



# EU-ToxRisk: Interactions with the OECD Chemical Safety Programme

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OECD Environment Health and Safety

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## Outline

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- IATA Case Studies Project
- PBK Guidance document
- DNT Guidance document
- AOP programme



# OECD IATA Case Studies Project

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- Under the OECD Working Party on Hazard Assessment
- Established in 2014, supersedes (CoCAP)
  - Aim to exchange information on NAMs
    - Scientific approaches
    - Application in a specific regulatory context
    - Establish common/best practices
- Also intended to provide a possible path to
  - NAM use in TGs
  - Defined Approaches
  - Testing Strategies
  - Testing Batteries



## IATA CSP is flexible

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- “Endorsement” by WPHA does not
  - indicate OECD Member Countries’ agreement to use
  - bind countries in any decision making
- Results are not covered by the Mutual Acceptance of Data

<b>Test Guideline</b>	+	<b>GLP</b>	=	<b>MAD</b>
Internationally harmonised <b>methods</b> for evaluating chemical safety		<b>Principles</b> and <b>conditions</b> under which laboratory studies are conducted, reported and recorded		Studies conducted using OECD TG and according to GLP fall under the <b>Mutual Acceptance of Data</b>

MAD is a legal agreement among all member and partner countries that share a common data requirement to accept the data generated by other member countries



# Purpose of Case Studies

- Increase experience with the use of IATA by developing case studies, which constitute examples that are fit for regulatory use.
- Create common understanding of using NAMs and the generation of considerations/guidance stemming from these case studies.

Previous Case studies are available;

<http://www.oecd.org/chemicalsafety/risk-assessment/iata-integrated-approaches-to-testing-and-assessment.htm>

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## Integrated Approaches to Testing and Assessment (IATA)

WHAT'S NEW

The [Integrated Approaches to Testing and Assessment \(IATA\) Case Studies Project](#) allows countries to share and explore the use of novel methodologies in Integrated Approaches to Testing and Assessment within a regulatory context.

[One new case](#) that illustrates an assessment workflow based on various types of non-animal test methods was published in 2021. In addition, an updated document that includes considerations of using methods in IATA was also published following the 6<sup>th</sup> case study review cycle. Since the project was launched in 2015, a total of 24 case studies and six considerations documents have now been finalised.

INTRODUCTION TO INTEGRATED APPROACHES TO TESTING AND ASSESSMENT (IATA)

### What are IATA?

IATA are pragmatic, science-based approaches for chemical hazard characterisation that rely on an integrated analysis of existing information coupled with the generation of new information using testing strategies.

IATA follow an iterative approach to answer a defined question in a specific regulatory context, taking into account the acceptable level of uncertainty associated with the decision context. There is a range of IATA - from more flexible, non-formalised judgment based approaches (e.g. grouping and read-across) to more structured, prescriptive, rule based approaches [e.g. Integrated Testing Strategy (ITS)].

IATA can include a combination of methods and can be informed by integrating results from one or many methodological approaches [(Q)SAR, read-across, in chemico, in vitro, ex vivo, in vivo] or omic technologies (e.g. toxicogenomics).

### Why IATA?

Current regulatory toxicity testing and assessment approaches remain to a large extent based on a checklist of in vivo tests, conducted in accordance with standardised test guidelines or protocols such as OECD Test Guidelines.

While this approach has evolved over the past half century, it is unlikely to efficiently meet legislative mandates that require increased numbers of chemical assessments to be undertaken without a concomitant increase in the use of animals and resources.

New approaches are necessary to close the gap between the number of chemicals in use and the number assessed to date.

### Why we use AOPs for IATA?

IATA can include a combination of methods and can be informed by integrating results from one or many methodological approaches [(Q)SAR, read-across, in chemico, in vitro, ex vivo, in vivo] or omic technologies (e.g. toxicogenomics).

Many testing approaches do not result in a mechanistic understanding of the induced toxicity. This is particularly the case with non-animal testing approaches and understanding the relationship between what is tested and the apical toxicity endpoint being predicted. This is one of the reasons why results from novel approaches are not yet widely and consistently used for regulatory decision-making.

An objective and systematic framework is needed to characterise the individual biological and toxicological relevance of novel methods in predicting an adverse effect. The same framework could inform their potential use in combination with other tools and methods to benefit from an integrated approach. The Adverse Outcome Pathway (AOP) concept can be applied as a framework to develop IATA.

IATA based on the AOP concept

MIE → KE 1 → KE 2 → KE n → AO

Level of Biological Organisation: Molecular, Organism, Cellular, Tissue, Organ, Organism, Population

Types of information: in silico/in chemico, in vitro, in vivo, field and epidemiological studies



## Information included in Considerations Documents

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- Based on the experiences gained from all case studies evaluated in the annual cycle, considerations documents are drafted that:
  - summarize the lessons learned from the different case studies
  - describe the key points and considerations of the review
  - identify need for further guidance
  - provide revised templates for RAX and IATA
  - discuss useful IATA tools

Previous Considerations Documents are available;

<http://www.oecd.org/chemicalsafety/risk-assessment/iata-integrated-approaches-to-testing-and-assessment.htm>



# IATA Experience to date (+ 8 CS in this review cycle)

Year-No. (Lead)	Assessment Approach	Endpoint	AOP <sup>1</sup>	IATA Topics			Reference
				UR <sup>2</sup>	NAM <sup>3</sup>	L/N <sup>4</sup>	
2020-1 (BIAC)	Safety assessment workflow	Repeated dose toxicity	X	X	X	X	OECD, 2021a
2019-1 (BIAC)	Safety assessment workflow Read-across	Reproductive toxicity	X	X	X	X	OECD, 2020a
2019-2 (BIAC)	Read-across	Repeated dose toxicity	X	X	X		OECD, 2020b
2019-3 (BIAC)	Read-across	Repeated dose toxicity	X	X			OECD, 2020c
2019-4 (BIAC)	Read-across	Repeated dose toxicity	X	X	X		OECD, 2020d
2019-5 (BIAC)	Read-across	Repeated dose toxicity	X	X	X	X	OECD, 2020e
2019-6 (BIAC)	Read-across	Developmental toxicity	X	X	X	X	OECD, 2020f
2019-7 (BIAC)	Read-across	Neurotoxicity	X	X	X		OECD, 2020g
2019-8 (BIAC)	Read-across	Neurotoxicity	X	X	X	X	OECD, 2020h
2018-1 (Japan)	Read-across	Reproductive toxicity	X	X			OECD, 2019b
2018-2 (US)	Prioritisation and screening	Oestrogenicity	X	X	X	X	OECD, 2019c
2017-1 (Canada/US)	Prioritisation and hazard characterisation	Oestrogenicity	X	X	X	X	OECD, 2018b
2017-2 (Canada)	Prioritisation of chemicals	Ecotoxicity	X	X	X	X	OECD, 2018c
2017-3 (JRC)	Read-across	Genotoxicity for nano-TiO <sub>2</sub>		X	X		OECD, 2018d
2017-4 (ICAPO)	Read-across	Repeated dose toxicity		X	X	X	OECD, 2018e
2016-1 (Japan)	Read-across	Repeated dose toxicity		X	X		OECD, 2017b
2016-2 (US)	Grouping for cumulative risk assessment	Neurotoxicity	X		X		OECD, 2017c
2016-3 (ICAPO)	Read-across	Repeated dose toxicity		X	X	X	OECD, 2017d
2016-4 (ICAPO)	Read-across	Repeated dose toxicity		X	X	X	OECD, 2017e
2016-5 (JRC/BIAC)	Safety assessment workflow	Repeated dose toxicity	X		X		OECD, 2017f
2015-1 (Canada/US)	Read-across	Mutagenicity	X	X			OECD, 2016b
2015-2 (Canada)	Read-across	Repeated dose toxicity		X	X		OECD, 2016c
2015-3 (Japan)	Read-across	Repeated dose toxicity	X	X			OECD, 2016d
2015-4 (Japan)	Read-across	Bioaccumulation		X		X	OECD, 2016e

## 2014-2020

- 24 Cases studies have been published on OECD website

## 2021 = 7<sup>th</sup> cycle

- 8 new case studies
  - 5 DNT
  - 1 NGRA Skin Sens
  - 1 inhalation toxicity
  - 1 transcriptomics for ED



# Benefits for the EU-ToxRisk

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## **5** Case studies published in the OECD

Environment, Health and Safety Publications  
Series on Testing and Assessment

**5-8** Regulators from OECD member countries provided feedback

**40** Experts from OECD member countries attended the final meeting, and additional number of regulators reviewed the case studies at WPHA level

## IATA CS Review Cycles

- Fixed Schedule
- Structure: based on templates
- Set review questions
- Regular meetings that allows interaction with regulators





# Benefits for OECD IATA Case Studies Project

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EU-ToxRisk contributed to the considerations document

- feedback to improve our **Templates**
- develop section on **AOPs**
  - use of endorsed vs non-endorsed AOPs,
  - use of AOP networks
  - mapping of *in silico* and *in vitro* assays used in IATA
  - use of AOP based testing strategy
- areas for developing further **Guidance**
  - how to report data from NAMs (e.g. docking/modelling approaches, PBK modelling, gene expression data)
  - justification of negative prediction



## Tools to build confidence in NAMs

- Description of applicability domain/uncertainty
  - Due to lack of information
  - Due to limitation of methods
- SOP or standardised execution of the method
- Demonstration of reproducibility
- Predictive capacity of method(s) against robust reference chemicals
- Standardized reporting

### Relationship to in vivo tox

- Rationale described
- Limitations?

### Detailed protocol

- Publically available
- Reproducible

### Intralab [Interlab]

- Variability over time

### Performance

- Reference chemicals
- Relevance to target spp/available tox information

### Review

- Data documentation



# Standardized Templates and Reporting Formats

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- IATAs
  - General template
  - Read across template
  - Guidance for building blocks in IATA
- Defined Approaches
  - to be used in IATA
  - New GL includes elements to stand-alone DA use
- QSARs
  - QSAR Model Reporting Formats
  - QSAR Prediction Reporting Formats
  - Expanding to be generalizable to in silico models
- Omics
  - Transcriptomics Reporting Framework
  - Metabolomics Reporting Framework
- OECD Harmonised Templates (OHTs) for chemical safety data
  - ~130 standard reporting formats for information used in risk assessment
  - GL and non-GL studies
  - Chemically agnostic
- AOPs
- PBK models
- Various guidance on how to use



# EU-ToxRisk Templates

- ToxTemp
- Read across template
- Other?



## Template for the Description of Cell-Based Toxicological Test Methods to Allow Evaluation and Regulatory Use of the Data

*Alice Krebs<sup>1,2</sup>, Tanja Waldmann<sup>1</sup>, Martin F. Wilks<sup>3</sup>, Barbara M. A. van Vugt-Lussenburg<sup>4</sup>, Bart van der Burg<sup>4</sup>, Andrea Terron<sup>5</sup>, Thomas Steger-Hartmann<sup>6</sup>, Joelle Ruegg<sup>7</sup>, Costanza Rovida<sup>8</sup>, Emma Pedersen<sup>9</sup>, Georgia Pallocci<sup>1,8</sup>, Mirjam Luijten<sup>10</sup>, Sofia B. Leite<sup>11</sup>, Stefan Kustermann<sup>12</sup>, Hennicke Kamp<sup>14</sup>, Julia Hoeng<sup>14</sup>, Philip Hewitt<sup>15</sup>, Matthias Herzler<sup>16</sup>, Jan G. Hengstler<sup>17</sup>, Tuula Heinonen<sup>18</sup>, Thomas Hartung<sup>8,19</sup>, Barry Hardy<sup>20</sup>, Florian Gantner<sup>21</sup>, Ellen Fritsche<sup>22</sup>, Kristina Fant<sup>9</sup>, Janine Ezendam<sup>10</sup>, Thomas Exner<sup>20</sup>, Torsten Dunkern<sup>23</sup>, Daniel R. Dietrich<sup>24</sup>, Sandra Coecke<sup>11</sup>, Francois Busquet<sup>8,25</sup>, Albert Braeuning<sup>26</sup>, Olesja Bondarenko<sup>27</sup>, Susanne H. Bennekou<sup>28</sup>, Mario Beilmann<sup>29</sup> and Marcel Leist<sup>1,2,8</sup>*

<sup>1</sup> *in vitro* Toxicology and Stemcell Research, Dept inaugurated by the Doerenkamp-Zbinden Foundation, University of Konstanz, Konstanz, Germany; <sup>2</sup> Konstanz Research School Chemical Biology (KoRS-CB), University of Konstanz, Konstanz, Germany; <sup>3</sup> Swiss Centre for Applied Human Toxicology, University of Basel, Basel, Switzerland; <sup>4</sup> BioDetection Systems BV, Amsterdam, The Netherlands; <sup>5</sup> European Food Safety Authority, Parma, Italy; <sup>6</sup> Investigational Toxicology, Drug Discovery, Pharmaceuticals, Bayer AG, Wuppertal, Germany; <sup>7</sup> Department of Organismal Biology, Uppsala University, Uppsala, Sweden; <sup>8</sup> CAAT-Europe, University of Konstanz, Konstanz, Germany; <sup>9</sup> RISE Research Institutes of Sweden, Göteborg, Sweden; <sup>10</sup> Centre for Health Protection, National Institute for Public Health and the Environment (RIVM), Bilthoven, The Netherlands; <sup>11</sup> European Commission, Joint Research Centre (JRC), Ispra, Italy; <sup>12</sup> F. Hoffmann – La Roche, Pharma Research and Early Development, Pharmaceutical Sciences – Roche Innovation Center, Basel, Switzerland; <sup>13</sup> Experimental Toxicology and Ecology, BASF SE, Ludwigshafen, Germany; <sup>14</sup> Philip Morris International R&D, Novato, CA, USA; <sup>15</sup> Non-Clinical Safety, Merck KGaA, Darmstadt, Germany; <sup>16</sup> German Federal Institute for Risk Assessment, Dept. Chemical Safety, Berlin, Germany; <sup>17</sup> Leibniz Research Centre for Working Environment and Human Factors (IfU), Technical University of Dortmund, Dortmund, Germany; <sup>18</sup> FITCAM, Faculty of Medicine and Life Sciences, Tampere University, Tampere, Finland; <sup>19</sup> Johns Hopkins University, Center for Alternatives to Animal Testing (CAAT), Baltimore, MD, USA; <sup>20</sup> Edelweiss Connect GmbH, Technology Park Basel, Basel, Switzerland; <sup>21</sup> Translational Medicine & Clinical Pharmacology, Boehringer Ingelheim Pharma GmbH & Co. KG, Biberach, Germany; <sup>22</sup> IfU – Leibniz Research Institute for Environmental Medicine, Düsseldorf, Germany; <sup>23</sup> Crunthal GmbH, Aachen, Germany; <sup>24</sup> Human and Environmental Toxicology, University of Konstanz, Konstanz, Germany; <sup>25</sup> ALERTox SPRL, Ixelles, Bruxelles, Belgium; <sup>26</sup> German Federal Institute for Risk Assessment, Dept. Food Safety, Berlin, Germany; <sup>27</sup> Laboratory of Environmental Toxicology, National Institute of Chemical Physics and Biophysics, Tallinn, Estonia; <sup>28</sup> The National Food Institute, Technical University of Denmark, Kgs. Lyngby, Denmark; <sup>29</sup> Boehringer Ingelheim Pharma GmbH & Co. KG, Nonclinical Drug Safety, Biberach, Germany

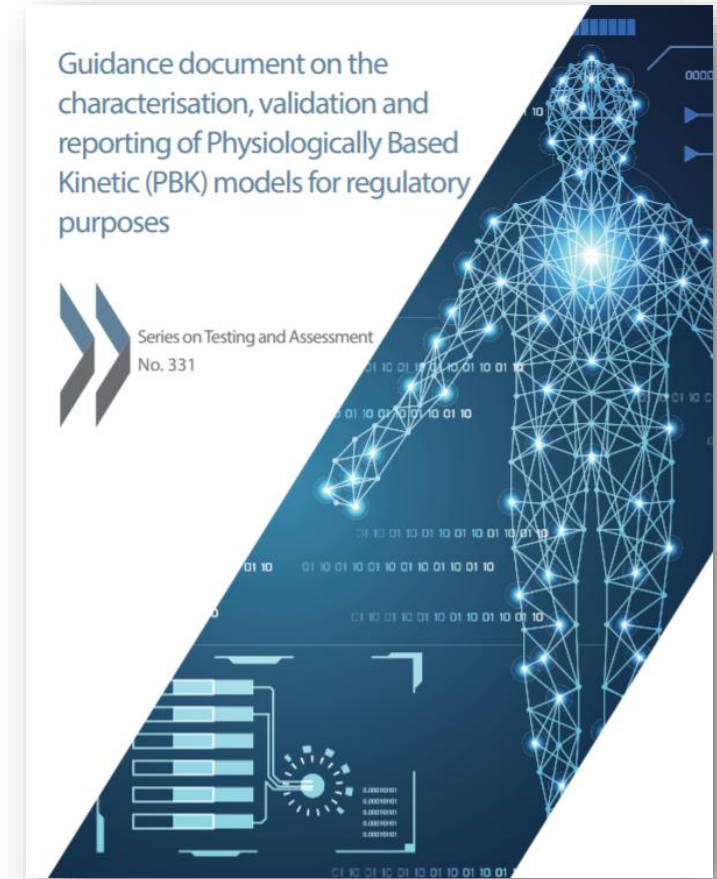
### Abstract

Only few cell-based test methods are described by Organisation for Economic Co-operation and Development (OECD) test guidelines or other regulatory references (e.g., the European Pharmacopoeia). The majority of toxicity tests still



# Guidance document on PBK modelling

**1 Case study from** EU-ToxRisk that uses the template for reporting models and the checklist for evaluating their validity and applicability

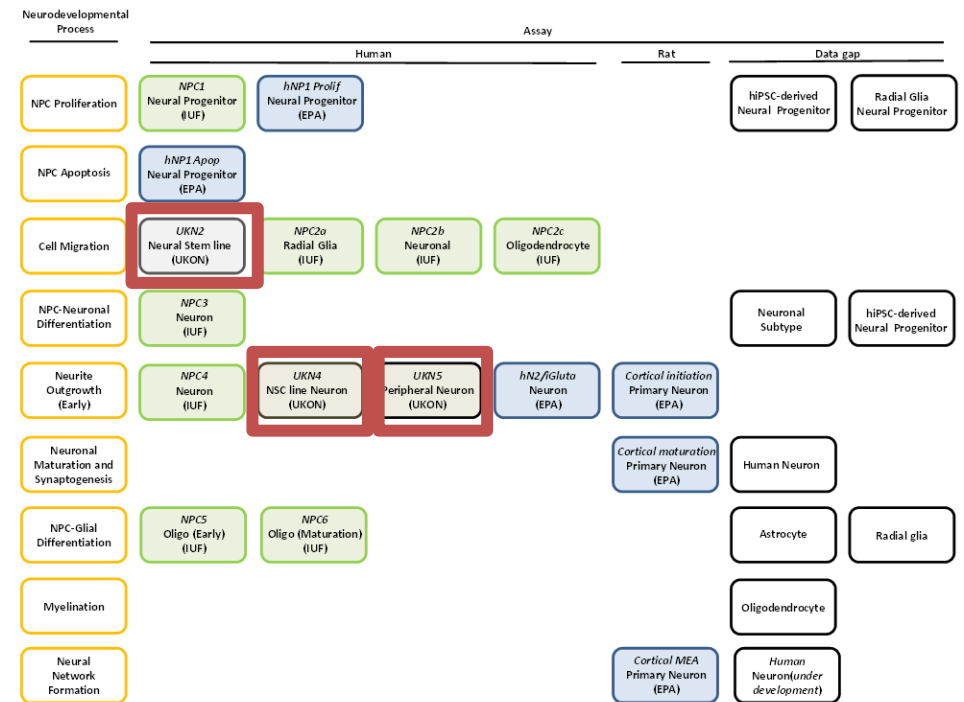




# DNT In vitro Battery Guidance Document

**2 DNT IATA case studies** to be published in 2022, showing how to use the DNT IVB and additional EU-ToxRisk tools

**3 In vitro assays from the EU-ToxRisk toolbox** are part of the battery and they might undergo validation





## AOP programme

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- Members of EU-ToxRisk consortium became members of EAGMST and its subgroups
- EU-ToxRisk provided content in some KEs and KERs

**23** AOPs in designing face

**12** AOPs developed

**61** KEs and **68** KERs

**7** AOPs in the AOP-Wiki



## Invitation to ASPIS

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- Provide a **short update** on the projects annually at the WPHA June meeting.
- Create a mechanism of **WPHA feedback** on deliverables intended to be used by regulators

**You're  
Invited!**





# Thanks For Listening



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