The state of safety science

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The Author and the Institute

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- Member of SCCS (Scientific Committee for Consumer Safety) of the EU since 2000
- Member of Cosmetics Committee at BfR
- Member of Plastics Committee at BfR
- Member of Working Group Textiles at BfR

Federal Institute for Risk Assessment (BfR)

Tasks: “Identifying risks - protecting health”

1. Assessment of existing risks
2. Identification of new risks
3. Recommendations on risk reduction
4. Risk communication

SCCS Scientific Committee on Consumer Safety

- 76/768/EEC Cosmetics Directive Article 8:

  SCC "Scientific Committee on Cosmetics",

  scientific advice to the EU Commission
- 1978 **SCC** established
- 1997 successor **SCCNFP**
- 2004 **SCCP**
- 2009 **SCCS** (Scientific Committee on Consumer Safety)

Evaluation of cosmetic ingredients

Cosmetics Regulation (EC) No. 1223/2009

Safety of cosmetic products

Article 3
A cosmetic product made available on the market shall be safe for human health when used under normal or reasonably foreseeable conditions of use

Elements of regulation

1. *Positive lists*
2. *Negative lists*
3. *Product labelling*
4. *Product dossier*
5. *Inventory*

The safety assessment of cosmetic products is based on the safety of the ingredients.

Risk assessment of cosmetic products

- Information on the ingredients
- Exposure to the product
- *In vitro* tests of the formulation
- Tests with probands
- Risk assessment in a safety report by a qualified responsible person, kept in a product information file

Task of manufacturer / distributor, controlled by member states‘ market surveillance authorities!

Ingredients: elements of risk assessment

1. Hazard assessment
2. Dose-response relationship
3. Exposure assessment
4. Risk characterisation

<u>Basis: Dossier of Industry</u>

- Specification (including contamination and stability)
- Toxicological data
- Human experience

<u>Formal requirements:</u> OECD-Guideline
GLP
SCCS Notes of Guidance
SCCS Opinions

Risk assessment of cosmetic ingredients: Notes of Guidance *SCCS/1501/12*

1. Mutagenicity / carcinogenicity

- **Genotoxicity**
- (Carcinogenicity)

2. Percutaneous absorption

3. Systemic toxicity

- Acute toxicity
- Subchronic toxicity
- Reprotoxicity
  - developmental
  - (reproductive)
- (Chronic toxicity)

3. Dermatotoxicity

- Skin and eye irritation
- **Skin sensitisation**
- Phototoxicity UV-filter (irritation, mutagenicity, sensitization)

4. **Toxicokinetics**

data not regularly provided

Exclusion of carcinogenic substances: testing genotoxicity / mutagenicity

Nota bene: *Use of CMR substances is prohibited in cosmetics.*

Base set, 3 *in vitro* tests

1. Testing for gene mutation potential with bacteria
2. Testing gene mutation potential with mammalian cells
3. *In vitro* micronucleus test or chromosome aberrations

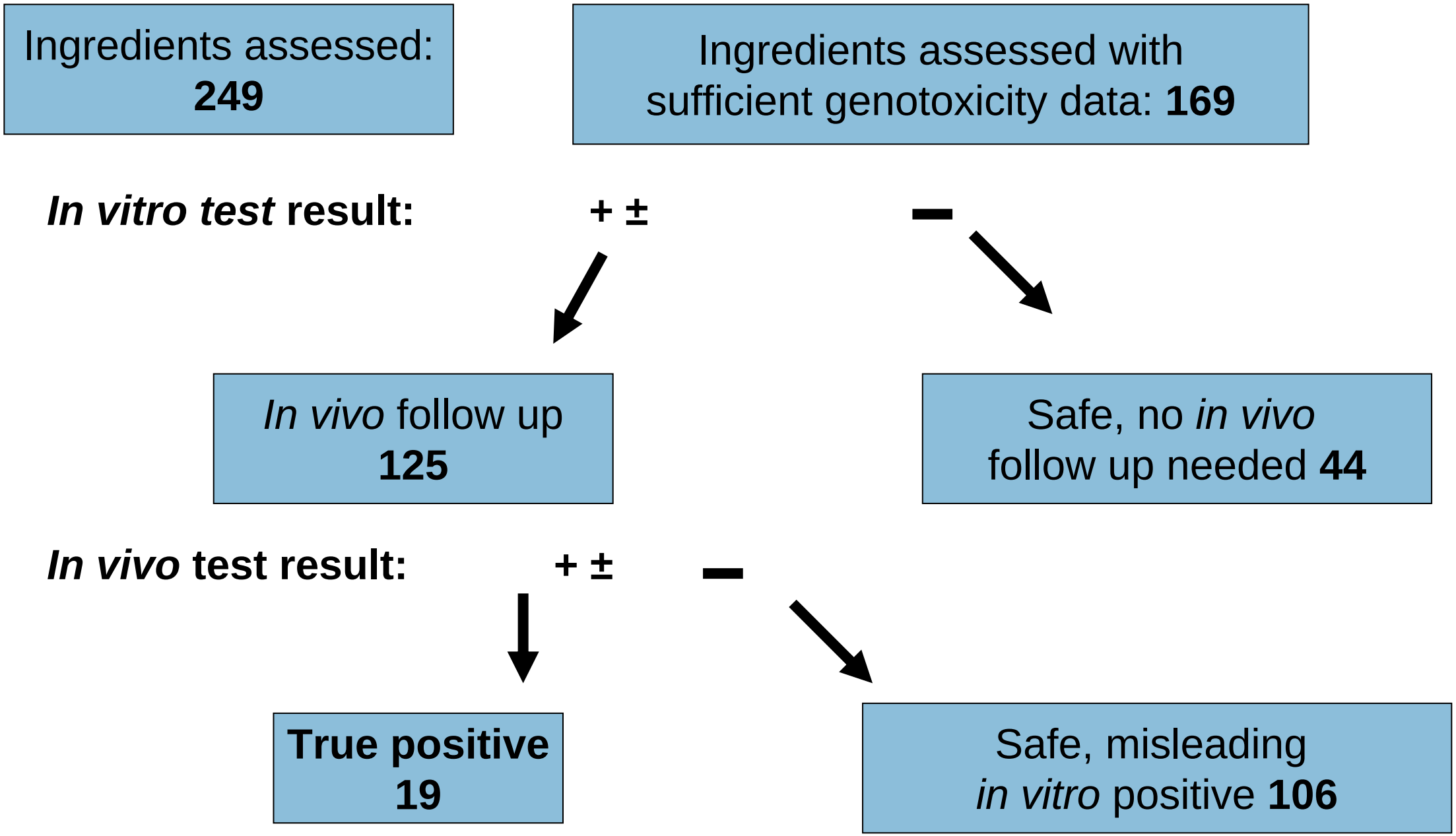
In the case of positive results further tests (in vivo) necessary

In vivo tests

UDS-Test
Micronucleus test
Chromosome aberrations
COMET-Assay

Genotoxicity testing without animals?

- **Retrospective analysis of SCCS assessments 2000-2012 (V. Rogiers)**



Genotoxicity testing without animals

Options to reduce misleading positives were proposed:

ECVAM 2006, 2013, BfR 2010, EFSA 2011, SCCS 2013

- Reduction of the number of base tests
- Optimisation of test methods
  (cell lines, top concentration, toxicity)
- Overruling Ames-positives *in vitro*
- Development of new methods (COMET, skin models,
  HET-MN test)

- ***From todays experience derogations from the animal testing ban are needed.***

- ***Alternatively, a higher level of uncertainty may be accepted.***

Skin sensitisation and contact allergy

- So far there are no regulatory accepted non-animal approaches for skin sensitisation (EURL ECVAM 2013).

- Sensitisation is triggered by complex mechanisms and various steps are involved: a single *in vitro* method may not be able to assess this endpoint.

- An integrated testing strategy is needed adressing 3 key events:
  - Covalent binding to protein
  - Keratinocyte inflammatory response
  - Activation of dendritic cells.

- Predictivity is promising when combining methods.

- Problems: skin barrier, metabolism and potency not covered.

- *In silico* models are not sufficiently accurate to predict sensitisation

Systemic (organ) toxicity, risk assessment of ingredients

1. **Hazard:** (Evidence: Human data > *in vivo* > *in vitro* > *in silico*)

2. **Dose response:** No Observed Adverse Effect Level (**NOAEL** from an animal study)

3. **Exposure:** Systemic Exposure Dose (**SED** from an *in vitro* dermal absorption study)

4. **Risk characterisation:** Margin of Safety (**MoS = NOAEL / SED**)

If MoS > 100 the substance is considered safe

Systemic (organ) toxicity and NOAEL

- Many cosmetic ingredients are considerably dermally absorbed, that means: systemic exposure dose (SED) is not negligible.
- In these cases the safety is to be assessed by MoS calculation (see REGULATION (EC) No 1223/2009 *ANNEX I* COSMETIC PRODUCT SAFETY REPORT. 8. Toxicological profile of the substances)

  All significant toxicological routes of absorption shall be considered as well as the systemic effects and margin of safety (MoS) based on a no observed adverse effects level (NOAEL) shall be calculated. The absence of these considerations shall be duly justified.

- No test methods have been submitted to EURL ECVAM for repeated dose toxicity testing. Considering the scientific challenges for the development of alternatives in this area, no methods are expected within the short and mid-term and consequently no validation studies are planned for the moment (EURL ECVAM 2013).

Further aspects

- There is a broad agreement in the society as well as in the scientific community to implement the 3R strategy refinement, reduction and *replacement* in hazard assessment.
- Validated *replacement* alternatives are available yet for several hazards: skin and eye irritation, phototoxicity, dermal absorption, genotoxicity, carcinogenicity and embryotoxicity
- In contrast to hazard, risk is a quantitative term and this has to be addressed also by alternative methods.
- By use of the TTC approach an exposure dose with low concern of systemic toxicity can be set dependent on the structure. For non-oral exposures an internal TTC has to be defined.
- Predictive toxicology without using animals needs a mechanistic understanding of the toxic events (adverse outcome pathway) in order to develop alternative tools. To date, there is only limited regulatory acceptance of the available methods.

Conclusion

- Safety science is developing fast. However, it is a long way to a safety science without using animals.
- Modern technologies (e.g. computational toxicology, “omics”, integrated test strategies) are being developed (e.g. SEURAT, Tox21). However, the predictivity and reliability of these alternative methods has to be ensured.
- The SCCS takes responsibility of cosmetic ingredients safety for the consumer. As long as animal free methodology is incomplete the use of animal data is still needed.
- Relevant toxicological data may be generated elsewhere, e.g. with REACH. The SCCS needs full access to the respective studies for its own sound and independent assessment.

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Safety assessment without animals:

The challenge is to ensure both consumer safety and innovation

Thank you for your attention

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References

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Bauch et al. (2011) Intralaboratory validation of four in vitro assays for the prediction of the skin sensitizing potential of chemicals

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EFSA (2011) Scientific opinion on genotoxicity testing strategies applicable to food and feed safety assessment

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Kirkland et al. (2007) In vitro approaches to develop weight of evidence (WoE) and mode of action (MoA) discussions with positive in vitro genotoxicity results

Mehling et al. (2012) Non-animal test methods for predicting skin sensitization potentials

SCCS/1517/13 Memorandum on Scientific Evaluations and Opinions to be adopted by the SCCS

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SEURAT-1

Paracelsus (1493-1541):
"The dose makes the poison"

Towards the Replacement of *in vivo* Repeated Dose Systemic Toxicity Testing

Toxicology in the 21st century:
Mechanism-driven Toxicology
defines the safe dose

Volume 3
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