EU-ToxRisk: Interactions with the OECD Chemical Safety Programme

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OECD Environment Health and Safety
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BETTER POLICIES FOR BETTER LIVES

Outline

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

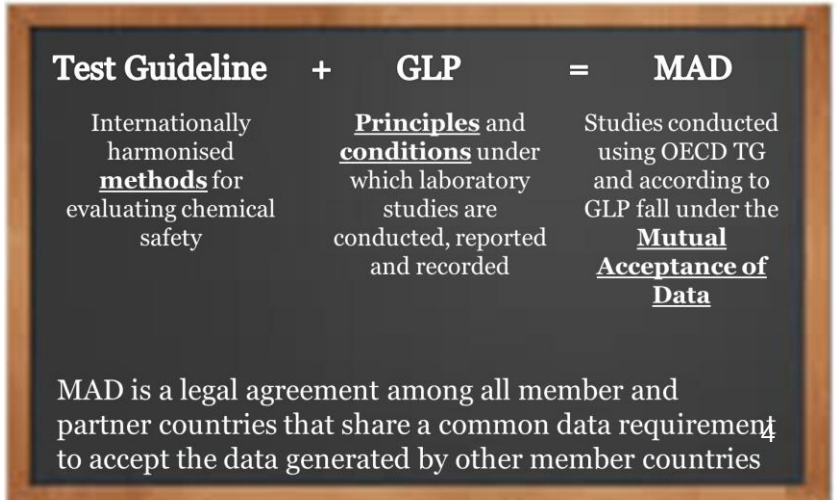
OECD IATA Case Studies Project

- 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

- "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



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

Information included in Considerations Documents

- 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	IATA Topics				Reference
			AOP[1]	UR[2]	NAM[3]	L/N[4]	
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_2		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 = 7th cycle

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

Benefits for the EU-ToxRisk

5 Case studies published in the OECD
Environment, Health and Safety Publications Series on Testing and Assessment

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

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

Benefits for OECD IATA Case Studies Project

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

- 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?

Bench Marks!

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

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

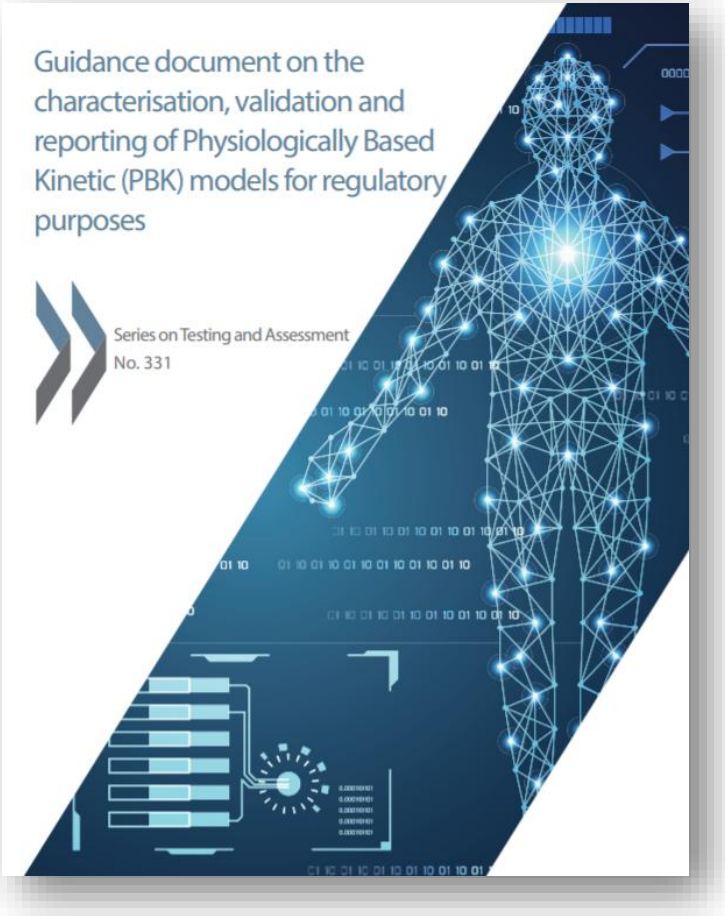
[1]In vitro Toxicology and Biomedicine, Dept inaugurated by the Doerenkamp-Zbinden Foundation, University of Konstanz, Konstanz, Germany; [2]Konstanz Research School Chemical Biology (KoRS-CB), University of Konstanz, Konstanz, Germany; [3]Swiss Centre for Applied Human Toxicology, University of Basel,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

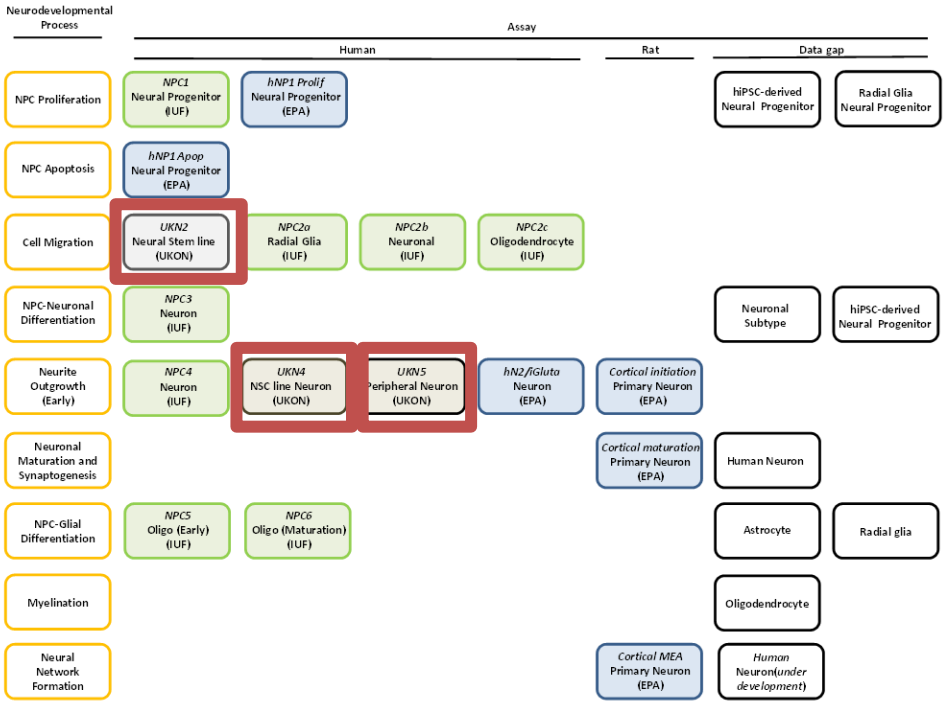
1 Case study from EU-ToxRisk that uses the template for reporting models and the checklist for evaluating their validity and applicability



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

- 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

- 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

Thanks For Listening

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