Status of OECD activities:

Development of a PBTG for Defined Approaches for skin sensitisation

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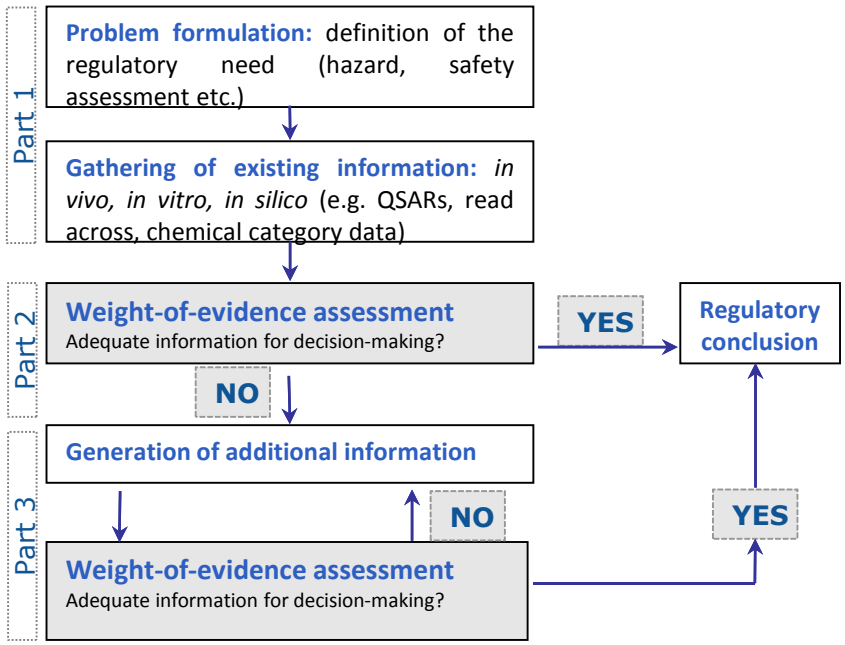
The European Commission's science and knowledge service

Joint Research Centre

European Commission

IATA generic framework



- ✓ Moving away from one-to-one replacement
- ✓ Overcomes limitation of single in vitro assays/increases confidence in outcome
- ✓ AOP framework will be used increasingly to combine assays and other data/predictions
- ✓ Development of IATA case studies
  - submitted by countries, industry
  - review cycles organised, with discussions and meetings,
  - case studies are published regularly

Adapted from OECD 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. 2017.

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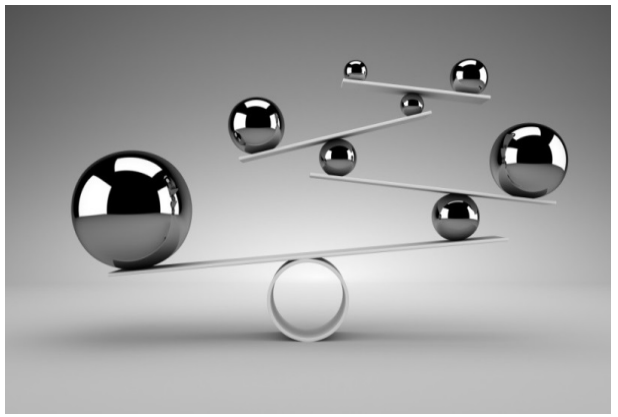
IATA assessment process

- ✓ IATA are flexible tools and for this reason they cannot be described in OECD TGs
- ✓ They are not formally part of the Test Guideline program, and thus not part of MAD
- ✓ Strong support to continue developing testing methodologies covered by MAD



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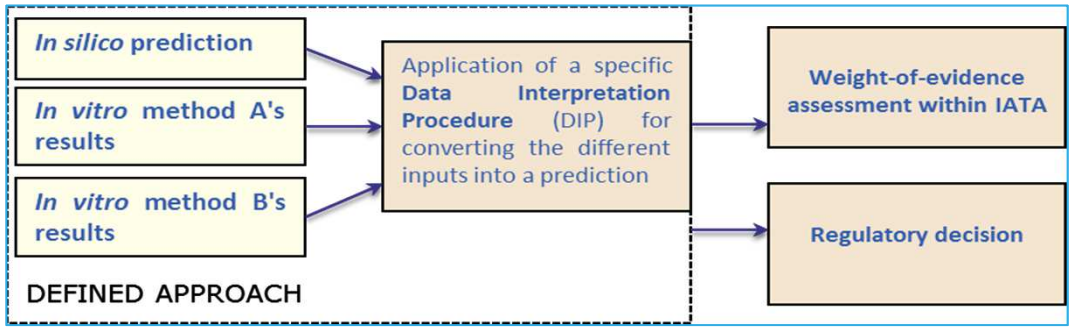
Defined Approaches



A Defined Approach consists of a fixed data interpretation procedure (DIP) applied to data generated with a defined set of information sources (formalised decision-making approach)

OECD Guidance Documents No. 255

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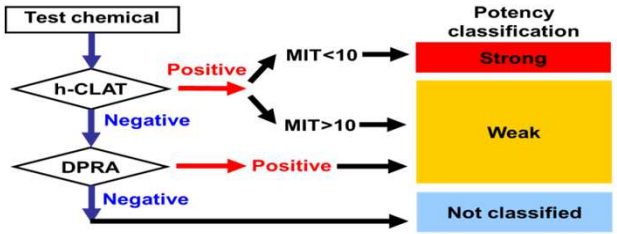
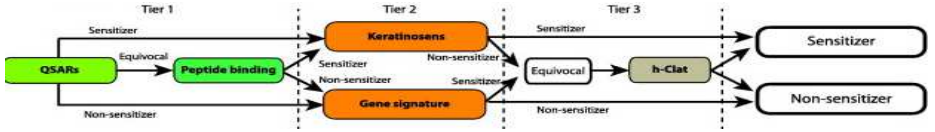
Defined Approaches



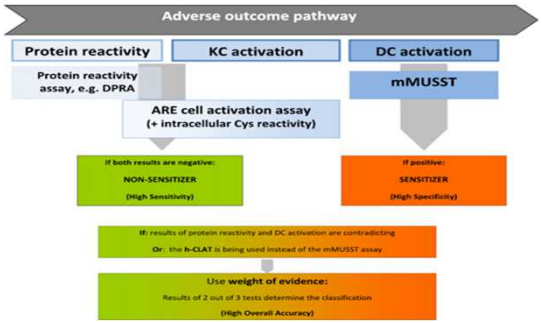
Van der Veen et al. (2014) Regul. Toxicol. Pharmacol.: STS



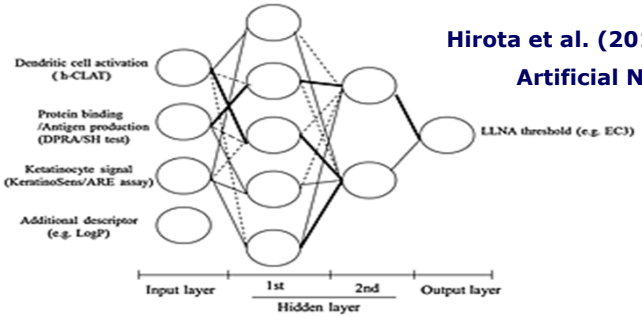
Takenouchi et al. (2015) J. Appl. Toxicol.: STS & ITS

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

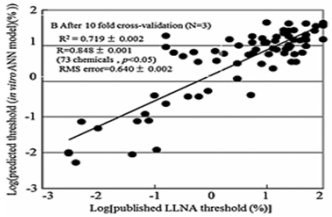
Potency: Total battery score		
	Strong :	7
	Weak :	2-6
	Not classified :	0-1

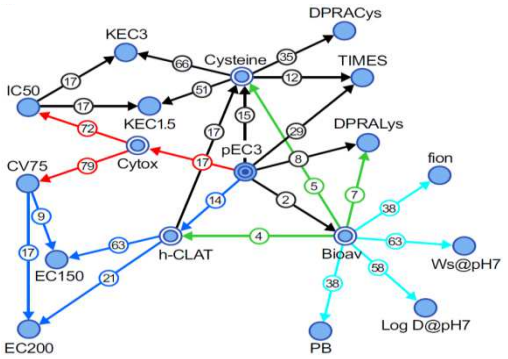


Bauch et al. (2012) Regul. Toxicol. and Pharmacol.: 2 out of 3



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





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

Defined Approaches – Case Studies

					MIE	KE2	KE3			
	Case Study	Bioavailability	Phys-chem properties	*In silico*	Protein binding /reactivity	Events in Keratinocytes	Events in DC	Events in T cells	Adverse effect	Others
1	Sensitiser potency prediction Key event 1+2 (**Givaudan**)		X	TIMES SS	Cor1C420-assay	TG 442D				
2	The artificial neural network model for predicting LLNA EC3 (**Shiseido**)		X		SH Test	AREc32 assay	TG 442E			
3	ITS/DS for hazard and potency identification of skin sensitisers (**P&G**)	penetration (PBPK model)	X	TIMES SS	TG 442C	TG 442D	TG 442E U937 test	TG 429		
4	Tiered system for predicting sensitising potential and potency of a substance (STS) (**Kao Corporation**)				TG 442C		TG 442E			
5	Score-based battery system for predicting sensitising potential and potency of a substance (ITS) (**Kao Corporation**)			DEREK Nexus	TG 442C		TG 442E			
6	IATA for skin sensitisation risk assessment (**Unilever**)	penetration modified OECD TG428			modified OECD TG428					
7	Weight of evidence in vitro ITS for skin hazard identification (**BASF**)				TG 442C	TG 442D LuSens	TG 442E m-MUSST			
8	STS for hazard identification of skin sensitisers (**RIVM**)			Various	TG 442C	TG 442D HaCaT gene signature	TG 442E			
9	IATA (**Dupont**)		X	Various	TG 442C glutathione depletion assay	TG 442D	TG 442E U937	TG 429	TG 406	E.g. Skin Irr/Corr, Ames
10	Decision strategy (**L'Oréal**)		X	Various	TG 442C	TG 442D ARE-Nrf2 Assay	U-SENS™ PGE2 Assay			
11	Integrated decision strategy for skin sensitisation hazard (**ICCVAM**)		X	OECD Toolbox			TG 442E			
12	Consensus decision tree model for skin sensitisation hazard prediction (**EC JRC**)			TIMES SS Dragon						

Annex 1 to Guidance Document No. 256

- Some based fully on *in vitro* methods, some on *in silico*, some combine both
- The *in vitro* methods are mainly OECD Test Guidelines, but some are not
- Algorithms used to combine data to make a prediction vary in complexity

OECD Guidance Documents (GD) on Defined Approaches

GD 255 Templates for reporting

GD 256 Case studies

Six defining principles:

1. Defined endpoint
2. Defined purpose
3. Description of the underlying rationale, including mechanistic basis (e.g. AOP)
4. Description of the individual information sources used
5. Description of how the individual information sources are processed
6. Consideration of the known uncertainties

OECD Project – PBTG on Defined Approaches

- Submitted to the OECD in November 2016 by the EU (European Commission – DG JRC), the US (NICEATM, EPA, CPSC) and Canada (Health Canada) with the support from other ICATM partners

- Proposal adopted included in the work plan of the OECD Test Guidelines Programme in 2017 (project 4.116)

The WNT requested to be strongly involved in the implementation of the project

- Meeting of the OECD Working Group of the National Coordinators for the Test Guidelines Programme Ispra, Italy 13-15 December 2017

    - Definition of *evaluation criteria* to judge the scientific validity of DAs and their suitability to be included in an OECD instrument covered by MAD

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DA Evaluation Framework

Structure

- DA elements
- Information provided:
  - S/NS
  - GHS cat 1A
  - GHS cat 1A and 1B
  - Point of departure for QRA

Relevance

- Mechanistic coverage

Predictive Capacity

- Performance compared to reference data

Reliability

- Reproducibility

Applicability

- Technical limitations
- Chemical space

Complexity

- Data Interpretation Procedure

Transparency

- Availability of elements

New OECD Expert Group on DAs for Skin Sensitization

- First Teleconference: 9 April 2018
- 52 members
  - Project Leads (EU/JRC, US, Canada)
  - OECD Secretariat
  - BIAC, ICAPO
  - 10 member countries

DA Evaluation Framework

- Revised according to all comments received
- Template developed to apply evaluation framework to Group I DAs (Sens ITS, Kao STS, Kao ITS v1 & v2)
- Volunteers from EG DASS to apply evaluation framework templates
    - Information contained in reporting template (GD 255 Annex)
- Outcome of review returned to leads/OECD by 4 June
- Discuss lessons learned during next EG DASS TC: mid-June 2018

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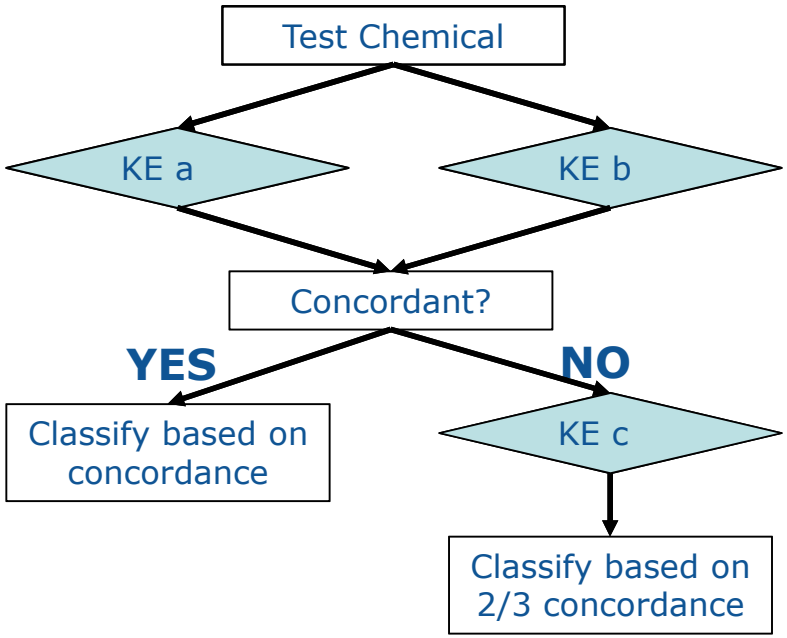
BASF Sens ITS



- No weighting of individual methods, or defined order of testing
- Covers 3 AOP KEs:
  - KE1 (**TG 442C**, e.g. DPRA)
  - KE2 (**TG 442D**, e.g. KeratinoSens™, LuSens)
  - KE3 (**TG 442E**, e.g. hCLAT, U-SENS™)

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Kao ITS DA

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

Kao ITSv1.0

Hazard identification (S/NS)
3 Potency classes:
NS, Strong and Weak

- Score-based system
- Depends on hCLAT, DPRA, DEREK

Kao ITSv2.0

- Depends on hCLAT, DPRA, OECD Toolbox

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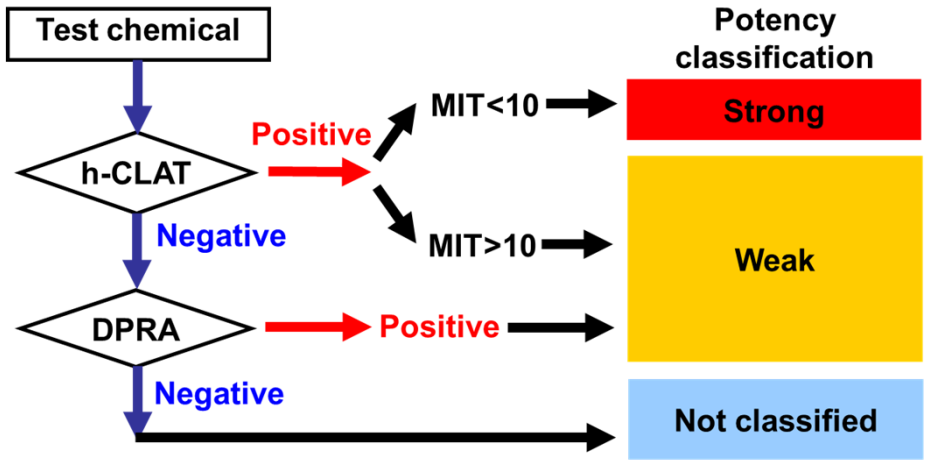
KAO STS



- Prediction can be derived after first tier
- Covers 2 AOP KEs:
  - KE 3 (**TG 442E**, h-CLAT)
  - KE 1 (**TG 442C**, DPRA)

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Expert subgroups working on topics identified in Dec 2017 WNT meeting

- **Uncertainty analysis: first TC 19 March 2018 (JRC led)**
  LLNA variability & propagating in vitro variability through DAs
- **Applicability Domain: first TC 19 April 2018 (JRC led)**
  Assessing AD of all elements and applying to DAs
- **Variability in human data (ICCVAM SSWG led)**

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Further Steps

- Select DAs for inclusion in Group II review
- Request EG volunteers to apply the evaluation framework to Group II DAs
  - Next round of evaluations: mid-Sept 2018

- Timeline for overarching project
  - Status report at OECD EG meeting on Skin Sensitization: Nov 2018
  - In depth discussion at WNT Special Session: Dec 2018

Stay in touch

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