INTEGRATED APPROACHES FOR TESTING AND ASSESSMENT OF CHEMICALS FOR REGULATORY DECISION-MAKING

Bob Diderich, OECD
Cat-APP Final Workshop, 6 September 2018, Brussels

BETTER POLICIES FOR BETTER LIVES

Regulators want to …

- Accelerate the pace of risk assessment
- Access new, more predictive information
- Have more data
- Make better use of existing data

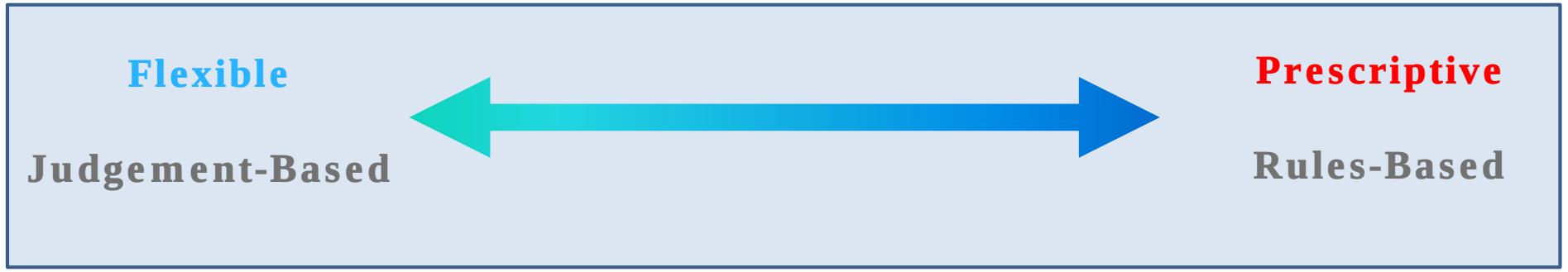
- Make good regulatory decisions

➢ Shift in national legislations:
~~Testing~~ Information requirements

Integrated approaches to testing and assessment (IATA)

- Pragmatic, science-based approaches for chemical hazard characterization
- Follow an iterative, integrative approach to answer a defined question in a specific regulatory context
  - take into account the acceptable level of uncertainty associated with the decision context
- Can include a combination of methods and can be informed by integrating results from one or many methodological approaches

Types of IATA – A Continuum



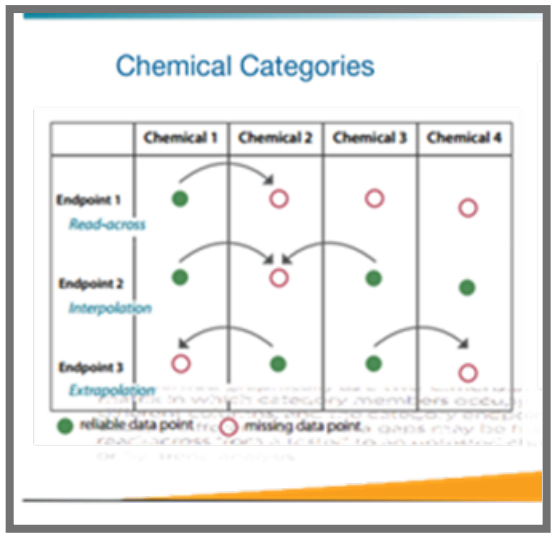
Non-formalised approaches

e.g. grouping and read-across

Structured approaches

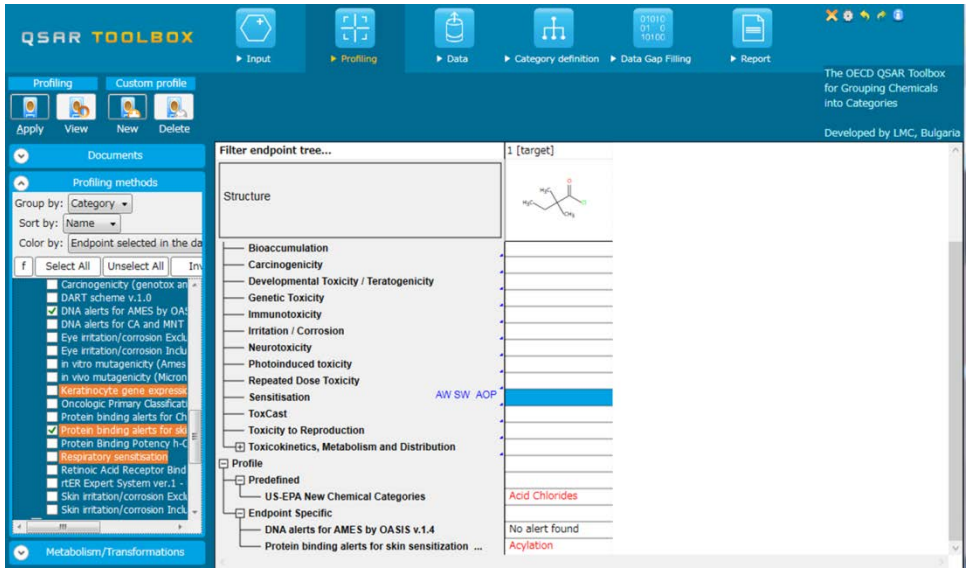
e.g. Integrated Testing Strategy

Regulators already applying:

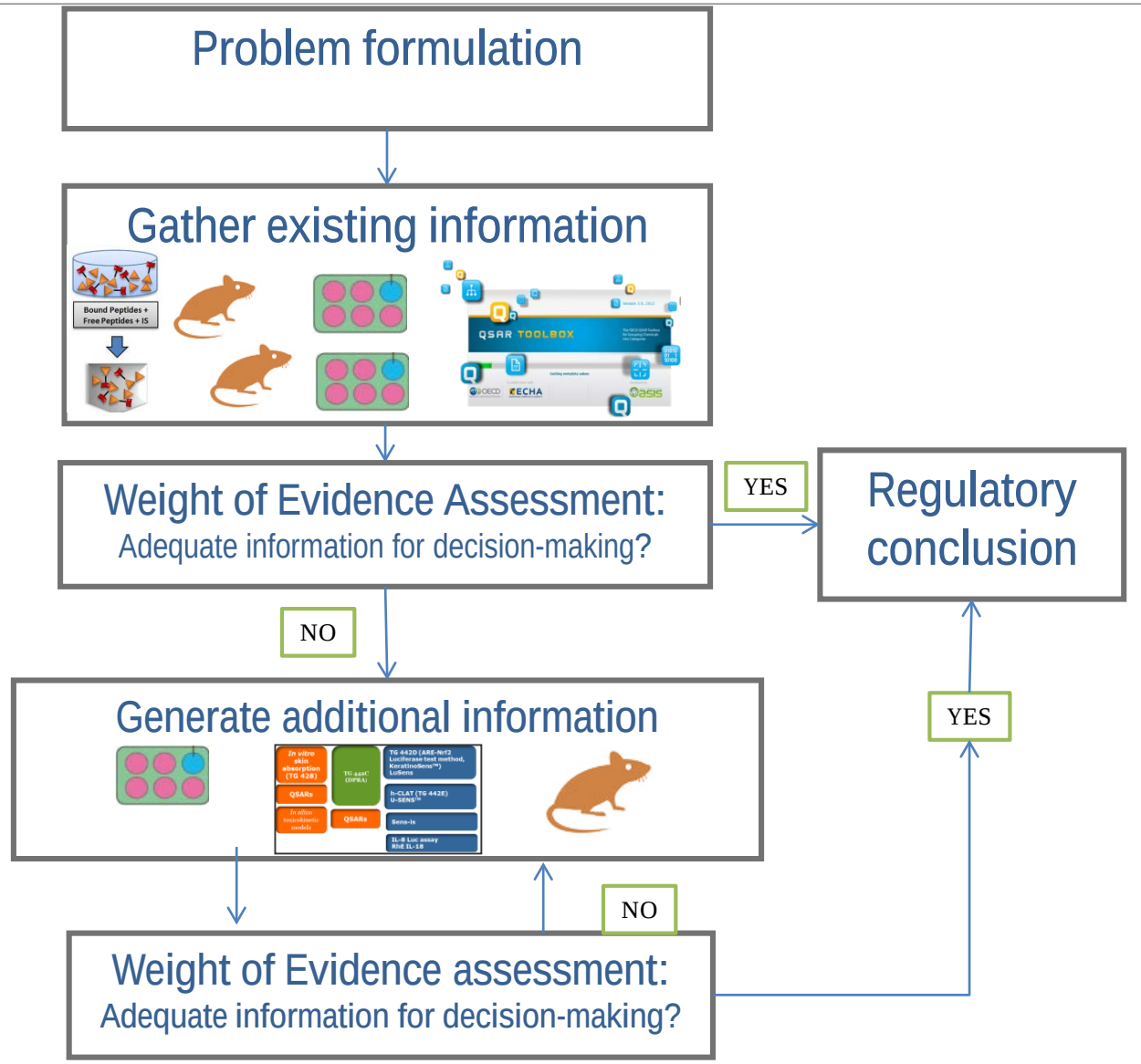


in vitro

MOA/mechanistic

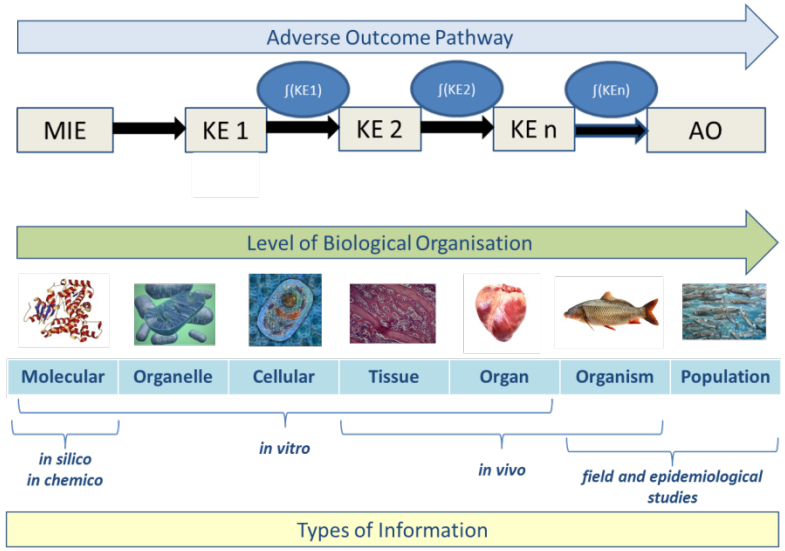


General workflow in Integrated Approaches to Testing and Assessment (IATA)



Reconcile IATA with MAD

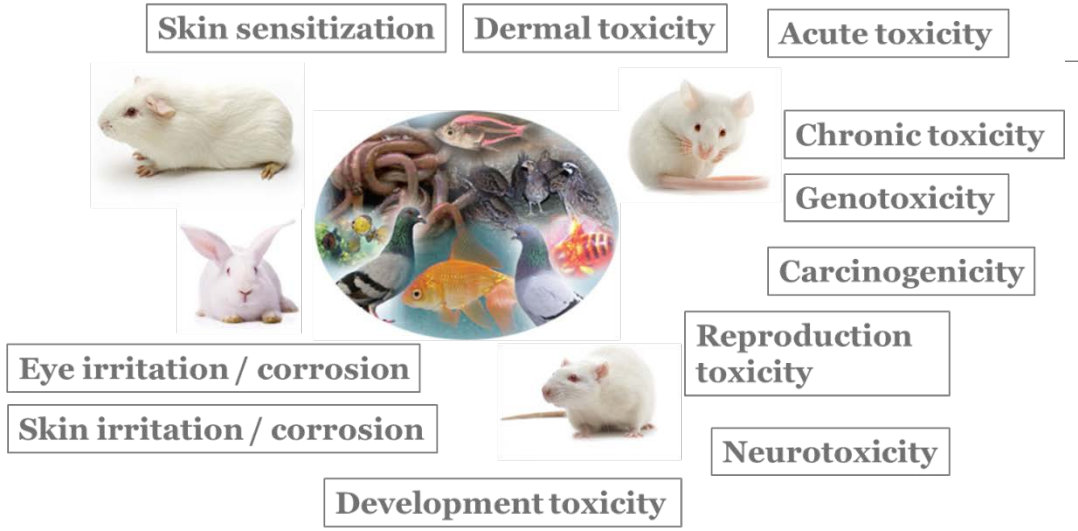
The AOP concept can be used as a framework for the development of Integrated approaches to testing and assessment (IATA)

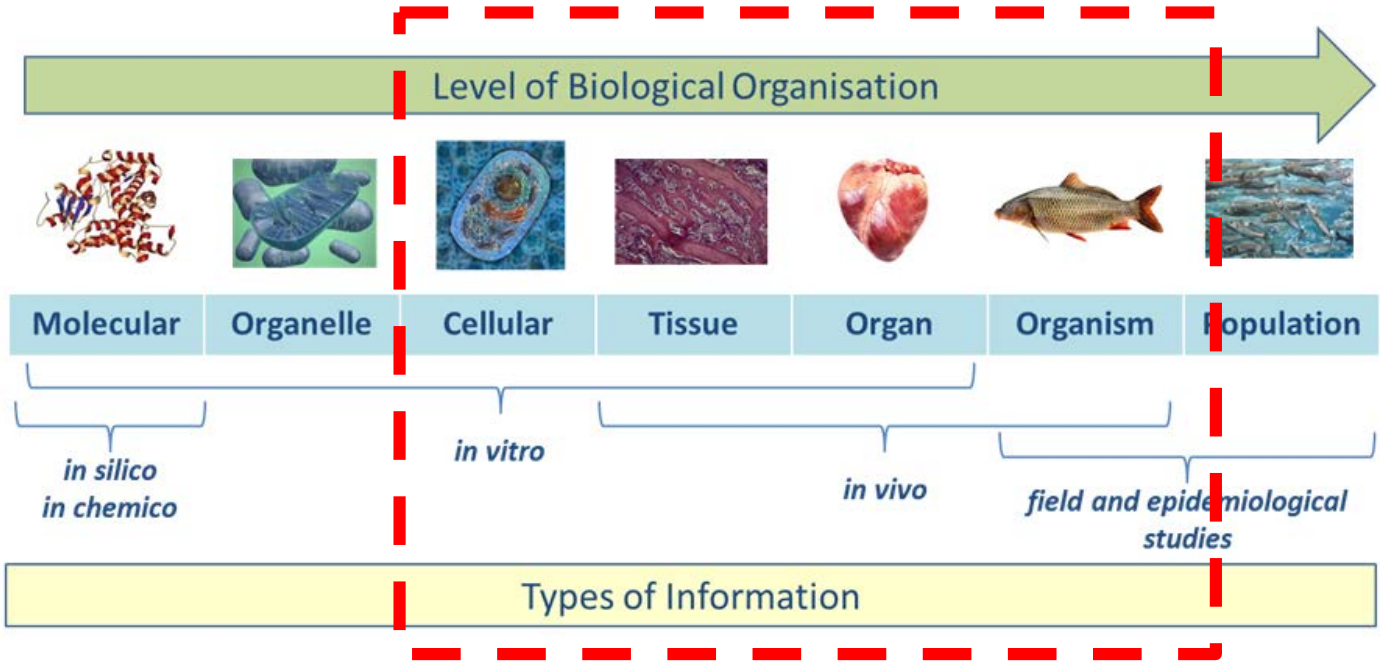


Guidance document for the use of Adverse Outcome Pathways in developing Integrated Approaches to Testing Assessment (IATA)

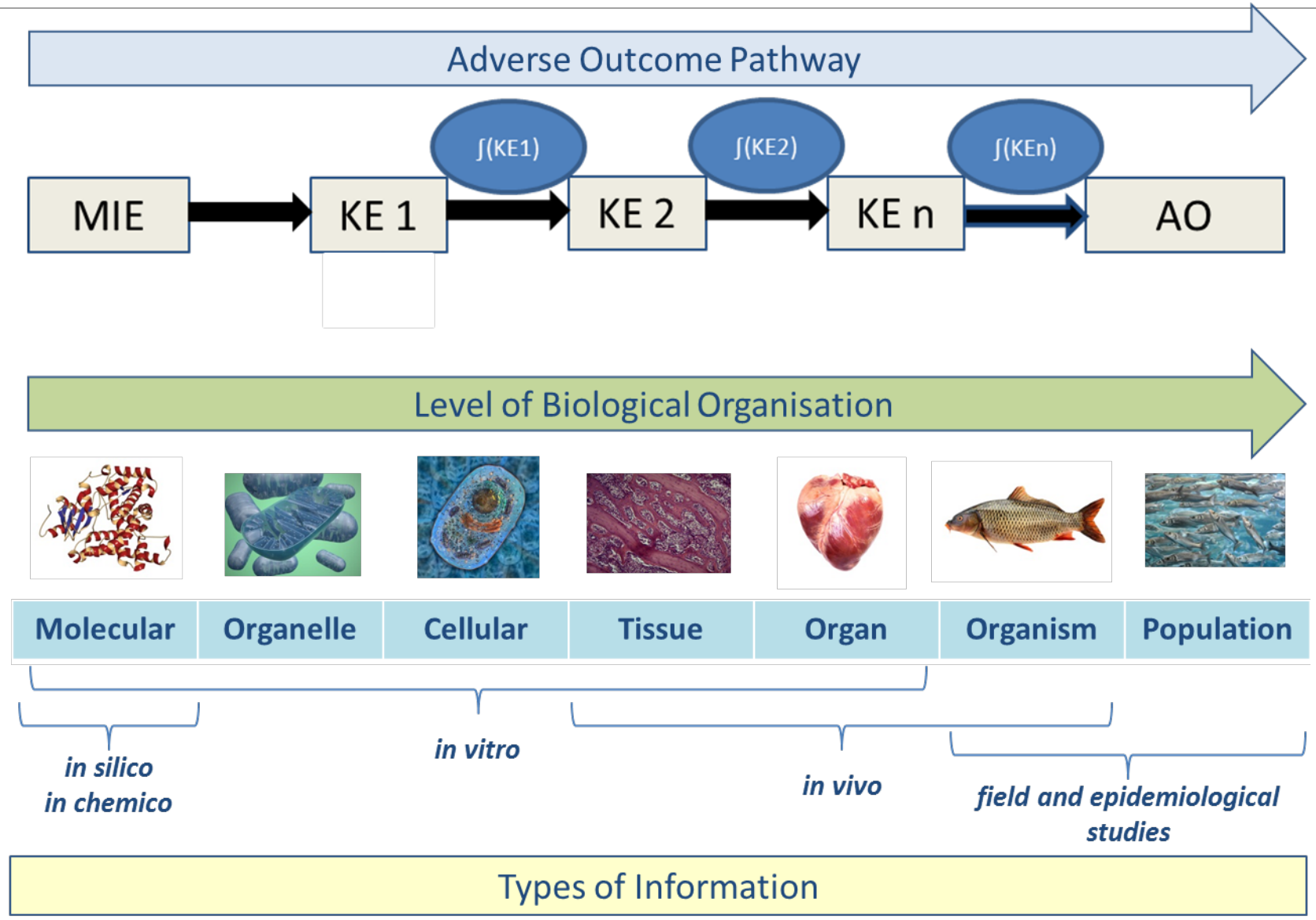
Current Regulatory Toxicity Testing

To a large extent based on in vivo tests, conducted in accordance with standardised test guidelines or protocols such as OECD Test Guidelines.

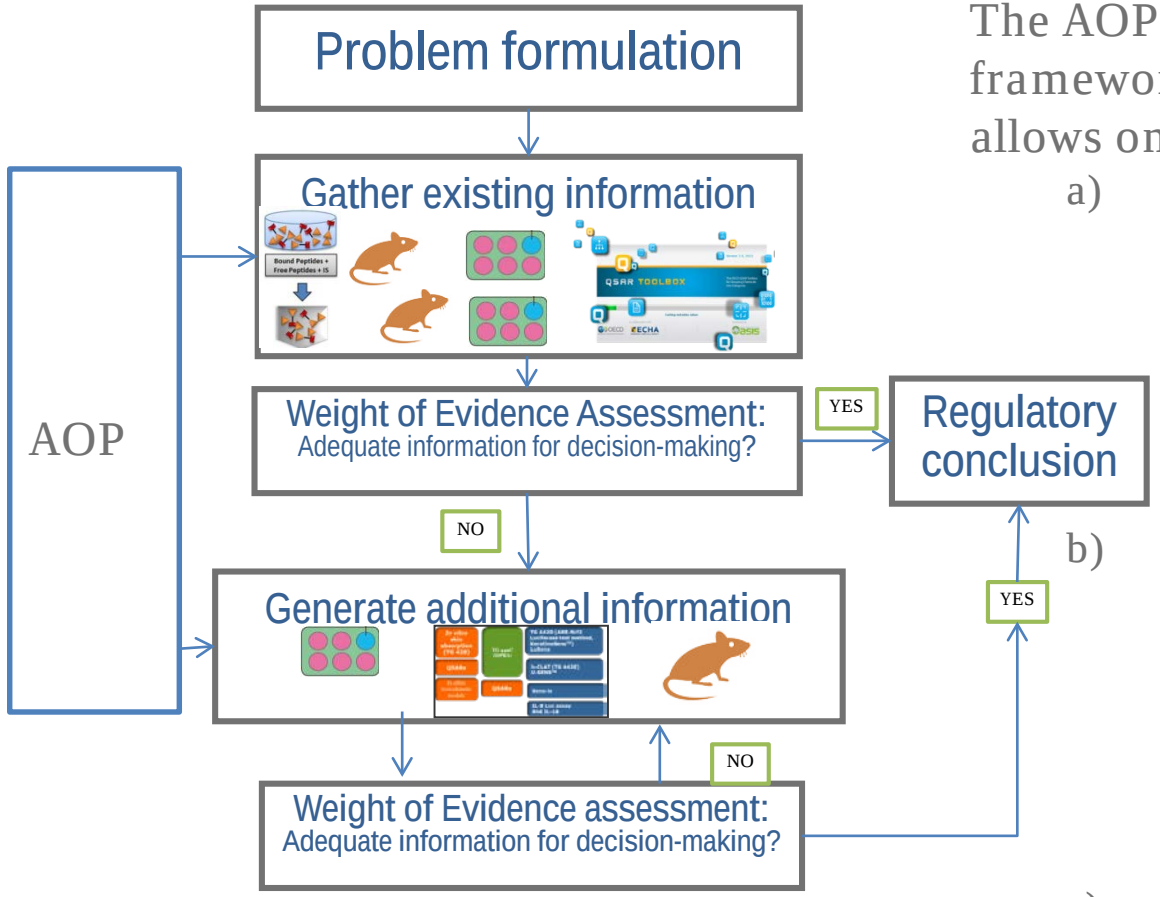




Linking of MIEs, Early KEs and their testing results to Adverse Outcomes



IATA based on the AOP concept



The AOP concept can be applied as a framework to develop IATA as it allows one to:

a) evaluate in a structured way the existing information that is available for the chemical(s) of interest and possibly conclude on the hazard based on existing information;

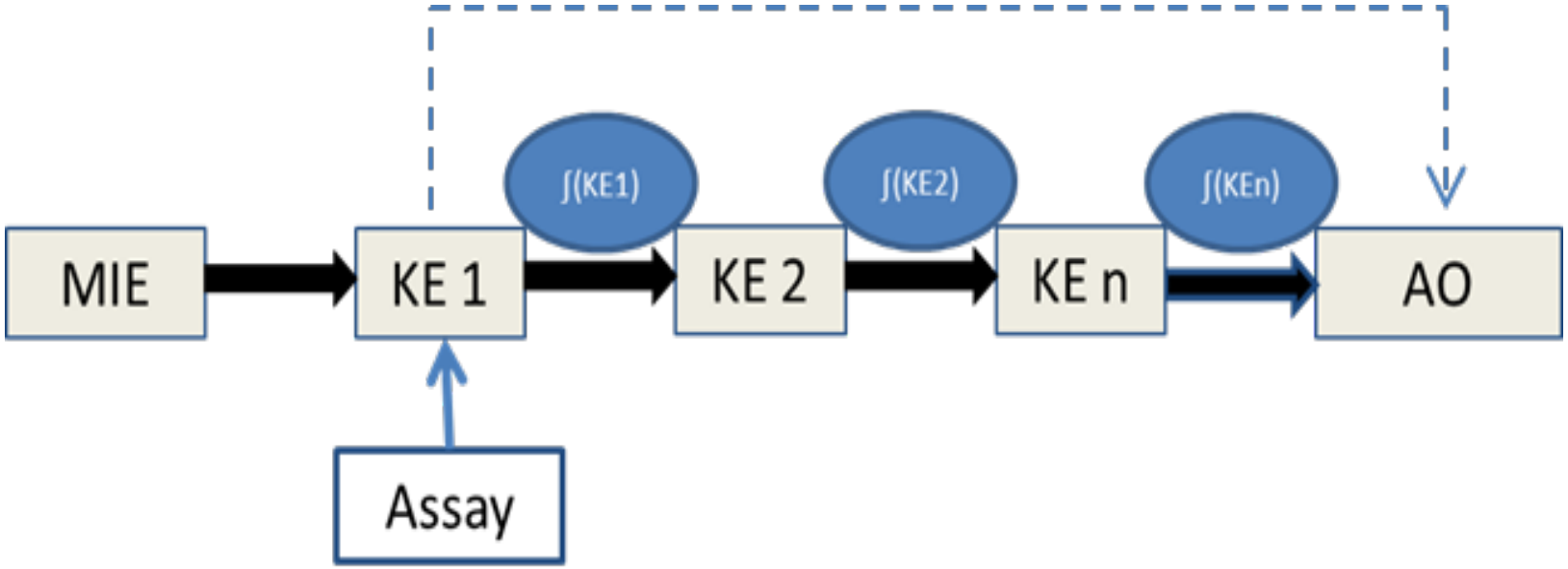
b) identify and generate the type of information that might be required to increase the confidence level concerning evidence of a particular hazard; and

c) iteratively determine if additional information is required to make a regulatory decision

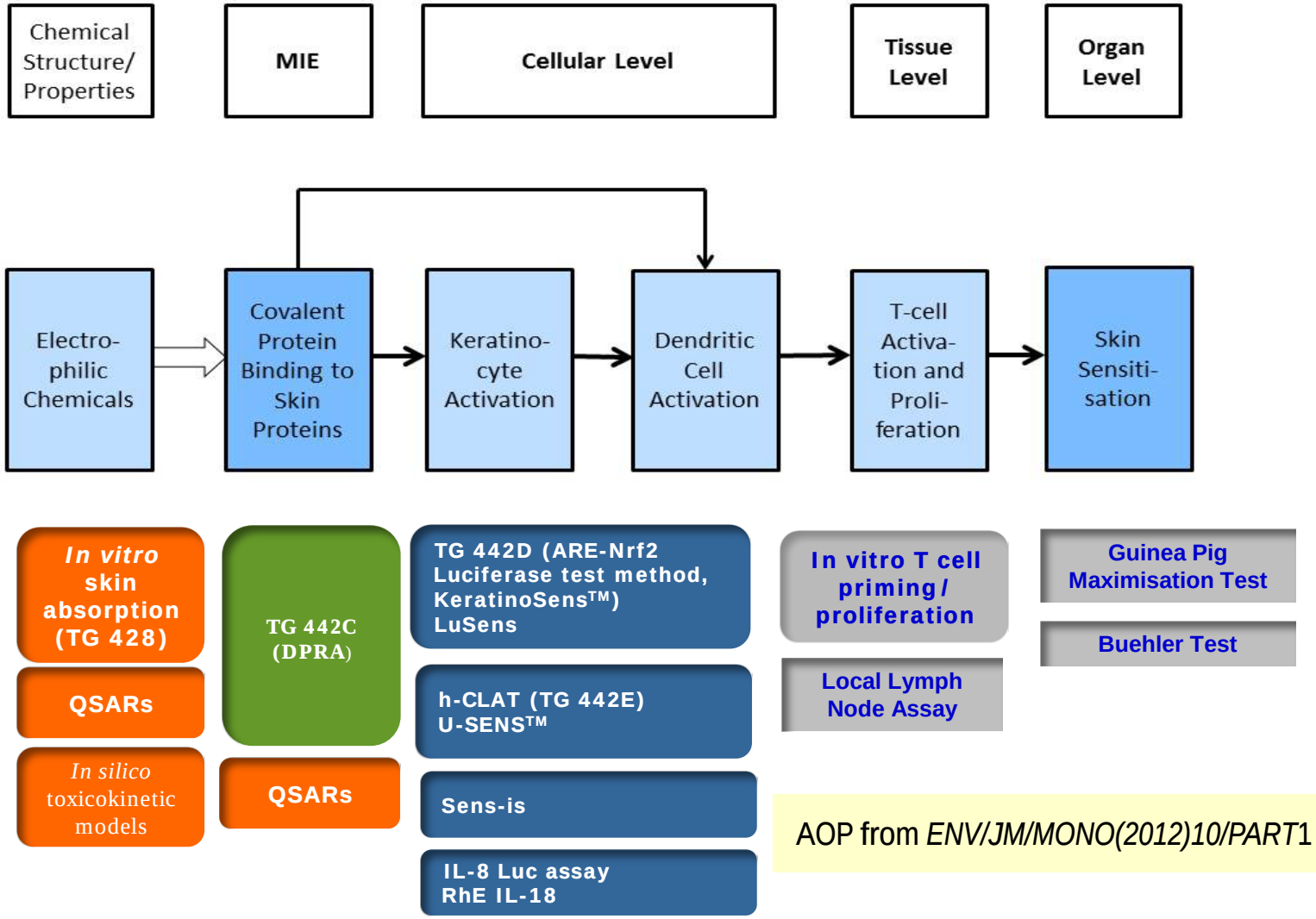
Examples of how AOPs can be used in the development of IATA

- Development of (Q)SARs
- Grouping of chemicals into chemical categories
- Development of testing strategies
- Interpretation of results from non-standard test methods
- Selection of methods for Test Guideline development/refinement

Selection of methods for Test Guideline development/refinement



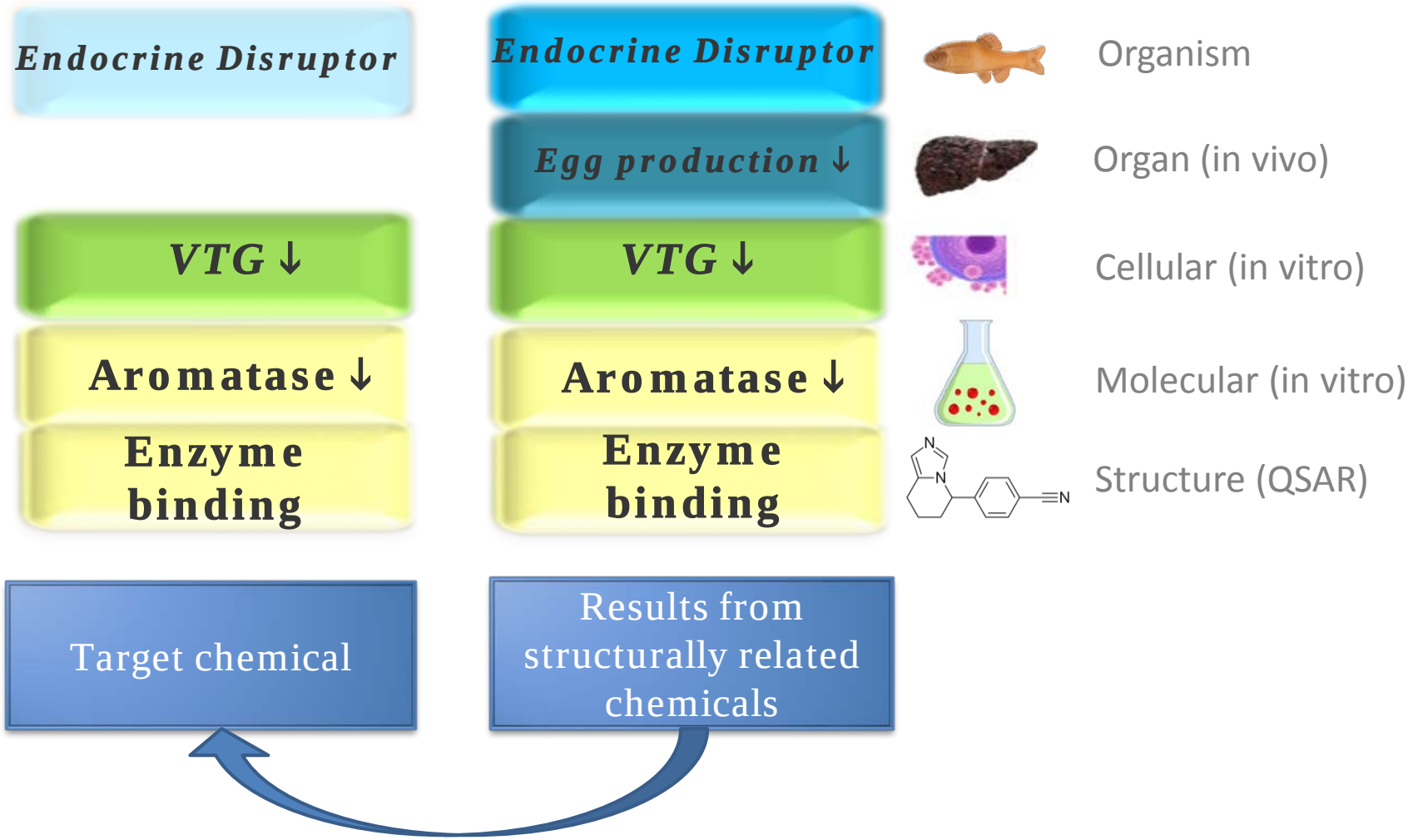
Skin sensitisation AOP and alternative method toolbox



AOP from *ENV/JM/MONO(2012)10/PART1*

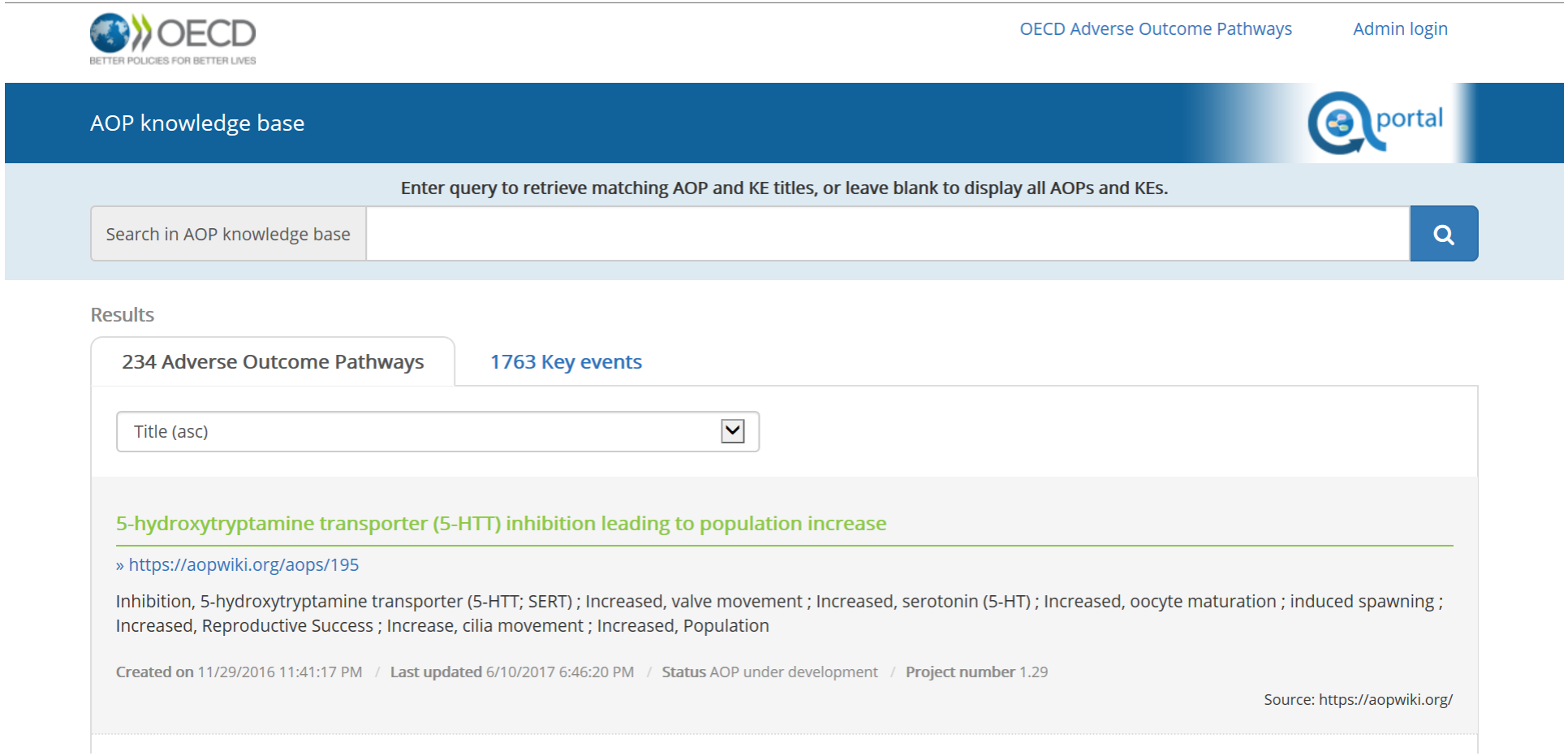
https://aopwiki.org/wiki/index.php/Aop:40

Read-across based on mechanistic understanding



AOP Knowledge Base

http://aopkb.oecd.org/



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 of using novel methodologies and the generation of considerations/guidance stemming from these case studies

Deliverables:

- Case studies followed by guidance documents on approaches

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

Summary of the Case Studies Reviewed in the First and Second Review Cycles

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**

Identified areas for potential development of guidance (1)

Guiding Principles for Establishing Weight of Evidence for the Evaluation of Chemicals

- Establish practical "universal" guiding principles for formulating a weight of evidence (WoE) for both prioritization and assessment of chemicals under different context dependent regulatory and non-regulatory scenarios
- Applicable to individual assessment endpoints and overall conclusions
- Applicable to ecological and human health evaluation

Timelines: Draft reviewed by review team and being updated by core writing team. Projected to be sent to WPHA in Q4 2018 for review.

Identified areas for potential development of guidance (2)

- Uncertainty framework
  - Overall uncertainty resulting from the combined uncertainties of each IATA component and data types
- When to generate *in vitro* data to support read-across
- Use and reporting of results of alternative methods (cheminformatics tools, HTS and HTTK assays)

Future

- Continue the development of AOPs and review case-studies on the practical application of IATAs

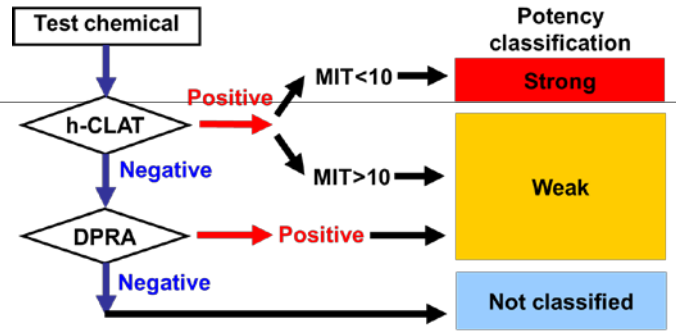
- Further examples of the application of AOPs to inform IATA in various regulatory contexts
  - as the number of documented AOPs increase at different stages of development (i.e. putative, quantitative etc.)

Further Information

- Website
  - http://www.oecd.org/chemicalsafety/
- IATA and AOPs
  - http://www.oecd.org/chemicalsafety/testing/adverse-outcome-pathways-molecular-screening-and-toxicogenomics.htm
- EHS Newsletters (sign up to receive automatically)
  - http://www.oecd.org/chemicalsafety/environment-health-safety-news.htm

THANK YOU FOR YOUR ATTENTION

Skin sensitisation: many possibilities of combining information

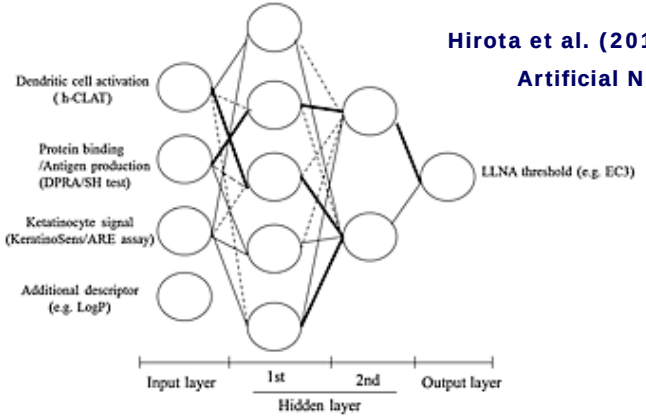


Takenouchi et al. (2015) J. Appl. Toxicol.: STS & ITS

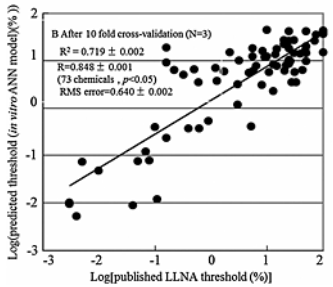
Score	h-CLAT MIT	DPRA depletion	DEREK
3	≤10 µg/mL	≥42.47%	-
2	>10, ≤150 µg/mL	≥22.62, <42.47%	-
1	>150, ≤5000 µg/mL	≥6.376, <22.62%	Alert
0	not calculated	<6.376%	No alert

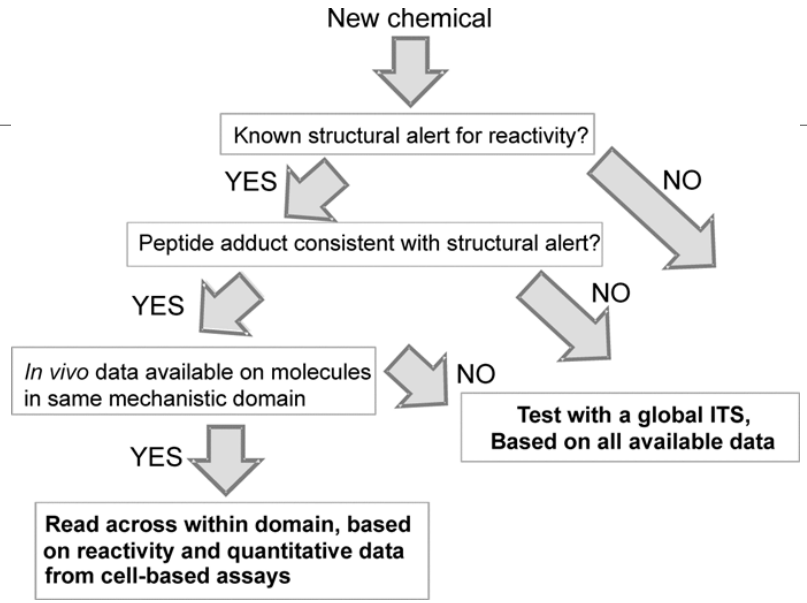
Potency: Total battery score

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

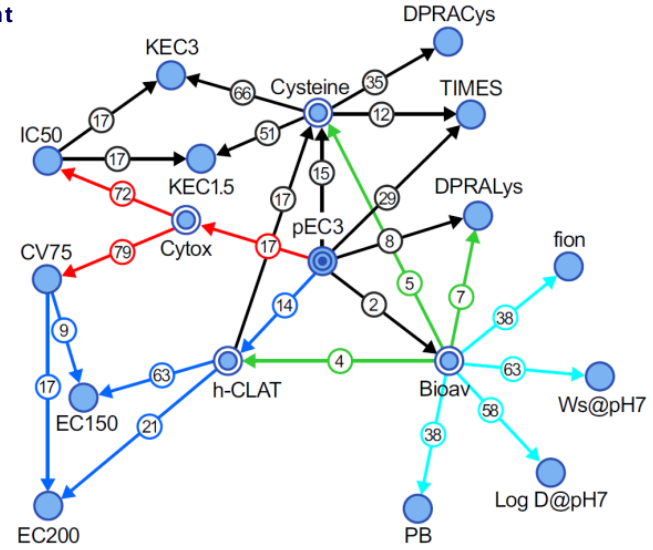


Hirota et al. (2015) J. Appl. Toxicol.:
Artificial Neural Network





Natsch et al. (2015) Toxicological Science
Global/domain-based asssessment



Jaworska et al. (2015) Arch. Toxicol.:
Bayesian Network

Defined Approaches in IATA

A defined approach to testing and assessment consists of a fixed data interpretation procedure (DIP) used to interpret data generated with a defined set of information sources, that can either be used on its own, or together with other information sources within an IATA, to satisfy a specific regulatory need.

- **Guidance Document** on the Reporting of Defined Approaches to be Used within Integrated Approaches to Testing and Assessment ENV/JM/MONO(2016)28

- **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 ENV/JM/MONO(2016)

  - Includes exemplification of reporting with **12 skin sensitisation case studies**

Now underway in the WNT: EC/US/CAN - Performance Based Test Guideline around the best performing *Defined Approaches*