

ACUTE SKIN IRRITATION AND SKIN CORROSION

WHAT DIFFERENCES?

Irritation



Local and *reversible* inflammatory response to skin injury caused by direct contact with a substance

Clinical signs:

Oedema
Erythema
Itching, Pain

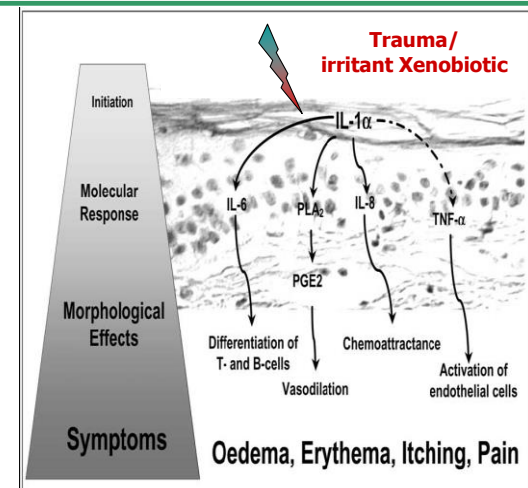
Corrosion

Potential of a substance to induce *irreversible* damage to skin.

Clinical signs:

Necrosis through the epidermis and the dermis
And *idem* irritation signs in surrounding areas

- Protein and lipids modification
- Dehydration
- Membrane modifications
- Release mediators pool
- mRNA transcription
- Protein synthesis (mediators)
- Interaction with other cells
- Increased lipid synthesis
- Abnormal differentiation
- Hyper-proliferation
- Irreversible membrane damage
- Cell death



Boelsma & Ponc: *Dermatopharmacology of topical preparations*. Springer, 2000, p.37

T. Welss et al., *Toxicology in Vitro* 18 (2004) 231-243

UN GHS/ EU CLP/ TDG CLASSIFICATIONS

		1.5	2.0	2.3			4.0
	P.I.I.						
EU DSD	No label	R38		Cause burns (R34)	Cause severe burns (R35)		
UN GHS / EU CLP	No Category		Cat.2	Cat.1C	Cat.1B	Cat.1A	
Regulations Dangerous Goods				Class 8 PG III	Class 8 PG II	Class 8 PG I	
	Not classified		Irritant	Corrosive			



Not classified	Irritant	Corrosive 1C/1B	Corrosive 1A
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P.I.I. = Primary Irritation Index

OECD TG404: Max reaction score = 4.0 - Cat.2 and 3: Mean score (24, 48 and 72hrs) for at least 2/3 tested animals – Cat.1: at least 1 animal

Corrosive substances and mixtures; Class 8 Packaging Groups – PG I: very dangerous; PG II: medium danger; PG III: minor danger

TDG: transportation of dangerous Goods



Stand alone test methods using Human Reconstructed Epidermis (RhE)

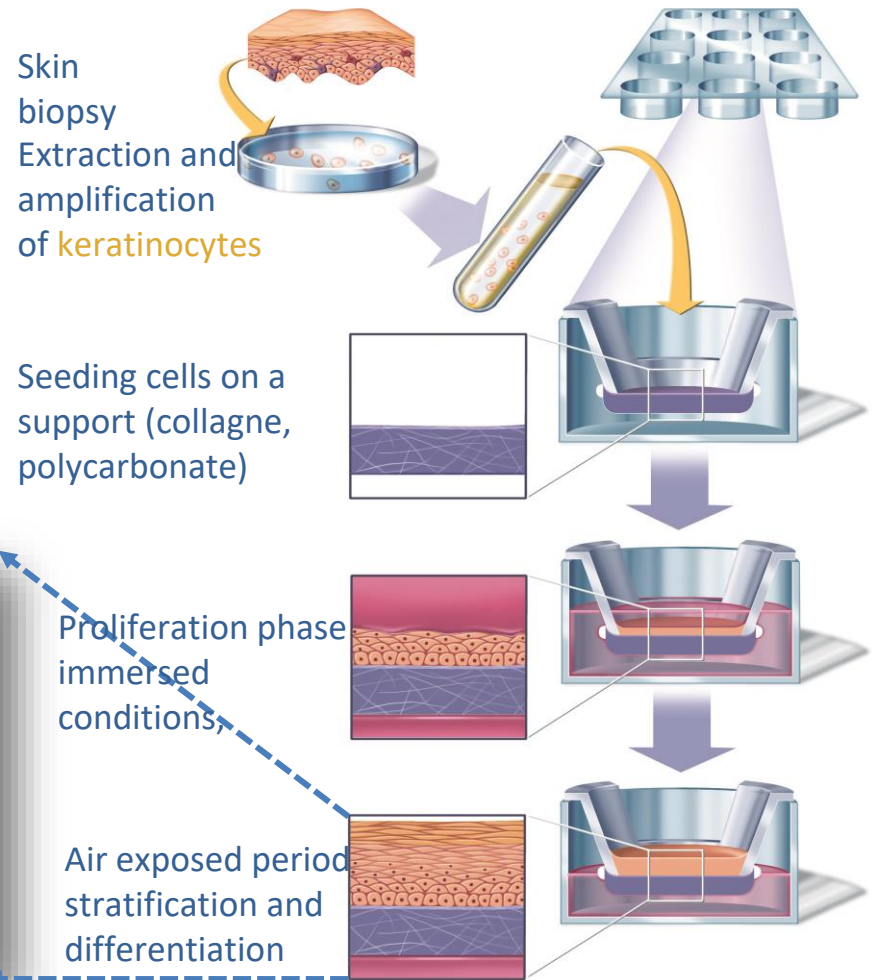
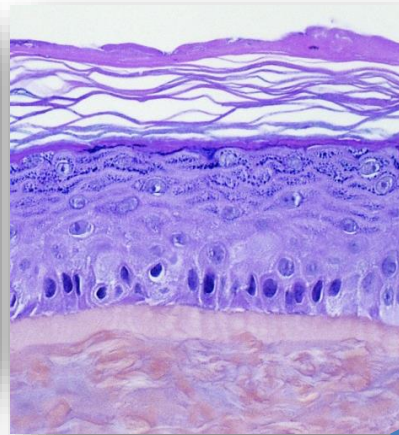
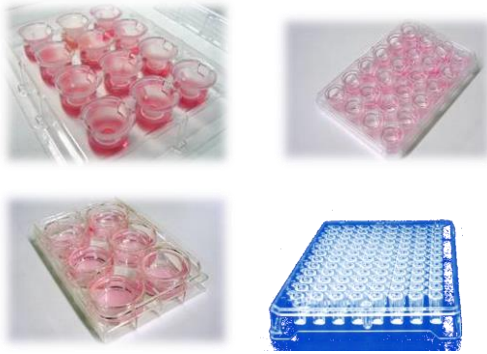
SKIN CORROSION & SKIN IRRITATION



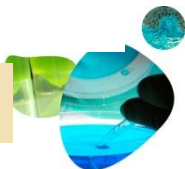
IN VITRO RECONSTRUCTION PROCESS

MAIN STEPS

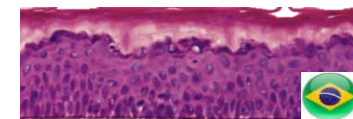
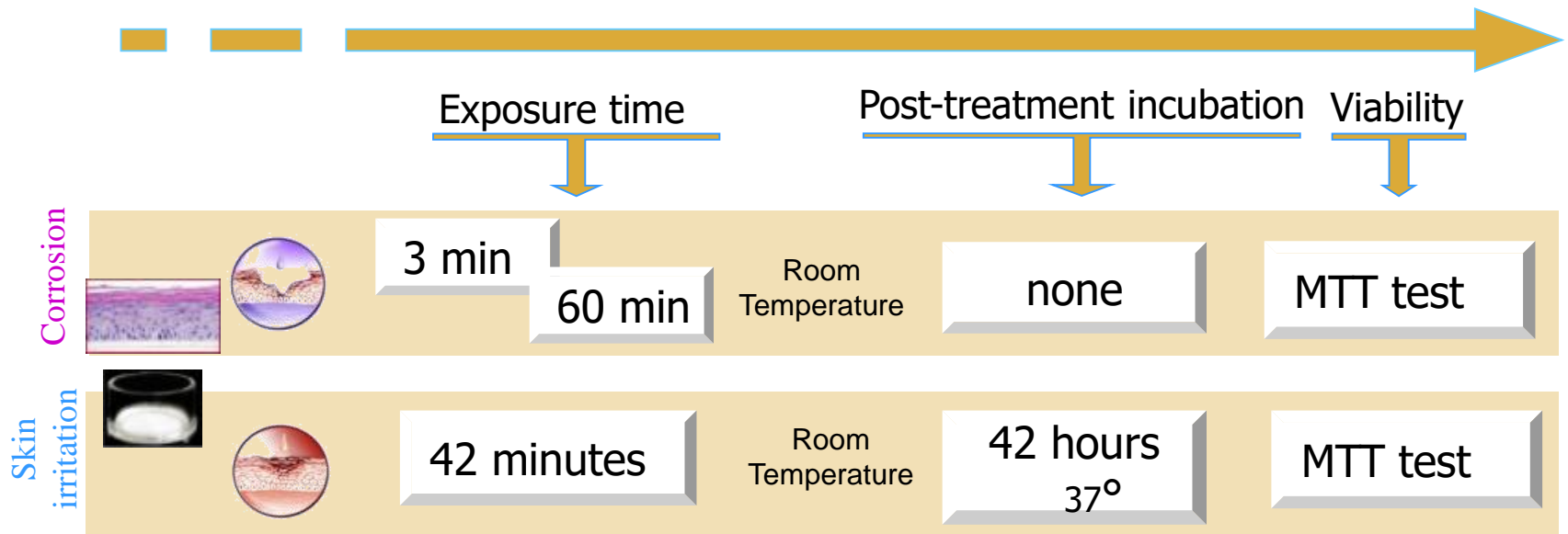
Human Reconstructed Epidermis (RHE)



Industrialization is a must have



- Each test chemical was applied topically onto tissues. At the end of the treatment period, cytotoxicity was determined by the MTT conversion test.
- Adapted controls were added for MTT reducers and coloring/tissue staining test substances.



Industrialized Reconstructed Epidermis in Rio/Brazil

❑ Prediction Models

<u>Skin Corrosion</u>		3 min exposure	1 h exposure
Corrosive	Cat. 1A	< 15% (independent of results obtained at 1 h)	
	Cat. 1B-and-1C	≥15%	<15%
Non Corrosive		≥ 15%	≥15%

Skin Irritation

Irritant (Category 2): viability ≤ 50 %

Non-Irritant: viability > 50 %

❑ Performances

	Skin Corrosion (n=84)	Skin irritation (n=60)
REPRODUCIBILITY	93%	98%
SENSITIVITY	94 %	90 %
SPECIFICITY	74 %	80 %
ACCURACY	85 % (2 classes) 71% (3 classes)	85 %

Corrosion

OECD/OCDE

431

Adopted:
29 July 2016

OECD GUIDELINE FOR THE TESTING OF CHEMICALS

In vitro skin corrosion: reconstructed human epidermis (RHE) test method

INTRODUCTION

1. Skin corrosion refers to the production of irreversible damage to the skin manifested as visible necrosis through the *epidermis* and into the *dermis*, following the application of a test chemical [as defined by the United Nations (UN) Globally Harmonized System of Classification and Labelling of Chemicals (GHS)] (1). This updated Test Guideline 431 provides an *in vitro* procedure allowing the identification of non-corrosive and corrosive substances and mixtures in accordance with UN GHS (1). It also allows a partial sub-categorisation of corrosives.

2. The assessment of skin corrosion potential of chemicals has typically involved the use of laboratory animals (OECD Test Guideline 404 (TG 404); originally adopted in 1981 and revised in 1992, 2002 and 2015) (2). In addition to the present TG 431, two other *in vitro* test methods for testing corrosion potential of chemicals have been validated and adopted as OECD Test Guidelines 430 (3) and 435 (4). Furthermore, the *in vitro* OECD TG 430 (3) has been adopted for testing skin irritation potential (4).

Irritation

OECD/OCDE

439

Adopted:
28 July 2015

OECD GUIDELINES FOR THE TESTING OF CHEMICALS

In Vitro Skin Irritation: Reconstructed Human Epidermis Test Method

INTRODUCTION

1. Skin irritation refers to the production of reversible damage to the skin following the application of a test chemical for up to 4 hours [as defined by the United Nations (UN) Globally Harmonized System of Classification and Labelling of Chemicals (GHS)] (1). This Test Guideline (TG) provides an *in vitro* procedure that may be used for the hazard identification of irritant chemicals (substances and mixtures) in accordance with UN GHS Category 2 (1) (2). In member countries or regions that do not adopt the optional UN GHS Category 3 (mild irritants), this Test Guideline can also be used to identify non-classified chemicals. Therefore, depending on the regulatory framework and the classification system in use, this Test Guideline may be used to determine the skin irritancy of chemicals either as a stand-alone replacement test for *in vivo* skin irritation testing or as a partial replacement test within a testing strategy (3).

Broad application to chemicals, pesticides, drugs, cosmetics, medical devices, ...



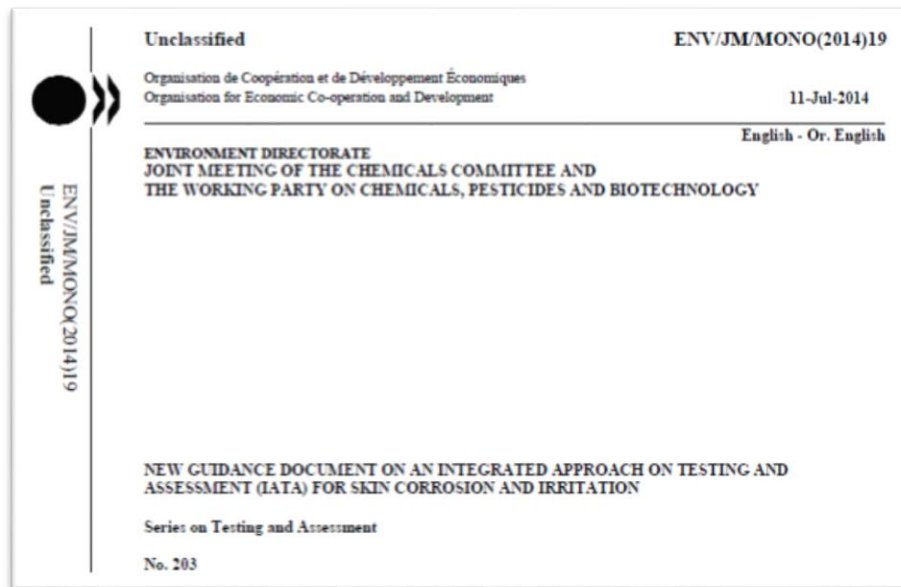
*FROM a stand alone test method
TO Integrated approach on testing
And Assessment (IATA)*

SKIN CORROSION & SKIN IRRITATION





OECD IATA : GD 203

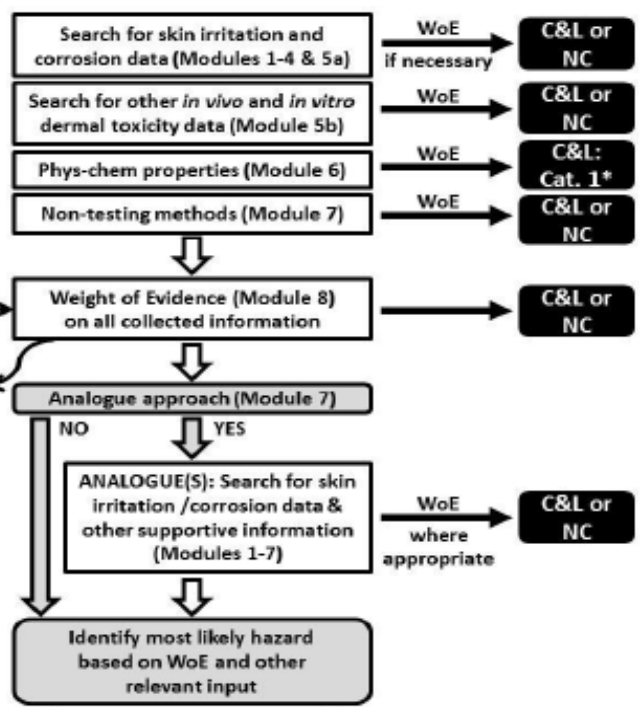


Guidance Document # 203 on an Integrated Approach on Testing and Assessment (IATA) for skin corrosion and irritation.

Provide guidance on how to integrate all existing and newly generated information into a modular approach for Classification and Labelling



PARTS 1 & 2



PART 3



8 modules

Part 1:
Collection and evaluation of existing data covering human, *in vivo* and *in vitro* data, physico-chemical properties and non-testing methods (i.e.. Read-across, QSAR, grouping)

Part 2:
a Weight-of-evidence (WoE) analysis, for decision-making on C&L

If the WoE analysis in the IATA is inconclusive and prospective testing is required

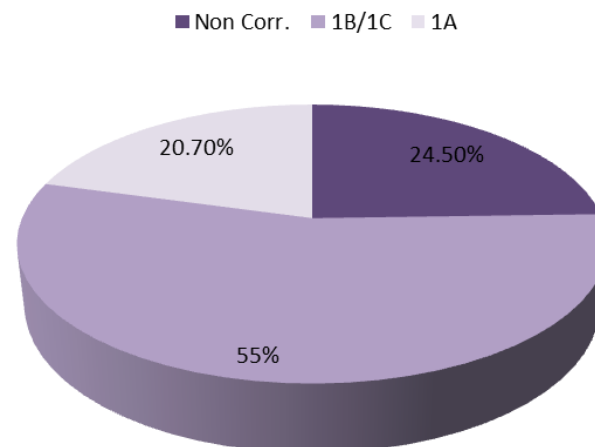
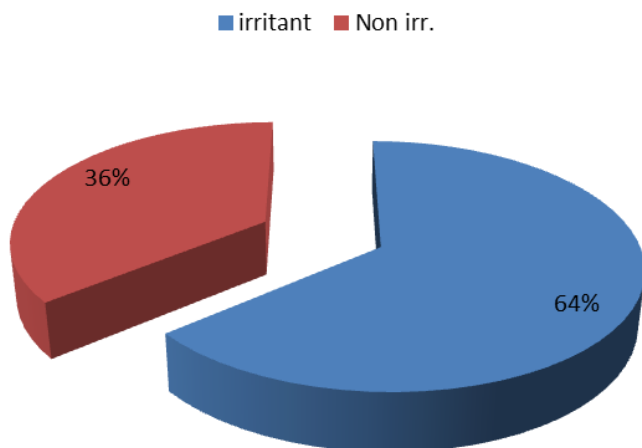
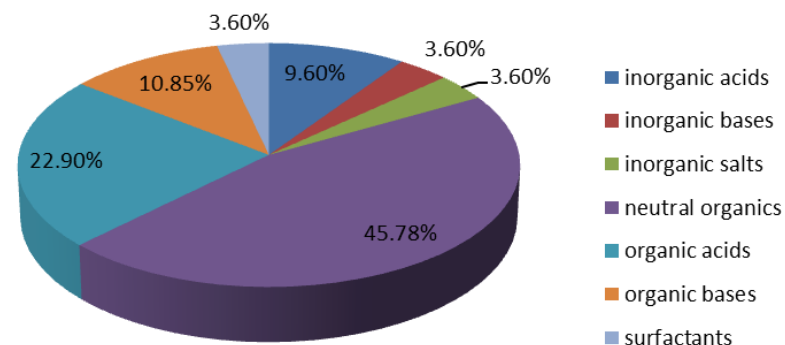
A Top-Down or Bottom-Up Sequential *in vitro* testing strategy
OECD TG 431, 439 skin irritation / corrosion
Using SkinEthic RHE test methods



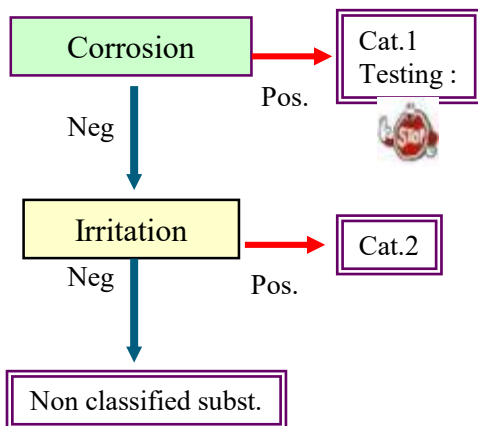


CHEMICALS DATASET

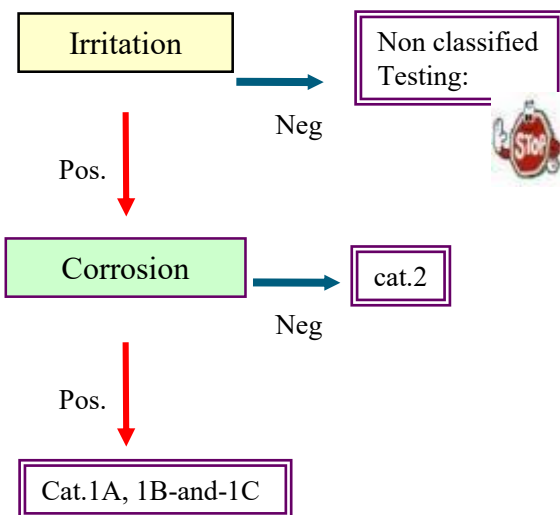
A total of **83** chemicals (~ 680 dataset) with *in vivo* data according to the OECD GD 203 were tested using the formally adopted *in vitro* SkinEthic™ RHE test methods for skin irritation (OECD TG 439) and skin corrosion (OECD TG 431)



TOP-DOWN BOTTOM-UP APPROACHES



Top Down		In Vivo				Sum
		Non Class.	Cat. 2	Cat. 1B-1C	Cat. 1A	
TG 431	Cat. 1A	0	0	2	9	11
↓	Corrosive	0	0	1	0	1
TG 439	Cat. 1B-1C	0	0	18	10	28
	Cat. 2	1	10	2	0	13
	Non Class.	25	4	1	0	30
Sum		26	14	24	19	83



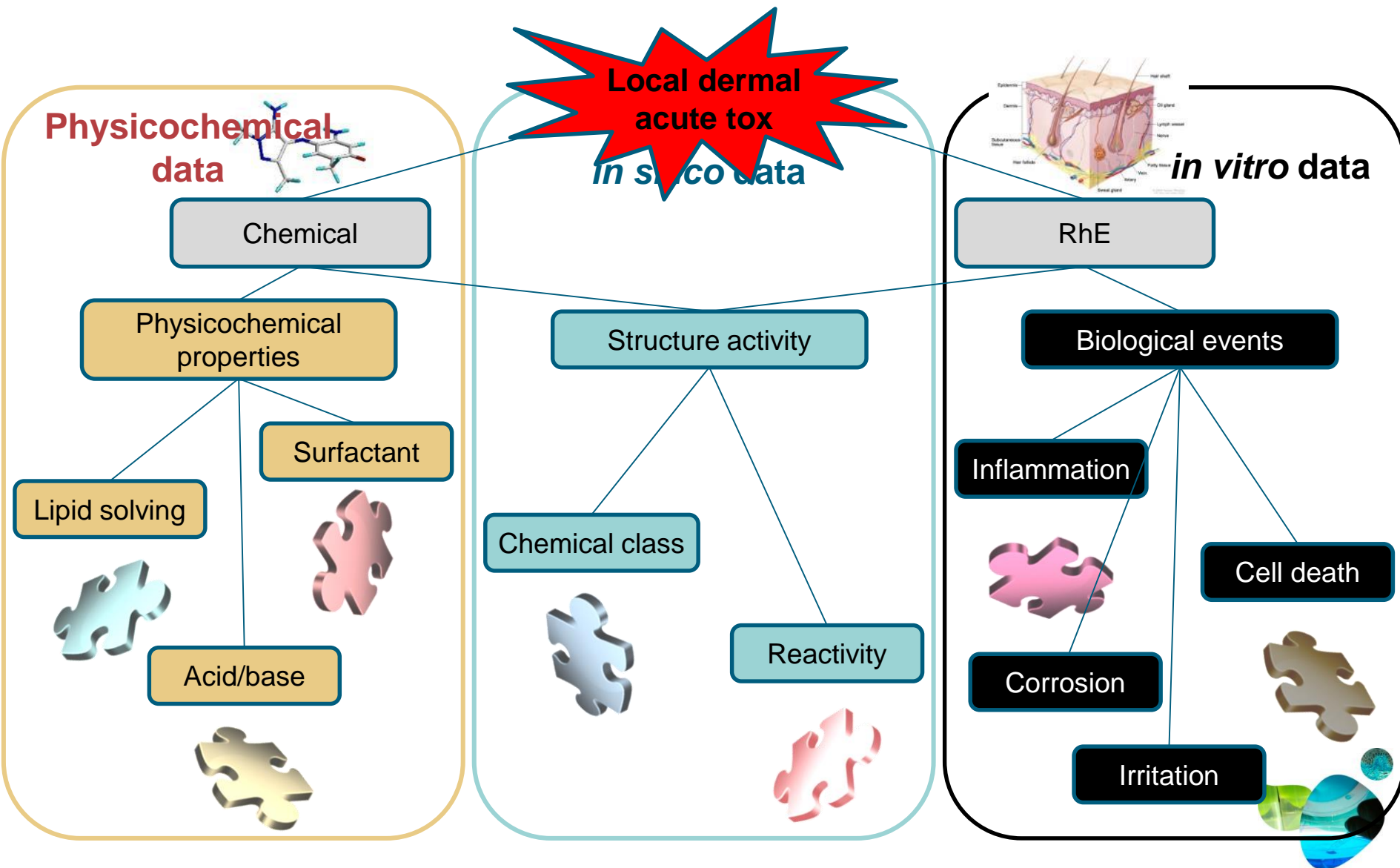
Bottom Up		In Vivo				Sum
		Non Class.	Cat. 2	Cat. 1B-1C	Cat. 1A	
TG 439	Non Class.	25	4	1	0	30
↓	Cat. 2	1	10	2	0	13
TG 431	Cat. 1B-1C	0	0	18	10	28
	Corrosive	0	0	1	0	1
	Cat. 1A	0	0	2	9	11
Sum		26	14	24	19	83

High similar predictive capacities in both the bottom-up and top-down testing sequences 

*FROM Integrated approach on testing
And Assessment (IATA)
TO Application*

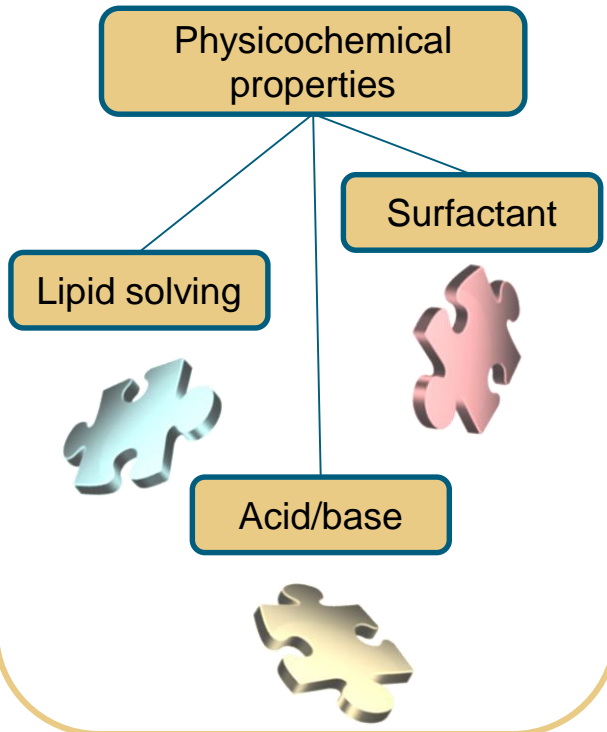
SKIN CORROSION & SKIN IRRITATION



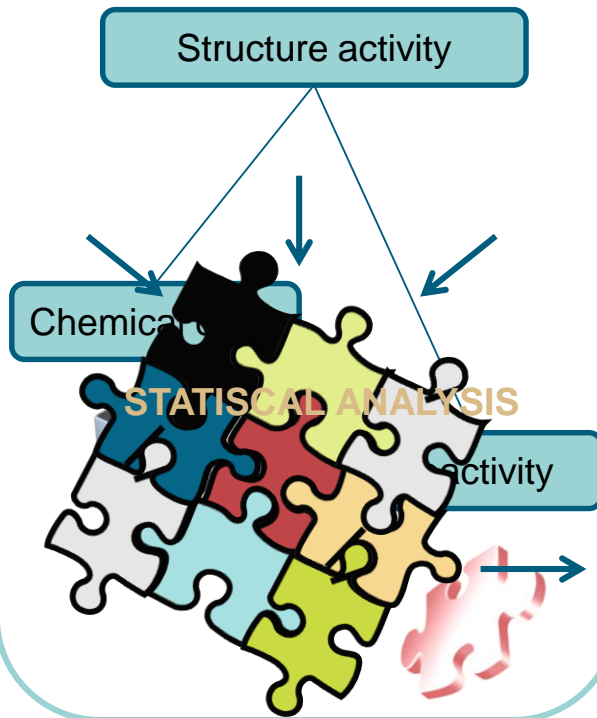


TO BUILT AN INTEGRATED (& INTELLIGENT) TESTING STRATEGY

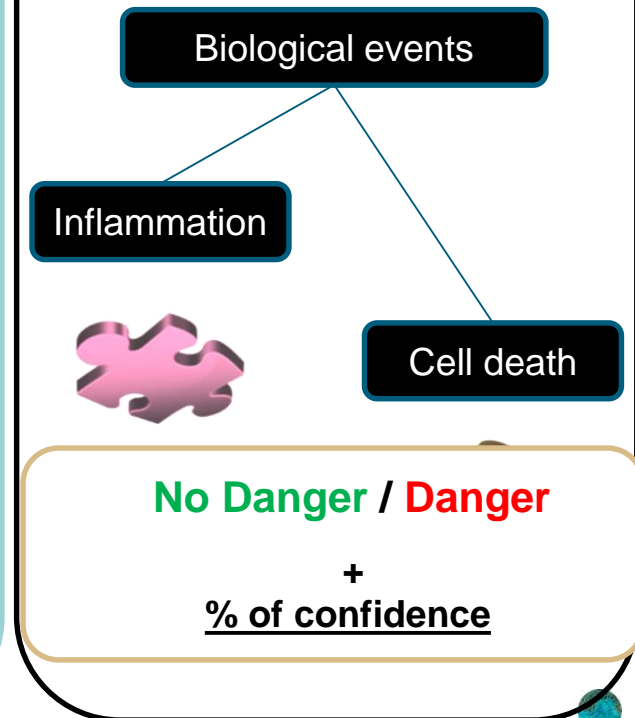
physicochemical data



in silico data



in vitro data



- ✓ SkinEthic™ RHE tissues are produced in Brazil (www.episkin.com)
- ✓ No Intellectual Property Rights nor license fee applied on the test methods: skin irritation/corrosion
- ✓ Protocols are freely accessible through European Commission website:
[<https://ecvam-dbalm.jrc.ec.europa.eu/methods-and-protocols>]
- ✓ High safety standards demonstrated: Reliable and relevant to identify chemicals according to UN GHS classification
- ✓ Applicable to the testing of all types of chemicals
- ✓ **Adopted for regulatory purposes**
 - in the OECD Test Guidelines TG 431 and 439 for testing
 - in the OECD Guidance no. 203 on integrated approaches to testing and assessment

The SkinEthic™ RHE model showed to provide accurate and safe assessments of skin irritation and corrosion hazards, ensuring consumer safety.