UNIVERSITÀ DEGLI STUDI DI MILANO
DIPARTIMENTO DI SCIENZE FARMACOLOGICHE E BIOMOLECOLARI

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Understanding contact hypersensitivity: from mechanism to risk assessment

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LAYOUT OF THE PRESENTATION

- Contact hypersensitivity: the problem and the current animal models
- Mechanistic understanding of ACD and the development of in vitro models

ACD, Allergic Contact Dermatitis

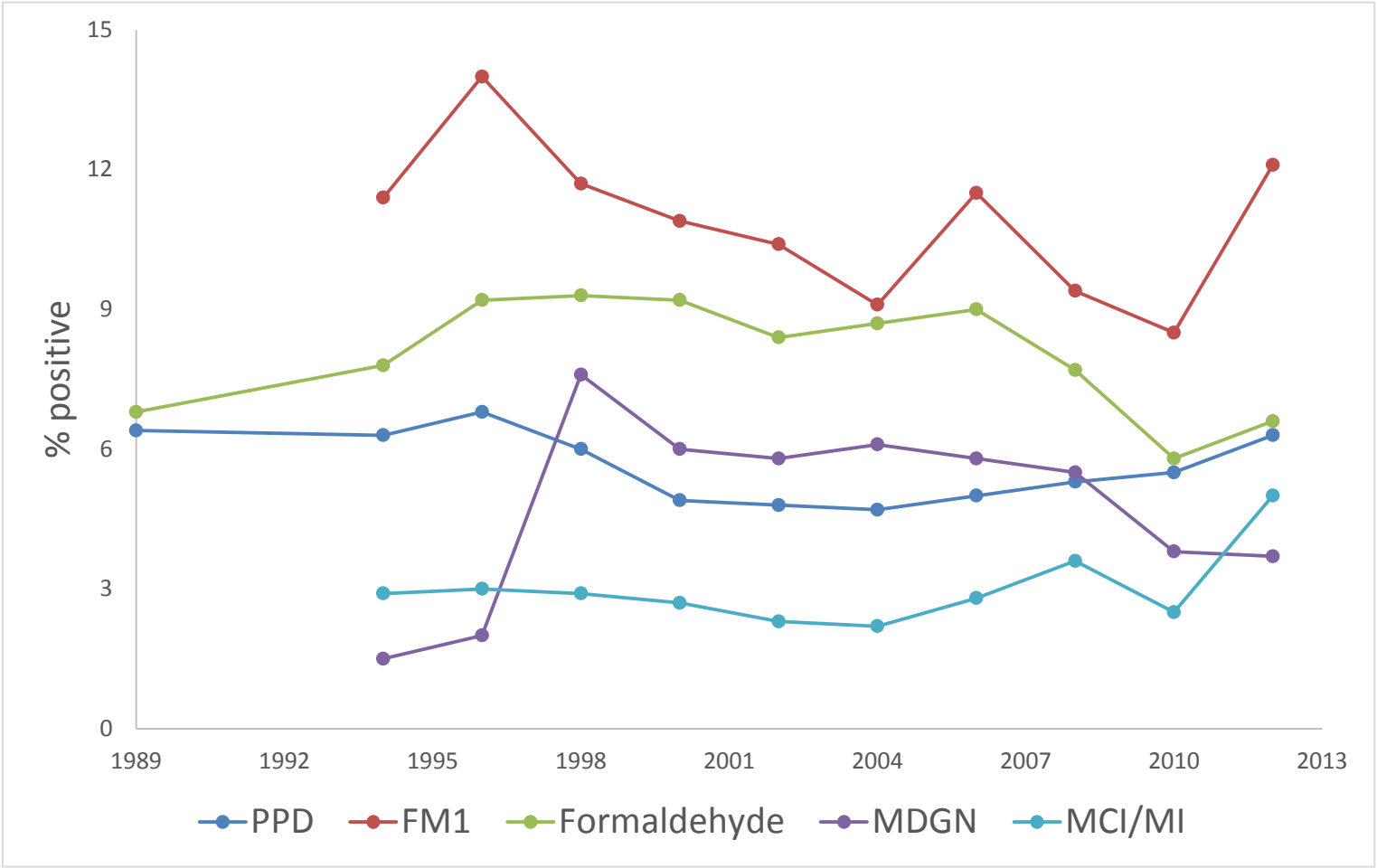
CHEMICAL ALLERGY

- The two most frequent manifestation of chemical-induced allergy are **contact hypersensitivity** and **respiratory sensitization**.
- Epidemiological studies suggest that the prevalence of contact allergy is ~15-20% (e.g. Peiser et al., 2012), making hypersensitivity reactions a major health problem in relation to environmental chemical exposure.

→ As a consequence chemical allergy is of considerable importance to the toxicologist, whom has the responsibility of identifying and characterizing the skin and respiratory potential of chemicals, and estimating the risk they pose to human health.

→ **Regulatory authorities worldwide require testing for allergic contact dermatitis (ACD) and appropriate hazard labeling to minimize exposures.**

Contact allergy to markers of cosmetic allergy over the 25 years in the USA



Basketter and Corsini, Cosmetics, 2016

MDGN, Methyldibromo glutaronitrile
MCI/MI Methylchloroisothiazolinone / methylisothiazolinone (preservatives)

Hypersensitivity: in vivo models

- Well established methods for contact and respiratory hypersensitivity
- Current models and assays as inadequate predictors for system hypersensitivity reaction

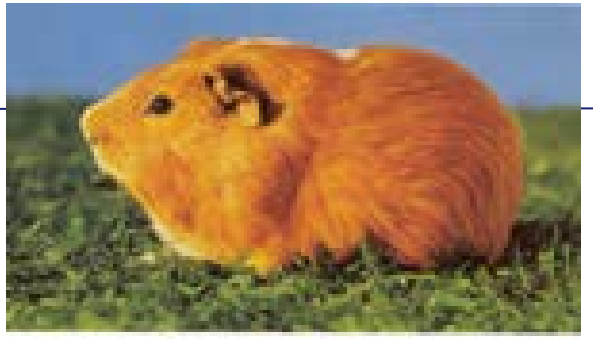
➢ Guinea Pig Tests
  - Maximization Test
  - Occlusive Patch Test
  - Respiratory Challenge
  - Systemic Anaphylaxix

➢ Mouse Tests
- **Local lymph node assay**
- Mouse Ear Swelling Test

Table 1. GHS Classification Categories for Skin Sensitizers

Category	Classification Criteria	LLNA EC3	Human Evidence (HRIPT or HMT)	GPMT Response	BT Response
1: Skin sensitizer	Evidence that skin sensitization occurs in a substantial number of people, or positive results from an appropriate animal test	NA	NA	NA	NA
1A: S skin sens					
1B: Other skin sensitizer	Low to moderate frequency of occurrence in humans, and/or low to moderate potency in animals. May consider severity.	>2%	Positive[2] response at >500 mg/cm^2	≥30% to <60% responders at >0.1% to ≤1% intradermal induction dose or ≥30% responders at >1% intradermal induction dose	≥15% to < 60% responders at >0.2% to ≤20% topical induction dose or ≥15% at >20% topical induction dose

The challenge is how to obtain the same quality of information using in silico or in vitro methods.



Abbreviations: BT = Buehler test; CPSC = U.S. Consumer Product Safety Commission; GPMT = guinea pig maximization test; HMT = human maximization test; HRIPT = human repeat insult patch test; LLNA EC3 = estimated substance concentration that produces a stimulation index of 3 in the murine local lymph node assay; NA = not applicable.

[1]Human evidence can also include diagnostic patch test data where there is a relatively high and substantial incidence of reactions in a defined population in relation to relatively low exposure or other epidemiology evidence where there is a relatively high and substantial incidence of allergic contact dermatitis in relation to relatively low exposure.

[2]Human evidence can also include diagnostic patch test data where there is a relatively low but substantial incidence of reactions in a defined population in relation to relatively high exposure or other epidemiology evidence where there is a relatively low but substantial incidence of allergic contact dermatitis in relation to relatively high exposure.

Non animal test for ACD

Four goals have been identified for a full replacement of skin sens

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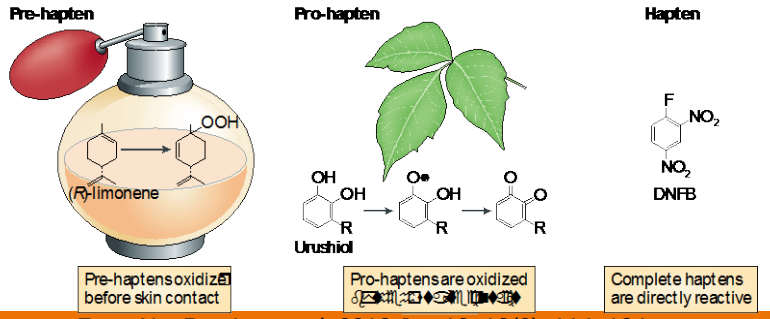
Potency is important as:

1. potency data can lead to improvements in hazard classification and so risk management
2. potency data can facilitate improved risk assessment for skin sensitization

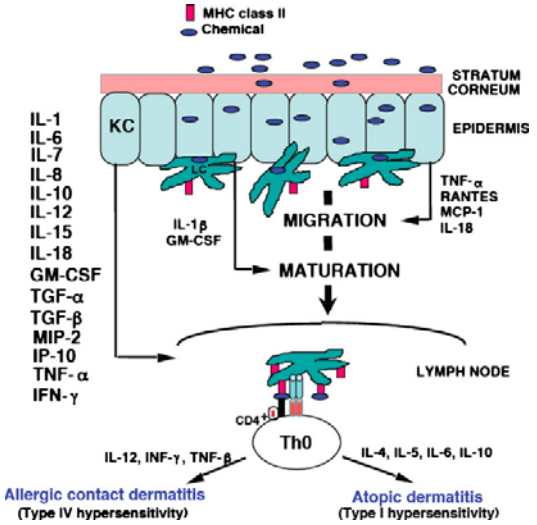


From Nat Rev Immunol. 2012 Jan 13; 12(2): 114–124.

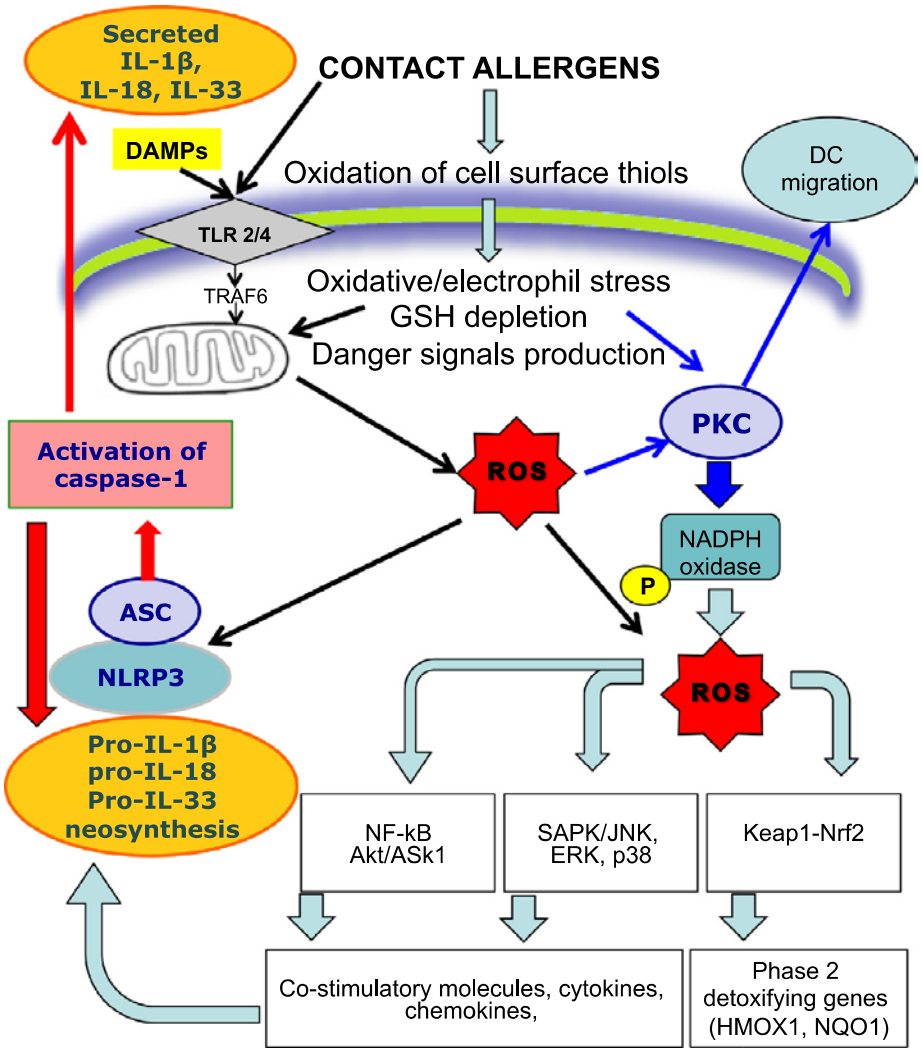
DEFINITION

- **<u>Allergic contact dermatitis</u>** (ACD) is a cell-mediated immune response to small molecular weight chemicals that contact and penetrate the skin.
- There are a variety of **characteristics** that determine whether a chemical can function as a contact sensitizer (or allergen):

  - ability to penetrate into the skin
  - reactivity with protein
  - epidermal and dermal inflammation
  - dendritic cell activation, migration to lymph nodes and recognition as antigenic by T cells.

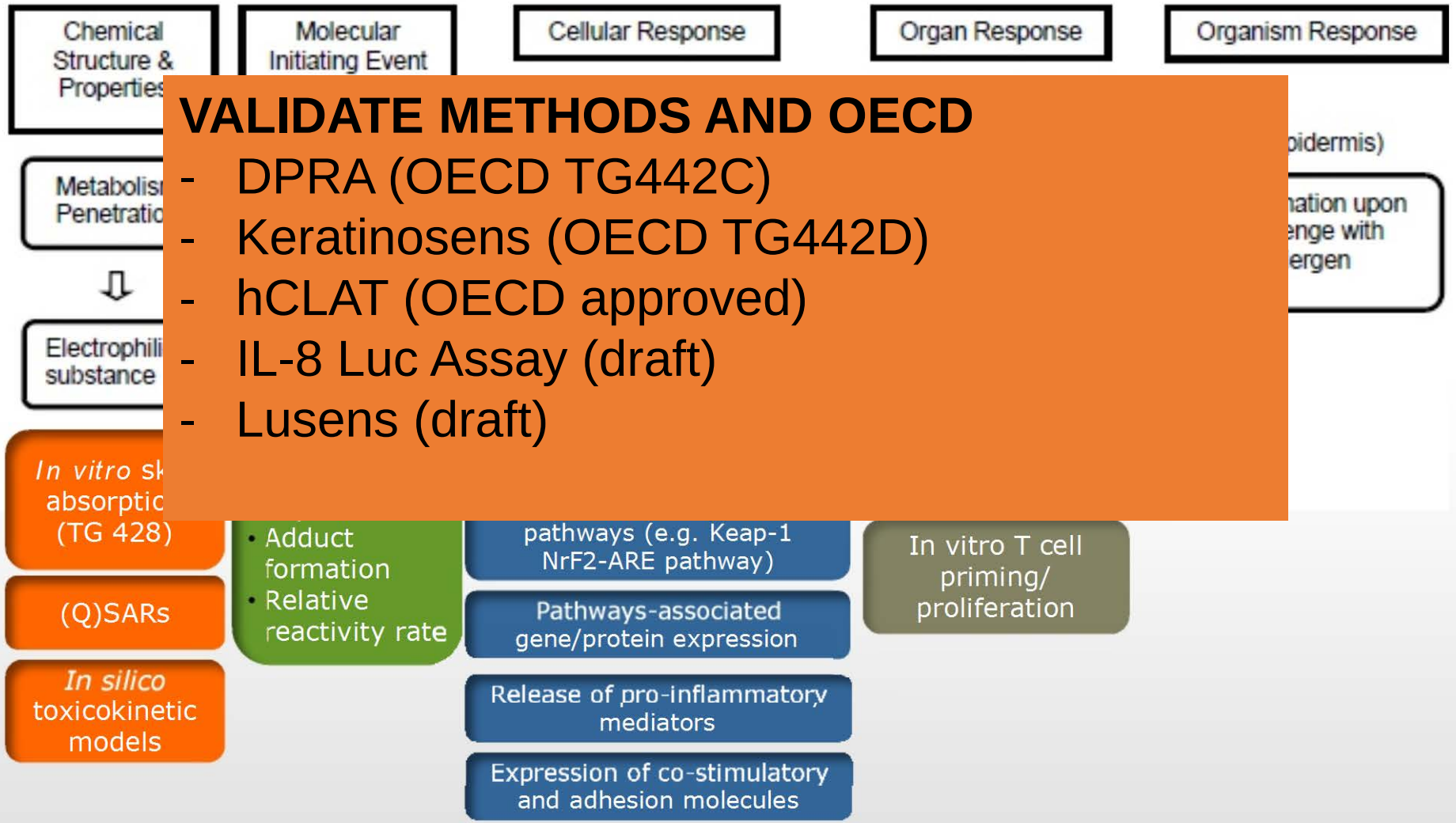


E. Corsini et al./Food and Chemical Toxicology 61 (2013) 74–81



uced DC/KC activation.

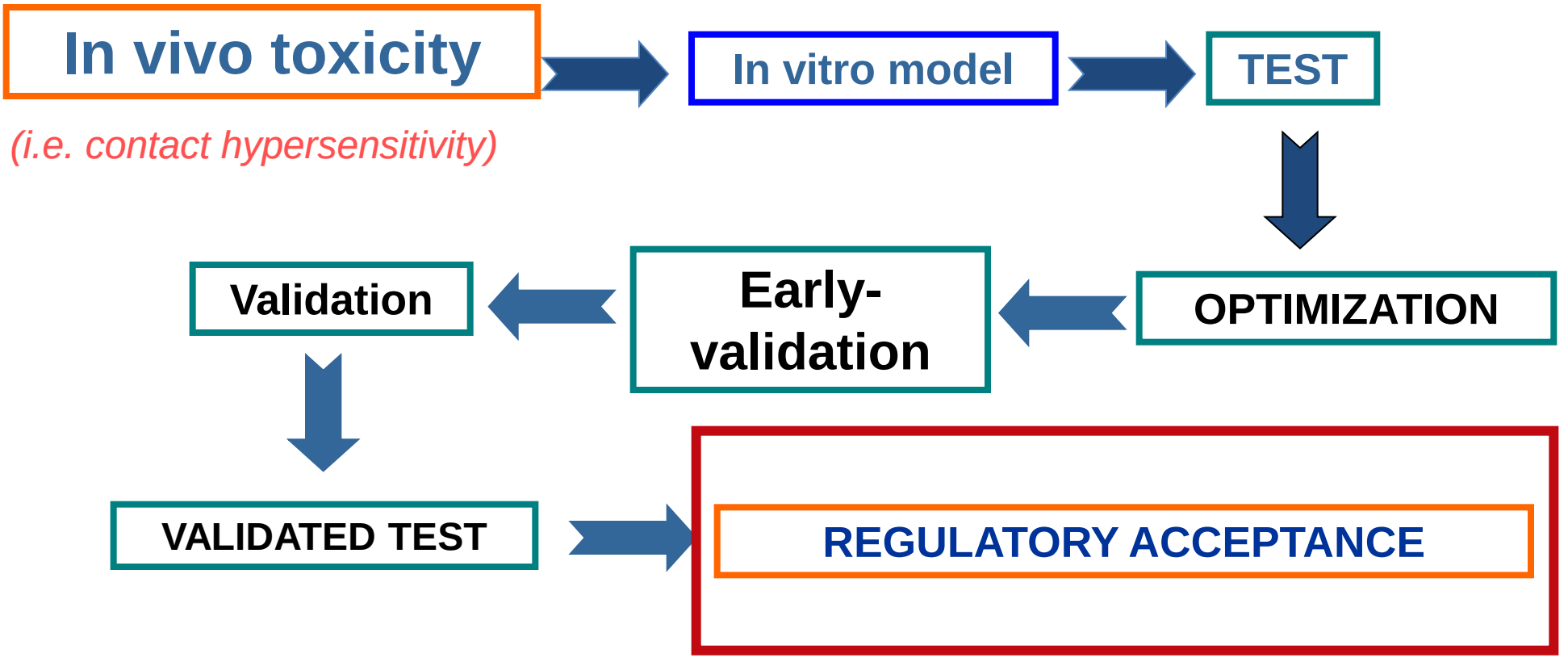
Toolbox of non-animal methods



VALIDATE METHODS AND OECD

- DPRA (OECD TG442C)
- Keratinosens (OECD TG442D)
- hCLAT (OECD approved)
- IL-8 Luc Assay (draft)
- Lusens (draft)

Development of alternative in vitro test



WHAT WE HAVE ACHIEVED AND WHAT WE NEED

- We have in vitro methods to support the discrimination between skin
- D
- T
safety assessment decisions

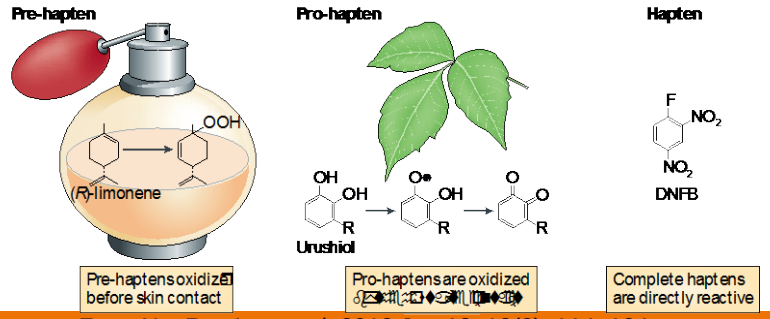
To achieve a complete replacement of animals in skin sensitisation assessment,

Currently validated methods are useful for hazard identification, classification and labelling.

IATA = Integrated Approaches to Testing and Assessment

ACD and gaps that remain to be filled

- Several in vitro methods to assess contact hypersensitivity are available.
- Five methods have been successfully validated.
- **GAPs:** bioavailability information (extrapolation of in vitro concentration to in vivo dose), applicability domains (solubility, metabolism, chemistry, respiratory allergens, mixtures, biologicals), potency.
- The identification of the mechanisms influencing the vigor of T cell responses, that can explain the strength of contact hypersensitivity reactions to weak, moderate, strong, and extreme sensitizers is a challenge still to be solved.



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CHEMICAL ALLERGY

A reduction of allergic contact dermatitis (ACD) can be achieved by:

- correct detection of skin sensitizers;
- characterization of potency;
- understanding of human skin exposure;
- application of adequate risk assessment and management strategies.

CONCLUSIONS

How to make contact allergy history:

- by improved risk assessment
- better education of risk assessors
- better education of consumers on the proper use of products
- better marketing surveillance by authorities to control proper product safety evaluation

THANK YOU FOR YOUR ATTENTION

QUESTIONS?

QRA is based on

1. Hazard identification: Determination of the No Expected Induction Sensitization Level (**NESIL**)
2. Application of Sensitization Assessment Factors (**SAF** 10-1000)
3. Determination of the Acceptable Exposure Level (AEL): **AEL = NESIL/SAF**
4. Determination of Consumer Exposure Level (**CEL**)
5. Acceptable Risk: **AEL≥CEL** or **AEL/CEL ratio ≥ 1**
6. **Risk management** (e.g. allergy warning labels)