Skin Sensitisation Overview/AOP and Guidance Document on the Reporting of IATA

Silvia Casati

Alternatives for Skin Sensitisation Testing and Assessment
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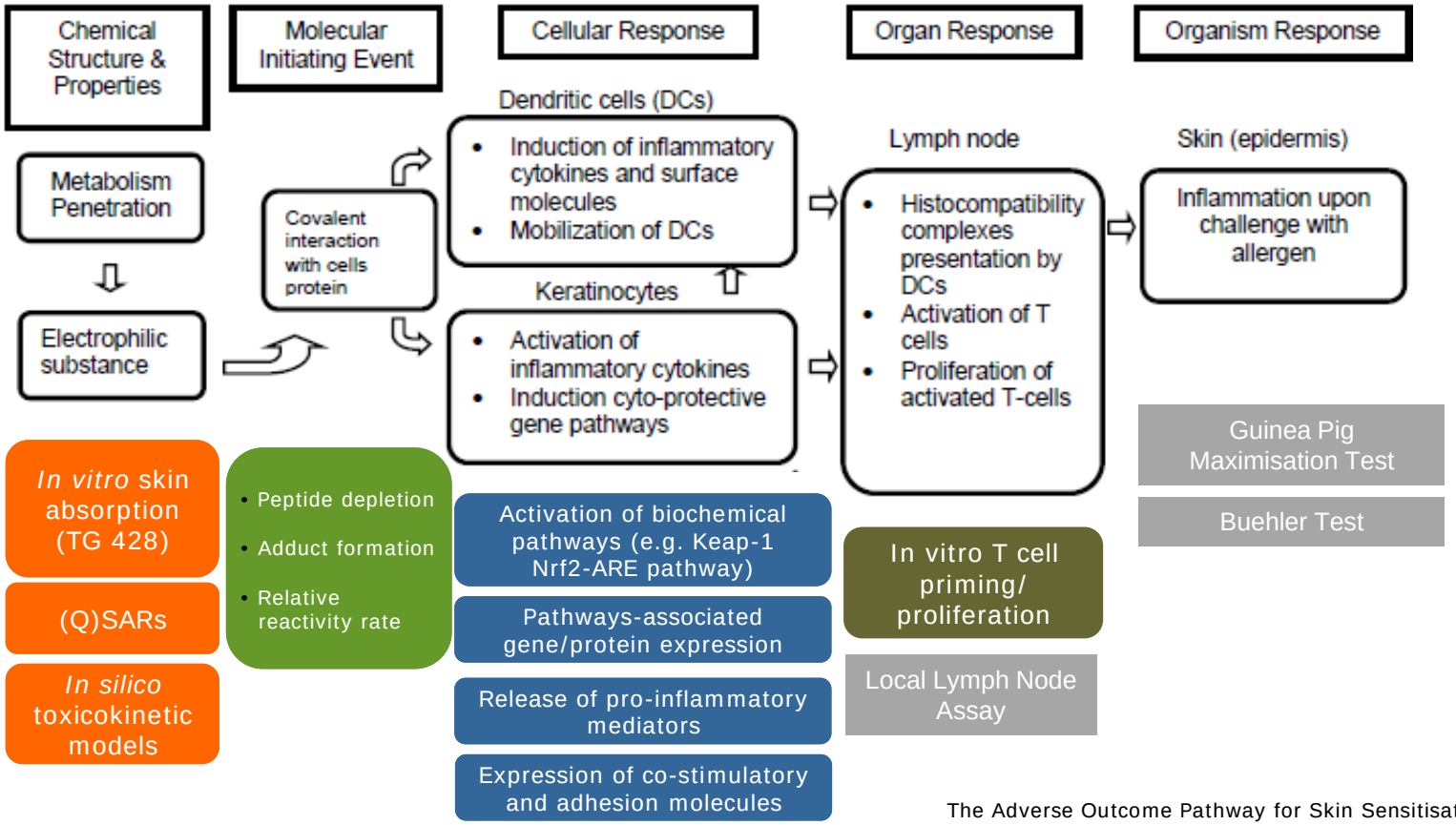
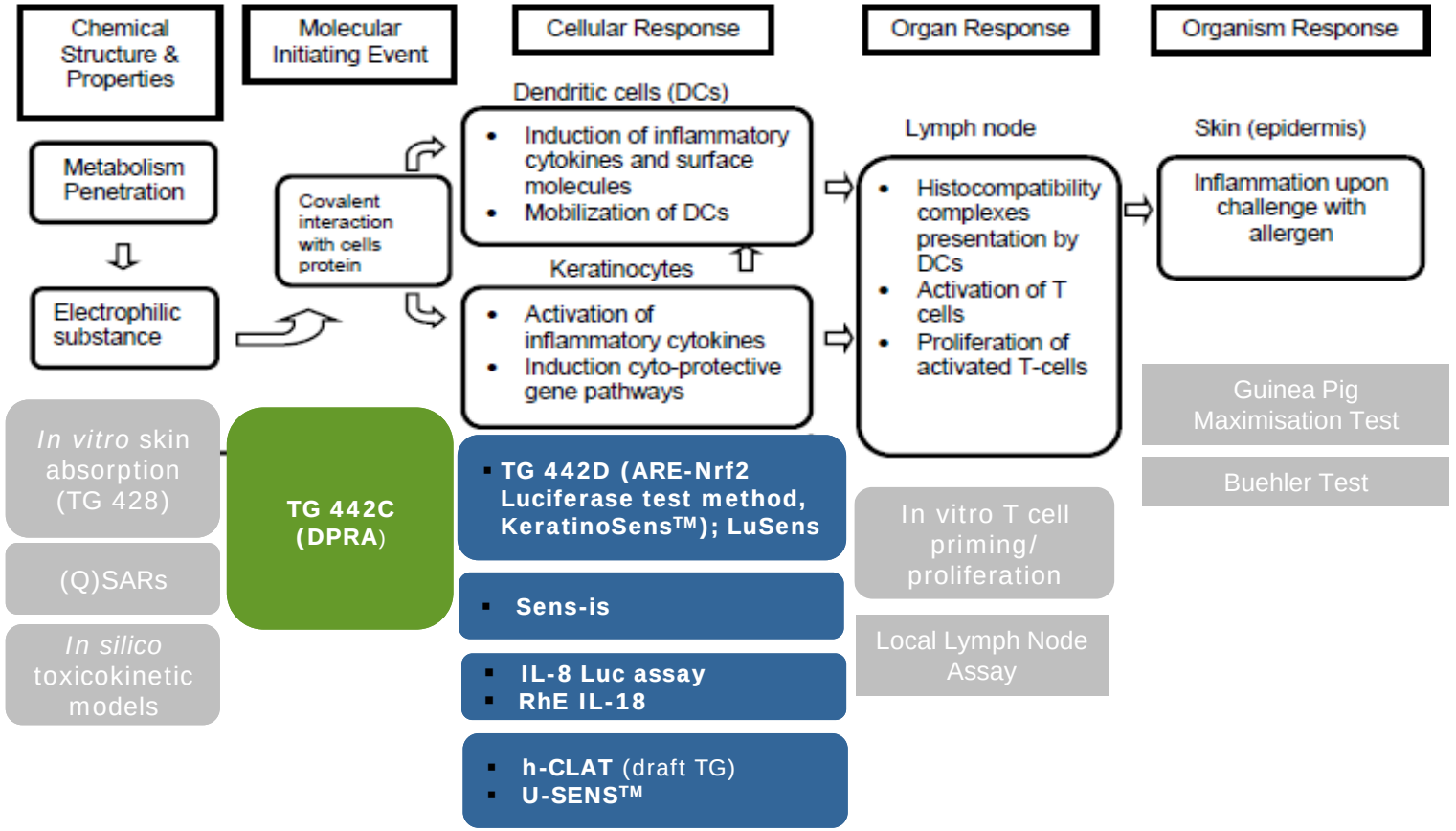
AOP and available toolbox of non-animal methods



The Adverse Outcome Pathway for Skin Sensitisation Initiated by Covalent Binding to Proteins; Part 1: Scientific Evidence Series on Testing and Assessment No.168 ENV/JM/MONO(2012)10/PART1

AOP and *some* of the more advanced non-animal methods

(i.e. OECD adopted, evaluated or under evaluation in ring trials)



Development of AOP-based IATA (using mechanistic methods)

- Several possibilities of combining information (context-specific and substance-tailored)
- Flexibility is foreseen in the construction and application of IATA (to allow use for multiple regulatory needs and wide chemical applicability)
- Some information will be covered by Mutual Acceptance of Data (MAD), but final decision will not
- There is therefore a risk of disharmonisation in the reporting, evaluation and application of IATA
- Proper guidance is crucial!

Differences between IATA for skin corrosion / irritation and for skin sensitisation

Skin corrosion / irritation	Skin sensitisation
In vitro methods developed to predict the apical endpoints i.e., skin corrosion or skin irritation	*In vitro* methods developed to predict key events along the skin sensitisation AOP
Information sources organised according to Modules i.e., human data, *in vivo* data, *in vitro* data, phys. chem. properties, non-testing methods	Information sources organised according to key events along the skin sensitisation AOP
Each *in vitro* method can be used on its own for regulatory decision making (C&L)	None of the *in vitro* methods can be used on its own (more dependent on data integration)
Additional testing follows a rather prescriptive scheme (top-down or bottom-up approaches)	Flexibility in the strategy used for additional testing (dependent on objective and test chemical)

Guidance Document on the reporting of IATA to facilitate consistent evaluation and application

Scope: To promote consistent application and evaluation of IATA within OECD member countries by providing guidance towards a harmonised approach for the reporting of IATA by delivering:

- A set of principles for describing and evaluating IATA *to facilitate the consideration of IATA's assessments in regulatory decision-making*
- Templates for reporting structured approaches to data integration and individual information sources used within IATA so that the same documentation format for describing and evaluating IATA and its elements
- Case-studies exemplifying consistent description of structured approaches to data integration for skin sensitisation and the information sources used therein, *to guide in the level of information needed to allow for their proper evaluation and application*

Structure of the Guidance Document

Part 1 Designed to introduce the purpose of the document, the general principles for the evaluation of IATA and the two templates for the reporting of structured approaches to data integration and individual information sources used within IATA (that could be in principle applicable to other areas)

Part 2 Designed to show how integrated approaches and information sources developed for the skin sensitisation endpoint should be documented (that would serve as example for other areas as well)

Six Principles: essential information for regulatory application of an IATA

Proposed to facilitate the consideration of IATA's assessments in regulatory decision-making.
IATA should be associated with the following set of information.

1. **A defined endpoint**
2. **A defined purpose**
3. **A description of the rationale underlying the construction of the IATA**
4. **A description of the individual information sources constituting the IATA**
5. **A description of how the individual information sources are integrated to derive the final prediction / assessment**
6. **A description of the known uncertainties associated with the IATA application**

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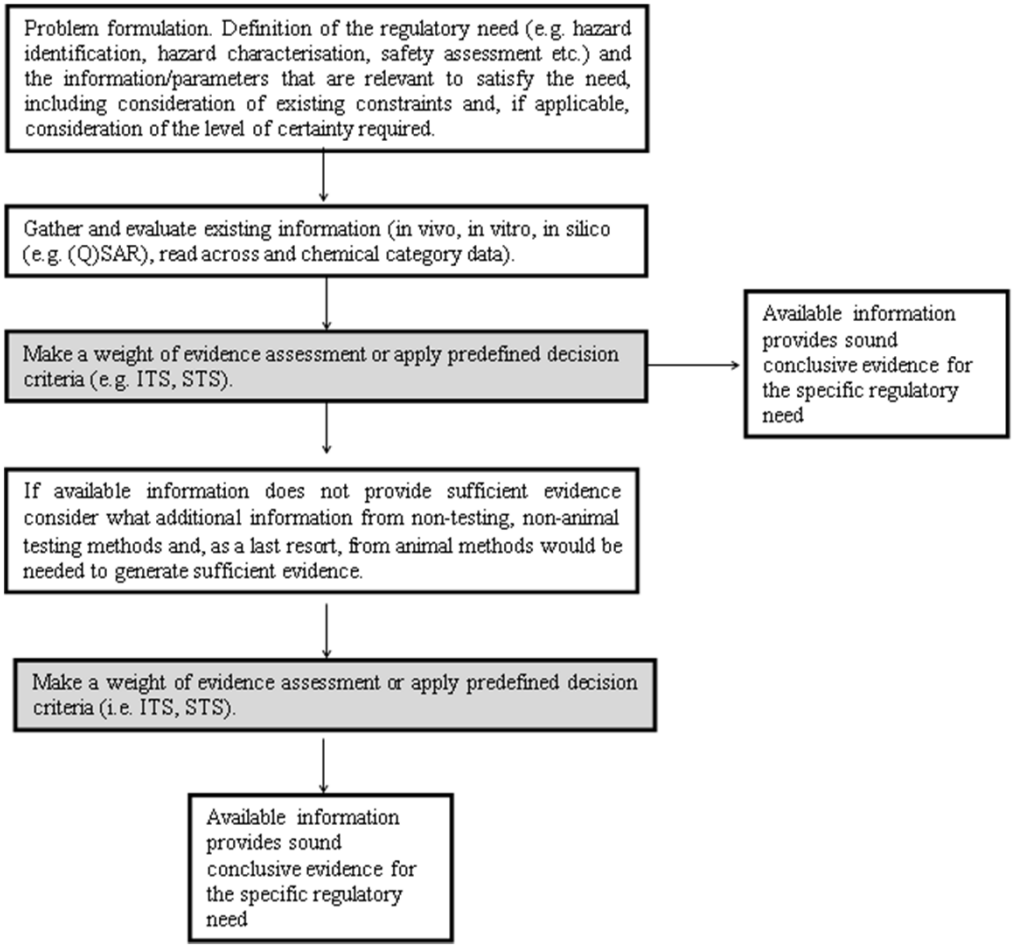
IATA general framework



Assessment process within IATA can be performed using a non-formalised WoE and/or predefined structured approaches to data integration (e.g. integrated testing strategies and sequential testing strategies)

Transparent documentation of the decision flow is essential for the evaluation and application of IATA

An example for a simple approach to the documentation of WoE is presented in Annex II of the OECD GD N. 203

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Structured approaches to data integration reporting format (RF)

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**	*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	**Process applied to the derive the prediction assessment**	*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 the approach**	*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 (and strengths) 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	**Known uncertainties associated with the application**	*how key assumptions related to model structure and information sources translate to prediction uncertainty described to the extent possible*

Template for reporting individual information sources

1	**Name**	*name and acronym*
2	**Mechanistic basis including AOP coverage**	*chemical – biological mechanism(s) addressed, linkage of the mechanism(s) to the predicted endpoint, biological relevance of the experimental system*
3	**Description**	*relevant aspects of the procedure; e.g. exposure time(s), concentration(s), replicates, concurrent controls*
4	**Response(s) measured**	*response(s) measured and measure(s)*
5	**Prediction model**	*clear description, modifications made to the original prediction model*
6	**Metabolic competence**	*if present how this relates to the in vivo situation*
7	**Status of development, standardisation, validation**	*standard test method, validated but not adopted, undergoing formal evaluation, non-validated but widely used*
8	**Technical limitations and limitations with regard to applicability**	*chemicals and chemical categories for which the information source is not applicable (technical limitations-wrong predictions)*
9	**Weaknesses and strengths**	*if possible compared to existing similar methods*
10	**Reliability**	*level of within- and between-laboratory reproducibility as characterised*
11	**Predictive capacity**	*expressed possibly by considering all existing evidence*
12	**Proprietary aspects**	*if not fully disclosed proprietary elements and their impact on wide implementation should be described*
13	**Proposed regulatory use**	*e.g. full replacement, partial replacement, screening*
14	**Potential role within IATA**	*potential weight within IATA, possibility to use the method on its own*

Elements of IATA for skin sensitisation

IATA Elements	
Exposure consideration	
Chemical descriptors	
Dermal bioavailability	Skin penetration Skin metabolism
AOP Key event 1: covalent interaction with cellular proteins	
AOP Key event 2: events in keratinocytes	Activation of biochemical pathways Pathways-associated gene expression Release of pro-inflammatory mediators
AOP key event 3: events in dendritic cells	Expression of co-stimulatory and adhesion molecules Pathways-associated gene expression Pathways-associated protein expression
AOP key event 4: Events in lymphocytes	
Adverse Outcome	
Others	

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Information sources within IATA for skin sensitisation

AOP key event 1: Covalent interaction with cellular proteins	

UNDER REVIEW	**Non-testing methods**
	• Protein binding/reactivity alerts (e.g. OECD Toolbox, Derek Nexus, Toxtree, TIMES-SS)
	• Others
	
	Testing methods
	• TG442C (Direct Peptide Reactivity Assay)
	• Adduct formation or relative reactivity rate, with or without metabolic activation, e.g
	  • Cor1C420 assay (Natsch and Gfeller, 2008)
	  • PPRA (Gerberick et al., 2009)
	  • Glutathion (Aptula et al. 2006)
	  • Others

AOP key event 2: events in Keratinocytes	
Activation of biochemical pathways	**Testing methods** • TG 442D (ARE-Nrf2 Luciferase Test Method-KeratinoSens™) • LuSens (Ramirez et al., 2014) • AREc32 cell line assay (Natsch and Emter, 2008). • Others
Pathways-associated gene expression	• Sens-is (Cottrez et al., 2015) • HaCaT gene signature (van der Veen et al., 2013) • SenCeeTox (McKim et al., 2012) • Others
Release of pro-inflammatory mediators	• RhE-IL-18 (Gibbs et al. 2013) • IL-8 Luc assay **(**Takahashi et al., 2011) • Others
AOP key Event 3: Events in Dendritic cell	
Expression of co-stimulatory and adhesion molecules	**Testing methods** • h-CLAT (Ashikaga et al., 2010, OECD draft TG available) • U-SENS™ (Piroird et al., 2015 • modified MUSST (Bauch et al., 2012) • PBMDC (Reuter et al., 2011) • Others
Pathways-associated gene expression	• GARD (Johansson et al., 2013) • VitoSens (Hooyberghs et al., 2008) • Others
Pathways-associated protein expression	• SensiDerm (Thierse et al., 2011) • Others

The IATA elements addressed and the type of information sources used to populate each individual IATA element may vary depending on:

- specific regulatory need
- substance under investigation

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IATA GD - reported case studies

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Case Study		Bioavailability	Physico-chemical 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 Nrf-2 Assay	U-SENS™ PGE2 Assay			
11	Integrated decision strategy for skin sensitisation hazard (**ICCVAM**)		X	OECD Toolbox			h-CLAT			
12	Consensus model for hazard identification (**EC-JRC**)			TIMES SS Dragon OECD Toolbox						

Structured approaches for data integration used within or constituting IATA for skin sensitisation

- 12 case studies documented in the GD
- Provide a perspective of how individual information sources and structured approaches to data integration used within or constituting an IATA should be reported
- Proposed for different purposes: *hazard identification, potency categorisation, potency prediction*
- Based on a variety of approaches for data integration/interpretation covering: *sequential testing strategies, regression models, 2 out of 3 WoE, scoring systems, machine learning approaches (e.g. artificial neural networks, support vector machines), Bayesian networks, etc.*
- All show improved predictivity with respect to the individual information sources
- Multitude of possibilities exist, which precludes the prescription of a one-fits-all solution
- Reporting in GD does not imply acceptance or endorsement, but harmonised reporting facilitates evaluation

Timelines

- **Q2 2013**: OECD IATA Drafting Group established
- **November 2013**: Release of 1st draft of Guidance Document by the EC
- **February 2014**: Drafting Group meeting at OECD
- **Q1 2014**: Compilation of case studies
- **June 2014**: Release of 2nd draft of Guidance Document by the EC
- **November 2014**: Release of 3rd draft of Guidance Document by the EC
- **November 2014**: Drafting Group meeting at JRC
- **Q1 2015**: Compilation of revised case studies (12 in total)
  - Hazard ID: BASF, Grace Patlewicz, L'Oréal, NICEATM, RIVM, EC-JRC
  - Potency prediction: Givaudan, Kao (2), P&G, Shiseido, Unilever
- **April 2015**: Release of 4th draft of Guidance Document by the EC
- **Q2 2015**: Final review of case studies and Guidance Document
- **Q3-Q4 2015**: Consultation of WNT and TF-HA & submission for adoption

Thank you for your attention!

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