IDC-2019,
May 13th-14th, Tokyo, Japan

Guidance on the use of alternative test methods for the safety assessment of cosmetics and quasi-drugs

Hajime Kojima, NIHS, Japan

Table 1. Test methods for safety evaluation of cosmetic ingredients defined by each cosmetic industry association.

		
JCIA safety evaluation guidance (2015)[8)]	**PCPC safety evaluation guideline (2014)[2)]**	**Cosmetic Europe, COLIPA guideline (2004)[1)]**
Single dose toxicity	Oral toxicity	Acute toxicity (oral or inhalation)
Repeat dose toxicity	Dermal toxicity	Sub-chronic toxicity (oral or inhalation)
—	Inhalation toxicity	
Primary skin irritation	Primary dermal irritation	Dermal irritation
Cumulative skin irritation	–	—
Skin sensitization	Dermal sensitization	Skin sensitization
Phtotoxicity	Phtotoxicity& Photoallegy	Phtotoxicity
Photosensitization		
Ocular irritation	Eye irritation	Eye irritation
Genotoxicity	Genotoxicity	Mutagenicity
Human patch test	Controlled use studies in human	Human data
—	—	Toxicokinetics
—	Mucous membrane irritation	Mucous membrane irritation
Skin absorption	Skin absorption	Dermal absorption
Reproductive and developmental toxicity	Reproductive and developmental toxicity	Reproductive toxicity, Carcinogenecity, Additional genotoxicity

Table 2. Test methods for safety evaluation of ingredients for regulatory use

			
Quasi-drug safety evaluation guidance（2008）[9)]	**SCCS safety evaluation guidance（2012）[3)]**	**Special cosmetic safety evaluation guideline[10)]**	**Functional cosmetic safety evaluation guideline[10)]**
Acute toxicity	Acute toxicity		Acute toxicity
Repeat dose toxicity (Sub-chronic, Chronic)	Repeat dose toxicity		
Reproductive toxicity	Reproductive toxicity		
Skin irritation	Corrosivity & irritation	Acute skin irritation	Primary skin irritation
	—	Cumulative skin irritation	—
Skin sensitization	Skin sensitization	Skin sensitization	Skin sensitization
	Phtoto-induced toxicity		Phtotoxicity
Photo sensitization		Photo sensitization	Photo sensitization
Mucous membrane irritation		Acute eye irritation	Eye or mucous membrane irritation
Genotoxicity	Mutagenicity/genotoxicity	Genotoxicity	
	Human data	Human patch test	Human patch test
		Controlled use studies in human	Human repeat insult patch test
ADME	Toxicokinetics		
	Dermal/percutaneous absorption		
Carcinogenecity	Carcinogenecity		

11 March 2013 Last updated at 17:23 GMT

EU bans sale of all animal-tested cosmetics

A complete ban on the sale of cosmetics developed through animal testing has taken effect in the EU.

The search for alternatives to animal testing goes on

The ban applies to all new cosmetics and their ingredients sold in the EU, regardless of where in the world testing on animals was carried out.

The 27 EU countries have had a ban on such tests in place since 2009. But the EU Commission is now asking the EU's trading partners to do the same.

Animal rights lobbyists said EU officials had "listened to the people".

The **anti-vivisection group BUAV and the European Coalition to End**

Related Stories

UK retains strict animal test law

Regulatory issue on alternative methods

- According to the MHLW notification, Japan in 2011, JaCVAM (Japanese Center for the Validation of Alternative Methods) decided to accelerate new *in vitro* testing methods to take advantage of this opportunity to strongly impact testing throughout Japan.
- Therefore, the members are coordinating the Guidance on the use of alternative test methods in safety assessment of cosmetics and quasi-drugs since 2012.
- The members have consists on dermatologists, delegates of cosmetic companies, the technical officers of PMDA (Pharmaceuticals and Medical Devices Agency) and specialists of NIHS (National Institute of Health Sciences) and this member is on-going to make drafting the guidance based on the OECD test guideline and/or JaCVAM evaluation document per each alternative test method.

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Members for the guidance

Classification	Name	Affiliation
Dermatologist	Tokio Nakada	Showa University, Fujigaoka Hospital, Japan
	Akiko Yagami	Fujita Health University School of Medicine, Japan
Regulator	Yukiko Hoshino	Pharmaceuticals and Medical Devices Agency, Japan
	Naofumi Iizuka	
	Takatoshi Nakamura	
	Shinichi Sekizawa	
	Kazutoshi Shinoda	
	Mio Yagi	
Researcher	Kenji Sugibayashi	Faculty of Pharmaceutical Sciences, Josai University, Japan
	Hiroaki Todo	
	Yoshiaki Ikarashi	National Institute of Health Sciences, Japan
	Hajime Kojima	
Industry	Daisuke Araki	Japan Cosmetic Industry Association, Japan
	Hitoshi Sakaguchi	
	Hitoshi Sasa	
	Mariko Sugiyama	

Guidances for alternative to animal testing

The following guidance documents have been approved by the MHLW.

- Guidance on the use of alternative test methods for skin-sensitization and phototoxicity in safety assessment of cosmetics and quasi-drugs (Appendix 1: Guidance on the use of LLNA for skin sensitisation test as an alternative test method in safety assessments of cosmetics and quasi-drugs, Appendix 2: Guidance on the use of the in vitro 3T3 NRU phototoxicity test as an alternative test method in safety assessments of cosmetics and quasi-drugs), dated April 26, 2012
- Guidance on the use of alternative test methods for skin-sensitization (LLNA:DA, LLNA:BrdU-ELISA) in safety assessments of cosmetics and quasi-drugs, dated May 30, 2013,
- Guidance on the use of the Bovine Corneal Opacity and Permeability (BCOP) test as an alternative method for testing ocular irritation in the safety assessment of cosmetics and quasi-drugs, dated February 4, 2014
- Points of consider for ocular irritation testing in the safety assessment of cosmetics and quasi-drug, dated February 27, 2015
- Guidance on use of the Isolated Chicken Eye (ICE) test as an alternative method for testing ocular irritation in the safety assessment of cosmetics and quasi-drugs, dated November 16, 2015
- Guidance on use of in vitro skin penetration assay (in vitro skin absorption assay) in the safety assessment of cosmetics and quasi-drugs, dated November 15, 2016
- Guidance on use of combination of in vitro skin sensitisation assays in the safety assessment of cosmetics and quasi-drugs, dated January 2018.
- Guidance on use of the Short Time Exposure (STE) test as an alternative method for testing ocular irritation in the safety assessment of cosmetics and quasi-drugs, dated December 18, 2018

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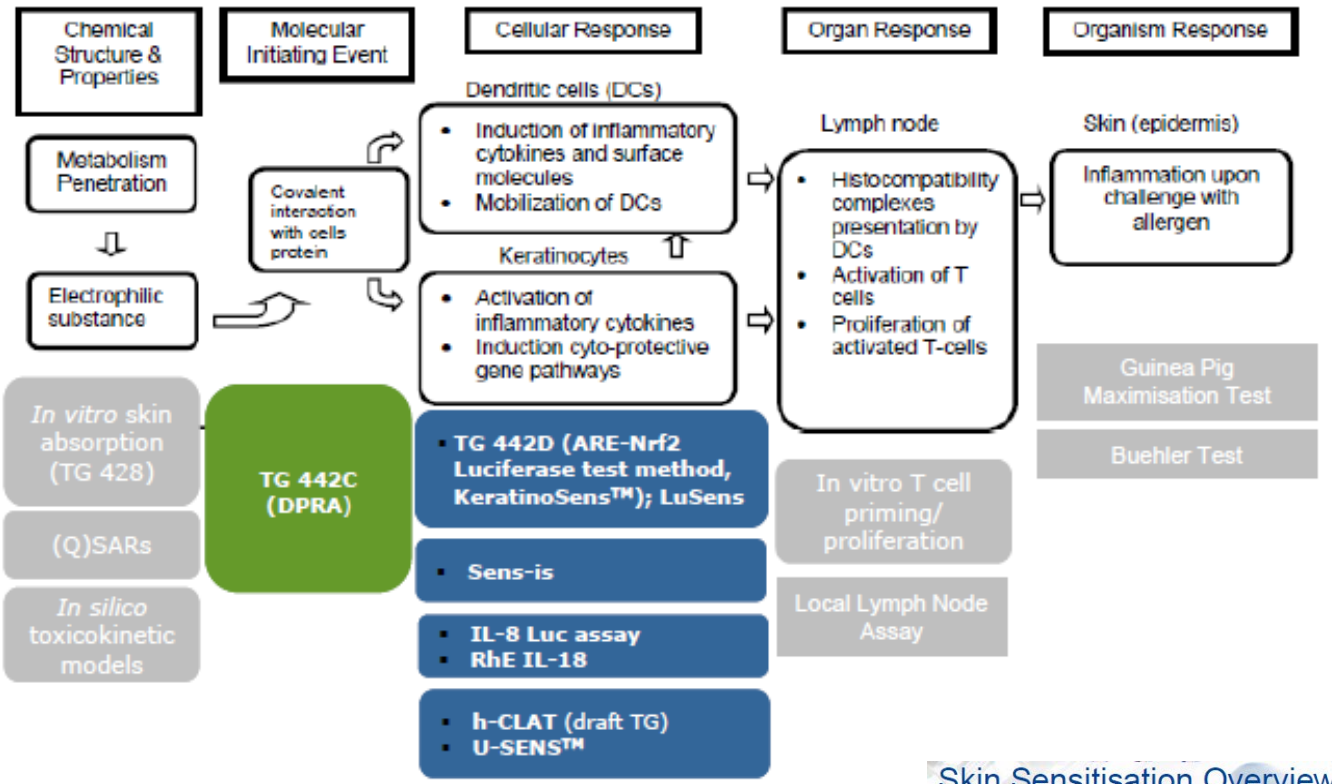
Guidance on use of combination of in vitro skin sensitisation assays in the safety assessment of cosmetics and quasi-drugs, dated January 2018.

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

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



OECD/OCDE **TG 442C**

Adopted: 4 February 2015

OECD GUIDELINE FOR THE TESTING OF CHEMICALS

In Chemico Skin Sensitisation: Direct Peptide Reactivity Assay (DPRA)

9. The test method described in this Test Guideline can be used, in combination with other complementary information, to support the discrimination between skin sensitisers (i.e. UN GHS Category 1) and non-sensitisers in the context of IATA. This Test Guideline cannot be used on its own, neither to sub-categorise skin sensitisers into subcategories 1A and 1B as defined by UN GHS (1), for authorities implementing these two optional subcategories, nor to predict potency for safety assessment decisions. However, depending on the regulatory framework, a positive result with the DPRA may be used on its own to classify a chemical into UN GHS category 1.

OECD/OCDE **442D**

Adopted:
25June 2018

KEY EVENT BASED TEST GUIDELINE 442D

8. The test methods described in this Test Guideline cannot be used on their own, neither to sub-categorise skin sensitisers into subcategories 1A and 1B as defined by UN GHS (1), for authorities implementing these two optional subcategories, nor to predict potency for safety assessment decisions. However, depending on the regulatory framework, positive results generated with these methods may be used on their own to classify a chemical into UN GHS category 1.

2. This Test Guideline describes in vitro assays that address mechanisms described under the second Key Event of the AOP for skin sensitisation, namely keratinocyte activation (2). The Test Guideline comprises test methods to be used for supporting the discrimination between skin sensitisers and non-sensitisers in accordance with the UN GHS (1). The test methods currently described in this Test Guideline are:

- The ARE-Nrf2 luciferase KeratinoSens™ test method (Appendix IA), and
- The ARE-Nrf2 luciferase LuSens test method (Appendix IB).

KEY EVENT-BASED TEST GUIDELINE

8. The test methods described in this Test Guideline cannot be used on their own, neither to sub-categorise skin sensitisers into subcategories 1A and 1B as defined by UN GHS (1), for authorities implementing these two optional subcategories, nor to predict potency for safety assessment decisions. However, depending on the regulatory framework, positive results generated with these methods may be used on their own to classify a chemical into UN GHS category 1.

2. This Test Guideline (TG) describes *in vitro* assays that address mechanisms described under the Key Event on activation of dendritic cells of the AOP for skin sensitisation (2). The TG comprises test methods to be used for supporting the discrimination between skin sensitisers and non-sensitisers in accordance with the UN GHS (1).

The test methods described in this TG are:

- Human Cell Line Activation test (h-CLAT)
- U937 cell line activation Test (U-SENS™)
- Interleukin-8 Reporter Gene Assay (IL-8 Luc assay)

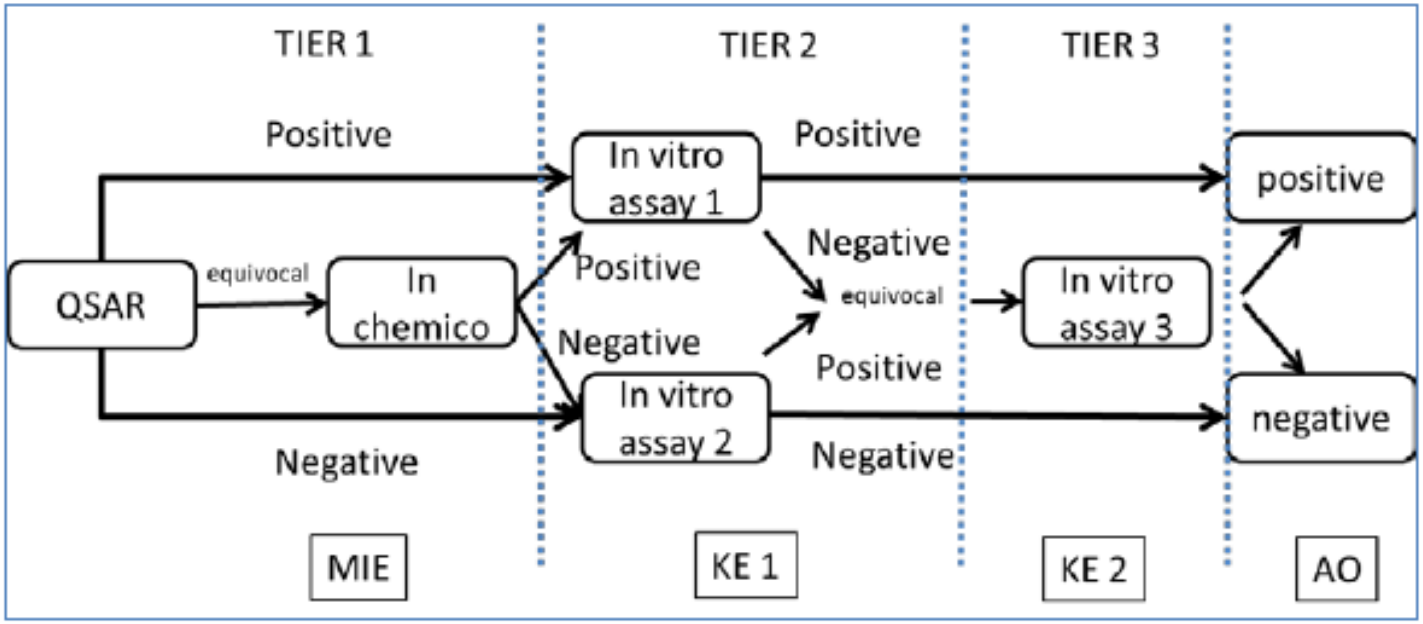


Figure 7. Use of an AOP in a testing strategy

GUIDANCE DOCUMENT FOR THE USE OF ADVERSE OUTCOME PATHWAYS IN DEVELOPING INTEGRATED APPROACHES TO TESTING AND ASSESSMENT (IATA)

Series on Testing & Assessment
No. 260

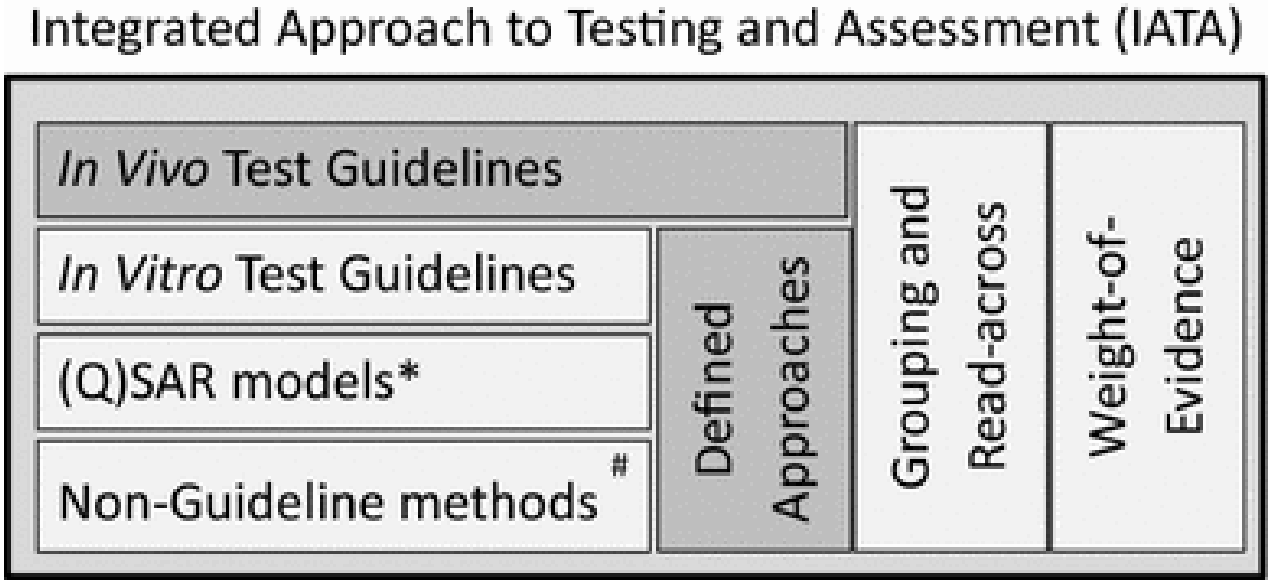


Fig. 1
Generic IATA elements and role of defined approaches within IATA. *Quantitative structure–activity (QSAR) models are usually characterised according to the five OECD principles for QSAR model validation (OECD 2007). #Non-guideline in vitro test methods should be described according to OECD Guidance Document No. 211

Archives of Toxicology
February 2018, Volume 92, Issue 2, pp 611–617 | Cite as

Standardisation of defined approaches for skin sensitisation testing to support regulatory use and international adoption: position of the International Cooperation on Alternative Test Methods

Just released!

Guidance on Reporting of Defined Approaches in Integrated Approaches to Testing and Assessment (IATA) and 12 Skin Sensitisation Case Studies

Guidance on principles for reporting defined approaches within IATA and an associated template have been published. A second guidance document illustrates how the reporting templates can be used to document a number of defined approaches (and information sources used within) in the area of skin sensitisation. This is exemplified via 12 case studies for skin sensitisation.

These can be found at the new IATA webpage: http://www.oecd.org/chemicalsafety/risk-assessment/iata-integrated-approaches-to-testing-and-assessment.htm

ENVIRONMENT, HEALTH
& SAFETY NEWS

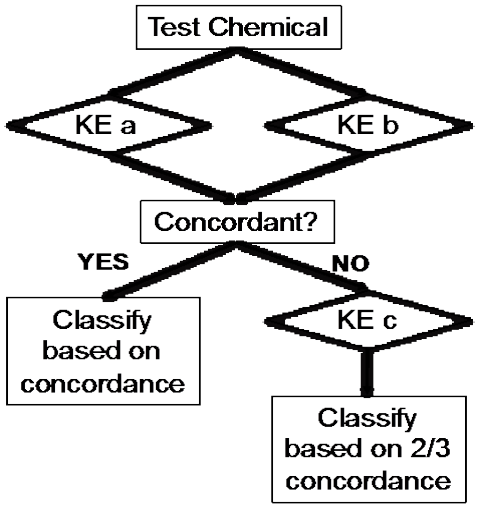
ENV/JM/HA(2016)11 – Annex 1

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

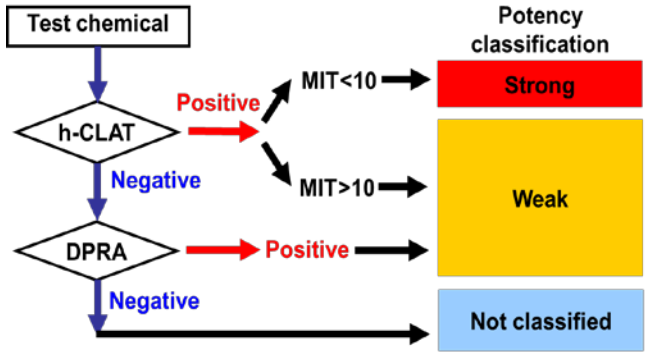
DRAFT GUIDELINE ON DEFINED APPROACHES FOR SKIN SENSITISATION

DAs included in the Guideline

For initial inclusion in this guideline, DAs using validated OECD in vitro test methods and simple, rule-based data interpretation procedures (DIPs) were considered. The following DAs, and their respective applications, are included in this guideline:



The "2 out of 3" defined approach.



The "KE 3/1 STS" defined approach

The "KE 3/1 ITS" defined approach

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

Historical Accuracy of Animal Tests Against Human Data

LLNA

Hazard	Potency (GHS)
72%-82%	54% - 60%

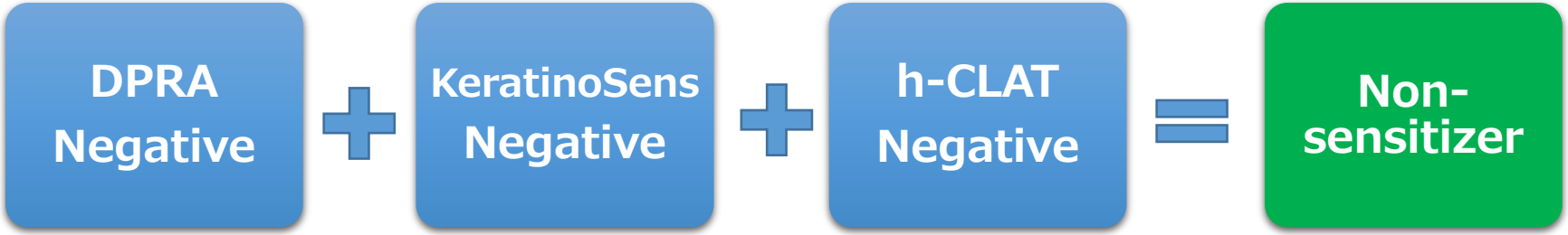
GPMT / Buehler

Hazard	Potency (GHS)
~72%	~60%

ICCVAM. 1999. NIH Publication No. 99-4494
ICCVAM. 2010. NIH Publication No. 11-7709
Urbisch et al. 2015. Reg Tox Pharm 71:337-351.
Hoffmann et al. 2017 in preparation

3 out of 3 for Bottom-up

"3 out of 3 for Bottom-up" could be used as **"one"** of testing strategies to identify non-sensitizers **as part of bottom-up approach**



	vs human data			vs LLNA			N
	Sensitivity (%)	Specificity (%)	Accuracy (%)	Sensitivity (%)	Specificity (%)	Accuracy (%)	
LLNA	91	64	82	-	-	-	111
3 out of 3 for bottom-up	97	35	81	99	43	86	100

Analyzed using data from Urbisch et al. 2015

- Inconsistent results of in vitro assays would require additional information to support the conclusion.
- **"3 out of 3 for Bottom-up"** is **not the only approach**. Additional testing strategies to identify non-sensitizers are also under discussion.

Summary

The members of guidance team have also contributed to the establishment of a guidance for skin sensitization based on Test Guidelines (TGs) and guidance documents in OECD.

Thank you for your attention