The European Commission's science and knowledge service

Joint Research Centre

Defined Approaches for Skin Sensitisation

S. Casati

9 November 2016

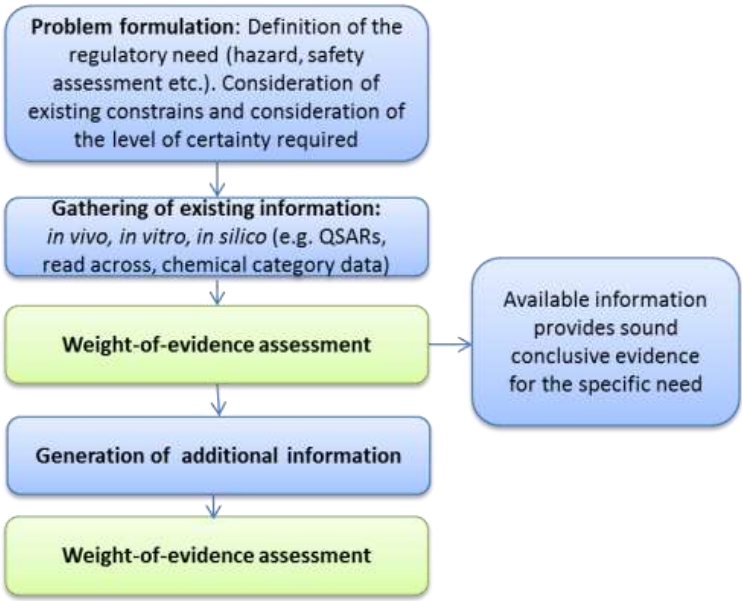
European Commission

Outline

- IATA definition
- Defined Approach (DA) definition
- OECD project on the reporting of DA
- Case studies overview

Integrated Approaches To Testing and Assessment (IATA)

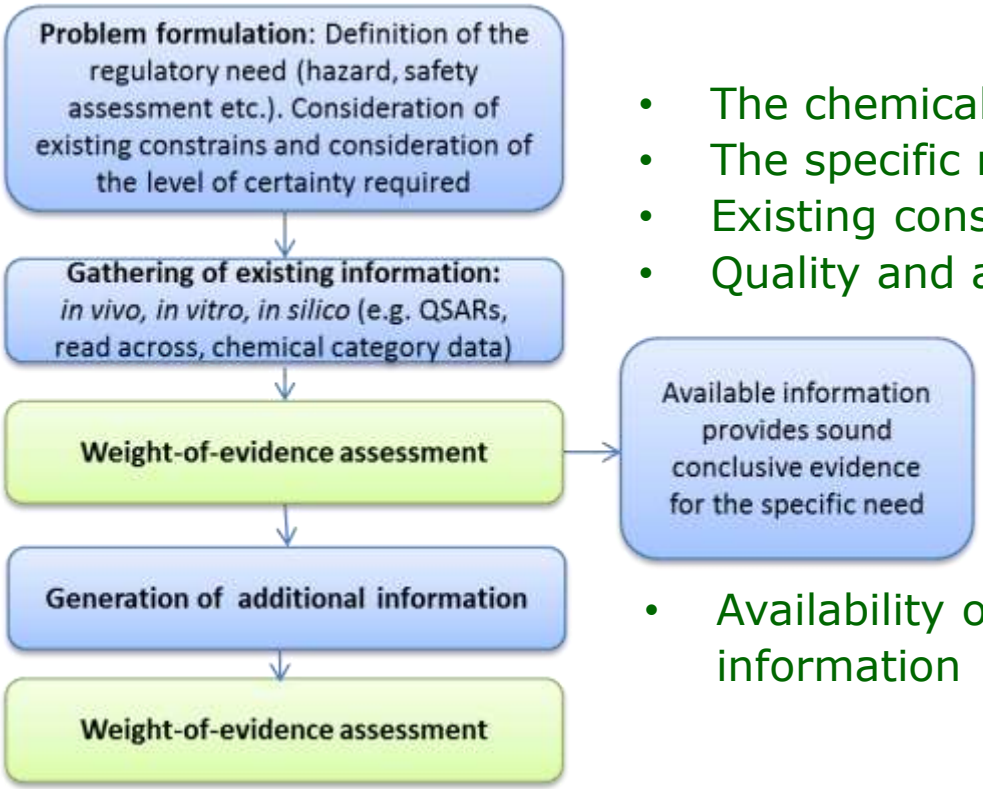
- Approach based on multiple information sources (i.e. physicochemical properties, non-testing methods - QSARs, read-across - testing methods – *in chemico, in vitro, in vivo*)
- Integrates and weights all relevant existing evidence and guides the target generation of new data where required to inform regulatory decisions
- Necessarily involves a degree of expert judgment , for example in the choice of the information sources to generate addition data and in the weighting of information



ENV/JM/MONO(2016)28

European Commission

Construction and Application of IATA

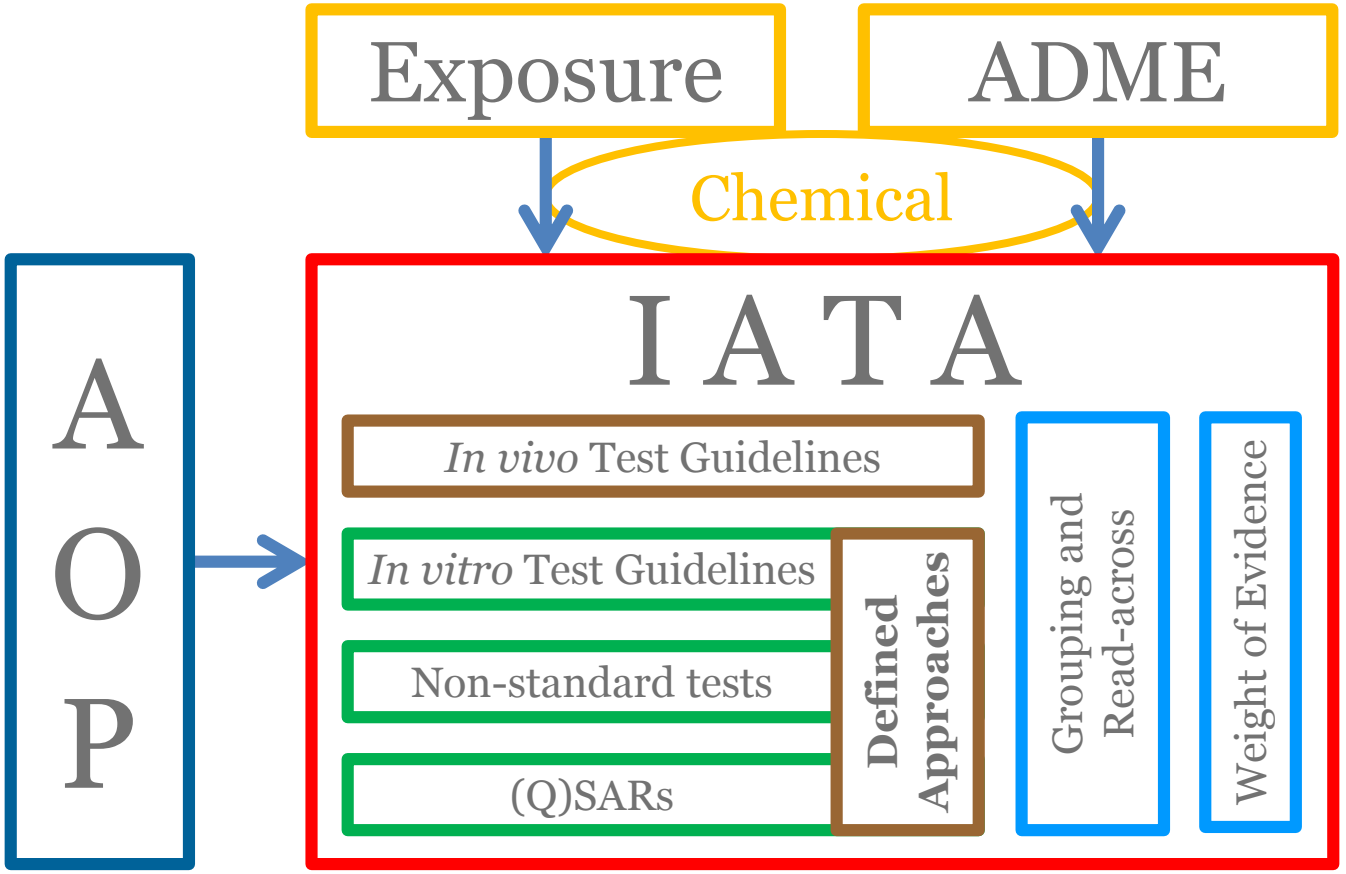


Depends on:

- The chemical under investigation
- The specific regulatory need
- Existing constrains
- Quality and adequateness of existing information

- Availability of methods to generate additional information

Integrated Approaches to Testing and Assessment (IATA)



European Commission

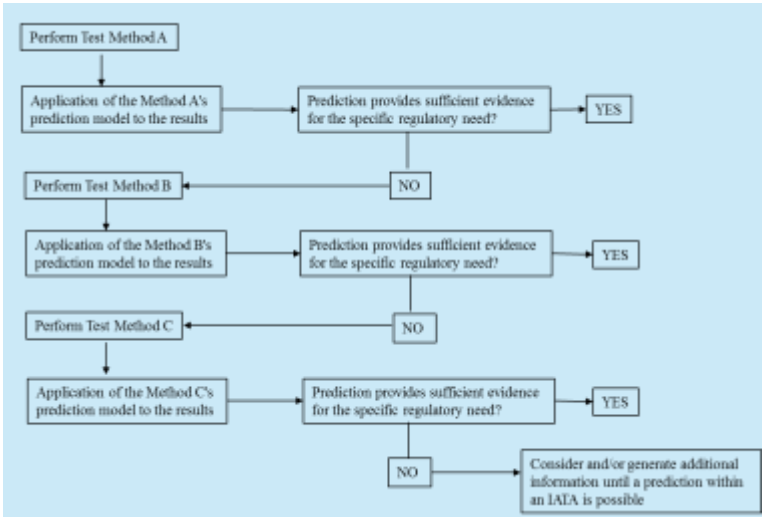
Defined approaches to be used within IATA

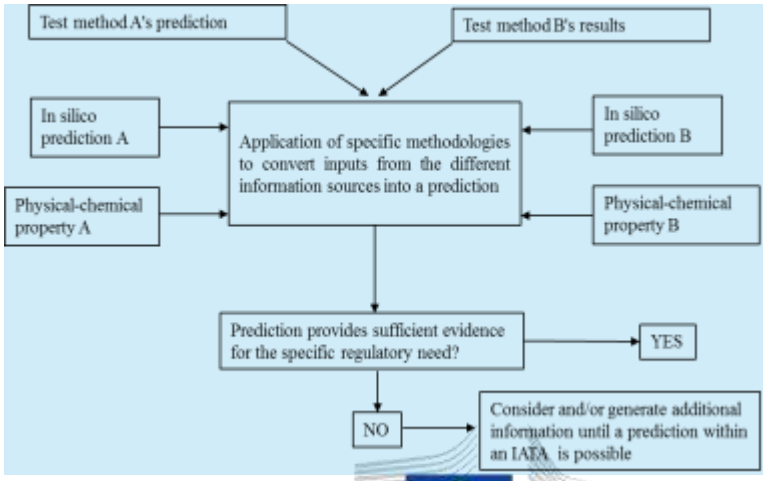
A defined approach to testing and assessment consists of a fixed data interpretation procedure (DIP) applied to data generated with a defined set of information sources (formalised decision-making approach)

The result can either be used on its own, or together with other information sources within an (IATA)

ENV/JM/MONO(2016)28

Sequential Testing Strategy

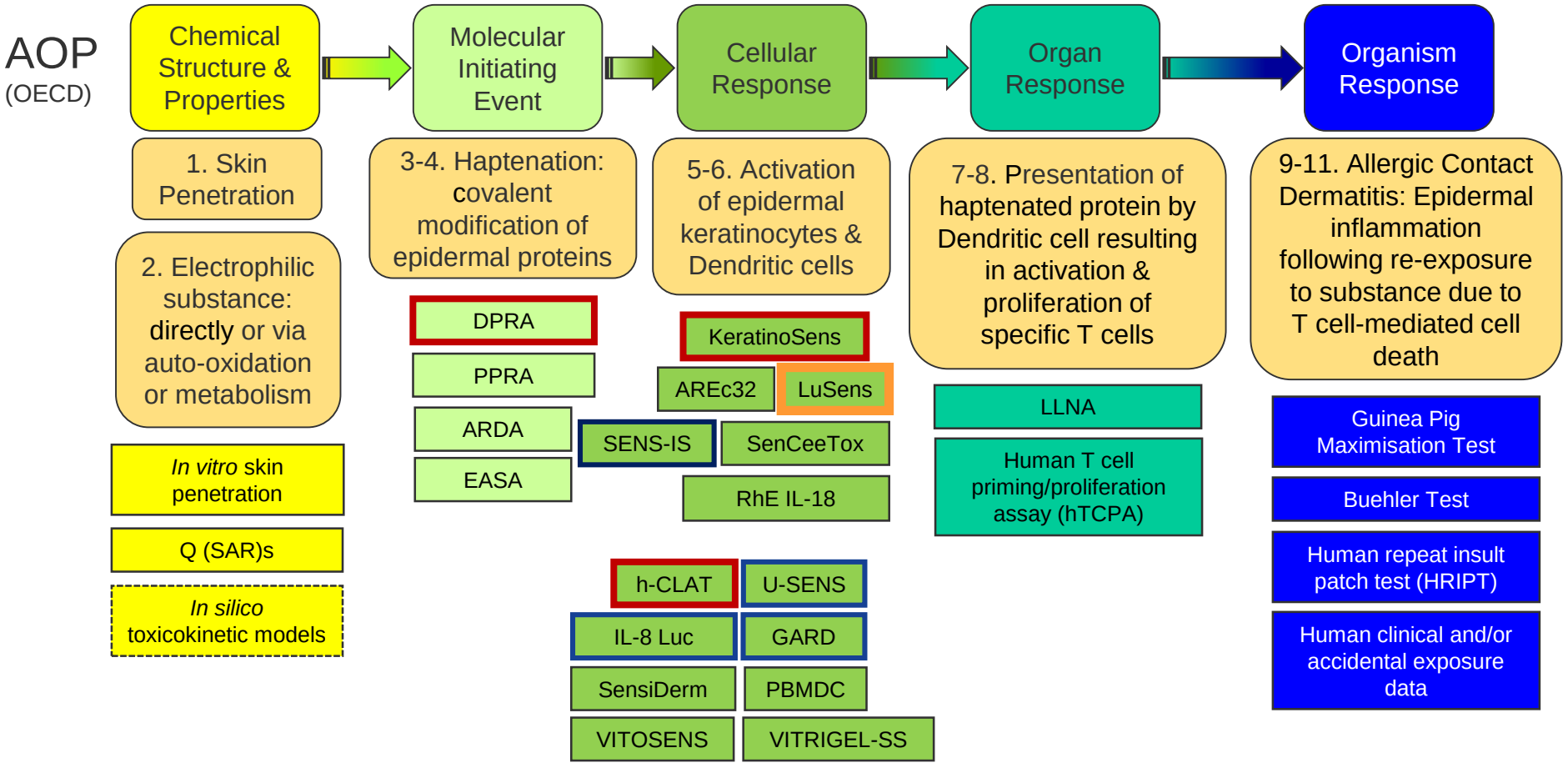




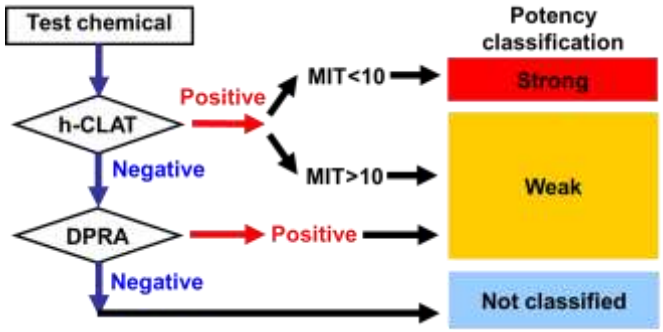
Integrated Testing Strategy

6

Grouping of Information Sources by Key Event



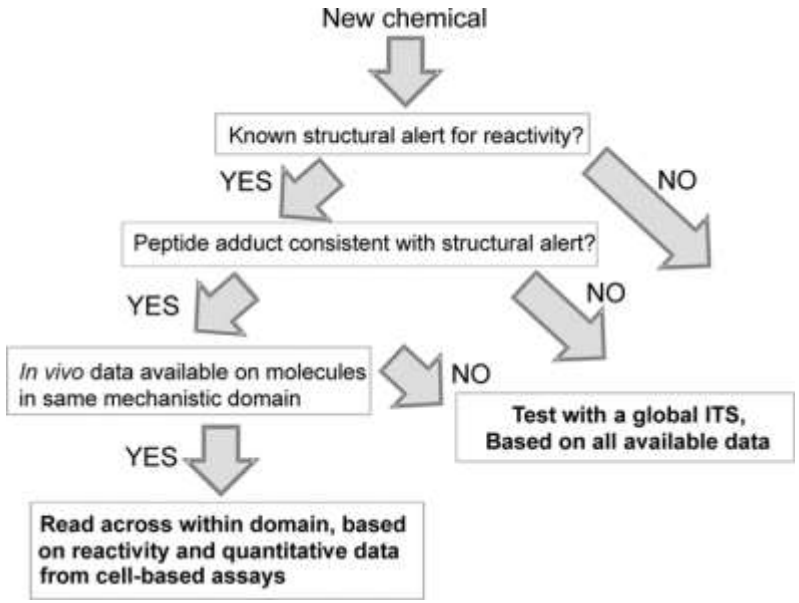
Skin sensitisation: many possibilities of combining information



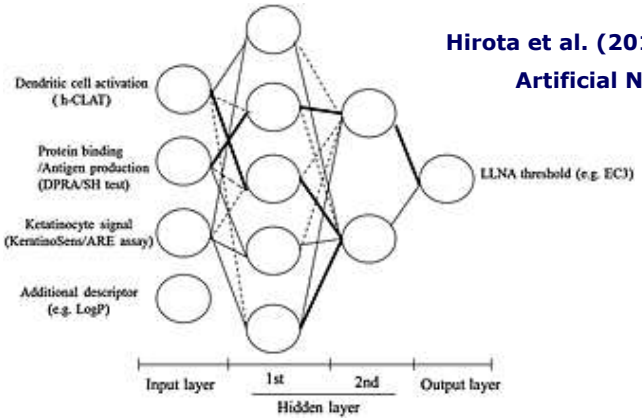
Takenouchi et al. (2015) J. Appl. Toxicol.: STS & ITS

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

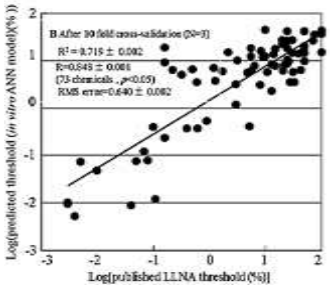
Potency: Total battery score		
	Strong :	7
	Weak :	2-6
	Not classified :	0-1

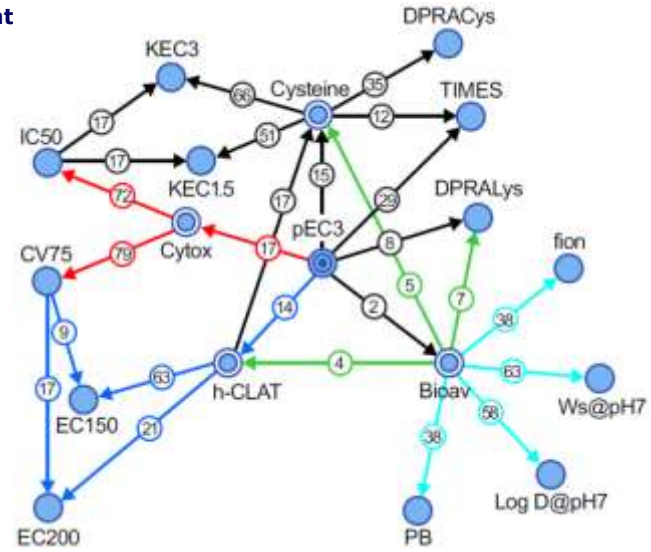


Natsch et al. (2015) Toxicological Science
Global/domain-based asssessment



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





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

OECD Guidance Documents on the reporting of Defined Approaches

To promote consistent description of defined approaches and facilitate their evaluation and acceptance within OECD member countries

- Principles for describing and applying defined approaches
- Template for reporting defined approaches — ***OECD ENV/JM/MONO(2016)28***
- Template for reporting individual information sources
- Case-studies - skin sensitisation — ***OECD ENV/JM/MONO(2016)29***
  - ✓ Illustration of how the reporting templates have been used to document a number (12) of defined approaches (and information sources used within) developed in the area of skin sensitisation
  - ✓ Guidance on the extent and level of reporting

Reporting Template for Defined Approaches

1	**Summary**	*concise overview of the approach*
2	**General information**	*identifier, date, authors, updates, references, proprietary aspects*
3	**Endpoint addressed**	*e.g. skin sensitisation*
4	**Purpose and regulatory relevance**	*e.g. screening, hazard assessment, potency prediction*
5	**Rationale underlying its construction**	*including reason for the choice of information sources and their linkage to known biological mechanisms (e.g. key events)*
6	**Brief description of the individual information sources used**	*including response(s) measured and respective measure(s), detailed descriptions in the dedicated template*
7	**Data interpretation procedure applied (DIP)**	*e.g. sequential testing strategies, regression models, 2 out of 3 WoE, scoring systems, machine learning approaches, Bayesian networks, etc…*
8	**Chemicals used to develop and test DIP**	*approach used for selection of training and test sets, relevant information on both sets: chemical names, composition, reference data (e.g. in vivo data), readouts, predictions*
9	**Limitations in the application of the approach**	*with regard to technical constrains or wrong predictions*
10	**Predictive capacity**	*misclassifications and unreliable predictions rationalised to the extent possible*
11	**Sources of uncertainty and impact on DIP's prediction**	*how uncertainties related to approach structure, information sources and benchmark data translate into prediction uncertainty*

ENV/JM/MONO(2016)29 – Annex 1

Case study		Purpose
1	An Adverse Outcome Pathway-based "2 out of 3" integrated testing strategy approach to skin hazard identification (BASF)	**Hazard identification**
2	Sequential Testing Strategy (STS) for hazard identification of skin sensitisers (RIVM)	**Hazard identification**
3	A non-testing Pipeline approach for skin sensitisation (G. Patlewicz)	**Hazard identification**
4	Stacking meta-model for skin sensitisation hazard identification (L'Oréal)	**Hazard identification**
5	Integrated decision strategy for skin sensitisation hazard (ICCVAM)	**Hazard identification**
6	Consensus of classification trees for skin sensitisation hazard prediction (EC-JRC)	**Hazard identification**
7	Sensitizer potency prediction based on Key event 1 + 2: Combination of kinetic peptide reactivity data and KeratinoSens® data (Givaudan)	**Potency prediction**
8	The artificial neural network model for predicting LLNA EC3 (Shiseido)	**Potency prediction**
9	Bayesian Network DIP (BN-ITS-3) for hazard and potency identification of skin sensitizers (P&G)	**Potency prediction**
10	Sequential testing strategy (STS) for sensitising potency classification based on in chemico and in vitro data (Kao Corporation)	**Potency prediction**
11	Integrated testing strategy (ITS) for sensitising potency classification based on in silico, in chemico, and in vitro data (Kao Corporation)	**Potency prediction**
12	DIP for skin allergy risk assessment (SARA) (Unilever)	**Potency prediction**

AOP mapping of Information sources

MIE KE2 KE3

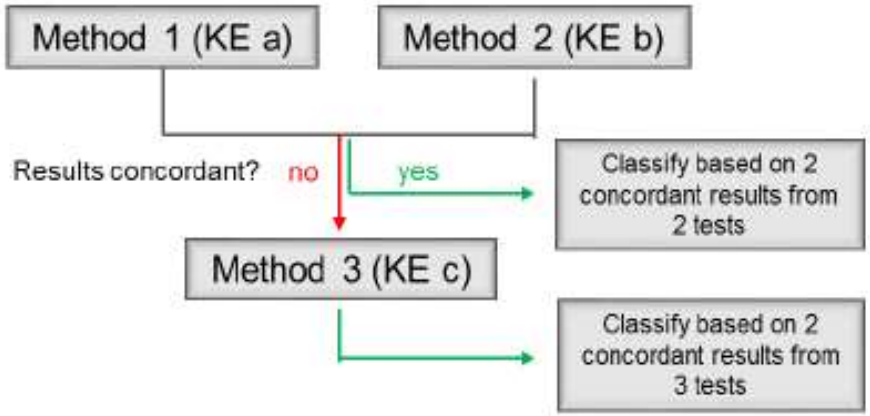
	Case Study	Bioavailability	Phys-chem properties	*In silico*	Protein binding /reactivity	Events in Keratinocytes	Events in DC	Events in T cells	Adverse effect	Others
1	Sensitiser potency prediction Key event 1+2 (**Givaudan**)		X	TIMES SS	Cor1C420-assay	TG 442D				
2	The artificial neural network model for predicting LLNA EC3 (**Shiseido**)		X		SH Test	AREc32 assay	h-CLAT			
3	ITS/DS for hazard and potency identification of skin sensitisers (**P&G**)	penetration (PBPK model)	X	TIMES SS	TG 442C	TG 442D	h-CLAT U937 test	TG 429		
4	Tiered system for predicting sensitising potential and potency of a substance (STS) (**Kao Corporation**)				TG 442C		h-CLAT			
5	Score-based battery system for predicting sensitising potential and potency of a substance (ITS) (**Kao Corporation**)			DEREK Nexus	TG 442C		h-CLAT			
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	h-CLAT m-MUSST			
8	STS for hazard identification of skin sensitisers (**RIVM**)			Various	TG 442C	TG 442D HaCaT gene signature	h-CLAT			
9	IATA (**Dupont**)		X	Various	TG 442C glutathione depletion assay	TG 442D	h-CLAT 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			h-CLAT			
12	Consensus decision tree model for skin sensitisation hazard prediction (**EC JRC**)			TIMES SS Dragon						

ENV/JM/MONO(2016)29-Annex 1

TG 442C : DPRA ; TG 442D : KeratinoSens™

DIP – some examples

2 out of 3 WoE BASF



Hazard identification (S/NS)

- No differential weighting of individual test methods
- No predefined sequential order of testing
- Usually DPRA and KeratinoSens™ are performed first since less expensive

Consensus Decision Tree Model -JRC

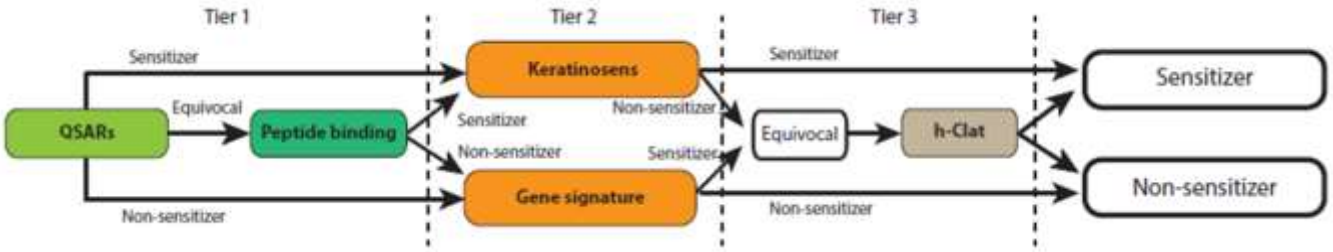
Output from DT-1	Output from DT-2	Consensus Prediction
1	1	1
1	0	1
0	1	1
0	0	0

Hazard identification (S/NS)

- Based entirely on *in silico* descriptors
- Prediction obtained by combining the outputs of the decision trees

Sequential Testing Strategies:

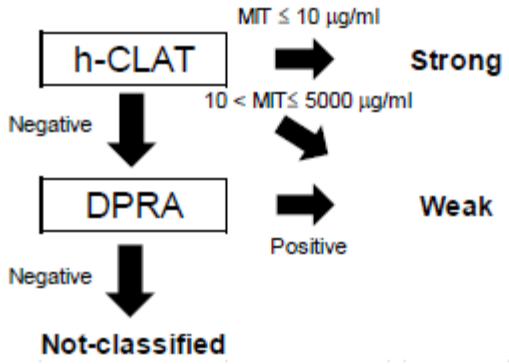
RIVM



Hazard identification (S/NS)

- At least two tiers needed to derive a prediction
- Final decision based on majority voting (2 out of 3 approach)

Kao

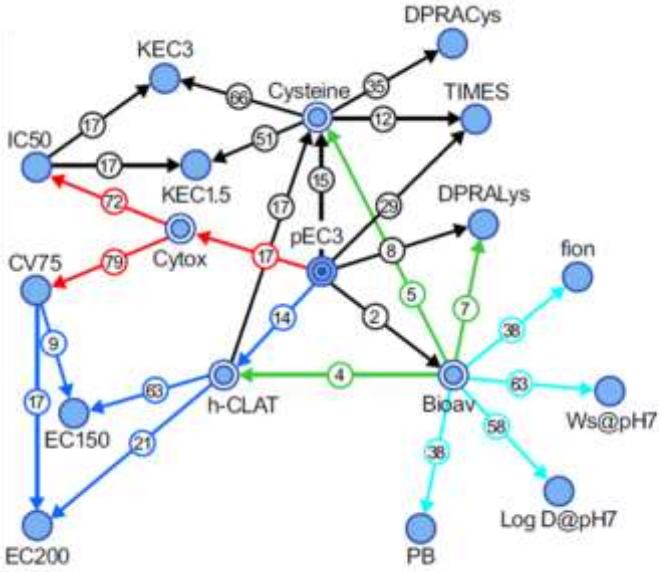


3 Potency classes: NS, Strong and Weak

Prediction can be derived after first tier

Integrated Testing Strategies:

Bayesian network ITS – P&G



- Gathering (available) data for all variables needed
- Integration of data inputs using Bayesian statistics within ITS structure
- Output = pEC3: potency probability distribution
- Conversion of the pEC3 to Bayes factors to determine the strenght of the evidence → final interpretation and prediction

4 Potency classes:

- NS
- Weak
- Moderate
- Strong and Extreme

Bayes Factor	Strength of evidence
<1	Negative (supports alternative)
1-3	Barely worth mentioning (weak)
3-10	Substantial
>30	Strong

European Commission

Wrap up

- Cases studies illustrate there are multiple ways to construct a defined approach and to process data
- DA make use of mechanistic data from one or more key event but DIP is usually data-driven
- Information on KE1 is used in all case studies
- Developed/tested with a substantial number of chemicals
- Show improved accuracy for predicting LLNA responses compared to the individual methods
- Are more relevant to predict human effects than the LLNA
- Provide useful information for potency categorisation/prediction
- LLNA variability never considered in the DA construction

European Commission

Thank you for your attention!

Joint Research Centre