Organisation for Economic Co-operation and Development

ENV/CBC/MONO(2023)31

Unclassified

English - Or. English

17 August 2023

ENVIRONMENT DIRECTORATE

CHEMICALS AND BIOTECHNOLOGY COMMITTEE

REPORT ON CONSIDERATIONS FROM CASE STUDIES ON INTEGRATED APPROACHES FOR TESTING AND ASSESSMENT (IATA)

Eighth Review Cycle (2022)

Series on Testing and Assessment
No. 385

JT03524207

OECD Environment, Health and Safety Publications

SERIES ON TESTING AND ASSESSMENT

NO. 385

REPORT ON CONSIDERATIONS FROM CASE STUDIES ON INTEGRATED APPROACHES FOR TESTING AND ASSESSMENT (IATA)

EIGHTH REVIEW CYCLE (2022)

IOMC

INTER-ORGANIZATION PROGRAMME FOR THE SOUND MANAGEMENT OF CHEMICALS

A cooperative agreement among FAO, ILO, UNDP, UNEP, UNIDO, UNITAR, WHO, World Bank and OECD

Environment Directorate

ORGANISATION FOR ECONOMIC COOPERATION AND DEVELOPMENT

Paris 2023

About the OECD

The Organisation for Economic Co-operation and Development (OECD) is an intergovernmental organisation in which representatives of 38 industrialised countries in North and South America, Europe and the Asia and Pacific region, as well as the European Commission, meet to co-ordinate and harmonise policies, discuss issues of mutual concern, and work together to respond to international problems. Most of the OECD's work is carried out by more than 200 specialised committees and working groups composed of member country delegates. Observers from several countries with special status at the OECD, and from interested international organisations, attend many of the OECD's workshops and other meetings. Committees and working groups are served by the OECD Secretariat, located in Paris, France, which is organised into directorates and divisions.

The Environment, Health and Safety Division publishes free-of-charge documents in twelve different series: **Testing and Assessment**; **Good Laboratory Practice and Compliance Monitoring**; **Pesticides**; **Biocides**; **Risk Management**; **Harmonisation of Regulatory Oversight in Biotechnology**; **Safety of Novel Foods and Feeds; Chemical Accidents; Pollutant Release and Transfer Registers; Emission Scenario Documents; Safety of Manufactured Nanomaterials;** and **Adverse Outcome Pathways.** More information about the Environment, Health and Safety Programme and EHS publications is available on the OECD's World Wide Web site (www.oecd.org/chemicalsafety/).

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

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

This publication is available electronically, at no charge.

- **Also published in the Series on Testing and Assessment: link**

For this and many other Environment, Health and Safety publications, consult the OECD's World Wide Web site (www.oecd.org/chemicalsafety/)

or contact:

OECD Environment Directorate,
Environment, Health and Safety Division
2 rue André-Pascal
75775 Paris Cedex 16
France

E-mail: ehscont@oecd.org

OECD Environment, Health and Safety Publications

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 to assess 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 Studies Project is to share experiences using NAMs by developing case studies, which illustrate examples of chemical assessments that are designed to address regulatory decision contexts. The case studies are reviewed on an annual cycle and discussed with experts who provide input on the technical and implementation aspects. From all case studies reviewed in each cycle, general considerations are summarised in a document to help create a common understanding of using novel methodologies and to highlight considerations around the development and implementation of IATAs.

This document reports the learnings and lessons from reviewing two case studies submitted in the 2022 eighth review cycle of the IATA Case Studies Project. The topics discussed in this document include each case study's strongest aspects and uncertainties. In addition, from the collective review of all IATA Case Studies submitted to date, this document also highlights topics for further guidance identified by reviewers.

These case studies 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 case studies should not be interpreted as an official regulatory decision made by the authoring Member Countries.

This document is published under the responsibility of the Chemicals and Biotechnology Committee of the OECD.

Table of contents

Tables

Figures

Abbreviations

ANN	Artificial Neural Network
AOP	Adverse Outcome Pathway
BIAC	Business at OECD
BMD	Benchmark dose
BN-ITS	Bayesian Network Integrated Testing Strategy
Cat.	Category
CLP	Classification, Labelling and Packaging
CoCAP	Cooperative Chemicals Assessment Programme
CS	Case Study
DA	Defined Approach
DAL	Defined approach liquid
DASS	Defined Approaches on Skin Sensitisation
DEA	Diethanolamine
DIP	Data interpretation procedure
DPRA	Direct Peptide Reactivity Assay
GHS	Globally Harmonized System of Classification and Labelling of Chemicals
h-CLAT	Human Cell Line Activation Test
HRIPT	Human repeat insult patch test
IATA	Integrated Approaches for Testing and Assessment
ITS	Integrated Testing Strategy
LLNA	Local lymph node assay
MoA	Mode of Action
MoE	Margin of exposure
MoIE	Margin of internal exposure
NAM	New Approach Method
NM	Nanomaterial
OECD	Organisation for Economic Co-operation and Development
PARC	Partnership for the Assessment of Risks from Chemicals
PBK	Physiologically Based Kinetic. PBK is synonymous of physiology-based pharmacokinetic (PBPK), physiologically-based biokinetic (PBBK) and physiologically-based toxicokinetic (PBTK).
PoD	Point of departure
(Q)SAR	(Quantitative) Structure-Activity Relationship
SARA	Skin Allergy Risk Assessment
STS	Sequential Testing Strategy
TG	OECD Test Guideline
UN	United Nations
WHO	World Health Organization
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 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] 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 case studies, 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 case studies.

Case studies 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 Case Studies Project Team. The discussion includes the strongest aspects, uncertainties, areas for further guidance, and possible uses of each case study in a regulatory context. Following each review cycle, approved studies are published, along with a Considerations document capturing the learnings and lessons stemming from case studies in the annual cycle, and of all case studies reviewed to date. The past seven review cycles of the project (2015-2021) included 32 case studies and seven Considerations 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 case studies 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 case studies should not be interpreted as official regulatory decisions made by the authoring Member Countries.

Two case studies were reviewed in the eighth review cycle (2022) (Table A B.1). This document briefly summarises each case study, the learnings and lessons in this (eighth) review cycle, and all 34 IATA Case Studies reviewed since the project began.

[1] OECD, Cooperative Chemicals Assessment Programme (CoCAP). http://www.oecd.org/chemicalsafety/risk-assessment/oecdcooperativechemicalsassessmentprogramme.htm

[2] OECD, IATA Case Studies Project. http://www.oecd.org/chemicalsafety/risk-assessment/iata-integrated-approaches-to-testing-and-assessment.htm

2 Learnings and Lessons

2.1. Learnings from the Eighth Review Cycle

This section describes the learnings gained through the review of the two case studies submitted in the 2022 eighth review cycle. In this review cycle, both case studies followed OECD Test Guideline (TG) Defined Approaches (DA). The first case study (CS2022-1[3]) demonstrated a Next Generation Risk Assessment (NGRA) framework for Diethanolamine (DEA) using information sources combined in DAs, including those described in the OECD Test Guideline Defined Approach for Skin Sensitisation (OECD TG 497) (OECD, 2021d)). The second case study (CS2022-2[4]) evaluated the potential eye hazard of four non-surfactant neat liquids following the approaches described in the OECD Test Guideline Defined Approach for Eye (OECD TG 467) (OECD, 2022j). Three topics, described in the subsections below, were selected as learnings from this review cycle during the expert discussion that took place at the eighth OECD IATA Case Study Project meeting on 15-16 November 2022.

2.1.1. How to understand different outcomes from multiple DAs.

CS2022-1 (OECD, 2023a) demonstrated how various information sources can be combined differently, in six DAs, and can lead to different conclusions regarding the potential of DEA to act as a skin sensitiser. Given that two of the six DAs included in OECD TG 497 (OECD, 2021d) (Integrated Testing Strategy (ITS) v1 and ITS v2) resulted in different predictions, this case study may be a good example to evaluate the divergent results from more than one DA.

Information sources were combined following the workflow of the DAs described in TG 497. The applicability domain of each assay or computational model must be considered to determine the most appropriate DA for a particular substance and the associated confidence in the DA result. This is recognised in TG 497 (OECD, 2021d), which notes: "*the applicability domain of the individual information sources used in the ITS DA are assessed, and this determines whether the ITS predictions can be considered conclusive (i.e., high confidence) or inconclusive (i.e., low confidence) for hazard identification and/or potency. These 'inconclusive' predictions may nevertheless be considered in a weight-of-evidence approach and/or within the context of an IATA together with other information sources*."

A negative outcome for skin sensitisation potential was obtained from the Direct Peptide Reactivity Assay (DPRA) and KeratinoSens™. A positive outcome for skin sensitisation was obtained from the U-SENS™ and h-CLAT. Due to the possibility that DEA could be a pro-hapten, using the DPRA and KeratinoSensTM data requires careful review, as this is a recognised limitation of these test systems (OECD 2018f; OECD 2021f).

[3] OECD, 2023a

[4] OECD, 2023b

In CS2022-1 (OECD, 2023a), differences in the results of the TG DAs were the result of differences in the *in silico* predictions (i.e., outcomes from Derek Nexus in ITS v1 and the OECD QSAR Toolbox in ITS v2). Derek Nexus predicted DEA to be a skin sensitiser and the outcome of ITS v1 (score of 2) was within the range of the United Nations Globally Harmonized System of Classification and Labelling of Chemicals (GHS) Category (Cat.) 1B for moderate to weak sensitisers. The OECD Toolbox v4.4 automated workflow for Defined Approaches on Skin Sensitisation (DASS) predicted DEA to be a non-sensitiser, and the outcome of ITS v2 (score of 1) was within the UN GHS range for substances that do not require classification (No Cat) range. Both the ITS v1 and ITS v2 include the DPRA as an information source, and as noted, DEA is considered out of domain, hence, the No Cat prediction from ITS v2 (score of 1) would be interpreted as inconclusive (OECD TG 497(OECD, 2021d)).

Considering the low confidence results of the DPRA and differing predictions of the ITSv1 and ITSv2, a conservative, weight of evidence approach would lead to the conclusion that DEA is more likely to be a weak/moderate skin sensitiser than a non-sensitiser based on positive h-CLAT and DEREK NEXUS result. Thus, in this case DEA is considered UN GHS Cat. 1B.

The authors also noted that ITS predictions may be influenced by the specific version of the *in silico* information sources, as *in silico* tools are regularly updated with new expert knowledge that may affect predictions. The authors noted that it is important to document the versions of *in silico* tools used in the risk assessment. Thus, the ITS in TG 497 (OECD, 2021d) are based on Derek Nexus v 6.1.0 and the OECD Toolbox v. 4.5 software.

In CS2022-1, the applicability of six different DAs (ITSv1, ITSv2, Artificial Neural Network (ANN), Sequential Testing Strategy (STS), Bayesian Network Integrated Testing Strategy (BN-ITS) and Skin Allergy Risk Assessment (SARA) model) was investigated. The authors did not choose to select a single DA for the DEA risk assessment, but rather, to use this case study as a demonstration that risk assessment with all DAs is possible. The selection of DAs to consider will depend on the following:

- accessibility to the DA,
- experience in the use of a certain DA,
- the type of prediction required from a DA (e.g., UN GHS classification or quantitative potency prediction),
- the existing NAM information available to populate a DA.

2.1.2. Development of a Fixed data interpretation procedure (DIP)

Both CS2022-1 and 2022-2 demonstrate the use of DAs consisting of select information sources used in a specific combination and combined using a fixed data interpretation procedure (DIP) to derive a prediction without the need for expert judgment. Compared to weight of evidence approaches used in an IATA which include an element of expert judgment, DAs are standardised, reproducible approaches that can become TGs. The OECD TG DAs accepted to date have included relatively simple, rules-based DIPs. However, more complex DIPs can address incomplete information sources, provide quantification of the uncertainty, and address the prediction coverage in the context of the applicability domain directly within the model prediction. Some considerations around Bayesian network models are described used in CS2022-1. It should be noted that the SARA DA is under considerations for including in an update to TG 497.

CS2022-1

In this case study, six DAs are applied, each with a unique DIP. Two DAs, the SARA model and BN-ITS, both of which are Bayesian network models and allow for the quantification of the uncertainty in the

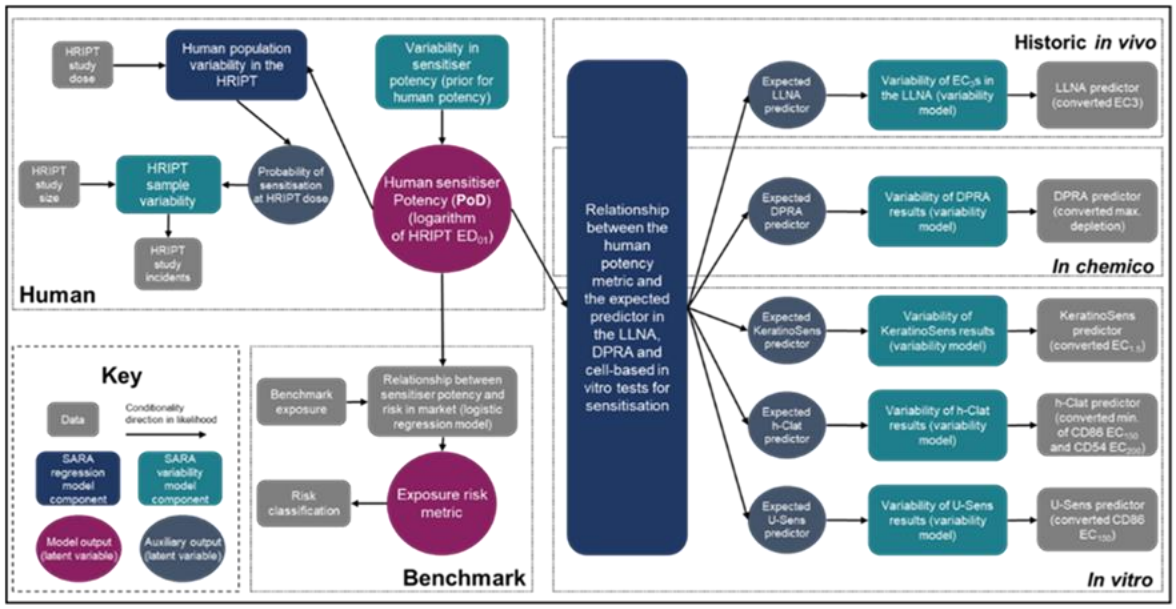
prediction, are summarised in the sections below. Because the BN model automatically assesses uncertainty based on the criteria, it eliminates judgment by the users. From a regulatory perspective, it is not necessary to individually assess the uncertainty of each prediction, but it is sufficient to determine an acceptable level of uncertainty based on the regulatory purpose.

SARA model

The SARA model (Gilmour et al., 2022) utilises a Bayesian multilevel modelling approach and has the following features:

- Utilises any combination of Human repeat insult patch test (HRIPT), LLNA, Direct Peptide Reactivity Assay (DPRA), KeratinoSens™, Human Cell Line Activation Test (h-CLAT) or U-SENS™ data, which allows the exploration of the value of NAM data (DPRA, KeratinoSens™, h-CLAT and U-SENS™) compared to *in vivo* data (LLNA and HRIPT) and a WoE across all available data.
- Sensitiser potency is expressed as the ED_{01} (the dose in µg/cm^2, predicted to sensitise 1% of an HRIPT population), with explicit quantification of the uncertainty in the prediction.
- Provides a probability that a consumer exposure scenario can be classified as low risk.
- Aims to derive a human sensitiser potency, in contrast to other DAs which characterise skin sensitisation potency by predicting the outcome of an LLNA.
- Provides a measure of the risk based on an exposure scenario, whereas, most of DAs aim to replace the animal test independently.

Figure 2.1. Schematic of the relationships between variables in the SARA DA (Reynolds and Gilmour et al, 2022



The Bayesian model in the SARA DA allows a quantitative description of uncertainty and attempts to account for the uncertainty in the strength of the relationship between the data sources. The fundamental

assumption behind this modelling approach is that there is a quantifiable relationship between the individual data sources (OECD, 2023a). However, the SARA risk metric should be used on a case-by-case basis within a weight-of-evidence framework to facilitate decisions on consumer safety and reach an overall risk assessment conclusion (Gilmour et al., 2022) (Reynolds and Gilmour et al., 2022).

For more details on how the Bayesian network model is interpreted in the SARA DAs, please refer to CS2022-1 (OECD, 2023a), CS2021-8 (OECD, 2022h) and Appendix A. of Supplementary data of Reynolds J and Gilmour et al. (2022).

BN-ITS

BN-ITS also uses a Bayesian Network (BN) and encoded skin sensitisation AOP structure and data related to KE 1 (DPRA), 2 (KeratinoSens™), 3 (h-CLAT) that represent the first three key events of the AOP. The potency probability distribution gives the predicted dose resulting in a simulation index (pEC3) in 4 potency classes and allows expressing the prediction as a probability distribution. Advantages of expressing the prediction as a probability distribution includes a quantification of uncertainty and removes prediction bias introduced by the training set potency distribution (Jaworska et al. 2015).

Other features of BN ITS are as follows (OECD, 2023a):

- uses information on metabolic transformation and auto-oxidation from TIMES-SS (*in silico*) in the prediction process.
- uses only relevant or available data for predictions since the BN-ITS can reason based on partial information. This allows explicit consideration of the applicability domains of individual assays. Data outside of domains can be excluded in the integrated prediction or treated with caution according to the prediction process.
- it is adaptive, as it can run with only partial evidence; it allows to add more evidence if needed to make a decision.
- assesses consistency in evidence and identifies conflict between input data.
- guides potential additional testing by quantifying the additional test information value before testing is commenced.

CS2022-2

CS2022-2 used two DAs which were recently adopted as OECD TG for investigating eye hazard potential of non-surfactant liquids (TG 467, 2022j). The CS used the combination of physicochemical properties and *in vitro* data (DAL-1) or *in vitro* data only (DAL-2) for a prediction. The physicochemical properties in DAL-1 were measured according to OECD TGs or predicted from QSARs.

Stand-alone in vitro methods included in OECD TG 467 (OECD, 2022j) cannot accurately predict moderate eye irritation (eye irritation, UN GHS Cat. 2). Therefore, these must be used as part of testing strategies that combine the strengths of individual *in vitro* test methods to address the required ranges of irritation potential covered by the rabbit eye test (TG 405) (OECD, 2021g; Scott et al., 2010).

- In circumstances where data on all the components of the DAs are available and are within the applicability domain of each component, the Bottom-Up (begins with test methods that can accurately identify non-irritants) or Top-Down (begins with test methods that can accurately identify severe irritants) approaches of DAs can be used. If the chemical is assumed a severe eye irritant, it is recommended to follow the Top-Down approach, and if the chemical is assumed not to cause eye irritation, it is recommended to follow the Bottom-Up approach.

- In circumstances where no data are available, the physicochemical properties can be estimated with QSAR models. If the exclusion rules[5] are not met, further testing is required depending on the recommendation of the Top-Down or Bottom-Up approaches.

CS2022-2 illustrated with four chemicals for which all components are available, and both Top-Down and Bottom-Up approaches of DAs were applied. The purpose of this case study demonstrates the applicability of the DAs and their potential to successfully distinguish between the 3 UN GHS categories for eye hazard identification.

CS2022-2 concluded overall uncertainty for DAL-1 and DAL-2 was low because the Top-Down and Bottom-Up approaches came to the same hazard assessment conclusion with a low uncertainty.

2.1.3. How to select the reference chemicals for IATA approaches.

The selection of a set of numerous structural and biological diverse reference chemicals is a critical element for evaluating the suitability of NAMs. In this section, a summary of how reference chemical selection affected the NAMs in the eighth review cycle is discussed briefly using 2022-2.

Reference chemicals of CS2022-1 are not described in detail in this section, however, information on the reference chemicals of for the skin sensitisation DAs (ITS v1 and ITSv2) can be found in OECD TG 497 (OECD, 2022d) and Supporting Document (OECD, 2022e).

Some general considerations regarding appropriate selection of reference chemicals are included In the Supporting Document for evaluation and review of TG 467 (OECD, 2022k), as identified by Barroso et al (2017). The following criteria should be considered when selecting the reference chemicals:

1) Chemicals that cover that range of GHS predictions (No. Cat., Cat. 2, and Cat. 1),
2) Important drivers of classification[6].
3) Purity of the chemicals.
4) Relevance of the chemicals, in terms of their representative functional and chemical classes and industrial use.

Although CS2022-2 describe a selection of reference chemicals which cover different organic functional groups rather than typical cosmetic ingredients, reviewers pointed out that main source of uncertainty was the selection and small number of the reference chemicals. This section summarises the relationship between the number of reference chemicals and the quality of the data using CS2022-2.

OECD (2005) states that a sufficient number of coded reference chemicals should be tested to exclude bias but does not provide specific numbers. In TG 467, the number of reference substances used to evaluate the DAL-1 and DAL-2 were between N=17 for Cat. 1, N=22 to 24 for Cat. 2 and at least N=46 for No Cat. The reference chemicals were selected based on the key criteria indicated above. The four chemicals for CS2022-2 were chosen from the set used to evaluate the DAs and met the criteria.

The supporting document (OECD, 2022k) noted uncertainty relating to the derived Cat. 1 and Cat. 2 accuracies (correct predictions), as compared with the No Cat. Accuracies, due to the lower number of reference chemicals within these categories. Unfortunately, because of the limited number of available

[5] OECD TG 467 (OECD, 2022j),

[6] As described by Barroso et al (2017), there are nine different criteria derived from the four tissue effects (corneal opacity (CO), iritis (IR), conjunctival redness (CR), and conjunctival chemosis (CC).) that can each independently drive the classification of a chemical

high quality Draize Eye test results with a Cat. 1 or Cat. 2 classifications, it was impossible to increase the number of chemicals. Applying the IATA to a larger number of (non-surfactant, liquid) chemicals would increase confidence in the result; however, using chemicals that meet the criteria is a higher priority.

2.2. Topics identified for further guidance development from all IATA Case Studies reviewed

Over the eight review cycles, the *Consideration* documents have identified priorities for identifies topics related to IATAs and new approach methods (NAMs) used within IATAs which could benefit from additional guidance. At the 8th OECD IATA CSP meeting in November 2022, the IATA CSP discussed to update the table of topics for additional guidance within the *Considerations* document to evaluate updated priorities, relevance, and provide feedback on the willingness to lead development of additional guidance based on feedback from WPHA and the Chemicals and Biotechnology Committee of the OECD. After the meeting, the Secretariat sent a survey to prioritise the topics identified in *Consideration* documents and endpoints to be addressed by NAMs to the IATA CSP team in November 2022 and sent the same request to the WPHA in March 2023. Please refer to ENV/CBC/HA(2023)7 for a summary of the survey results.

3 Conclusion

Two CSs were reviewed in the eighth review cycle of the project in 2022. Three consideration topics from the eighth review cycle are discussed in this document.

- How to understand different outcomes from multiple DAs in CS-2022-1?
- How is the fixed data interpretation procedure (DIP) applied to data to derive a prediction without the need for expert judgment in CS-2022-2?
- How to select the reference chemicals for IATA approaches?

Based on the review experience of all review cycles, priority areas for further developing guidance were identified. The Secretariat sent a survey to prioritise the topics identified in *Consideration* documents and endpoints to be addressed by NAMs to the IATA CSP and the WPHA in 2023. Further discussion will take place based on the result of this survey.

In summary, the considerations obtained from the two case studies in the eighth review cycle provided new knowledge on understanding the different results of DAs and variety of DIPs and selecting the reference chemical. These lessons and learnings provide key considerations for the use of the NAMs in the context of the IATAs, especially DAs.

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

References

Adriaens, E., Alépée, N., Kandarova, H., Drzewieckac, A., Gruszka, K., Guest, R., Willoughby, J.A. Sr., Verstraelen, S., Van Rompay, A.R. (2017). CON4EI: Selection of Reference Chemicals for Hazard Identification and Labelling of Eye Irritating Chemicals. Toxicol. In Vitro 44, 44-48. https://doi.org/10.1016/j.tiv.2017.06.001

Barroso J, Pfannenbecker U, Adriaens E, Alépée N, Cluzel M, De Smedt A, Hibatallah J, Klaric M, Mewes KR, Millet M, Templier M, McNamee P (2017). Cosmetics Europe compilation of historical serious eye damage/eye irritation in vivo data analysed by drivers of classification to support the selection of chemicals for development and evaluation of alternative methods/strategies: the Draize eye test Reference Database (DRD). Arch Toxicol (2017) 91:521–547.

Berggren, E. et al. (2017) 'Ab initio chemical safety assessment: A workflow based on exposure considerations and non-animal methods', Computational Toxicology. Elsevier, 4, pp. 31–44. doi: 10.1016/J.COMTOX.2017.10.001.

Blackburn, K. and S.B. Stuard (2014) A Framework to Facilitate Consistent Characterization of Read Across Uncertainty. Regulatory Toxicology and Pharmacology. Vol. 68, No. 3, pp 353-62.

Borenstein M, Hedges LV, Higgins JPT and Rothstein HR (2009). Introduction to meta-analysis. Wiley, Chichester, UK. CEE (Collaboration for Environmental Evidence)(2016). Systematic mapping. Available online: http://environmentalevidence.org/wp-content/uploads/2014/05/EE_InstructionsforAuthors_SYSTMAPS.pdf

Dent, M. P. et al. (2018) 'Principles underpinning the use of new methodologies in the risk assessment of cosmetic ingredients', Computational Toxicology, 7, pp. 20–26. doi: 10.1016/J.COMTOX.2018.06.001.

ECHA (2016), Practical guide. How to use and report (Q)SARs. Version. 3.1. Available

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, ECHA-17-G-17-EN, ECHA, Helsinki.

ECHA (2017b), Read-Across Assessment Framework (RAAF), ECHA-17-R-01-EN, ECHA, Helsinki.

EFSA(2014), Guidance on Expert Knowledge Elicitation in Food and Feed Safety Risk Assessment, EFSA Journal 2014;12(6):3734. https://www.efsa.europa.eu/fr/efsajournal/pub/3734

EFSA(2017), Guidance on the use of the weight of evidence approach in scientific assessments, EFSA Journal 2017;15(8):4971. https://www.efsa.europa.eu/en/efsajournal/pub/4971

EFSA (2018a), Guidance on Uncertainty Analysis in Scientific Assessments, EFSA Journal 2018;16(1):5123, 39 pp. https://doi.org/10.2903/j.efsa.2018.5123

EFSA (2018b) Principles and methods behind EFSA's Guidance on Uncertainty Analysis in Scientific Assessment. EFSA Journal 2018;16(1):5122, 282 pp. https://doi.org/10.2903/j.efsa.2018.5122

EU-ToxRisk (2018), Recommendations of the EU-ToxRisk Regulatory Advisory Board (RAB) on how to document case studies for regulatory evaluation

Gautier F, Tourneix F, et al (2020). Read-across can increase confidence in the Next Generation Risk Assessment for skin sensitisation: A case study with resorcinol. Regul Toxicol Pharmacol. 2020 Nov;117:104755. doi: 10.1016/j.yrtph.2020.104755. Epub 2020 Aug 13.

Gilmour N.; Reynolds J.; Przybylak K.; Aleksic M.; Aptula N.; Baltazar M.T.; Cubberley R.; Rajagopal R.; Reynolds G.; Spriggs S. et al. (2022) Next generation risk assessment for skin allergy: Decision making using new approach methodologies. Regulatory Toxicology and Pharmacology

Gilmour N & Kern PS, Alépée N, Boislève F, Bury D, et al. (2020) Development of a next generation risk assessment framework for the evaluation of skin sensitisation of cosmetic ingredients. Regulatory Toxicology and Pharmacology: 104721.

Gosling JP, Andy Hart H, Owen David M, Li J and MacKay C (2013). A Bayes linear approach to 25 weight-of-evidence risk assessment for skin allergy. Bayesian Analysis, 8, 169–186

IPCS (2005), International Programme on Chemical, Safety Workshop on Incorporating Uncertainty Variability into Risk Assessment (2000: Berlin, Germany); Chemical-Specific Adjustment Factors for Interspecies Differences and Human Variability: Guidance Document for Use of Data in Dose/Concentration-Response Assessment, Geneva, World Health Organization. https://apps.who.int/iris/handle/10665/43294.

J.S. Jaworska, A. Natsch, C. Ryan, J. Strickland, T. Ashikaga, M. Miyazawa. Bayesian integrated testing strategy (ITS) for skin sensitization potency assessment: a decision support system for quantitative weight of evidence and adaptive testing strategy. Arch. Toxicol., 89 (12) (2015), pp. 2355-2383, 10.1007/s00204-015-1634-2

Linkov I, Welle P, Loney D, Tkachuk A, Canis L, Kim JB and Bridges T(2011), Use of multicriteria decision analysis to support weight of evidence evaluation. Risk Analysis, 31, 1211–1225.

Linkov I, Massey O, Keisler J, Rusyn I and Hartung T (2015). From “weight of evidence” to quantitative data integration using multicriteria decision analysis and Bayesian methods. Altex, 32, 3–8.

Li Y and Ngom A (2015). “Data integration in machine learning,” Bioinformatics and Biomedicine (BIBM). 2015 IEEE International Conference on, Washington, DC, 2015, pp. 1665–1671.

OECD(2004) The report from the expert group on (Quantitative) Structure-Activity Relationships [(Q)SARs] on the principles for the validation of (Q)SARs. Series on Testing & Assessment No. 49. ENV/JM/MONO(2004)24, OECD, Paris. Available at https://www.oecd.org/chemicalsafety/testing/series-testing-assessment-publications-number.htm

OECD(2005) Guidance document on the validation and international acceptance of new or updated test methods for hazard assessment. Series on Testing & Assessment No. 34. ENV/JM/MONO(2005)14, OECD, Paris. Available at https://www.oecd.org/chemicalsafety/testing/series-testing-assessment-publications-number.htm

OECD (2007). Guidance Documents on the Validation of (Quantitative) Structure-Activity Relationship [(Q)SAR] Models. Series on Testing & Assessment No. 69. ENV/JM/MONO(2005)14, , Paris. Available at http://www.oecd.org/chemicalsafety/testing/series-testing-assessment-publications-number.htm

OECD (2014a). Guidance on Grouping of Chemicals, Second Edition, Series on Testing & Assessment No. 194. ENV/JM/MONO(2014)4, OECD, Paris. Available at http://www.oecd.org/chemicalsafety/testing/series-testing-assessment-publications-number.htm.

OECD (2014b). Weight of Evidence Assessment for the Skin Sensitisation Potential of 4-Isopropylaniline (Cumidine, CAS 99-88-7), Series on Testing & Assessment No. 199. ENV/JM/MONO(2014)5, OECD,

Paris. Available at http://www.oecd.org/chemicalsafety/testing/series-testing-assessment-publications-number.htm.

OECD (2014c). Guidance Document for Describing Non-Guideline In Vitro Test Methods, Series on Testing and Assessment No. 211. ENV/JM/MONO(2014)35, OECD, Paris. Available at http://www.oecd.org/chemicalsafety/testing/series-testing-assessment-publications-number.htm.

OECD (2016a). Report on Considerations from Case Studies on Integrated Approaches for Testing and Assessment (IATA), First Review Cycle (2015), Case Studies on Grouping Methods as a Part of IATA, Series on Testing & Assessment No. 250. ENV/JM/MONO(2016)48, OECD, Paris. Available at http://www.oecd.org/chemicalsafety/testing/series-testing-assessment-publications-number.htm.

OECD (2016b). Case Study on the Use of Integrated Approaches for Testing and Assessment for *In vitro* Mutagenicity of 3,3' Dimethoxybenzidine (DMOB) Based Direct Dyes, Series on Testing & Assessment No. 251. ENV/JM/MONO(2016)49, OECD, Paris. Available at http://www.oecd.org/chemicalsafety/testing/series-testing-assessment-publications-number.htm.

OECD (2016c). Case Study on the Use of Integrated Approaches for Testing and Assessment for Repeat Dose Toxicity of Substituted Diphenylamines (SDPA), Series on Testing & Assessment No. 252. ENV/JM/MONO(2016)50, OECD, Paris. Available at http://www.oecd.org/chemicalsafety/testing/series-testing-assessment-publications-number.htm.

OECD (2016d). Case Study on the Use of an Integrated Approach to Testing and Assessment for Hepatotoxicity of Allyl Esters, Series on Testing & Assessment No. 253. ENV/JM/MONO(2016)51, OECD, Paris. Available at http://www.oecd.org/chemicalsafety/testing/series-testing-assessment-publications-number.htm.

OECD (2016e). Case Study on the Use of an Integrated Approach to Testing and Assessment of the Bioaccumulation Potential of Degradation Products of 4,4'-Bis(Chloromethyl)-1,1'- Biphenyl, Series on Testing & Assessment No. 254. ENV/JM/MONO(2016)52, OECD, Paris. Available at http://www.oecd.org/chemicalsafety/testing/series-testing-assessment-publications-number.htm.

OECD (2016g). Users' Handbook supplement to the Guidance Document for developing and accessing Adverse Outcome Pathways, Series on Testing & Assessment No. 233, OECD Series on Adverse Outcome Pathways No. 1, ENV/JM/MONO(2016)12, OECD, Paris. Available at http://www.oecd.org/chemicalsafety/testing/series-testing-assessment-publications-number.htm.

OECD (2016h). Guidance Document on the Reporting of Defined Approaches to Be Used within Integrated Approaches to Testing and Assessment No. 255, ENV/JM/MONO(2016)28, OECD, Paris. Available at http://www.oecd.org/chemicalsafety/testing/series-testing-assessment-publications-number.htm.

OECD (2016i). Guidance Document on the Reporting of Defined Approaches and Individual Information Sources to Be Used within Integrated Approaches to Testing and Assessment (IATA) for Skin Sensitisation, Series on Testing and Assessment No. 256, ENV/JM/MONO(2016)29, OECD, Paris. Available at http://www.oecd.org/chemicalsafety/testing/series-testing-assessment-publications-number.htm.

OECD (2016j) Guidance Document for the use of Adverse Outcome Pathways in developing Integrated Approaches to Testing and Assessment (IATA), Series on Testing and Assessment No. 260, ENV/JM/MONO(2016)67, OECD, Paris. Available at http://www.oecd.org/chemicalsafety/testing/series-testing-assessment-publications-number.htm

OECD (2017a). Report on Considerations from Case Studies on Integrated Approaches for Testing and Assessment (IATA), Second Review Cycle (2016), Series on Testing & Assessment No. 270. ENV/JM/MONO(2017)22, OECD, Paris. Available at http://www.oecd.org/chemicalsafety/testing/series-testing-assessment-publications-number.htm.

OECD (2017b). Case Study on the Use of an Integrated Approach to Testing and Assessment for

Repeated-Dose Toxicity of Phenolic Benzotriazoles, Series on Testing & Assessment No. 271. ENV/JM/MONO(2017)23, OECD, Paris. Available at http://www.oecd.org/chemicalsafety/testing/series-testing-assessment-publications-number.htm.

OECD (2017c). Case Study on the Use of Integrated Approaches for Testing and Assessment for Pesticide Cumulative Risk Assessment & Assessment of Lifestage Susceptibility, Series on Testing & Assessment No. 272. ENV/JM/MONO(2017)24, OECD, Paris. Available at http://www.oecd.org/chemicalsafety/testing/series-testing-assessment-publications-number.htm.

OECD (2017d). Case Study on the Use of Integrated Approaches for Testing and Assessment of 90-Day Rat Oral Repeated-Dose Toxicity for Selected n-Alkanols: Read-Across, Series on Testing & Assessment No.273. ENV/JM/MONO(2017)25, OECD, Paris. Available at http://www.oecd.org/chemicalsafety/testing/series-testing-assessment-publications-number.htm.

OECD (2017e). Case Study on the Use of Integrated Approaches for Testing and Assessment of 90-Day Rat Oral Repeated-Dose Toxicity for Selected 2-Alkyl-1-alkanols: Read-Across, Series on Testing & Assessment No. 274. ENV/JM/MONO(2017)26, OECD, Paris. Available at http://www.oecd.org/chemicalsafety/testing/series-testing-assessment-publications-number.htm.

OECD (2017f). Chemical Safety Assessment Workflow Based on Exposure Considerations and Non-Animal Methods, Series on Testing & Assessment No. 275. ENV/JM/MONO(2017)27, OECD, Paris. Available at http://www.oecd.org/chemicalsafety/testing/series-testing-assessment-publications-number.htm.

OECD (2017g) Guidance Document on the Reporting of Defined Approaches and Individual Information Sources to be Used within Integrated Approaches to Testing and Assessment (IATA) for Skin Sensitisation, Available at https://www.oecd-ilibrary.org/content/publication/9789264279285-en.

OECD (2018a). Report on Considerations from Case Studies on Integrated Approaches for Testing and Assessment (IATA), Third Review Cycle (2017), Series on Testing & Assessment No. 289. ENV/JM/MONO(2018)25, OECD, Paris. Available at http://www.oecd.org/chemicalsafety/testing/series-testing-assessment-publications-number.htm.

OECD (2018b). Case Study on the Use of Integrated Approaches for Testing and Assessment (IATA) for Estrogenicity of Substituted Phenols, Series on Testing & Assessment No. 290. ENV/JM/MONO(2018)26, OECD, Paris. Available at http://www.oecd.org/chemicalsafety/testing/series-testing-assessment-publications-number.htm.

OECD (2018c). Prioritisation of chemicals using the Integrated Approaches for Testing and Assessment (IATA)-based Ecological Risk Classification, Series on Testing & Assessment No. 291. ENV/JM/MONO(2018)27, OECD, Paris. Available at http://www.oecd.org/chemicalsafety/testing/series-testing-assessment-publications-number.htm.

OECD (2018d). Case Study on Grouping and Read-across for Nanomaterials Genotoxicity of Nano-TiO_2, Series on Testing & Assessment No. 292. ENV/JM/MONO(2018)28, OECD, Paris. Available at http://www.oecd.org/chemicalsafety/testing/series-testing-assessment-publications-number.htm.

OECD (2018e). A Case Study on the Use of Integrated Approaches for Testing and Assessment for Sub-Chronic Repeated-Dose Toxicity of Simple Aryl Alcohol Alkyl Carboxylic Esters: Read-Across, Series on Testing & Assessment No. 293. ENV/JM/MONO(2018)29, OECD, Paris. Available at http://www.oecd.org/chemicalsafety/testing/series-testing-assessment-publications-number.htm.

OECD (2018f). Test No. 442D: In vitro Skin Sensitisation, OECD, Paris. Available at https://www.oecd-ilibrary.org/content/publication/9789264229822-en.

OECD (2018g). Guidance Document on Good In Vitro Method Practices (GIVIMP). , Series on Testing & Assessment No. 286. OECD, Paris. Available at https://www.oecd-ilibrary.org/environment/guidance-document-on-good-in-vitro-method-practices-givimp_9789264304796-en?itemId=/content/publication/9789264304796-

en&_csp_=19b7fbedc5127ff0a5ec1cb241841ac0&itemIGO=oecd&itemContentType=book

OECD (2019a). Report on Considerations from Case Studies on Integrated Approaches for Testing and Assessment (IATA), Fourth Review Cycle (2018), Series on Testing & Assessment No. 307. ENV/JM/MONO(2019)26, OECD, Paris. Available at http://www.oecd.org/chemicalsafety/testing/series-testing-assessment-publications-number.htm.

OECD (2019b). Case Study on the Use of an Integrated Approach to Testing and Assessment for Testicular Toxicity of Ethylene Glycol Methyl Ether (EGME)-Related Chemicals, Series on Testing & Assessment No. 308. ENV/JM/MONO(2019)27, OECD, Paris. Available at http://www.oecd.org/chemicalsafety/testing/series-testing-assessment-publications-number.htm.

OECD (2019c). Case Study on the Use of Integrated Approaches for Testing and Assessment for Estrogen Receptor Active Chemicals, Series on Testing & Assessment No. 309. ENV/JM/MONO(2019)28, OECD, Paris. Available at http://www.oecd.org/chemicalsafety/testing/series-testing-assessment-publications-number.htm.

OECD (2019d), Guiding Principles and Key Elements for Establishing a Weight of Evidence for Chemical Assessment, Series on Testing and Assessment No. 311, ENV/JM/MONO(2019)31, OECD, Paris. Available at http://www.oecd.org/chemicalsafety/testing/series-testing-assessment-publications-number.htm.

OECD (2020a). Case Study on use of an Integrated Approach to Testing and Assessment (IATA) and New Approach Methods to Inform a Theoretical Read-Across for Dermal Exposure to Propylparaben from Cosmetics, Series on Testing & Assessment No. 320. ENV/JM/MONO(2020)16, OECD, Paris. Available at http://www.oecd.org/chemicalsafety/testing/series-testing-assessment-publications-number.htm.

OECD (2020b). Case Study on the use of Integrated Approaches for Testing and Assessment for Systemic Toxicity Arising from Cosmetic Exposure to Caffeine, Series on Testing & Assessment No. 321. ENV/JM/MONO(2020)17, OECD, Paris. Available at http://www.oecd.org/chemicalsafety/testing/series-testing-assessment-publications-number.htm.

OECD (2020c). Case Study on the Use of Integrated Approaches for Testing and Assessment for 90-Day Rat Oral Repeated-Dose Toxicity of Chlorobenzene-Related Chemicals, Series on Testing & Assessment No. 322. ENV/JM/MONO(2020)18, OECD, Paris. Available at http://www.oecd.org/chemicalsafety/testing/series-testing-assessment-publications-number.htm.

OECD (2020d). Case Study on the Use of Integrated Approaches for Testing and Assessment to Inform Read-Across of p-Alkylphenols: Repeated-Dose Toxicity, Series on Testing & Assessment No. 323. ENV/JM/MONO(2020)19, OECD, Paris. Available at http://www.oecd.org/chemicalsafety/testing/series-testing-assessment-publications-number.htm.

OECD (2020e). Case Study on the Use of Integrated Approaches to Testing and Assessment for 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, Series on Testing & Assessment No. 324. ENV/JM/MONO(2020)20, OECD, Paris. Available at http://www.oecd.org/chemicalsafety/testing/series-testing-assessment-publications-number.htm.

OECD (2020f). Case Study on the Use of Integrated Approaches to Testing and Assessment for Read-Across Based Filling of Developmental Toxicity Data Gap for Methyl Hexanoic acid, Series on Testing & Assessment No. 325. ENV/JM/MONO(2020)21, OECD, Paris. Available at http://www.oecd.org/chemicalsafety/testing/series-testing-assessment-publications-number.htm.

OECD (2020g). Case Study on the Use of Integrated Approaches to Testing and Assessment for Identification and Characterisation of Parkinsonian Hazard Liability of Deguelin by an AOP-based Testing and Read Across Approach., Series on Testing & Assessment No. 326. ENV/JM/MONO(2020)22, OECD, Paris. Available at

http://www.oecd.org/chemicalsafety/testing/series-testing-assessment-publications-number.htm.

OECD (2020h). Case Study on the Use of Integrated Approaches to Testing and Assessment for Mitochondrial Complex-III-Mediated Neurotoxicity of Azoxystrobin - Read-Across to Other Strobilurins, Series on Testing & Assessment No. 327. ENV/JM/MONO(2020)23, OECD, Paris. Available at http://www.oecd.org/chemicalsafety/testing/series-testing-assessment-publications-number.htm.

OECD (2020i). Report on Considerations from Case Studies on Integrated Approaches for Testing and Assessment (IATA) - Fifth Review Cycle on Testing & Assessment No. 328. ENV/JM/MONO(2020)24, OECD, Paris. Available at http://www.oecd.org/chemicalsafety/testing/series-testing-assessment-publications-number.htm

OECD (2020j). Overview of Concepts and Available Guidance related to Integrated Approaches to Testing and Assessment (IATA), Series on Testing and Assessment No. 329, OECD, Paris. Available at http://www.oecd.org/chemicalsafety/risk-assessment/concepts-and-available-guidance-related-to-integrated-approaches-to-testing-and-assessment.pdf

OECD (2021a). Case Study on the Use of the use of Integrated Approaches for Testing and Assessment for the Systemic Toxicity of Phenoxyethanol when included at 1% in a body lotion, Series on Testing & Assessment No. 349. ENV/CBC/MONO(2021)35, OECD, Paris. Available at https://www.oecd.org/officialdocuments/publicdisplaydocumentpdf/?cote=ENV/CBC/MONO(2021)35&docLanguage=En

OECD (2021b). Guidance Document on Characterisation, Validation and Reporting of PBK models for Regulatory Purposes, Series on Testing & Assessment No. 331, OECD, Paris. Available at https://www.oecd.org/officialdocuments/publicdisplaydocumentpdf/?cote=ENV-CBC-MONO(2021)1&doclanguage=en

OECD (2021c). Report on Considerations from Case Studies on Integrated Approaches for Testing and Assessment (IATA) - Sixth Review Cycle, Series on Testing & Assessment No. 350. ENV/CBC/MONO(2021)36, OECD, Paris. Available at https://www.oecd.org/officialdocuments/publicdisplaydocumentpdf/?cote=ENV-CBC-MONO(2021)36&doclanguage=en

OECD (2021d). Guideline No. 497: Defined Approaches on Skin Sensitisation, OECD, Paris. Available at https://www.oecd.org/env/guideline-no-497-defined-approaches-on-skin-sensitisation-b92879a4-en.htm

OECD (2021e). Supporting document to the OECD Guideline 497 on Defined Approaches for skin sensitisation. Series on Testing & Assessment No. 336. ENV/CBC/MONO(2021)11, OECD, Paris. Available at https://www.oecd.org/chemicalsafety/testing/series-testing-assessment-publications-number.htm

OECD (2021f) Guideline No. 442C: In Chemico Skin Sensitisation: Assays addressing the Adverse Outcome Pathway key event on covalent binding to proteins, OECD Guidelines for the Testing of Chemicals, Section 4, OECD Publishing, Paris, https://doi.org/10.1787/9789264229709-en.

OECD (2021g). Guideline No. 405: In Vivo Eye Irritation/Serious Eye Damage, OECD, Paris. Available at https://www.oecd.org/env/test-no-405-acute-eye-irritation-corrosion-9789264185333-en.htm#:~:text=Test%20No.%20405%3A%20Acute%20Eye%20Irritation%2FCorrosion%20This%20method,is%20intended%20preferably%20for%20use%20with%20albino%20rabbit.

OECD (2022a). Case study for the integration of in vitro data in the developmental neurotoxicity hazard identification and characterisation using deltamethrin as a prototype chemical, Series on Testing & Assessment No.362. ENV/CBC/MONO(2022)24, OECD, Paris. Available at http://www.oecd.org/chemicalsafety/testing/series-testing-assessment-publications-number.htm

OECD (2022b). Case study for the integration of in vitro data in the developmental neurotoxicity hazard identification and characterisation using flufenacet, Series on Testing & Assessment No.363. ENV/CBC/MONO(2022)25, OECD, Paris. Available at http://www.oecd.org/chemicalsafety/testing/series-testing-assessment-publications-number.htm

OECD (2022c). Case study on the use of integrated approaches to testing and assessment for DNT to prioritize a class of compounds using Organophosporus flame retardants, Series on Testing & Assessment No.364. ENV/CBC/MONO(2022)26, OECD, Paris. Available at http://www.oecd.org/chemicalsafety/testing/series-testing-assessment-publications-number.htm

OECD (2022d). Case Study on the use of Integrated Approaches for Testing and Assessment for developmental neurotoxicity hazard characterisation of acetamiprid, Series on Testing & Assessment No.365. ENV/CBC/MONO(2022)27, OECD, Paris. Available at http://www.oecd.org/chemicalsafety/testing/series-testing-assessment-publications-number.htm

OECD (2022e). Case Study on the use of Integrated Approaches for Testing and Assessment for developmental neurotoxicity hazard characterisation of imidacloprid and the metabolite desnitro-imidacloprid, Series on Testing & Assessment No. 366. ENV/CBC/MONO(2022)28, OECD, Paris. Available at http://www.oecd.org/chemicalsafety/testing/series-testing-assessment-publications-number.htm

OECD (2022f). Case Study on the use of Integrated Approaches to Testing and Assessment for potential Systemic Toxicity and Estrogen Receptor Activation of a Group of Bisphenols and Select Alternatives, ,Series on Testing & Assessment No. 373, ENV/CBC/MONO(2022)43. OECD, Paris. Available at http://www.oecd.org/chemicalsafety/testing/series-testing-assessment-publications-number.htm

OECD (2022g). Case Study Using a New Approach Methodology (NAM) for Refining Inhalation Risk Assessment from Point of Contact Toxicity of the Pesticide, Chlorothalonil, Series on Testing & Assessment No. 367, ENV/CBC/MONO(2022)31, OECD, Paris. Available at http://www.oecd.org/chemicalsafety/testing/series-testing-assessment-publications-number.htm

OECD (2022h). Case Study on the Use of Integrated Approaches for Testing and Assessment for skin sensitisation: Demonstrating the Next Generation Risk Assessment Framework using Geraniol, Series on Testing & Assessment No. 368, OECD, ENV/CBC/MONO(2022)32, Paris. Available at http://www.oecd.org/chemicalsafety/testing/series-testing-assessment-publications-number.htm

OECD (2022i). Report on considerations from case studies on Integrated Approaches for Testing and Assessment (IATA), Series on Testing & Assessment No. 369, OECD, ENV/CBC/MONO(2022)36, Paris. Available at http://www.oecd.org/chemicalsafety/testing/series-testing-assessment-publications-number.htm

OECD (2022j). Test No. 467: Defined Approaches for Serious Eye Damage and Eye Irritation, OECD, Paris. Available at https://www.oecd.org/chemicalsafety/test-no-467-defined-approaches-for-serious-eye-damage-and-eye-irritation-28fe2841-en.htm

OECD (2022k). Supporting Document for Evaluation and Review of Test Guideline 467 on Defined Approaches (DAs) for Serious Eye Damage / Eye Irritation. Series on Testing & Assessment No. 354, OECD, ENV/CBC/MONO(2022)10, Paris. Available at http://www.oecd.org/chemicalsafety/testing/series-testing-assessment-publications-number.htm

OECD (2023a). Case Study on the Use of Integrated Approaches for Testing and Assessment for skin sensitisation of Diethanolamine: Application of a Next Generation Risk Assessment Framework, Series on Testing & Assessment No. 374, OECD, ENV/CBC/MONO(2023)5, Paris. Available at http://www.oecd.org/chemicalsafety/testing/series-testing-assessment-publications-number.htm

OECD (2023b). Case Study on the use of Integrated Approaches for Testing and Assessment for "Eye hazard identification" of "non-surfactant neat liquids" Series on Testing & Assessment No. 375, OECD, ENV/CBC/MONO(2023)6, Paris. Available at http://www.oecd.org/chemicalsafety/testing/series-testing-assessment-publications-number.htm

Reynolds J and Gilmour N, Baltazar MT, Reynolds G, Windebank S and Maxwell G (2022). Decision making in next generation risk assessment for skin allergy: using historical clinical experience to benchmark risk. Case study on the use of IATA for skin sensitization: NGRA framework using Geraniol: Regulatory Toxicology and Pharmacology, Volume 134, October 2022, 105219

SCCS (2018) 'Scientific Committee on Consumer Safety (SCCS) Notes of Guidance for the Testing of Cosmetic Ingredients and their Safety Evaluation 10th revision, 24-25 October 2018, SCCS/1602/18'.

SCCS (2021) The SCCS Notes of Guidance for the testing of Cosmetic ingredients and their Safety Evaluation. 10th revision.

https://ec.europa.eu/health/sites/default/files/scientific_committees/consumer_safety/docs/sccs_o_250.pdf

Schultz TW, Amcoff P, Berggren E, et al. (2015). A strategy for structuring and reporting a read-across prediction of toxicity. Regul Toxicol Pharmacol. Vol. 72, No. 3, pp. 586-601. doi:10.1016/j.yrtph.2015.05.016

Scott, L., Eskes, C., Hoffmann, S., Adriaens, E., Alépée, N., Bufo, M., Clothier, R., Facchini, D., Faller, C., Guest, R., Harbell, J., Hartung, T., Kamp, H., Le Varlet, B., Meloni, M., McNamee, P., Osborne, R., Pape, W., Pfannenbecker, U., Prinsen, M., Seaman, C., Spielmann, H., Stokes, W., Trouba, K., Van den Berghe, C., Van Goethem, F., Vassallo, M., Vinardell, P., Zuang, V. (2010). A Proposed Eye Irritation Testing Strategy to Reduce and Replace In Vivo Studies Using Bottom-Up and Top-Down Approaches. Toxicol. In Vitro 24, 1-9.

Small MJ (2008). Methods for assessing uncertainty in fundamental assumptions and associated models for cancer risk assessment. Risk Analysis, 28, 1289–1308.

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 case studies. Computational Toxicology, Vol. 9, pp. 1-11 https://doi.org/10.1016/j.comtox.2018.10.003

U.S. EPA. (2006) Approaches For the Application of Physiologically Based Pharmacokinetic (PBPK) Models and Supporting Data In Risk Assessment (Final Report). U.S. Environmental Protection Agency, Washington, D.C., EPA/600/R-05/043F

U.S. EPA (2011), Recommended use of body weight3/4 as the default method in derivation of the oral reference dose. Risk Assessment Forum. United States Environmental Protection Agency, Washington, D.C., EPA/100/R11/0001.

U.S. EPA (2019). FIFRA Scientific Advisory Panel Meeting Minutes and Final Report No. 2019-01 Peer review on evaluation of a proposed approach to refine the inhalation risk assessment for point of contact toxicity: a case study using a new approach methodology (NAM) December 4 and 6, 2018 FIFRA Scientific Advisory Panel Meeting. https://www.regulations.gov/document/EPA-HQ-OPP-2018-0517-0030

U.S. EPA (2021). Chlorothalonil: revised human health draft risk assessment for registration review https://www.regulations.gov/document/EPA-HQ-OPP-2011-0840-0080

U.S. National Toxicology Program (2018) NTP Research Report on National Toxicology Program Approach to Genomic Dose-Response Modeling.

WHO (2010) Harmonization Project Document No. 9: Characterization and application of physiologically based pharmacokinetic models in risk assessment. Geneva: World Health Organization.

WHO (2018), Guidance document on evaluating and expressing uncertainty in hazard characterization, 2nd edition. https://apps.who.int/iris/handle/10665/259858

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, No 1, pp 67-81.

Annex A. Questions for authors and reviewers of Case Studies included in the eighth review cycle

Six countries/stakeholders (Australia, Canada, Germany, Italy, Japan, and the Netherlands) participated to review in the eighth review cycle. The authors used templates to document the case studies (Annex D, Annex E and Annex F). The template for the case studies on read-across (Annex D) 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 case studies (Annex E) was developed to fit case studies with multiple components, such as adverse outcome pathways (AOPs), Mode of Action (MoA), Defined Approaches (DAs), Workflows, and Grouping /Read-Across. The PBK template (Annex F) 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 case studies 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 eighth review cycle are indicated below (Table A A.1).

Table A A.1. Guided reviewer questions for eighth (2022) IATA Case Study review cycle

Part I: Guided Questions for Review of Case Studies	
	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?
	Does the template work well? Would you use approaches in this case study in your regulatory context? If no, please provide any explanation and required additional information,
	What additional information / data could facilitate acceptance the approaches in your regulatory context,

	Are there specific topic areas in the case study that could benefit from the development of further guidance for application or interpretation?
	Are there tools in the case study that you would like the author to demonstrate?
	Other comments
Part III:	Guided Questions for global acceptance
	Endpoint/ Scope
	Country/ Agency of reviewer
	Regulatory need for chemical/sector
	Applicable for reviewer.
	If no, are there useful aspects of the case study?
	Is there additional information that would make the IATA applicable?

The reviewers' comments and the revised case studies were discussed at the eighth meeting of the IATA Case Studies Project (16 November 2022), in order to finalise the case studies and summarise the learnings and lessons.

Annex B. Summary of results of the review of Case Studies included in the eighth review cycle

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

Table A B.1. Case Studies Reviewed in the Eighth Review Cycle (2022)

No.	Title	Endpoint	Purpose of Use	References
2022-1	Case Study on the Use of Integrated Approaches for Testing and Assessment for skin sensitisation of Diethanolamine: Application of a Next Generation Risk Assessment Framework	Skin sensitisation	to demonstrate the impact of inconsistent NAM information on a hypothetical risk assessment scenario for a leave-on product (0.8% DEA in a non-spray deodorant) that is a more complex scenario than in previous case studies.	OECD, 2023a
2022-2	Case Study on the use of Integrated Approaches for Testing and Assessment for "Eye hazard identification" of "non-surfactant neat liquids"	Eye damage/irritation	to illustrate the applicability of the DAs for serious eye damage and eye irritation integrated in the TG 467 (OECD, 2022a).	OECD, 2023b

Annex Section B.1 summarises answers regarding a potential regulatory use of the two CSs from reviewers (Australia, Canada, Germany, Italy, Japan, and the Netherlands). Annex Sections B.2 and B.3 summarise the review results of the two CSs.

B.1 Potential regulatory application of two CSs in 2022 review cycle

Table A B.2 and Table A B.3 show review results regarding the potential regulatory application replied to by reviewers (Australia, Canada, Germany, Italy, Japan and the Netherlands). More detailed responses on regulatory application are described in Annex Section B.2.

Table A B.2. Potential regulatory application of CS2022-1

CS 2022-1: Application of a Next Generation Risk Assessment (NGRA) framework for skin allergy: a case study for Diethanolamine

ENDPOINT/ SCOPE of reviewer's organisation (e.g. prioritization, hazard id, hazard characterization, POD, etc.; and for which chemical sector, e.g. pesticide, TSCA, REACH, cosmetics, etc.)	COUNTRY/ AGENCY OF REVIEWER	REGULATORY NEED FOR CHEMICAL/ SECTOR e.g. GHS classification, MOA, NOEL, etc.)	ARE THERE ENDPOINT-SPECIFIC DATA REQUIREMENTS FOR The Case study ENDPOINT? IF SO, IS THIS A BARRIER TO USING THIS IATA IN REGULATORY ASSESSMENT?	APPLICABLE FOR REVIEWER?	IF NO, ARE THERE USEFUL ASPECTS OF THE CASE STUDY?	IS THERE ADDITIONAL INFORMATION THAT WOULD MAKE THE IATA APPLICABLE?
Hazard characterisation of industrial chemicals	Australia	GHS classification and risk assessment	This is an endpoint requiring data for two activities under the *Industrial Chemicals Act 2019*: 1) For Categorisation of chemicals to consider the introduction category of an unlisted chemical; 2) For assessment applications requiring a certificate to introduce the chemical in Australia.	Applicable (can be considered as part of a weight of evidence approach too) – AICIS cosmetic ingredient assessments have used DA in the OECD GL 497. However, having no potency value compared to LLNAs is a limitation for quantitative risk assessment.	The DA in the OECD GL would be given more weight than the other non-GL DAs.	Additional guidance on: Determining PODs/exposure limits for weak and moderate sensitisers in cosmetics Selecting an appropriate DA when multiple options are available Additional information on analogue potency data to compare the classification category from different DAs would have been useful.

Risk assessment of new substances	Canada	MOA, NOAEL, POD; Toxicity assessment of new substances	There are data requirements for this endpoint under the New Substances Notification Regulations (NSNR). A barrier exists when inconsistent results are obtained for different methods, or when a POD cannot be derived to conduct a quantitative risk assessment for skin sensitisation.	Yes.		Specific guidance for handling inconsistent results of different methods, and for handling haptens would help with the applicability of the IATA.
hazard characterization for Pesticide/ Biocide Regulation	Germany, BfR	GHS categorization, Risk mitigation measures	There data requirements for this endpoint. However, the CS does investigate OECD validated methods (namely ITSv1 and v2 acc. to OECD TG 497). Other DAs investigated are currently being tested for inclusion into OECD TG 497. Thus, no barriers exist.	only partly	It is a good example of how to deal with substances that have clear and good data regarding the use of NAM data.	1) In general, it would be advantageous if the discussion of results was elaborated further. Especially since results differ for different approaches. In regulatory work, the handling of different data sources with different results is extremely relevant. Thus, at least some recommendation on how to deal with equivocal results should be attempted. 2) When conducting case studies on a proposed framework all aspects of the framework should be included to create "real-life" case studies. In both case studies, read-across was not considered although it is part of the NGRA. This somehow defeats the purpose of a case study on the application of a defined framework.
Hazard identification, REACH/CLP	Italy	Classification	There are data requirements for this endpoint. Major barriers are training of assessors and building	Not yet mature to be fully applied.		Building confidence through implementation of use cases.

			regulatory confidence.			
Hazard identification for chemicals including cosmetics	Japan, NIHS	Hazard identification	In case that a target substance is within in vitro/in silico applicability domains, there is no barrier. If not, in vivo data (TG429 etc.) is required.	Applicable only for hazard identification so far.	Seven approaches were selected as the case studies listed in the OECD guidance document No. 256 in 2017, and this is the strongest point of the case study.	This case study was developed under the assumption that analogue information is not available. In order to reduce uncertainty in this approach, it is useful to use analogue information when it is available.
Risk assessment and management of chemical substances	National Institute for Public Health and the Environment (RIVM, The Netherlands		The methods are currently not designed for risk assessment, and the basis for deriving a POD is not sufficient reliable yet.	Partly	The description of the DAs, there main characteristics and the outcome of the methods is presented very clear and concise. The authors did a great job in communicating complex information.	Guidance and justification on the use of a specific DA and validation data showing the predictivity of all the DAs for risk assessment would have been helpful.

Table A B.3. Potential regulatory application of CS 2022-2

CS 2022-2: Case Study on the use of Integrated Approaches for Testing and Assessment for “Eye hazard identification” of “non-surfactant neat liquids”

ENDPOINT/ SCOPE	COUNTRY/ AGENCY OF REVIWER	REGULATORY NEED FOR CHEMICAL/ SECTOR	ARE THERE ENDPOINT-SPECIFIC DATA REQUIREMENTS FOR THIS ENDPOINT? IF SO, IS THIS A BARRIER TO USING THIS IATA IN REGULATORY ASSESSMENT?	APPLICABLE FOR REVIEWER?	IF NO, ARE THERE USEFUL ASPECTS OF THE CASE STUDY?	IS THERE ADDITIONAL INFORMATION THAT WOULD MAKE THE IATA APPLICABLE?
Hazard characterisation of industrial chemicals	Australia	GHS classification and risk assessment	This is an endpoint requiring data for two activities under the *Industrial Chemicals Act 2019*: 1) For Categorisation of chemicals to consider the introduction category of an unlisted chemical; 2) For assessment applications requiring a certificate to introduce the chemical in Australia	Applicable	N/A	Further testing of the approach with additional chemicals would increase confidence in using the approach for hazard characterisation.
Risk assessment of new substances	Canada	Toxicity assessment of new substances	No.	Yes. Eye irritation data are not required under the New Substances Notification Regulations (NSNR) for chemicals and polymers, but these data are received with some regularity for substances in products that may involve inadvertent eye exposure or intentional near-eye exposure.	Because the case study methodology follows a validated OECD defined approach under OECD TG 467, this approach would be acceptable to the New Substances Program assuming the guideline was followed properly.	No.
hazard characterization for Pesticide/	Germany, BfR	GHS categorization, Risk mitigation measures	yes data requirements exist but these are no barrier for the regulatory assessment of single substances	only partly	It is a good example of how to deal with substances that have clear and good data	In order to be able to apply the case study more in a regulatory context, borderline example substances are particularly

Biocide Regulation					regarding the use of NAM data.	interesting. This would also be a good point to explain how to deal with mixtures and to propose solutions for the assessment strategy. These would significantly improve the handling in everyday regulatory practice and strengthen the safety of handling NAM data on the regulatory side.
Hazard identification, REACH/CLP	Italy	Classification	There are data requirements for this endpoint. Major barriers are training of assessors and building regulatory confidence.	Not yet mature to be fully applied.		Building confidence through implementation of use cases.
Hazard characterisation for chemicals under chemical regulation	Japan, NIHS	Hazard identification	The DA is under evaluation.	Under consideration	This case study could be useful for evaluation of the DA.	The test guideline 467 could be used if relevant information is available. However, additional case studies or guidance how borderline results could be treated may be needed.
Risk assessment and management of chemical substances	National Institute for Public Health and the Environment (RIVM, The Netherlands	GHS/CLP	At the GHS there is agreement on an update of the criteria on the use of *in vitro* methods and defined approaches (expected to be published in the 10th revision in 2023). The CLP regulation is more open to the type of data that can be used in general as reference is made to the OECD TGs in general and the use of other types of data.	Partly	It is good to see that there is a clear intended regulatory purpose.	

B.2 Review Results for CS 2022-1: Case Study on the Use of Integrated Approaches for Testing and Assessment for skin sensitisation of Diethanolamine: Application of a Next Generation Risk Assessment Framework

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

- Comparing the outcome from multiple DAs
- Exploring a substance where a clear answer regarding skin sensitisation potential has not been obtained through NAMs
- Description of the DAs, their main characteristics and the outcome of the individual methods

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

- The relevance of the DAs for a potential pro-hapten.
- NAM data for the substance examined
- The inconsistency of the risk assessment, 2 un-safe versus 4 safe results.
- The inconsistency of the classification for DEA, 3 DAs predict a non-sensitiser and 3 a weak/moderate sensitiser
- limited information on metabolism.

The main comments on the potential use of the case study in other Member Countries' regulatory contexts are as follows:

- ***Australia:*** The case study is useful to understand the NGRA framework and how individual cosmetic products could be assessed for safety. In Australia (AICIS) ingredient-based risk assessments need to consider consumer exposure from multiple cosmetic product types containing the same chemical. Often higher concentrations than actual use levels are requested to be considered. When using specific assays, TGs and GLs, more weight is given to OECD adopted methods/GLs, compared to others available. Considering the 6 DAs used in this case study, the ITS DA is likely to be considered more favourably over others, as the DAs in the OECD GL 497 have been validated for regulatory purposes. In addition, in the regulatory context often a chemical is notified as used in multiple cosmetic products and consumers use those products simultaneously. Therefore, such scenarios need to be considered when introducers request approval for a specific chemical in multiple cosmetic product types at various concentrations

  Additional information that may facilitate acceptance is guidance on how to decide a maximum acceptable level for a weak/moderate skin sensitiser in various cosmetic product types. Currently AICIS uses an approach similar to the International Fragrance Association (IFRA) Quantitative Risk Assessment (QRA) (with LLNA or HRIPT data).

- ***Canada:*** Yes, the approaches used in this case study could be used in the Health Canada's Chemical Management Plan. Specifically, skin sensitization data are requirements of specific regulations for chemicals and polymers. Defined approaches under OECD test guideline 497 may be received to meet that data requirement. If the approach(es) taken are well justified and documented, they can be acceptable to meet the data requirement.

Additional information or data is not necessary to facilitate acceptance of the approach, assuming that the approach taken is well documented and explained and uncertainties discussed and, if possible, addressed.

While skin sensitization is not applicable in the Environment and Climate Change Canada (ECCC) regulatory context for ecological risk assessment under the Canadian Environmental Protection Act, 1999 (CEPA), the general aspects of the tiered framework, the application of WoE, and account of uncertainties are highly relevant and applicable to this Canadian regulatory context.

- ***Germany:*** Two of the DAs are part of OECD GL 497. Others are part of OECD GD 256. The inconsistency of the results for the different DAs in this case study, however, makes the interpretation of results difficult.

  Since ITS DAs are part of a TG, these approaches will have to be used in our regulatory context more often in the future. However, considering the inconsistent outcome of the risk assessment in this case study, confidence in the method described is rather low (at least for 'difficult' substances).

  Additional information on the level of confidence to be assigned to individual methods (similar to the P-value for SARA) could facilitate decision making in terms of selection of the appropriate method.

- ***Italy:*** Overall, the case study shows the applicability for hazard identification purposes.

- ***Japan:*** Currently, it would be difficult to use these approaches in our regulatory context.

  Precise guidance for particular substances that have the potential to be metabolized and to be a hapten could be needed.

  This approach is new. It should be tested for other substances to confirm its scientific validity, and assessors should be trained to understand this type of approach.

  Cosmetic habits are influenced by culture. Therefore, the use scenario should be different for each region. For Japan, we will consider the use scenario in Japan, so the following information will be helpful.

  Yamaguchi, M., Araki, D., Kanamori, T., Okiyama, Y., Seto, H., Uda, M., Usami, M., Yamamoto, Y., Masunaga, T., Sasa, H.: Actual consumption amount of personal care products reflecting Japanese cosmetic habits. Journal of Toxicological Science, 42 (6): 814, 2017.

- ***The Netherlands:*** The DAs that are included in the new OECD test guideline DASS are usable for hazard assessment, but they cannot currently be used for risk assessment in a NGRA. This is due to the fact that these methods are not designed for risk assessment and the step used to calculate a POD warrants further scientific scrutiny.

  In addition, this case does not resolve the question whether or not DEA is a skin sensitizer or how to choose the most appropriate DA if there are conflicting results.

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

- Selecting an appropriate DA in case of obtaining differing outcomes.
- How to deal with substances that may or may not be out of the applicability domain of single assays employed in the DAs

Overviews of the case study are as follows.

This case study aims to apply the NGRA framework for 0.8% DEA in a non-spray deodorant that is a more complex scenario than the previous case study (OECD, 2022h). The reason of "more complex scenario" is the existing NAM results of DEA were inconsistent with respect to sensitisation potential (Hoffmann et al. 2022). Within the case study, six DAs (Integrated Testing Strategy (ITSv1, ITSv2), Artificial Neural Network (ANN), Sequential Testing Strategy (STS), Bayesian Network Integrated Testing Strategy (BN-ITS) and Skin Allergy Risk Assessment (SARA) model) were applied to obtain skin sensitisation hazard potential and potency predictions. 2/6 DAs ((ITSv1, ITSv2) were adapted as OECD Guideline No. 497: Defined Approaches on Skin Sensitisation (OECD, 2021d).

The inconsistencies in the NAM information led to different results of the DA and the risk assessment. 4/6 DA (ITSv2, ANN, STS, BN-ITS) concluded safe as result of risk assessment, while 2/6 DA (ITSv1 and SARA) concluded un-safe. This different result of the risk assessment was caused by the design and objective of the individual DA. Three DA (ITSv2, STS, BN-ITS) predicted DEA as a non-sensitiser, while others predicted a weak or moderate skin sensitisation on either a continuous potency scale (ANN, SARA) or a potency category (ITSv1).

In conclusion, this IATA case study demonstrates that the NGRA framework can be applied to this complex case, and the NGRA framework helps to explain conducted approach and the reasons.

Please refer to (OECD, 2023a) for more information on the case study.

B.3 Review Results for CS2022-2: Case Study on the use of Integrated Approaches for Testing and Assessment for "Eye hazard identification" of "non-surfactant neat liquids"

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

- The thorough and transparent uncertainty analysis
- The detailed schemes and consistent prediction results (Annex A of OECD, 2023b)
- The integration of the two DAs and both the Bottom-Up and Top-Down approach used.

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

- The data quality used in the DAs (*in vitro, in silico* and from public sources)
- The selection of the reference chemicals (Cat. 1 and Cat. 2)
- The small number of reference chemicals. Applying the IATA to a larger number of (non-surfactant, liquid) chemicals would increase confidence in the results).

The main comments on the use of the case study in other Member Countries' regulatory contexts are as follows:

- ***Australia:*** Testing the approach with a larger number of chemicals would increase confidence in using the approach to categorise chemicals (under United Nations (UN) Globally Harmonized System of Classification and Labelling of Chemicals (GHS)).
- ***Canada:*** Approaches used in this case study can be used in Canada's Chemical Management Plan context. Although eye irritation data is not required under specific regulations, information is received or found regularly for substances in products that may involve inadvertent eye exposure or intentional near-eye exposure. Because the methodology follows a validated OECD-defined approach under TG 467, this approach

would be acceptable to the New Substances Program assuming the guideline was correctly followed.

Additional information or data would not be required for this approach to be accepted.

- ***Germany:*** The case study provides an illustrative example for identifying the hazard categories. In the regulatory context, the TGs are of greater relevance, as they list not only the possibilities but also the general limitations. In order to be able to apply the case study more in a regulatory context, borderline substances are particularly interesting. Furthermore, representative substances of different structural characteristics would certainly also be very interesting.
- ***Italy:*** Overall, the case study shows the applicability for hazard identification purposes.
- ***Japan***: The test guideline 467 could be used if relevant information is available. But additional case studies or guidance how borderline results could be treated may be needed.

  TG 467 "Defined Approach for serious eye damage and eye irritation" has been published in 2022, and a supporting document is available as OECD GD 354 (OECD 2022k)..

  Essentially, it is desirable that this case study be prepared prior to development of the guideline and used to facilitate the discussion in WNT. It is recommended that this case study will be used effectively in the ongoing discussion and be added to the Guideline as the supporting materials.
- ***The Netherlands:*** Classification of substances and mixtures is based on the criteria in GHS and their implementation in national legislation which is in our case Classification, Labelling and Packaging (CLP). The GHS classification criteria for eye hazards (revision 9) do not currently include the use of *in vitro* methods, physical/chemical properties and defined approaches. GHS states that *in vitro* alternatives that have been validated and accepted should be used to make classification decisions (paragraph 3.3.2.2.3). This would include the *in vitro* TGs but not allow the use of the physical/chemical properties. The DAs could be considered as a type of Weight-of-evidence evaluation. However, at the GHS sub-committee there is already agreement on an update of the GHS criteria including the use of *in vitro* methods and defined approaches. This is expected to be published in the 10th revision in 2023. The CLP regulation is more open to the type of data that can be used in general as reference is made to the OECD TGs in general and the use of other types of data in article 9.2 and 9.3. Therefore, such information can be used. However, acceptance would be facilitated by updating CLP based on revision 10 of GHS.

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

- The criteria for the selection of model substances for application or interpretation of DA.

Overviews of the case study are as follows.

This case study developed to illustrate the application of both DAs in TG 467 to assess the eye hazard potential of non-surfactant neat liquids (hereinafter referred to as DAL-1 and DAL-2). The eye hazard potential of four neat liquids (two No Cat., one Cat. 2, and one Cat. 1) was determined based on the results of physicochemical properties and the results of OECD TG *in vitro* test methods. DAL-1, applicable to neat liquids only, combines 4 physicochemical properties with a reconstructed human cornea-like epithelium (RhCE) test method (EpiOcular™ EIT or SkinEthic™ HCE EIT; OECD TG 492), and the Bovine Corneal Opacity and Permeability laser light-based opacitometer (BCOP LLBO) test method (OECD TG 437). DAL-

2, applicable to neat liquids and to liquids and solids dissolved in water, is based on the combination of the BCOP LLBO and the Short Time Exposure test method (STE, OECD TG 491).

For each chemical, the final prediction using variants of the DAs was concordant with the *in vivo* classification. In conclusion, these case study demonstrate applicability of the DAs and their potential to successfully distinguish between the 3 UN GHS categories for eye hazard identification.

Please refer to (OECD, 2023b) for more information on the case study.

Annex C. Summary of the case studies reviewed in all review cycles

This Annex summarises learnings and lessons from the 34 case studies of the IATA Case Studies project including the 32 case studies from the past seven review cycles. Some case studies include more than one endpoint/approach.

The target endpoints included:

- repeated dose toxicity (10 case studies),
- developmental neurotoxicity (5),
- systemic toxicity (6)
- neurotoxicity (3).
- estrogenicity (3),
- skin sensitisation (2),
- reproductive toxicity (2)
- genotoxicity & mutagenicity (2),
- bioaccumulation (1),
- developmental toxicity (1)
- ecotoxicity (1)
- eye irritation (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 (20 case studies),
- IATA workflow (14) *including* Developmental Neurotoxicity *(DNT)* (5) defined approach (4)

In addition, case studies reviewed also demonstrated examples of using;

- MoA/AOP approaches (27 case studies),
- describing uncertainty (32),
- application of NAMs (29), and
- deriving low/no toxicity prediction (16)

Table A C.1. Summary of the case studies reviewed in the past eight 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]	
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. • 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.	X	X	X		OECD, 2023b
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	X	X	X		OECD, 2022c

Year-No.	Assessment Approach	Endpoint	Usage classification	Key words provided by Authors	IATA Topics				Reference
					AOP*1	UR*2	NAM*3	L/N*4	
				• Flame retardants • Zebrafish					
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
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

Year-No.	Assessment Approach	Endpoint	Usage classification	Key words provided by Authors	IATA Topics				Reference
					AOP*1	UR*2	NAM*3	L/N*4	
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
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

Year-No.	Assessment Approach	Endpoint	Usage classification	Key words provided by Authors	IATA Topics				Reference
					AOP*1	UR*2	NAM*3	L/N*4	
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		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
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. Template for IATA Case Studies 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 case studies OECD, 2016b and 2016c).
- As the goal of the OECD IATA Case Studies project is to discuss case studies 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

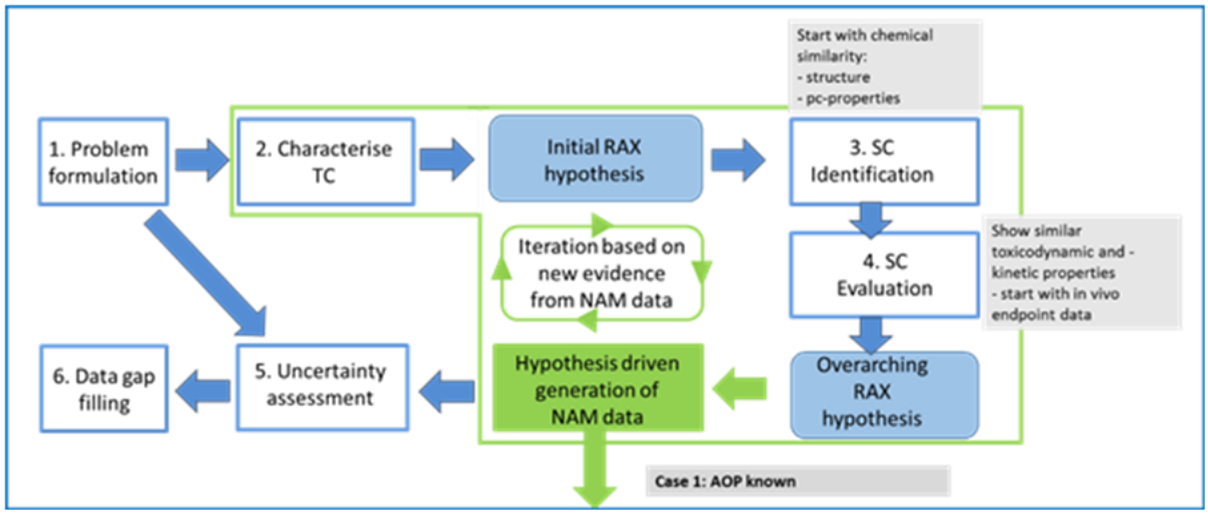
- The parameters to be considered for grouping and read-across of nanoforms and their relevance for human health and environmental endpoints are for example surface chemistry, size, shape and surface area, along with physical/chemical properties. (See *"1.2 Target chemicals"* of the case study 2017-3 (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 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.

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 D.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)].

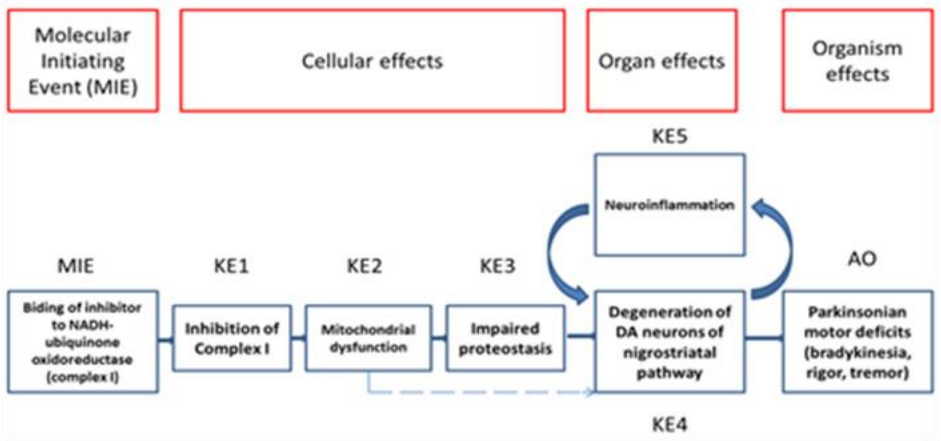
- These hypotheses can be argued by a number of elements as follows [See 3.2.3 “Elements for a read-across justification” of the grouping guidance (OECD, 2014a)]. Chemical identity and composition, including level of purity
  - Chemical identity and composition, including level of purity [See 3.2.3.1 “*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 D.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.

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

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

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

- 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.

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 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.

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 case studies[10]. One of the examples is Case Study 2018-1 (OECD, 2019b). More detailed or supporting information can be included in an Annex.

[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

- 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 experimentation (DB-ALM)[11]and U.S. 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

[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/

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].

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 case studies, 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 case studies 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

Factor	Uncertainty (low, medium, high)	Impact of uncertainty on hypothesis	Comment
Hypothesis used for the read-across			
Structural similarity			

[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

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 case studies 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 case studies 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 case studies 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 case studies 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 case studies. 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	QSAR1 (Target endpoint1)								
	QSAR2 (Target endpoint1)								
	QSAR3 (Target endpoint2)								
	QSAR4 (*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	QSAR1 (Target endpoint1)	result	result	result	result	result	result	result	result
	QSAR2 (Target endpoint1)	result	result	result	result	result	result	result	result
	QSAR3 (Target endpoint2)	result	result	result	result	result	result	result	result
	QSAR4 (*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 E. General Template for IATA case Studies - 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 case studies, 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*.

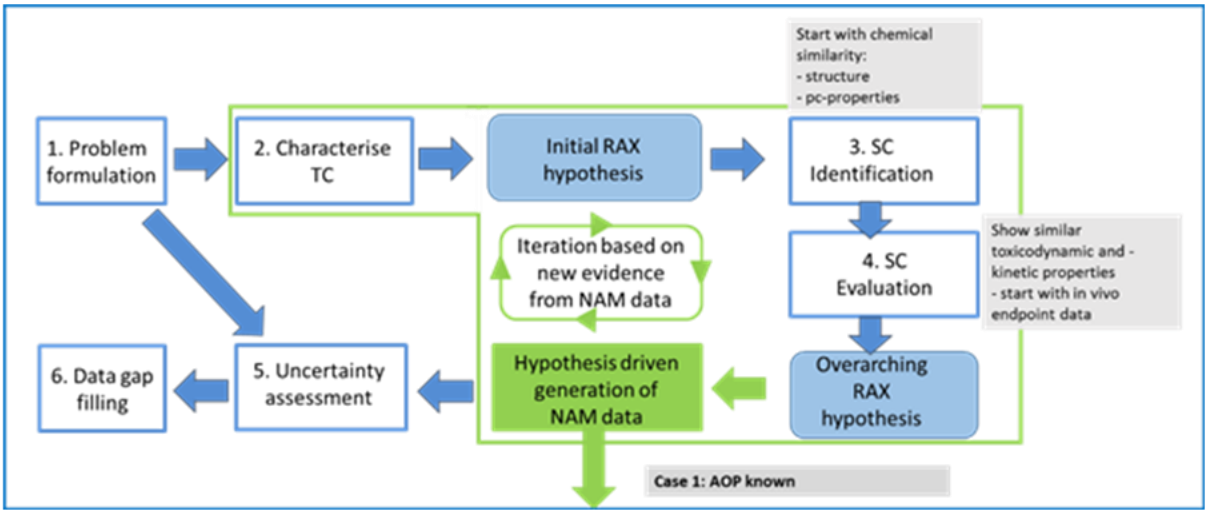
Tip

- 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 case studies OECD, 2016b and 2016c).
- As the goal of the OECD IATA Case Studies project is to discuss case studies 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 E.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.

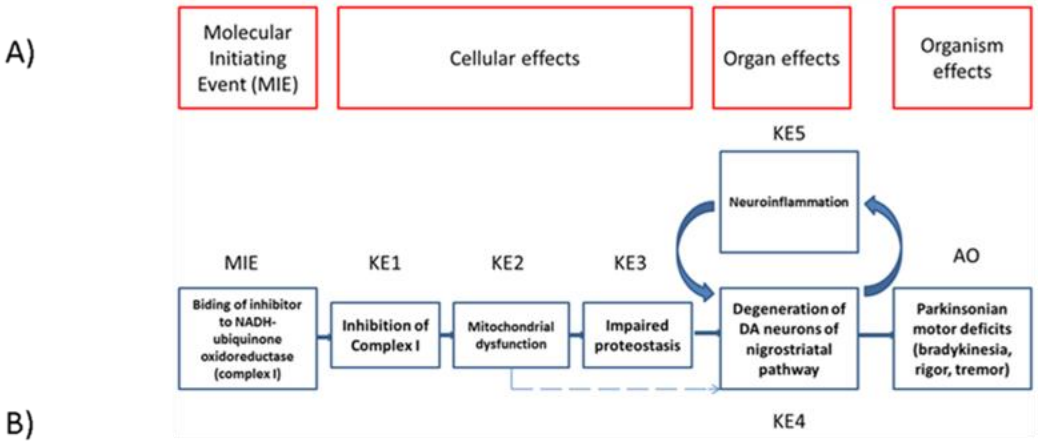
[17] AOP-KB. https://aopkb.oecd.org/

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

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

Figure A 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	

- **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 case studies 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 U.S. 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

[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/

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, 2019c). Please also refer to OECD guideline, "Defined Approaches on Skin Sensitisation" (OECD, 2021d)

- 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 case studies 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 case studies 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

[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

- 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.

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 Case Studies 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	IATA workflow, Fig. 3, Page 22	4. Approaches Used; Workflow	The workflow presented in this figure provides a clear and concise overview of

	Phenols			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 model, Fig.1, Page 16	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.
		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 on inhibition of the mitochondrial complex I of nigrostriatal neurons leading to parkinsonian motor deficits,	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

	AOP-based testing and read-across approach	Fig.2		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 F. 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.