OECD ACTIVITIES TO INCREASE THE UTILITY AND UPTAKE OF AOPS IN REGULATORY CONTEXTS ACROSS COUNTRIES

Science Advisory Committee on Alternative Test Methods
19-20 September 2019

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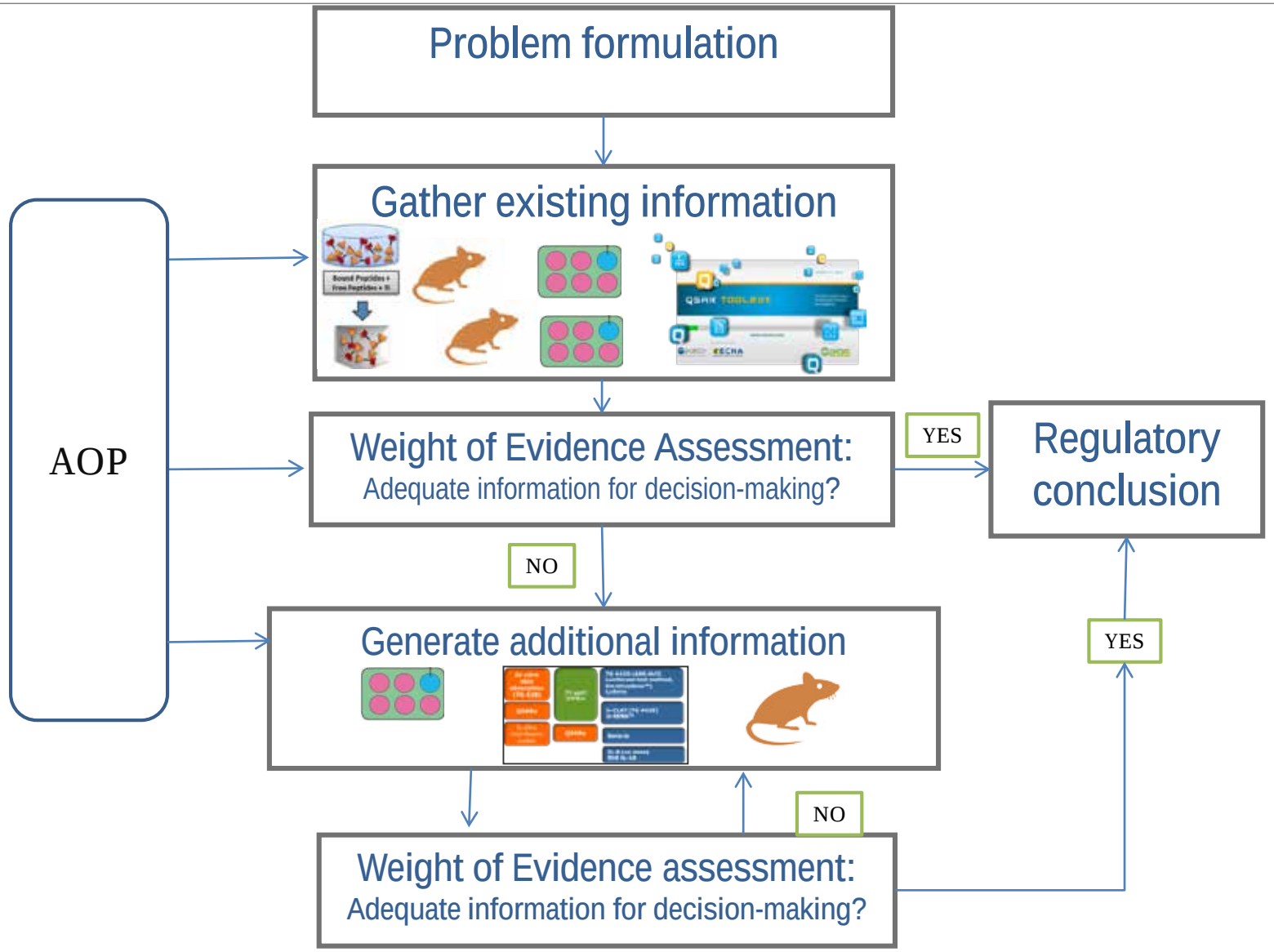
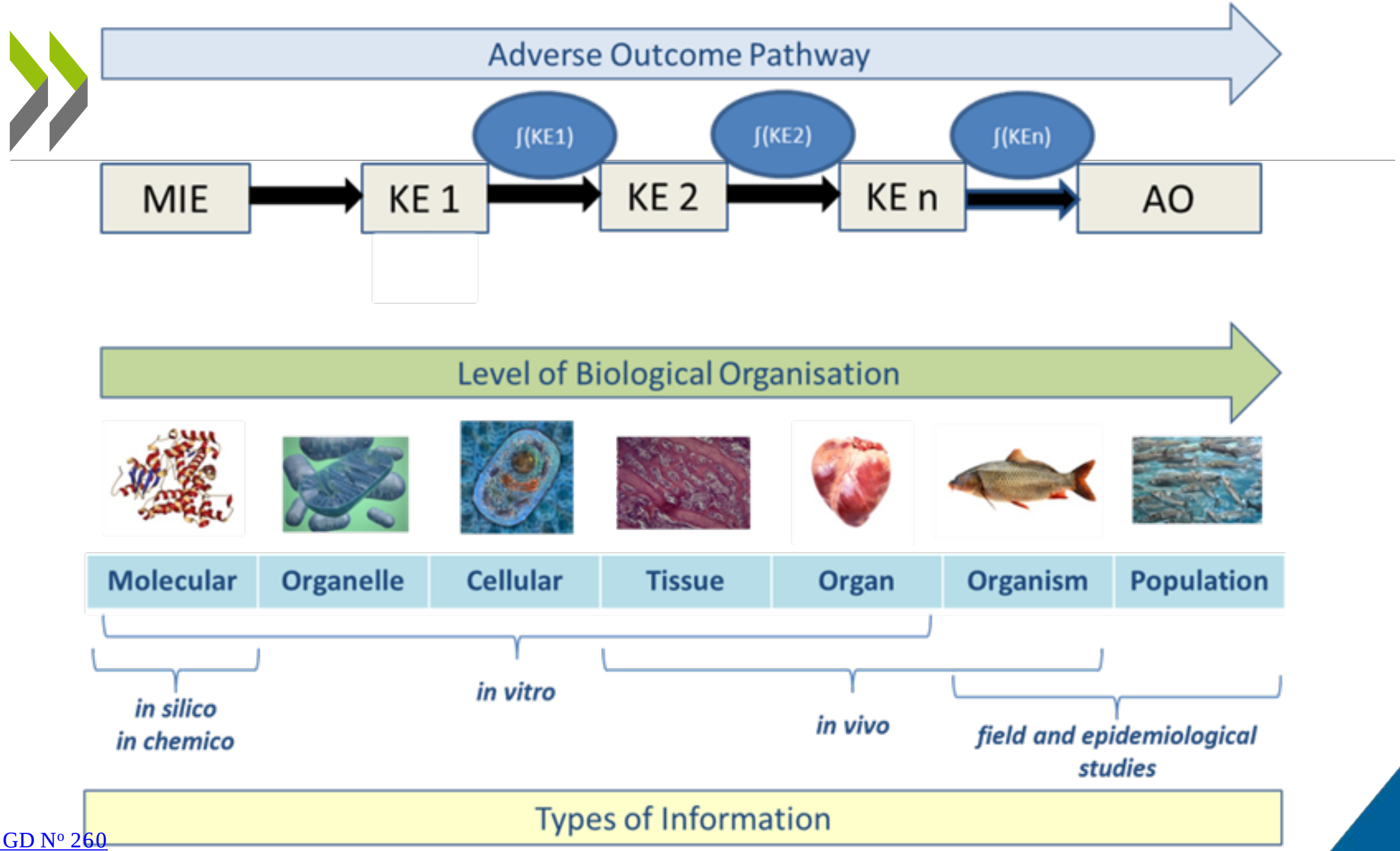
Head- Environment, Health and Safety Division
OECD

BETTER POLICIES FOR BETTER LIVES

Integrated Approaches to Testing and Assessment (IATA)





OECD GD Nº 260

OECD IATA Case Studies Project

Objective:

- Increase experience with the use of Integrated Approaches for Testing and Assessment by developing case studies, which constitute examples of predictions that are fit for regulatory use

- Create common understanding and develop guidance

Deliverables:

- Guidance documents on methodologies with associated case studies.

Year-No. (Lead)	Assessment approach	Endpoint	IATA topics				References
			AOP*1	UR*2	NAM*3	L/N*4	
2016-1 (Japan)	Read-across	Repeated dose toxicity		X	X		OECD, 2017a
2016-2 (US)	Grouping for cumulative risk assessment	Neurotoxicity	X		X		OECD, 2017b
2016-3 (ICAPO)	Read-across	Repeated dose toxicity		X	X	X	OECD, 2017c
2016-4 (ICAPO)	Read-across	Repeated dose toxicity		X	X	X	OECD, 2017d
2016-5 (JRC/BIAC)	Safety assessment workflow	Repeated dose toxicity	X		X		OECD, 2017e
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

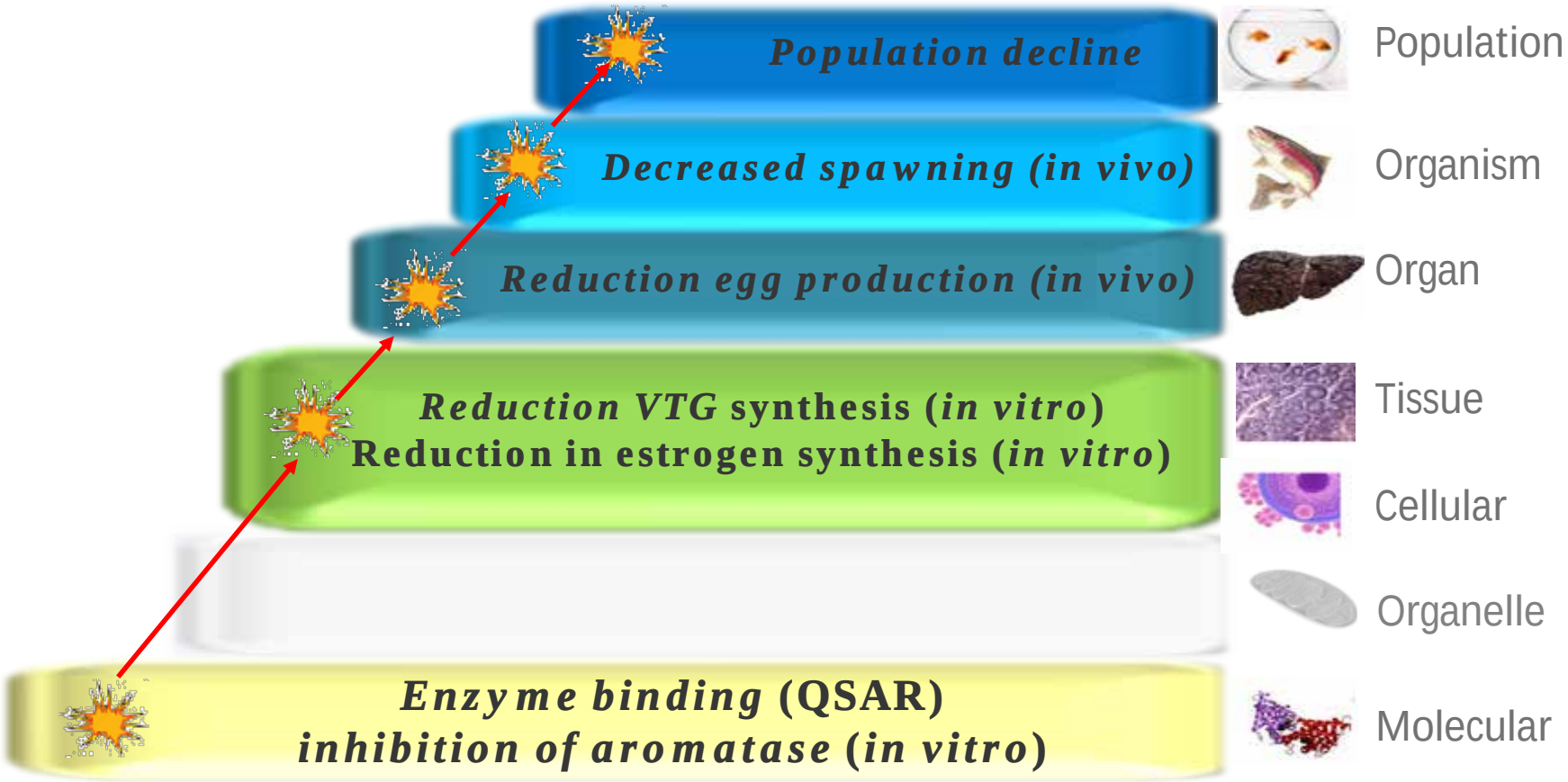
*1: AOP: Use of mode of action/adverse outcome pathways
*2: UR: Uncertainty reporting
*3: NAM: Use of new approach methodologies
*4: L/N: Low/no toxicity prediction

IATA Case Studies and AOPs …

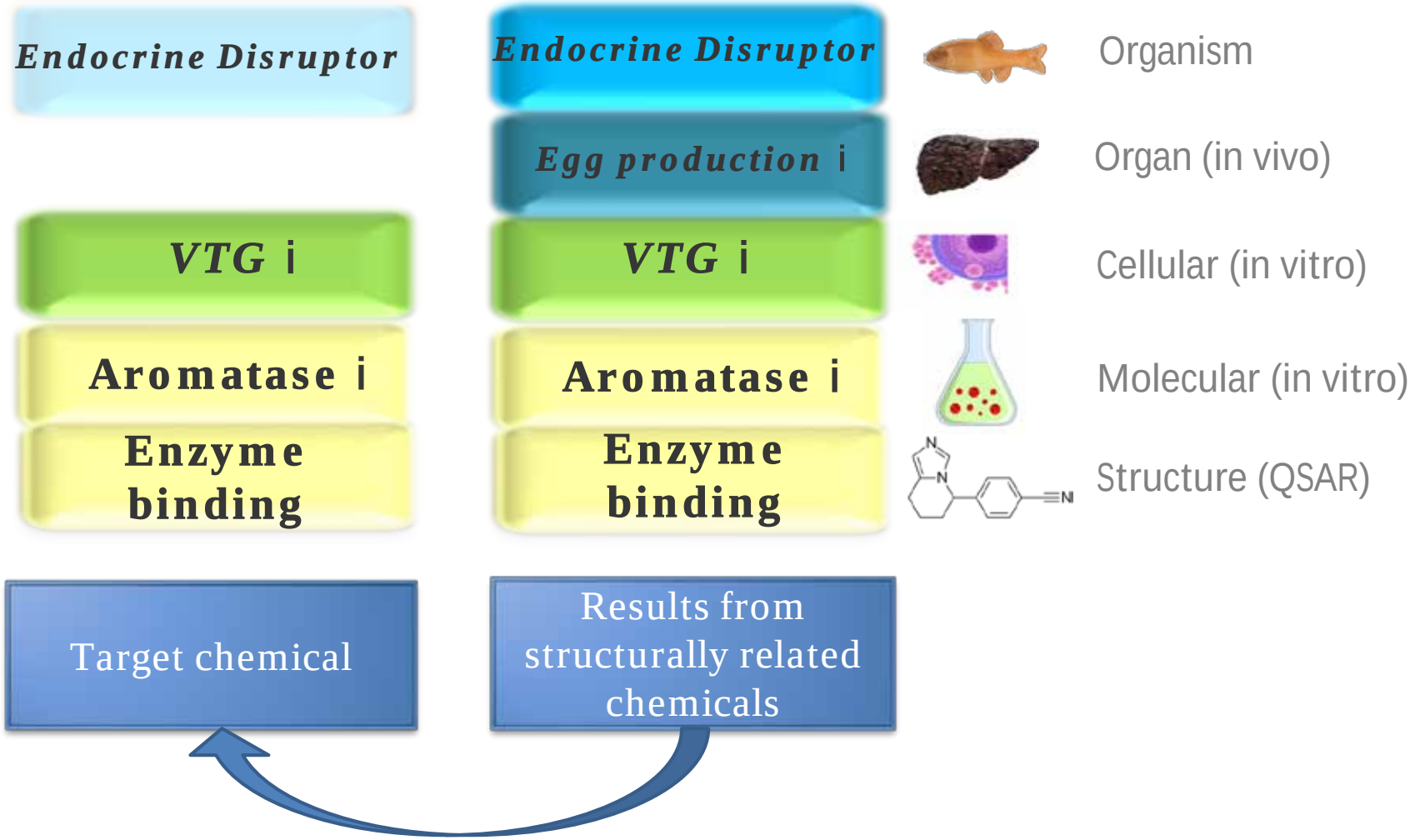
- IATA Case Studies Project
  - 8 case studies use AOP or mechanistic information
  - 2 include mechanism for endorsed AOP 38 - Adverse Outcome Pathway on Protein Alkylation Leading to Liver Fibrosis (AOP)
  - 2 link to AOPs under development, others had no relevant AOP in the wiki …
  - This round of case studies – almost all contain AOP/mechanistic thinking … often not on endorsed/active AOPs

POTENTIAL APPLICATIONS OF THE AOP CONCEPT

Early key events can be measured with non-animal tests, which can be used to predict the adverse outcome



Read-across based on mechanistic understanding



QSAR Toolbox (1)

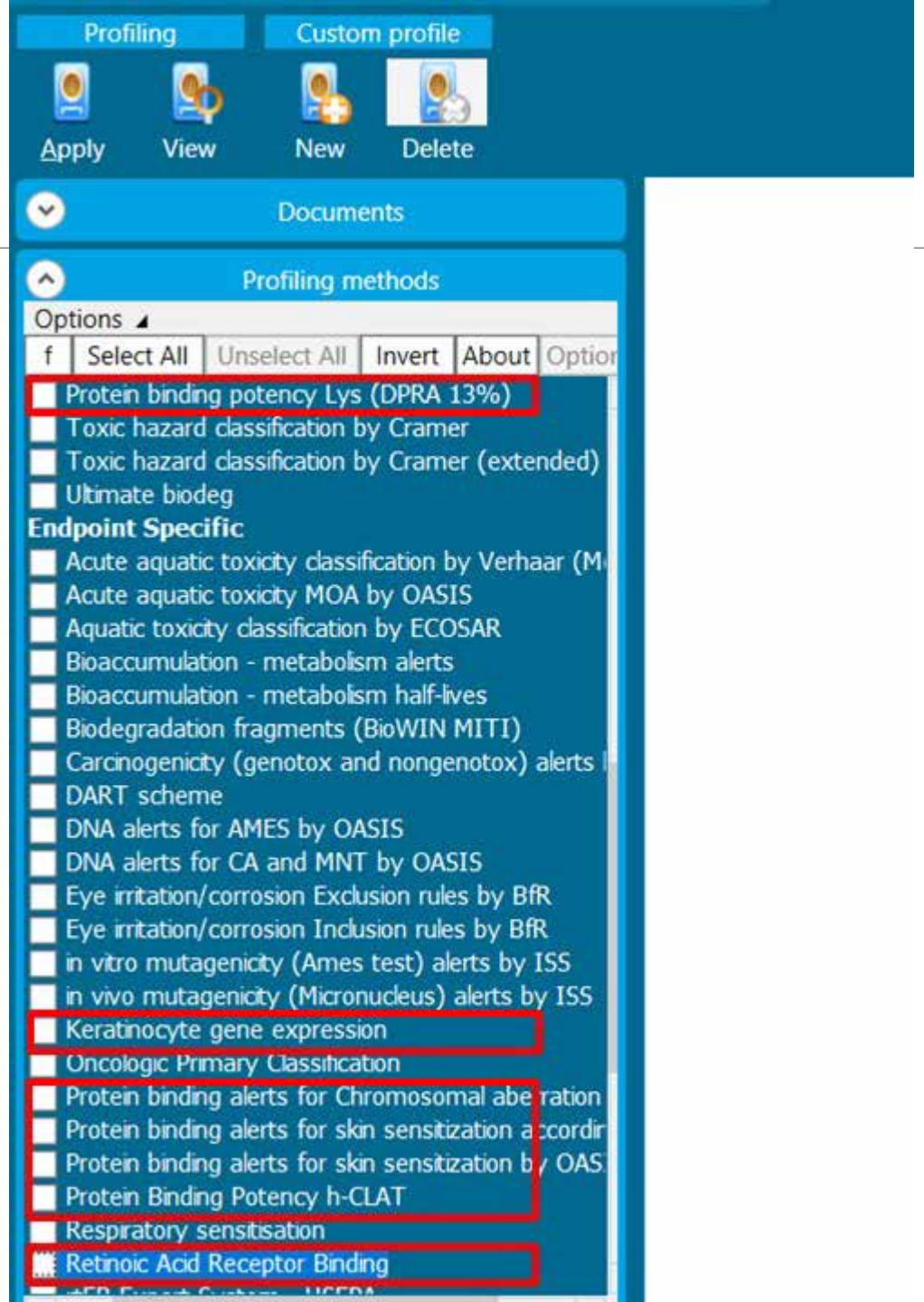
QSAR TOOLBOX

The OECD QSAR Toolbox for Grouping Chemicals into Categories

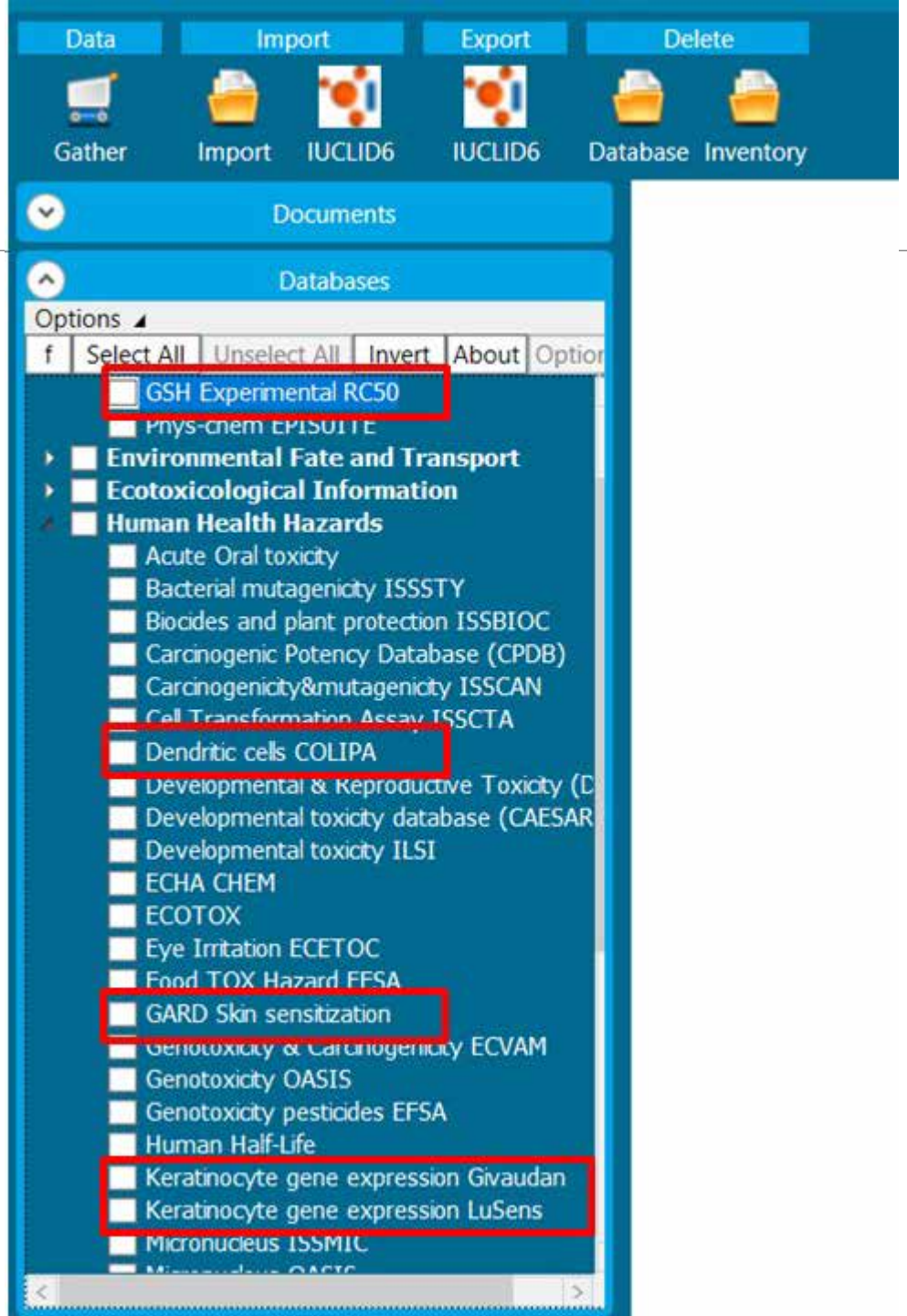
- Free software application to predict the properties of chemicals (version 4.3 launched in 2019)

- Estimate missing experimental values by read-across and trend analysis (grouping of similar chemicals, chemical categories)

www.oecd.org/env/hazard/qsar

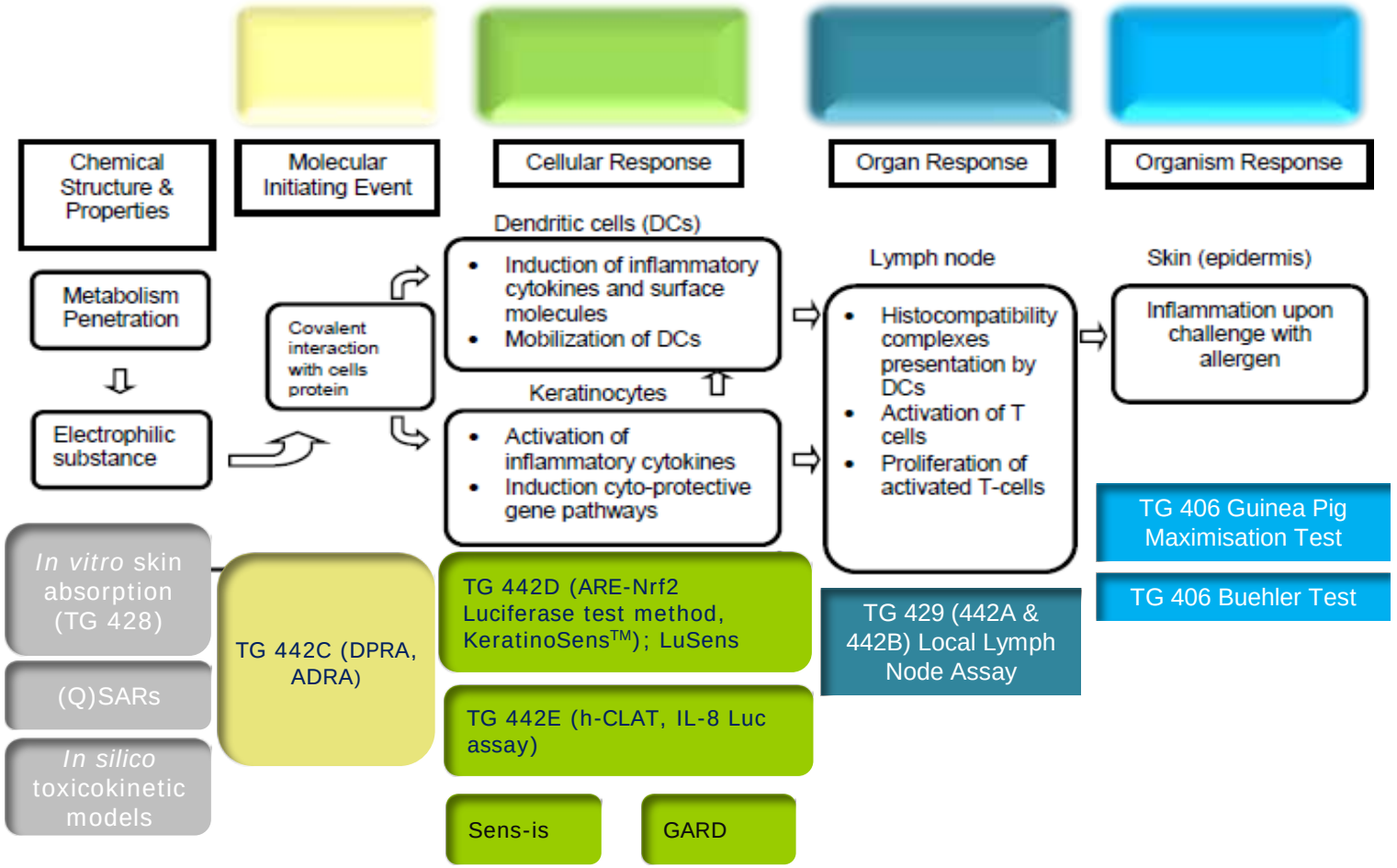


Profilers predicting results of key events

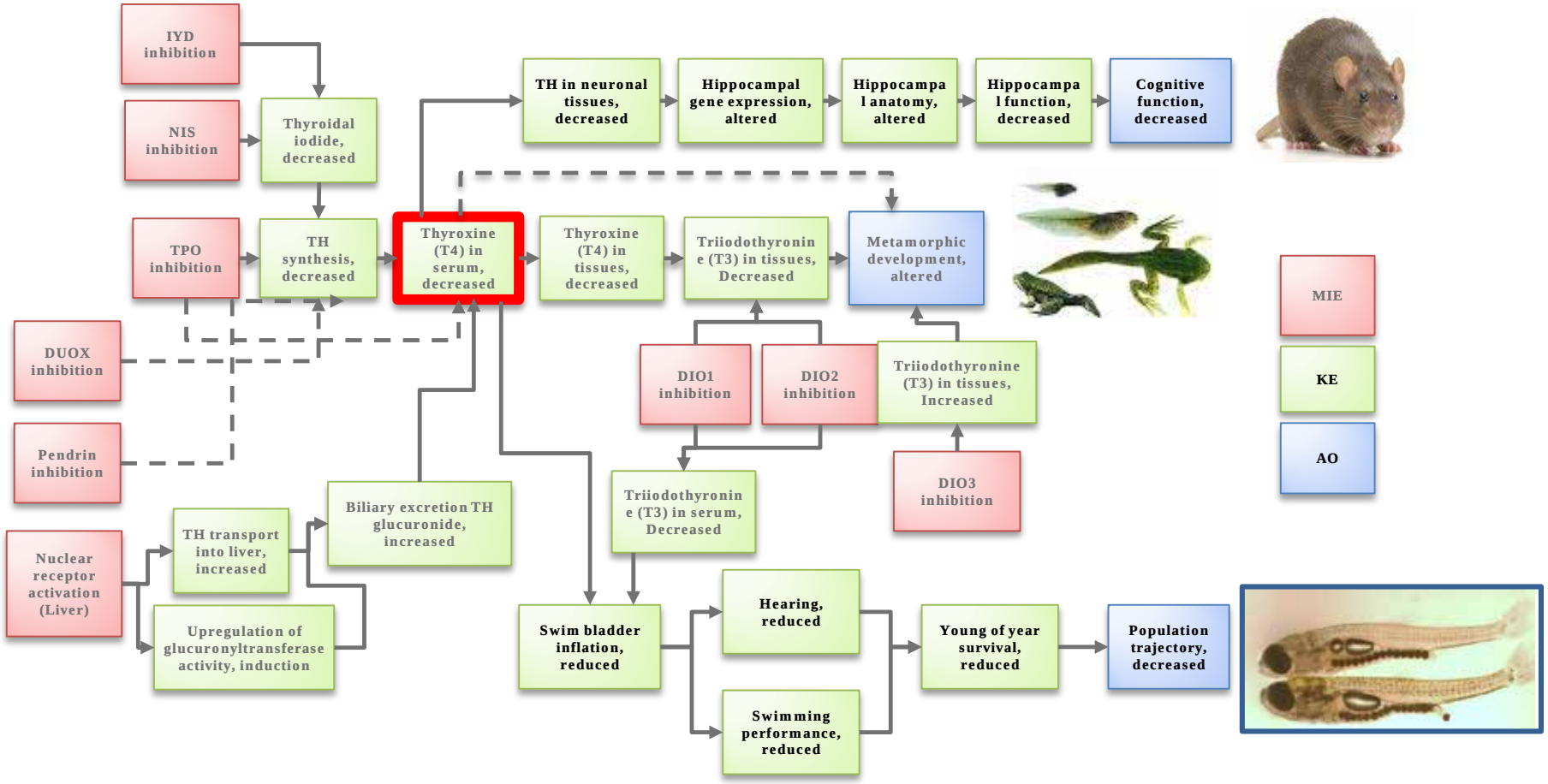


Databases with results from key events

Test Guideline Development (e.g. skin sensitisation)



Thyroid AOP Network: future opportunities for candidate *in vitro* assays, IATAs



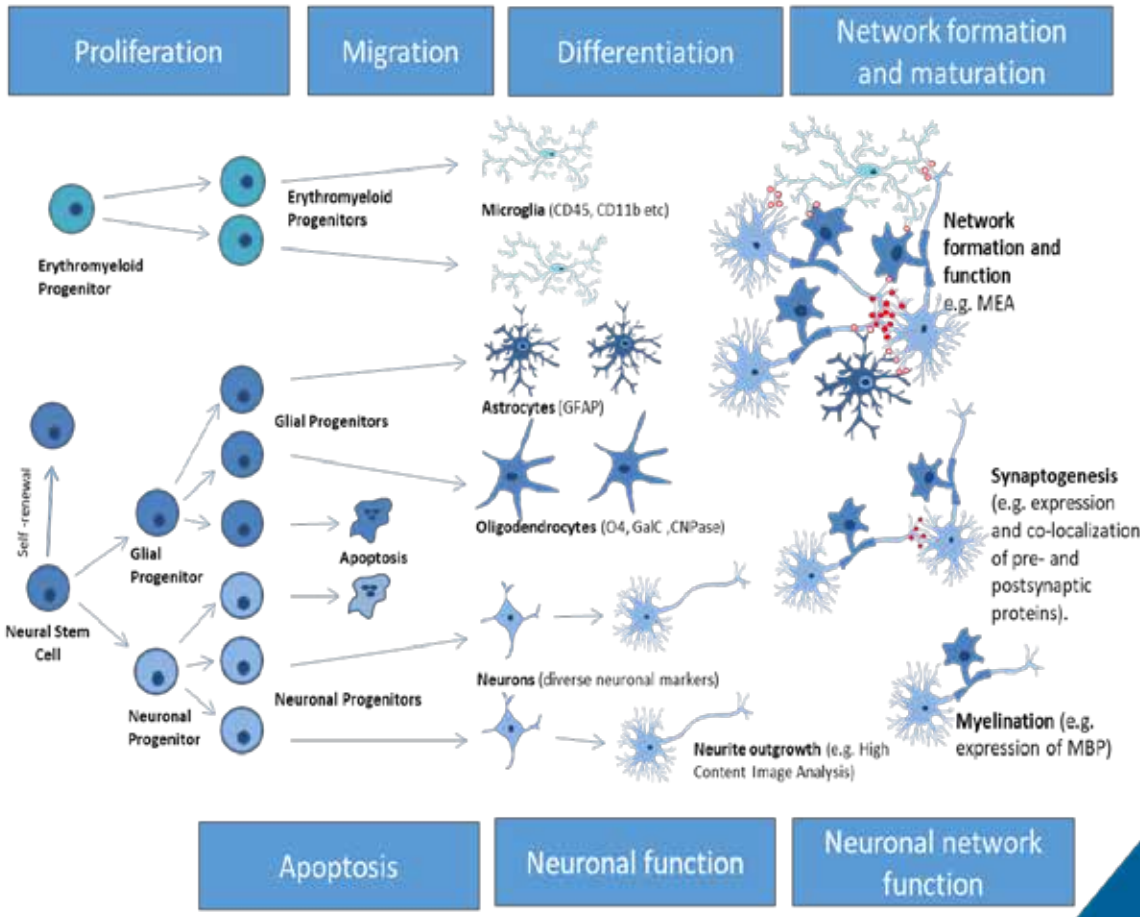
Slide courtesy of Jon Haselman, US EPA

Developmental neurotoxicity (DNT) project

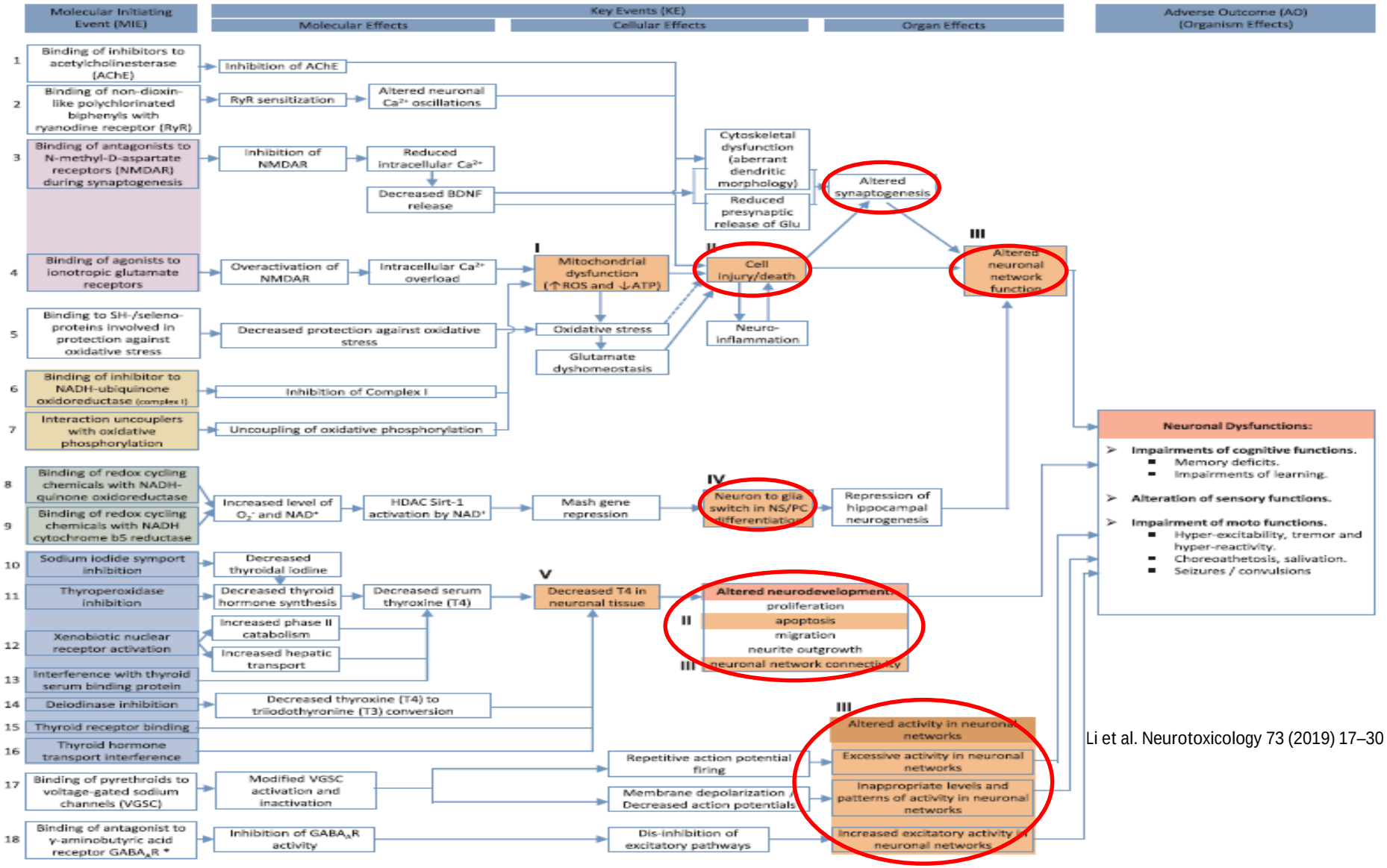
- Objective: to develop guidance on application and interpretation of *in vitro* developmental neurotoxicity assays and tiered approach to testing and assessment of DNT modalities not related to endocrine system

  - Lead Consortium: EFSA, Danish EPA, US EPA, EC-JRC

Key neurodevelopmental processes: mapping of in vitro assays



Graphic representation of 18 DNT-related AOPs



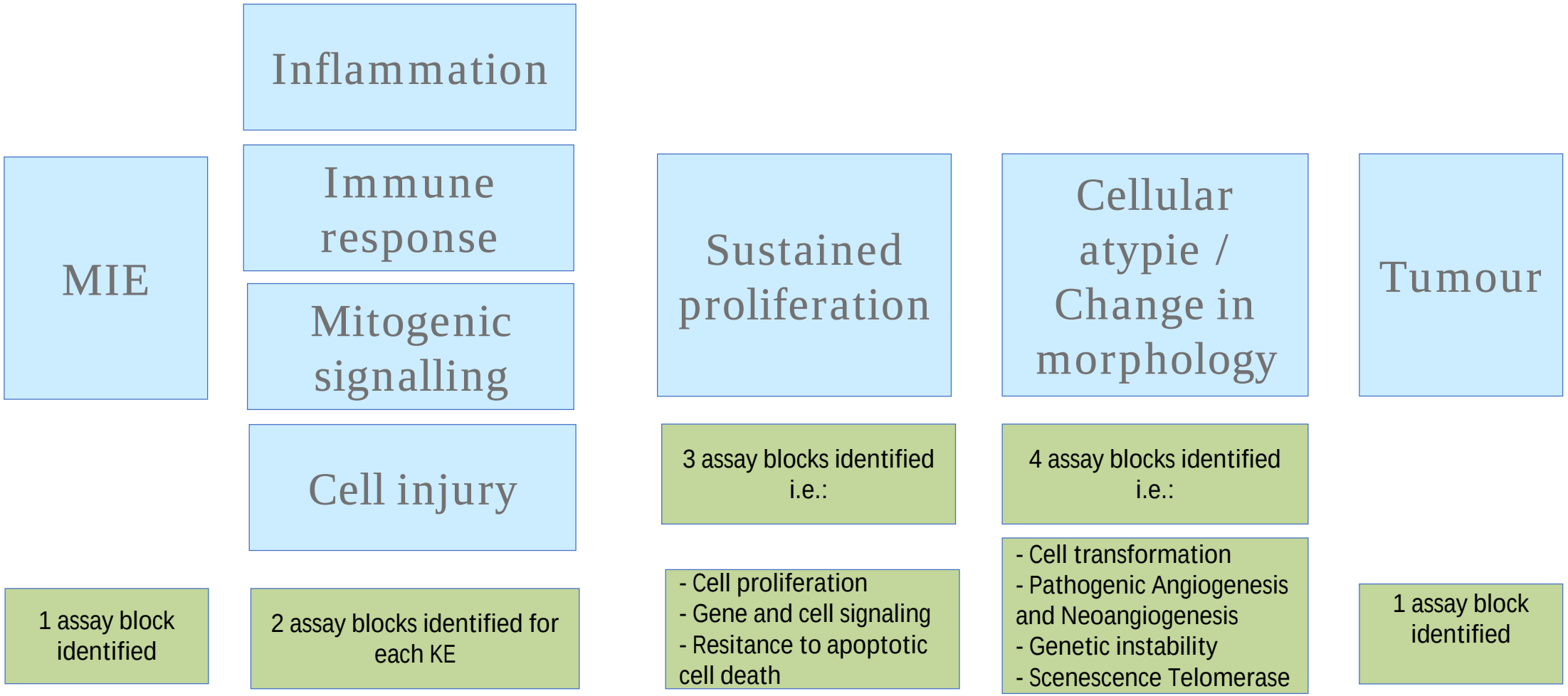
Li et al. Neurotoxicology 73 (2019) 17–30

IATA project for non-genotoxic carcinogens (NGTxC)

- Led by the UK
- Three cancer models considered: liver, colon and lung
- NGTxC flow developed using the AOP construct:
  - Simple
  - Pragmatic
  - Accomodate most NGTx cancer theories and understanding

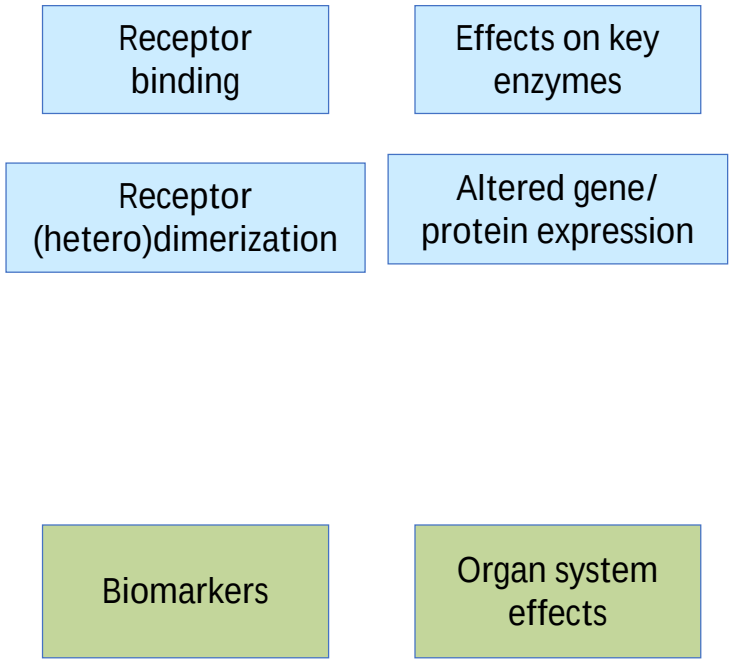
Objective: develop a scoping document to characterise *in vitro* assays and their level of readiness for further standardisation

Simplified NGTxC AOP flow

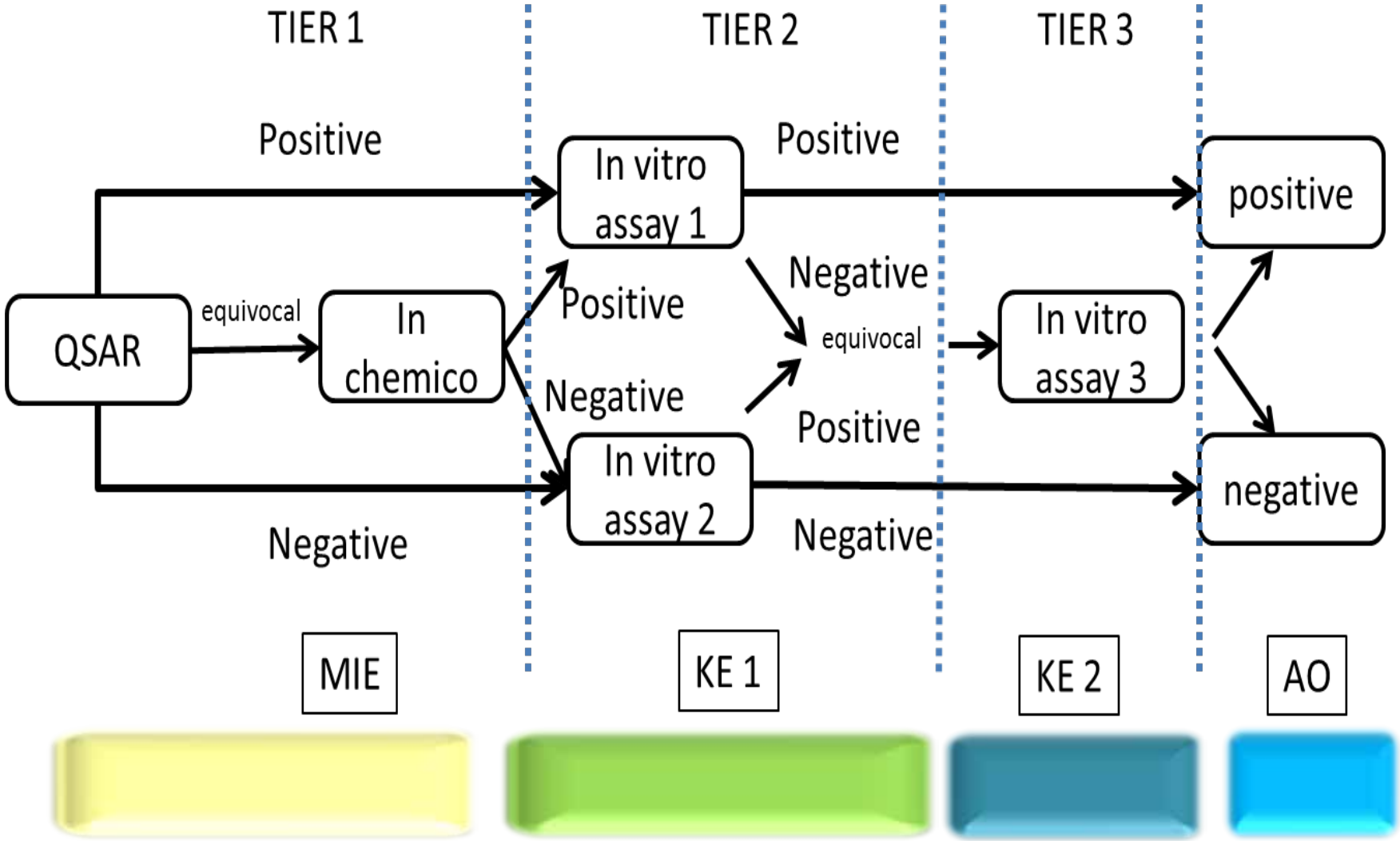


IATA-related endocrine projects: Retinoid signalling pathway

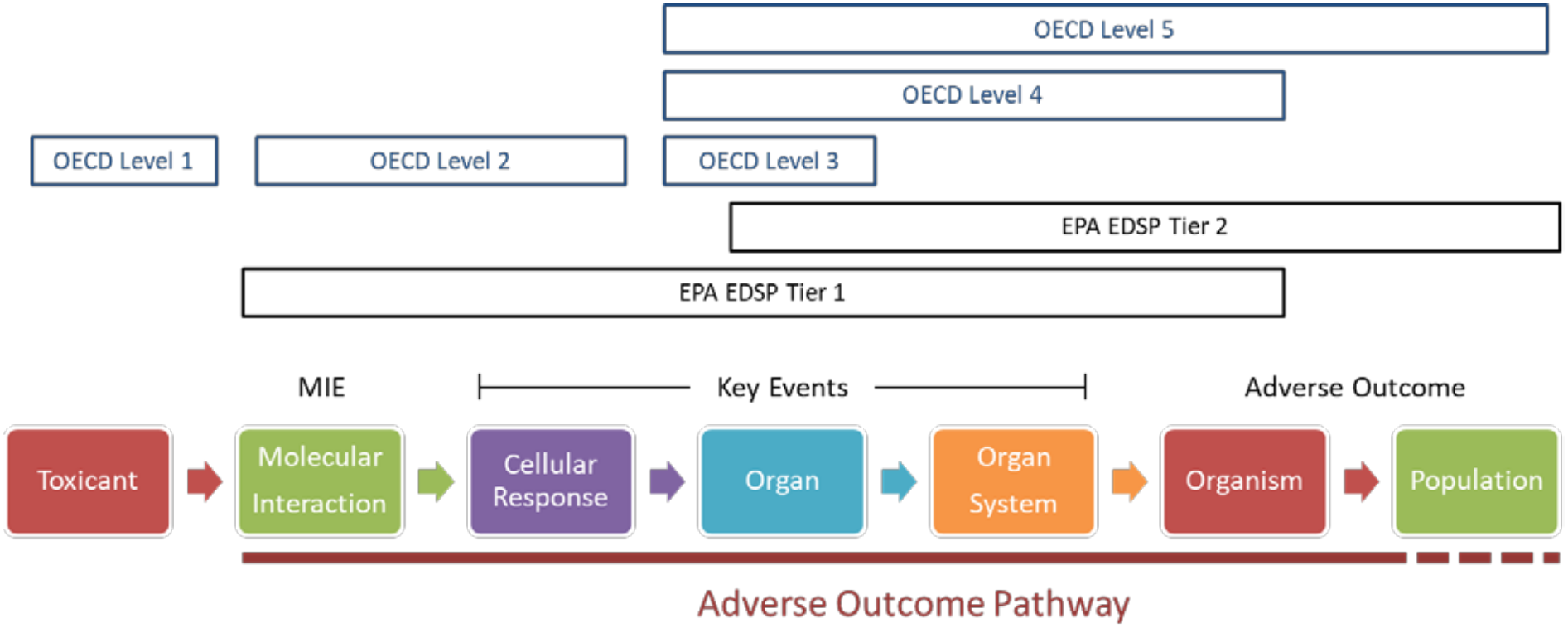
- Project to develop a Detailed Review Paper on retinoid pathway signalling
  - Led by Sweden/EC/Secretariat
- Overview of retinoid signalling biology
  - Detailed review of role of retinoid signalling in
    - female reproductive system,
    - male reproductive system,
    - central nervous system, and
    - skeletal system
- Objective: scope available assays
  - Link mechanistic data with apical responses for chemicals known to affect retinoid pathway signalling (case study approach)
  - Request input from expert group on:
    - Assays/endpoints for development
    - Regulatory interpretation
  - Given the complexity of the retinoid pathway, recommendations are likely to be a suite of assays in an IATA/screening battery/ITS



Development of Harmonised Testing Strategies or Defined Approaches

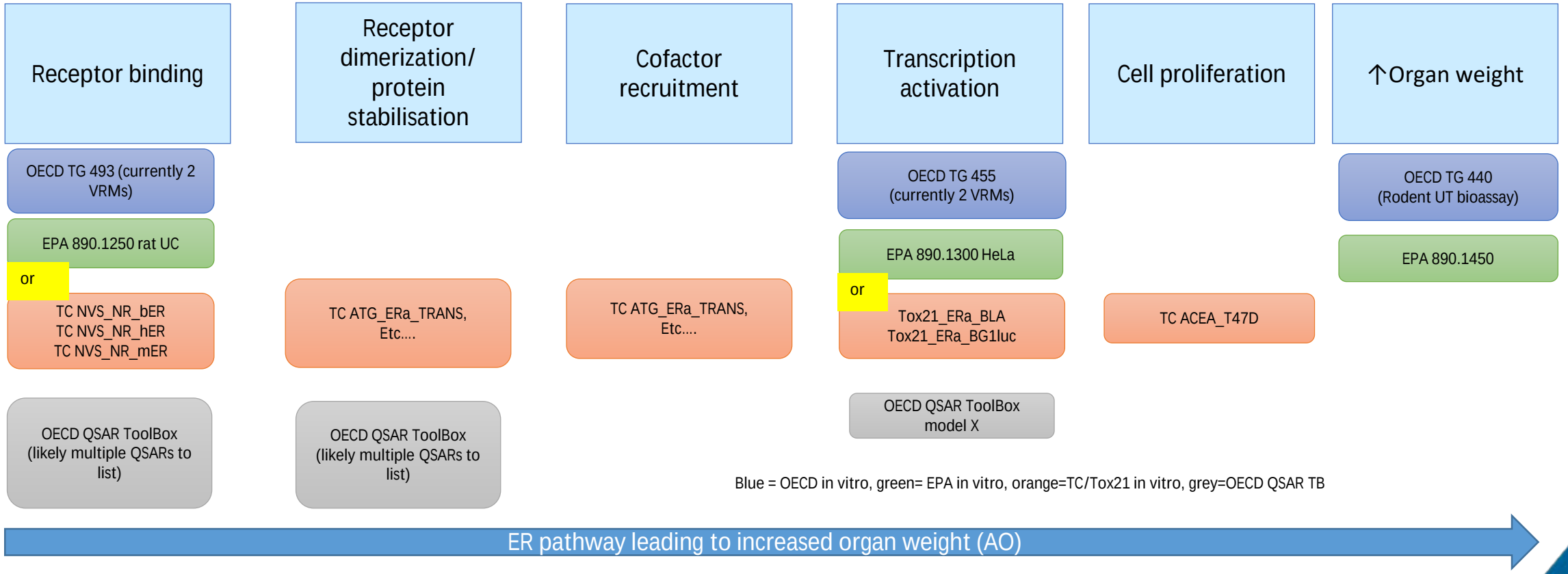


Endocrine Disruptor Screening and Testing: AOP thinking + testing strategies



Testing strategy developed around an AOP: ER pathway

- IATA case study project
  - Led US
  - Considered with a defined approach
  - Combines results form ≥ 4 in vitro assays to predict the rodent in vivo uterotrophic response



IATA versus Defined Approaches

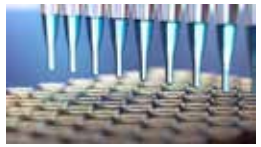
IATA	Defined Approaches
Designed in response to problem formulation	Designed to address pre-defined endpoint/prediction
Inputs are defined by user	Defined information sources
Sequence of input, next steps, decision context defined by user	Sequence defined and next steps are rule-based
Expert judgement for weighting data, interpreting data	Fixed data interpretation procedure
Conclusion may be open to interpretation	Regulatory conclusion is clear

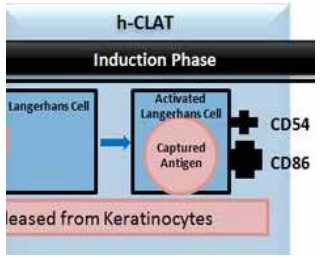
Defined Approach (DA) for Skin Sensitisation: General workflow

2017-2020: Developing a Guideline that predicts hazard and potency for skin sensitisation

TG 442E

TG 442C





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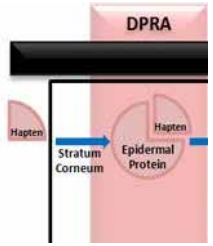

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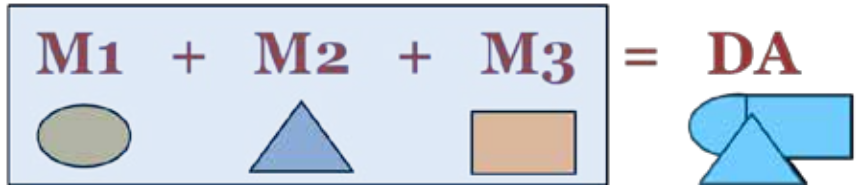
Score	h-CLAT MIT	DPRA depletion	OECD TB
3	≤10 µg/mL	≥42.47%	-
2	>10, ≤150 µg/mL	≥22.62, <42.47%	-
1	>150, ≤5000 µg/mL	≥6.376, <22.62%	Sens
0	not calculated	<6.376%	Non

Potency: Total battery score

Strong :	7
Weak :	2-6
Not classified :	0-1

Outcome of a discussion of QSAR experts- Nov. 2018

- A new approach for describing “applicability domain” of DAs is needed

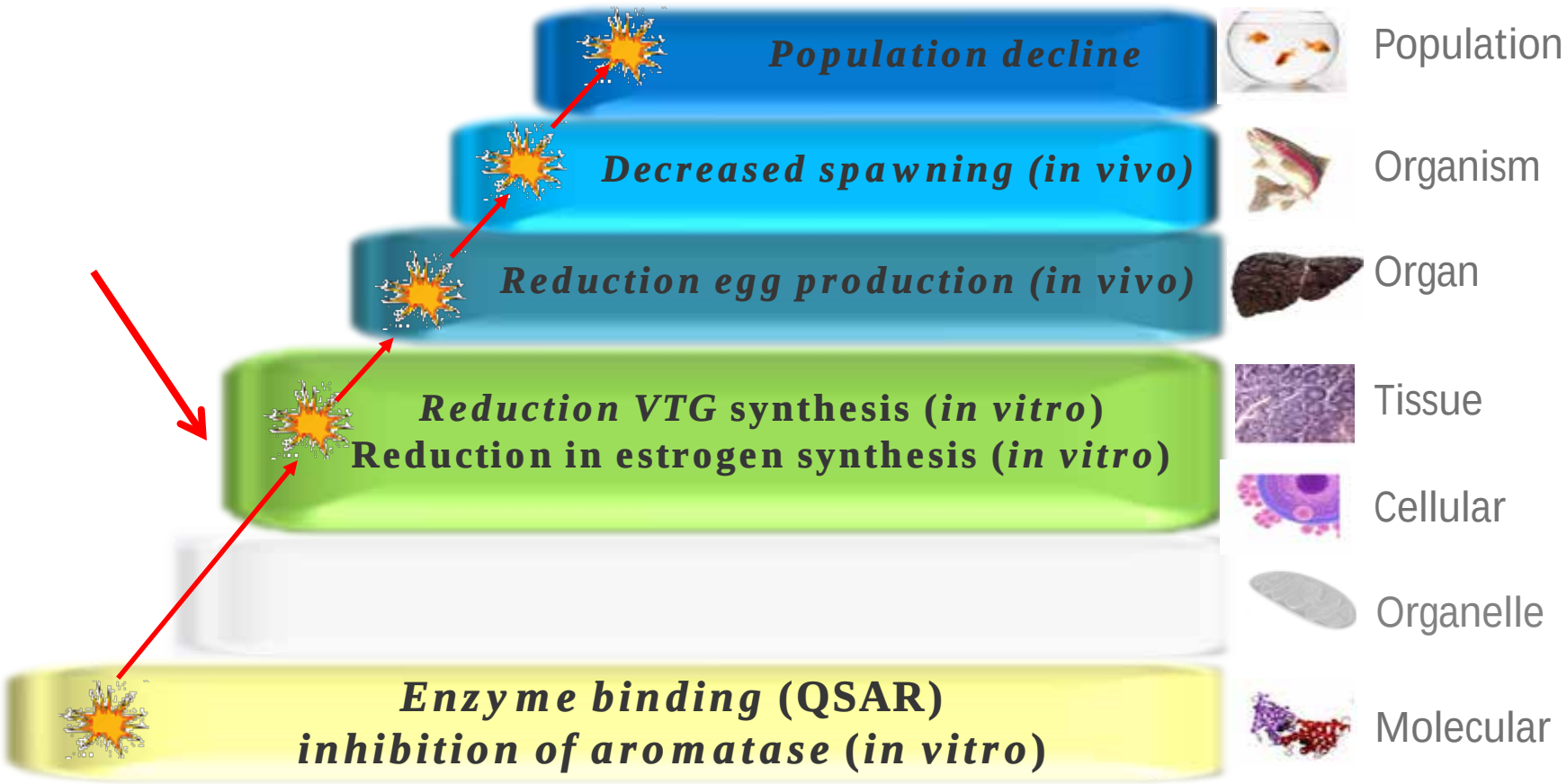


- Validation and transparency
- Proposal for QA reporting standards for in silico models and resulting predictions

QMRF + protocol ~ test guideline
QPRF ~ test report

- Proposal for rigid (or automated) protocol for generating predictions to remove expert judgement
  - New version of OECD QSAR TB will have a “skin sensitization for defined approaches” module
    - Included in next update of the TB (OCT 2019)

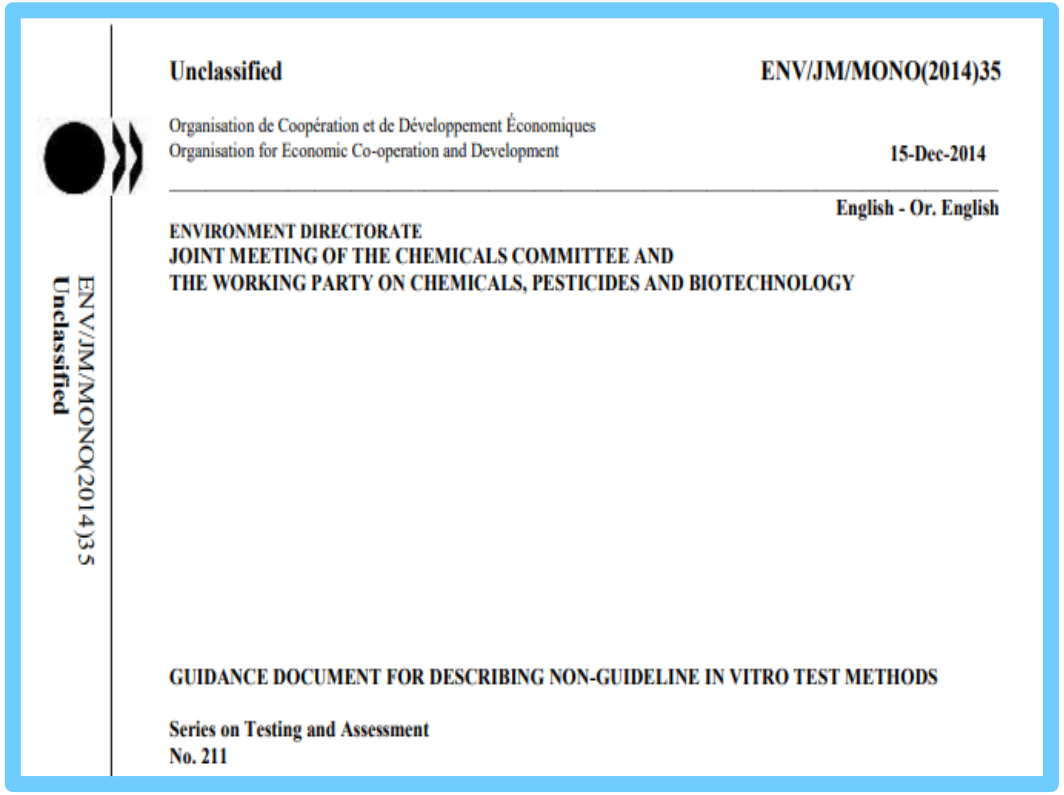
Interpretation of non-standard in vitro test results



GD 211 for describing Non-Guideline in vitro test methods

- "provide a short description (of an assay) indicating:
- firstly what key event within an existing or developing AOP, or in relation to a mechanism or mode of action, the assay is aiming to characterize (i.e. which level of biological organization the assay may be attributed (e.g. sub-cellular, cellular, tissue, organ or individual), and
- secondly where the assay might fit in the context of an existing regulatory hazard (i.e. adverse outcome)"

Represents an additional effort to give a role/ place to non-standardised methods



Unclassified ENV/JM/MONO(2014)35

Organisation de Coopération et de Développement Économiques
Organisation for Economic Co-operation and Development

15-Dec-2014

English - Or. English

ENVIRONMENT DIRECTORATE
JOINT MEETING OF THE CHEMICALS COMMITTEE AND
THE WORKING PARTY ON CHEMICALS, PESTICIDES AND BIOTECHNOLOGY

ENV/JM/MONO(2014)35
Unclassified

GUIDANCE DOCUMENT FOR DESCRIBING NON-GUIDELINE IN VITRO TEST METHODS

Series on Testing and Assessment
No. 211

http://www.oecd.org/officialdocuments/publicdisplaydocumentpdf/?cote=ENV/JM/MONO(2014)35&doclanguage=en

Criteria for AOP prioritisation

- 2012-2018: AOP development and review has been a proof-of-concept, open and based on opportunities
- 2019: prioritisation under discussion to ensure AOPs developed, reviewed and published will match the needs of countries
  - Is a Regulatory Need Identified?
    - Member country/agency priority
  - Is a Testing Strategy/Assays under development?
    - Help identify candidate in vitro assay or battery of assays or endpoints to standardise
  - Can it link to ongoing/future OECD projects on:
    - » WPHA IATA project
    - » Test Guidelines Programme workplan ?
  - Does it complement an existing network of AOPs addressing a regulatory endpoint?
  - Availability of people/resources to develop and review?

Outlook (1)

- Continuation of IATA Case Study Project
- OECD QSAR TB (2020-2025)
  - Addition of databases of results from KE (e.g. intermediate effects database by JRC)
- Testing strategies
  - DNT battery of in vitro assays
  - In vitro battery for immunotoxicity (just starting, first step DRP)
  - Follow-up for NGTxC
  - Adult neurotoxicity ?

Outlook (2)

- Defined Approaches
  - Skin Sensitisation: Mid-2020?
  - Eye irritation (ca. 2021)
- Prioritise AOP development and reviewing based on ongoing or upcoming OECD projects and regulatory needs. In parallel, encourage innovation and development of AOPs for future projects.