Template for Weight of Evidence / Uncertainty in Hazard Assessment https://echa.europa.eu/documents/10162//17169198/template_for_weight_of_evidence_en.docx

7. References

(*See OECD style guide third edition, p.56 "Bibliographical referencing: Sources and citations"*)

Annex

- Author can include supplemental or background data in an Annex in order to increase readability of case study if the data supports a particular aspect of the case study. The below table is an example of a summary table for *in vivo* data (Reference to Annex I and II in Case Study 2018-1 (OECD, 2019b); Annex IV in Case Study 2019-4 (OECD, 2020d)).

References	
Species/strain	
Sex	
Route of admin.	
Exposure period	
Doses	
GLP	
Test substance	
NOAEL	
Result	
Other findings	

- Author can provide a summary of methods and tools used in the case study, that a regulator may be less familiar with, such as an *in vitro* method, *in silico* ((Q)SAR) model or high throughput assay; or provide links to references of these methods for further information in order to increase readability of case study. The description should be sufficient for an expert, which a regulator may consult to get approval and better understanding of the methodology.

Appendix 5. List of CSs from Previous Cycles used as Example in the Template

Case Study No.	Case Study Title	Referred Information	Relevant template section	Why this example works well
2015-1	*In Vitro* Mutagenicity of 3,3' Dimethoxybenzidine (DMOB) Based Direct Dyes	1.1. Purpose of use, Page 10	2. Purpose; Purpose of use	The section provides a clear and concise overview of the purpose of use including the regulatory purpose. This helps the readers understand how much extent of the uncertainty is acceptable in the case study, which could be linked to the uncertainty assessment.
2015-2	Repeat Dose Toxicity of Substituted Diphenylamines (SDPA)	1.1. Purpose of use, Page 9	2. Purpose; Purpose of use	The section provides a clear and concise overview of the purpose of use including the regulatory purpose. This helps the readers understand how much extent of the uncertainty is acceptable in the case study, which could be linked to the uncertainty assessment.
2016-5	Chemical Safety Assessment Workflow Based on Exposure Considerations and Non-animal Methods	Schema of the chemical safety assessment workflow, Fig. 1, Page 11	4. Approaches Used; Workflow	The workflow presented in this figure provides a clear and concise overview of the case study, which helps to guide the reader through.
		TIER 0: Identification of the use scenario, chemical of interest and collection of existing information; use scenario, Page 11	5. Data/Information gathering; Exposure	This subsection describes the exposure scenario applied in the IATA such as use product, concentration and exposure route.
		4. Identification of analogues, suitability assessment and existing data, Page 13-14	4. Approaches Used; Read-across	This section describes the possibility for utility of read-across approach as one of the components in the case study.
		CHEMICAL SAFETY ASSESSMENT WORKFLOW PROPOSED, Page 11-24	5. Data/Information gathering; Summary text box	The summary textboxes provides a conclusion under each section, which makes readers understand what conclusion is observed.
2017-1	Estrogenicity of Substituted Phenols	IATA workflow, Fig. 3, Page 22	4. Approaches Used; Workflow	The workflow presented in this figure provides a clear and concise overview of the case study, which helps to guide the reader through.

		4.1. Analogue chemicals, Page 26-33	4. Approaches Used; Read-across	The section provides a clear and concise overview of approaches to select analogues with figures and tables in the workflow case study.
2017-2	Prioritization of chemicals using the Integrated Approaches for Testing and Assessment (IATA)-based Ecological Risk Classification	1. PURPOSE, Page 12	2. Purpose: target chemical	The section includes a clear and concise description of the target chemicals that 640 organic substances were evaluated based on the IATA and that the results of 3 chemicals were showed as example.
		Framework for the ecological risk classification, Fig.1, Page 15	4. Approaches Used; Workflow	The framework presented in this figure provides a clear and concise overview of the case study, which helps to guide the reader through.
		2.2. Hazard and exposure profiling in the ERC approach, Exposure profiling, Page 20-21	5. Data/Information gathering; Exposure	This subsection describes how exposure profiling was determined and provides the information on data source.
		3.3. Uncertainties identified in the ERC approach, Table 5, Page 34-35	6. Application of IATA; Uncertainty	This uncertainty table provides an overview of the uncertainty analysis for each element associated with the IATA-based prioritisation.
2017-3	Case study on grouping and read-across for nanomaterials genotoxicity of nano-TiO_2	SUMMARY, Page 8	Abstract / Synopsis / Executive summary	This summary is concise and includes the elements described in this template.
2018-1	Case Study on the use of Integrated Approaches for Testing and Assessment for Testicular Toxicity of Ethylene Glycol Methyl Ether (EGME)-Related Chemicals	Executive Summary, Page 7	Abstract / Synopsis / Executive summary	This summary is concise and includes the elements described in this template.
		Annex I and Annex II. Page 35-59,	Annex: A summary table for *in vivo* data	The summary table provides a robust summary for *in vivo* assay.
2018-2	Case Study on the Use of an Integrated Approach to Testing and Assessment for Identifying Estrogen Receptor Active Chemicals	Executive Summary, Page 7	Abstract / Synopsis / Executive summary	This summary is concise and includes the elements described in this template.
		1.2. Target Chemical, Page 13	2. Purpose: target chemical	The section includes a clear and concise description of the target chemicals that there are no specific target chemicals.
		Representation of the ER pathway and computational	4. Approaches Used; AOP	The figure provides a clear and concise overview of the putative AOP along with

		model, Fig.1, Page 16		testing for MIE/KE/AO applied in the case study, which helps to guide the reader through.
		3. Approaches Used, Page 15-16	4. Approaches Used; Defined approach	The description provides the hypothesis including element of defined approach.
		4. Data/Information Gathering, Page 17-24	5. Data/Information gathering; Defined Approach	This section describes an integrated battery of *in vitro* assays and a computational model with figures and tables, which provide an overview of data/information gathering procedure.
		5.4. Uncertainty, Table 5, Page 34-35	6. Application of IATA; Uncertainty	This uncertainty table provides an overview of the uncertainty analysis for each element associated with the IATA-based prioritisation.
2019-4	Case Study on the Use of Integrated Approaches for Testing and Assessment for Repeated-Dose Toxicity of p-Alkylphenols	Read-across workflow in this case study, Fig.1	3. Hypothesis for performing IATA; Figure for a Workflow	The figure provide a clear and concise workflow in this case study, which helps to guide the reader through.
		Overview of hepatotoxic mechanism of p-alkylphenols, Fig.3	4. Approaches Used; AOP	The figure provides a clear and concise overview of the putative AOP along with testing for MIE/KE/AO applied in the case study, which helps to guide the reader through.
		Annex IV	Annex: A summary table for *in vivo* data	The summary table provides a robust summary for *in vivo* assay.
2019-5	Prediction of a 90 day repeated dose toxicity study (OECD 408) for 2-Ethylbutyric acid using a read-across approach to other branched carboxylic acids	Overview of the six traditional assessment steps within the read-across assessment, Fig.2	3. Hypothesis for performing IATA; Figure for a Workflow	The figure provide a clear and concise workflow in this case study, which helps to guide the reader through.
		Overview on test systems used for hazard characterization, Fig.7	4. Approaches Used; AOP	The figure provides a clear and concise overview of the putative AOP along with testing for MIE/KE/AO applied in the case study, which helps to guide the reader through.
2019-7	Identification and characterization of parkinsonian hazard liability of deguelin by an AOP-based testing and read-across approach	AOP on inhibition of the mitochondrial complex I of nigrostriatal neurons leading to parkinsonian motor deficits, Fig.2	4. Approaches Used; AOP	The figure provides a clear and concise overview of the endorsed AOP along with testing for MIE/KE/AO applied in the case study, which helps to guide the reader through.

2019-8	Waiving of repeat-dose neurotoxicity study (TG 424) for azoxystrobin based on Read-Across to other strobilurins	AOP on the inhibition of mitochondrial complex III leading to neurotoxic effects, Fig.5.1	4. Approaches Used; AOP	The figure provides a clear and concise overview of the putative AOP along with testing for MIE/KE/AO applied in the case study, which helps to guide the reader through.
2020-1	Case Study on the use of Integrated Approaches for Testing and Assessment for the Systemic Toxicity of Phenoxyethanol when included at 1% in a body lotion	1.1. Purpose of use,	2. Purpose; Purpose of use	The section provides a clear and concise overview of the purpose of use. This helps the readers understand how much extent of the uncertainty is acceptable in the case study, which could be linked to the uncertainty assessment.
		IATA workflow, Fig. 2	4. Approaches used ; Workflow	The framework presented in this figure provides a clear and concise overview of the case study, which helps to guide the reader through.

Annex G. Physiologically Based Kinetic (PBK) Model Reporting Template

PBK Model Reporting Template sections	Brief description of information to report for each section
A. Name of model	Provide a title of the model. The same should be reported in the checklist.
B. Model developer and contact details	Contact details of model developer.
C. Summary of model characterisation, development, validation, and regulatory applicability	Please capture main points in a brief summary regarding the development, validation and regulatory application.
D. Model characterisation (modelling workflow) Step 1 – Scope and purpose of the model (problem formulation) Step 2 – Model conceptualisation (model structure, mathematical representation) Step 3 – Model parameterisation (parameter estimation and analysis) Step 4 – Computer implementation (solving the equations) Step 5 – Model Performance Step 6 – Model Documentation	Follow the 6 steps of the modelling workflow chapter two. Report in detail the model structure, model biologically plausibility, and parameters with assumptions and limitations, tables can be placed under section H. parameter tables. Under model performance report information on sensitivity analysis, predictive performance. Strategy on how the model validation was performed, e.g. using analogues or other sources or approaches should be reported in detail.
E. Identification of uncertainties model structure input parameters model output other uncertainties (e.g. model developed for different substance and/or purpose) *comparison with other existing PBK models (if available), list differences and/or compatibility*	For each step of the modelling workflow uncertainties should be reported. Use the information provided in the guidance to report and assess (e.g. table in figure 3.3. to capture information on sensitivity and uncertainty for input parameters). For each identified uncertainties, please rate how this uncertainty impacts the overall model applicability (i.e. low, medium or high impact).
F. Model implementation details software (version no) availability of code software verification / qualification	Information on the model equation solver/software to run the equation should be reported here.
G. Peer engagement (input/review)	Report the extent of peer engagement and review in development of the model.
H. Parameter tables	All information relevant to model parameterisation should be included here: physiological anatomical, physicochemical and biochemical. Report values and units and the source of the parameters (e.g. in case of *in vitro* studies detailed experimental conditions and motivation for choice of experimental conditions in case of non-guideline studies, in case of *in silico* studies add information on models).

References and background information publications links to other resources	Main reference and publications linked to development and description of the model

Please refer to the OECD guidance document of the PBK models (OECD, 2021b) for more information.