The Use of NAMs in Regulatory Assessments of Cosmetics Safety

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The views expressed in this presentation are not those of the SCCS

Cosmetics Safety

- Consumers buy and use cosmetics with a trust that they are safe.
- Cosmetics are used frequently and repeatedly in intimate contact with the body by vast majority of the population;
- Several cosmetic product types may be used in a day, and everyday:
  - oral-care (e.g. toothpaste, mouthwash)
  - skin-care (e.g. creams and lotions, cleansers, toners, moisturisers)
  - hair-care (e.g. shampoos/conditioners, hair dyes, hair sprays), etc.
  - make-up (e.g. foundations mascara, lipstick)
  - deodorant/antiperspirant, perfumes, fragrances …..
- Sub-standard cosmetics can harm consumer's health - ensuring safety is therefore of paramount importance.

The EU Regulatory Framework for Cosmetic Safety

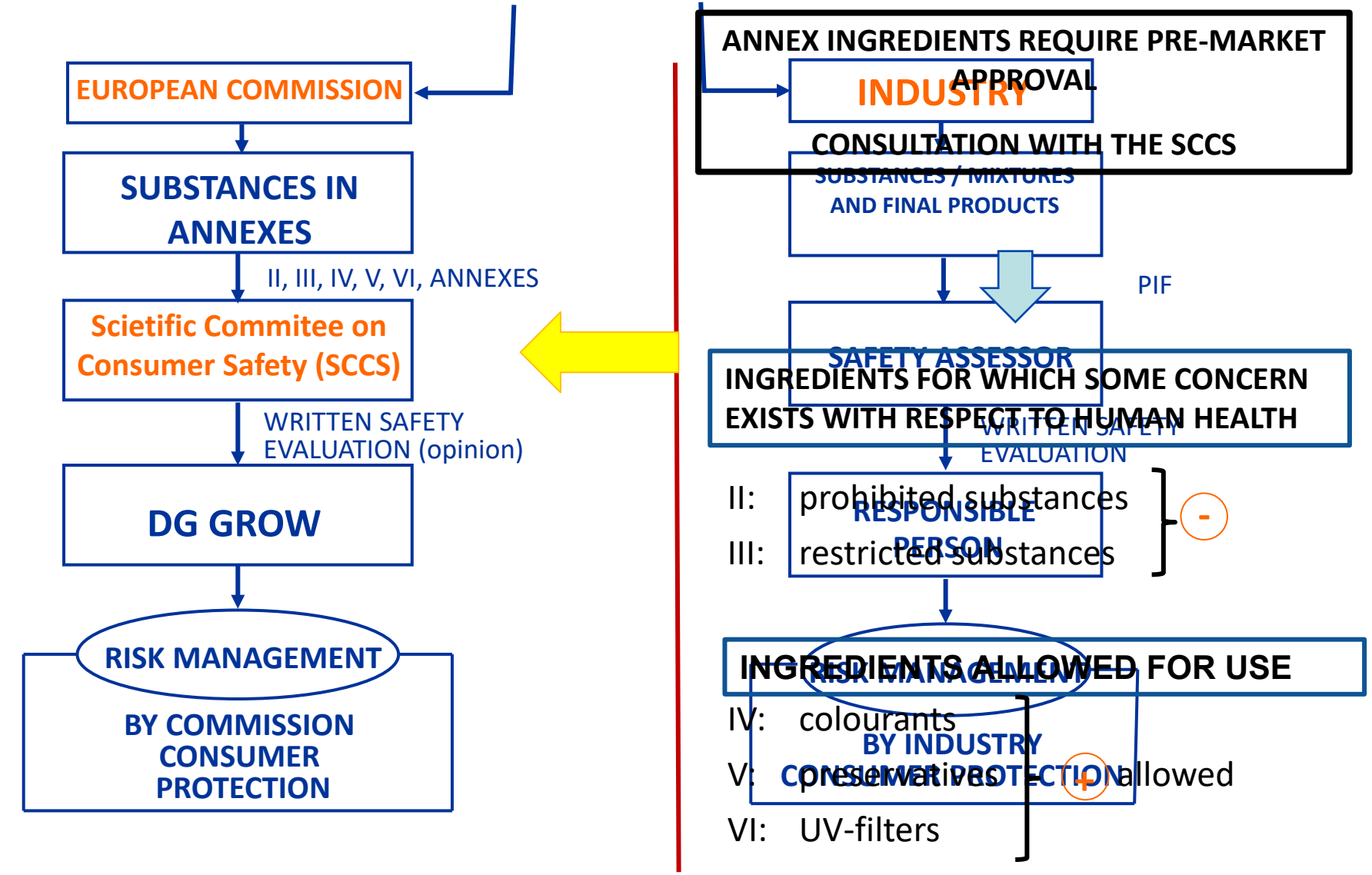
THE EUROPEAN COSMETICS REGULATION
Regulation (EC) No 1223/2009 of the European Parliament

- Cosmetics legislation requires that every cosmetic product placed on the market in Europe is SAFE to use.
- The manufacturer must ensure that cosmetic products undergo an expert scientific safety assessment before they are launched for sale.
- Safety is based on safe ingredients, and needs to be assessed on the basis of scientific evidence.

SAFETY EVALUATION

Authorisation

TWIN TRACK SYSTEM FOR EVALUATION OF SAFETY IN THE EU



Safety Assessment of Cosmetics in Europe

- An independent committee of experts (the SCCS) carries out risk assessment to advise the EC on the safety of cosmetic ingredients;
- The ingredients are then placed by the EC in one of the Annexes (i.e. banned, allowed, or allowed with restrictions);
- Hazard a cosmetic ingredient is assessed in a similar way to other regulations, but exposure from cosmetics is mainly through the dermal route;
- Some products may also give exposure through oral (toothpaste, mouthwash), or inhalation (sprays, aerosols).

Physicochemical properties

- Chemical identity
- Purity/impurity profile
- UV/Vis spectra
- Solubility (water/solvents)
- Melting/ freezing / boiling points
- Relative density
- Vapour pressure
- Surface tension
- Partition coefficient
- Flash point
- Flammability
- Self-ignition temperature
- Oxidising properties
- Granulometry

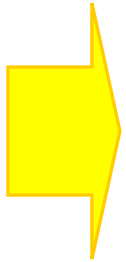
Exposure

- External Exposure
- Internal (systemic) exposure
  - Type of application (skin, oral, respiratory)
  - Concentration of the ingredient
  - Amount of the product used
  - Frequency of use
  - User groups

Toxicity

- Acute toxicity
- Skin and eye irritation/ corrosion, respiratory irritation
- Skin and respiratory sensitisation
- Repeated dose toxicity
- Reproductive and developmental toxicity
- Mutagenicity and carcinogenicity
- Other endpoints of special concern (phototoxicity, endocrine activity, etc)

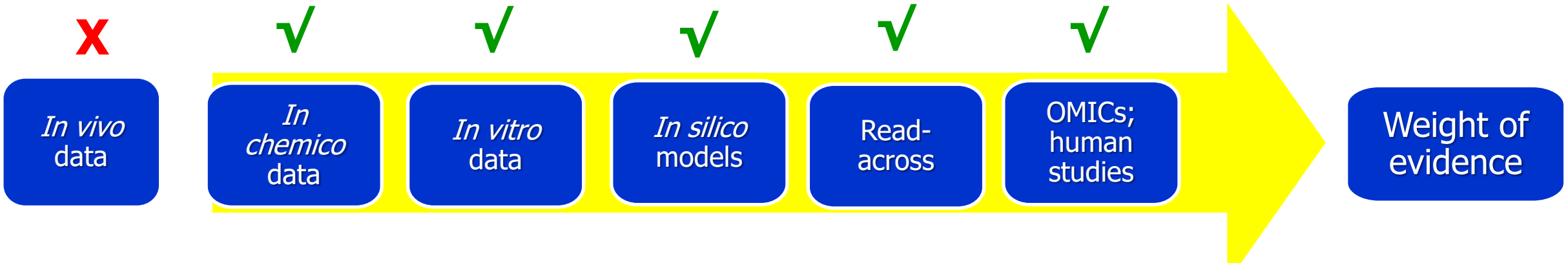
Substances of special Concern



- Carcinogenic, Mutagenic, Reproductive toxins (CMRs)
- Traces of prohibited substances
- Nanomaterials
- Endocrine disrupting substances

Safety Assessment of Cosmetics in the EU

- Safety assessment of cosmetics has historically been based on data from validated animal tests;
- From 11 March 2013, the EU Cosmetic Regulation has completely banned animal testing of cosmetic ingredients/products, and marketing of cosmetic ingredients/products tested on animals in Europe;
- New safety data for cosmetic ingredients needs to be derived from non-animal methods, with choices limited to **1R** (Replacement);

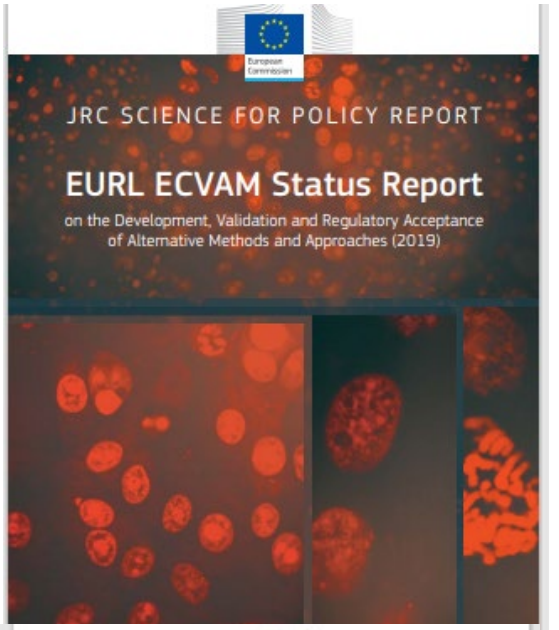


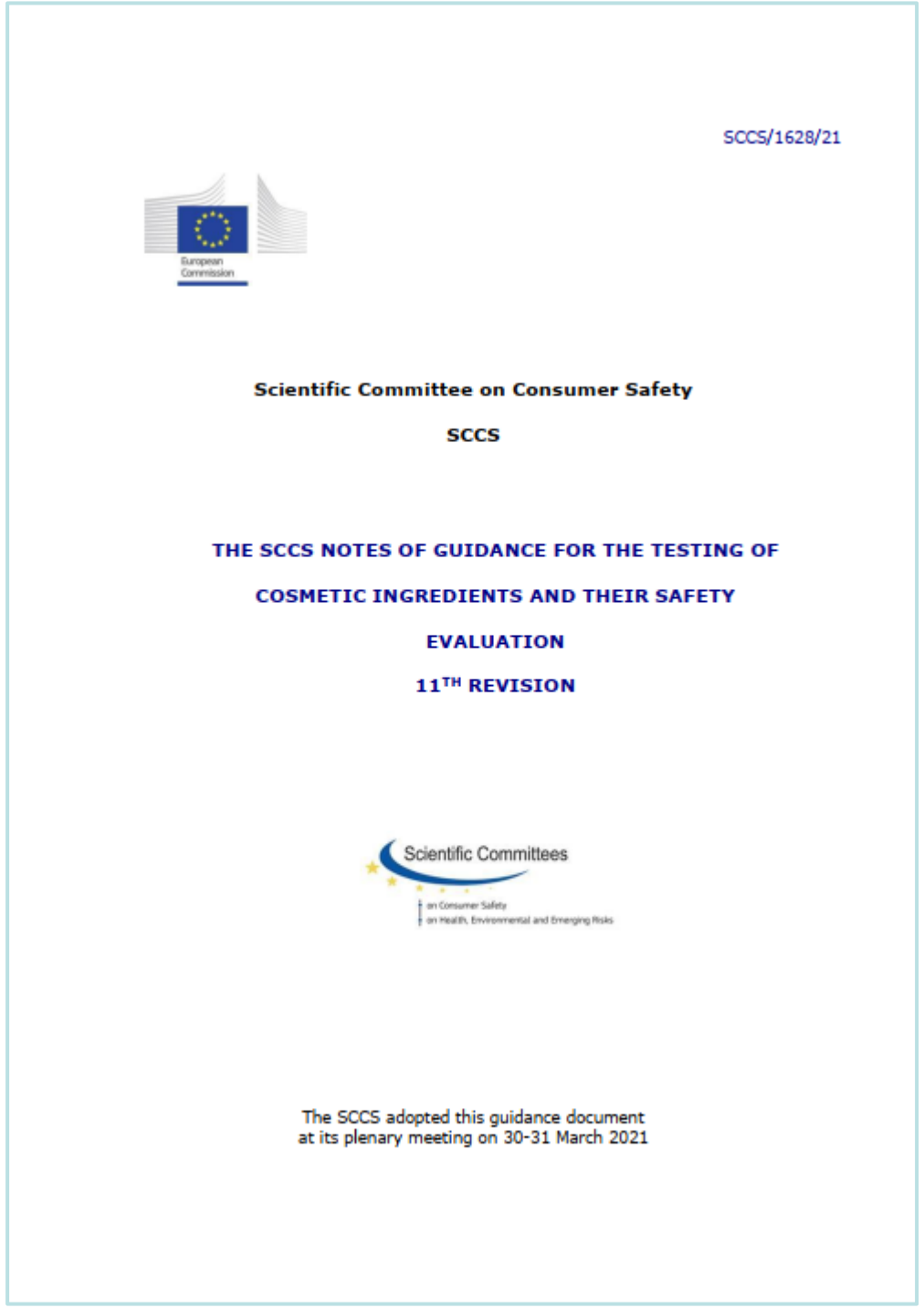
Limited Possibilities for the Use of Animal Data

- Applicants can only use data from animal studies to support safety of a cosmetic ingredient – if the tests had been carried out:
  - before 11 March 2013, or
  - to meet requirements under a different (non-cosmetic) regulatory framework (e.g. REACH);
- When developing an opinion, the SCCS can still use data from animal studies - even if carried out after the testing ban - if there is an indication of potential adverse effects on consumer's health.

Summary: *In Vitro* NAMs

- Only officially VALIDATED methods are accepted for use in regulatory risk assessments.
- Other methods may also be accepted, provided that they are demonstrated to be SCIENTIFCALLY-VALID.
- A number of validated in vitro tests are available (up-to-date information in the EURL ECVAM Status Reports).
- The use of a combination of in vitro tests in a testing strategy is generally more conclusive.
- Test results need to be used in a weight of evidence with all available data.



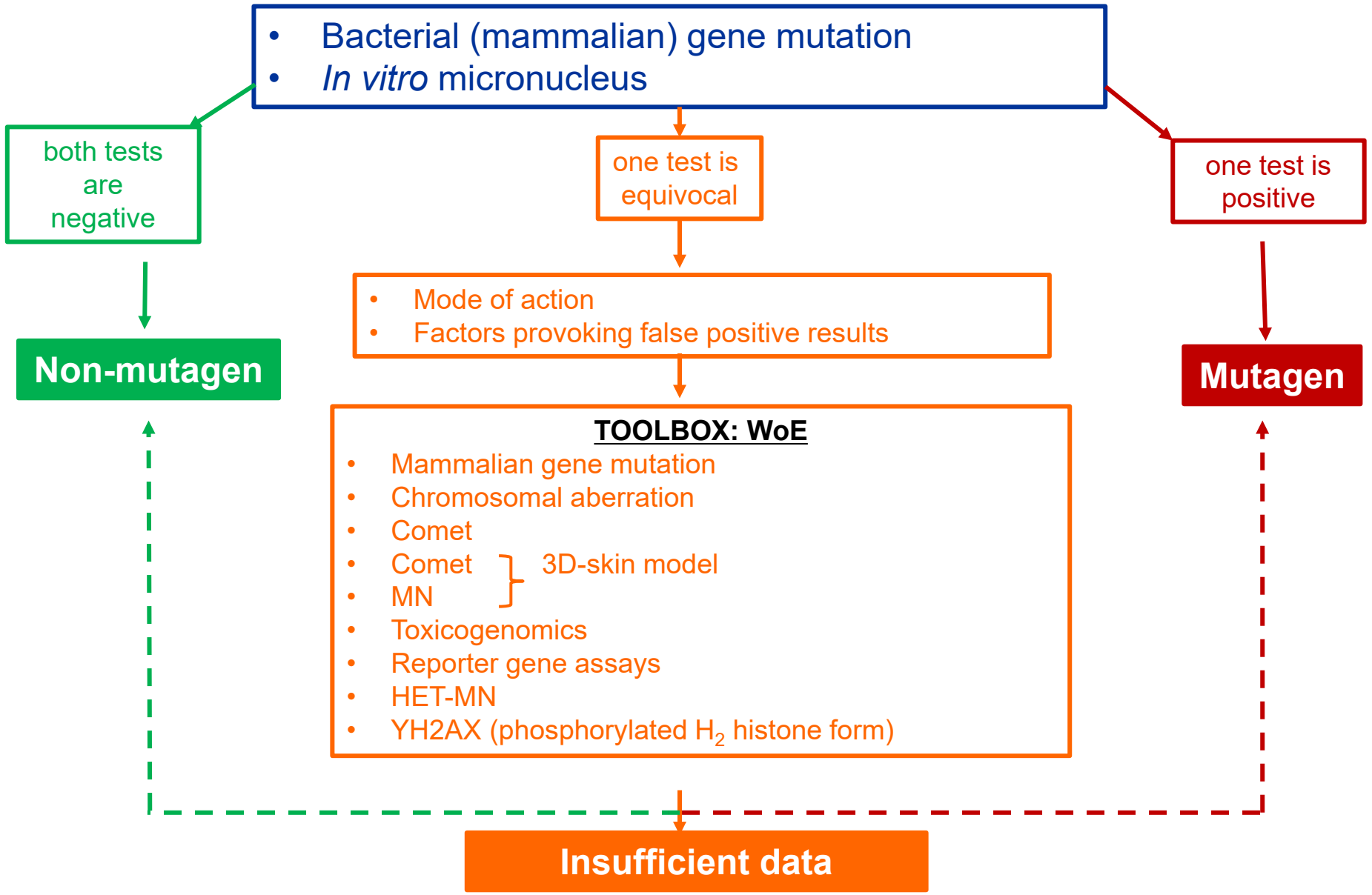


- **In chemico assessment:** physicochemical data
- **In silico modelling**: QSAR modelling and read-across – e.g. on genotoxicity/ mutagenicity
- **In vitro data**: e.g. skin irritation (Episkin); eye irritation (BCOP, HET-CAM, Epi Ocular, Neutral Red release test); phototoxicity (absorption spectrum and 3T3 NRUPT.
- **Toxicokinetics**: e.g. dermal absorption, frozen dermatomed human/pig skin
- **Oral absorption** (Caco-2 cells)
- **Genotoxicity/mutagenicity**: e.g. bacterial gene mutation test; in vitro micronucleus test in cultured human lymphocytes (mammalian cell gene mutation test in mouse lymphocytes)
- **Carcinogenicity**: e.g. cell transformation assay in Syrian Hamster cells (SHE assay)
- **TTC**: e.g. treshold of toxicological concern for fragrance ingredients

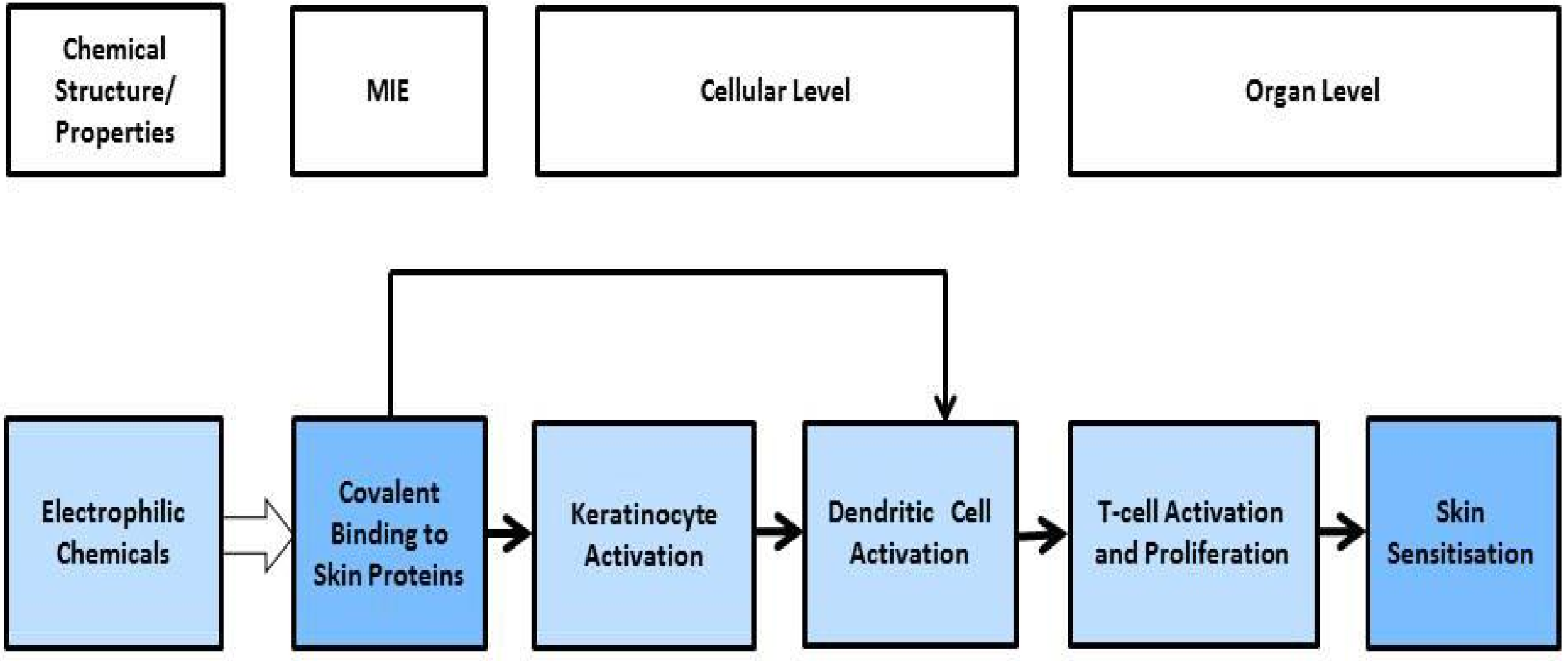
Available NAMs

Toxicological endpoint	*In silico* models/ read-across	Validated *in vitro* tests
Acute Toxicity	☑	☑
Skin corrosion/irritation	☑	☑
Skin sensitisation	☑	☑
Phototoxicity	☑	☑
Toxicokinetics	☑	☑A ☒DME
Repeated dose toxicity/ chronic toxicity	☑	☒
Reproductive & developmental toxicity	☑	☒
Mutagenicity/genotoxicity	☑	☑
Carcinogenicity	☑	☒ CTA
Endocrine activity	☑	☑EA ☒ED

TOOLBOX STRATEGY FOR GENOTOXICITY

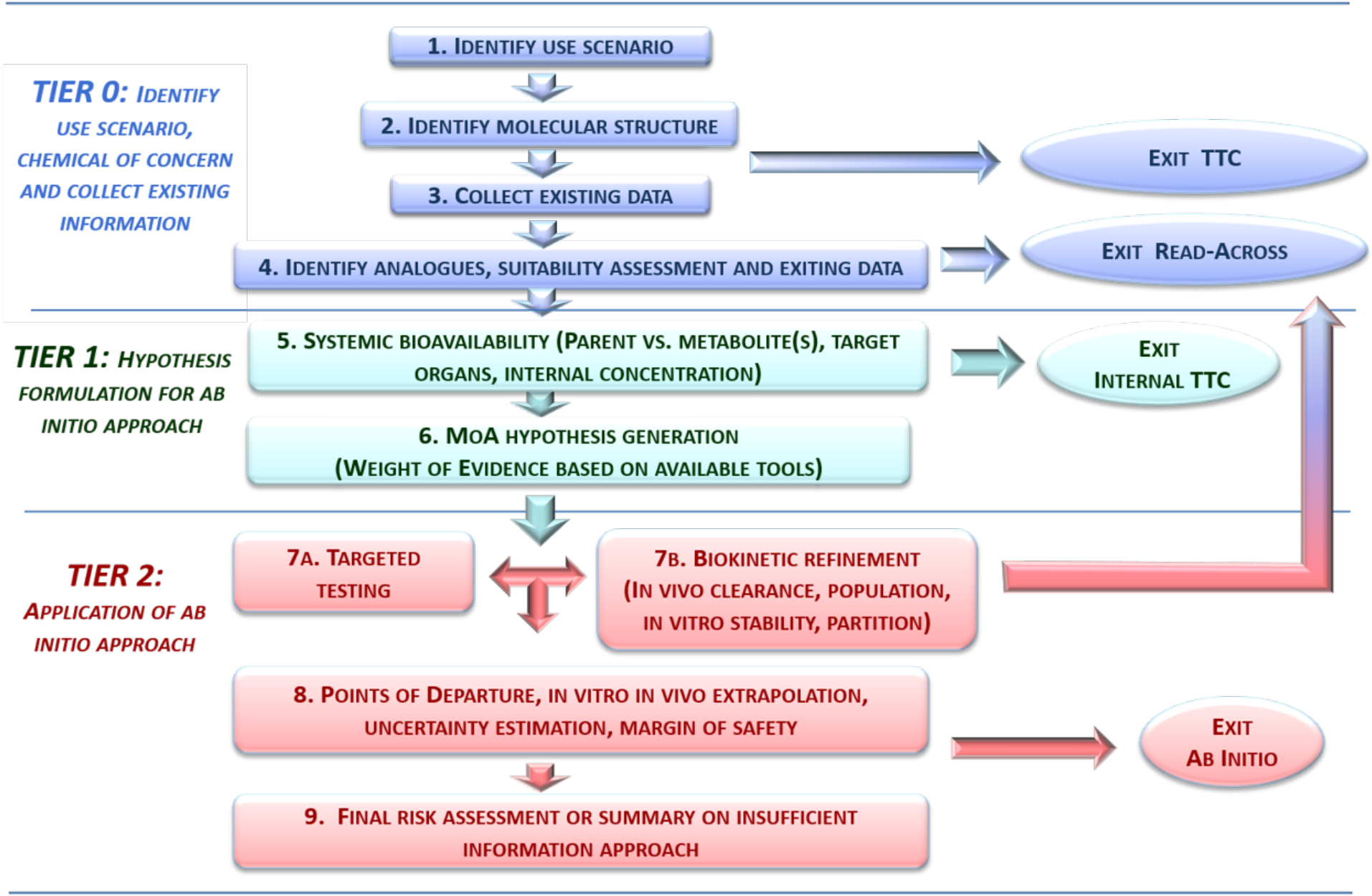


AOP: Covalent Protein Binding leading to Skin Sensitisation



NAMs for Assessment of Skin Sensitisation

AOP KE covered	OECD TGs/ EU test method	Test method
MIE (KE1): covalent binding to skin proteins	OECD 442C (2020) / EC B.59 In chemico skin sensitisation	Direct Peptide Reactivity Assay (DPRA) Amino acid derivative reactivity assay (ADRA)
KE2: keratinocyte activation	OECD 442D (2018) / EC B.60 In vitro Skin Sensitisation Assays addressing the KE on keratinocyte activation	ARE-Nrf2 Luciferase KeratinoSens™ Test Method The ARE-Nrf2 luciferase LuSens test method
KE3: dendritic cell activation	OECD 442E (2018) / EC B.72 In vitro Skin Sensitisation Assays addressing the KE on activation of dendritic cells.	Human Cell Line Activation test (h-CLAT) U937 Cell line Activation Test (U-SENS™) Interleukin-8 Reporter Gene Assay (IL8-Luc assay)



Proposed framework for New Generation Risk Assessment (NGRA)
(adopted from Berggren *et al.*,2017 and Dent *et al.*, 2018

Use of NAMs in SCCS Assessments

- **<u>In chemico</u>:** used in all cases

- **<u>In silico</u>:** limited use so far
  - derivatives of p-phenylene diamine hair dyes (methoxy-methyl and hydroxy-propyl) read across data for genotoxicity/mutagenicity
  - for fertility study of salicylic acid: read across data from studies on methyl- and acetylsalicylate

- **<u>In vitro</u>:** used in virtually all cases

  For local toxicity
  - skin irritation (*e.g. Episkin®)*
  - eye irritation: BCOP, HET-CAM, Epi Ocular, Neutral Red release

  For sensitisation
  - phototoxicity: absorption spectrum & 3T3 NRUPT

Use of NAMs in SCCS Assessments

- Toxicokinetics: - dermal absorption - frozen dermatomed human/pig skin
  - oral absorption - Caco-2 model of gut epithelium (not validated)
- Genotoxicity/mutagenicity:
  - bacterial gene mutation test
  - *in vitro* MN test in cultured human lymphocytes
  - folow up mammalian cell gene mutation test in mouse lymphocytes to resolve any doubts.
- Carcinogenicity:
  - cell transformation assay in Syrian Hamster Embryo cells (SHE)
- TTC (Treshold of Toxicological Concern);
  - use for impurities so far (non-carcinogenic and carcinogenic)

Summary

- The EU regulatory ban on animal testing has posed a challenge to risk assessment of cosmetics – limiting the options for methods to only 1R (Replacement);
- Therefore, increasing reliance on NAMs - validated as well as scientifically-valid methods;
- Currently available NAMs mostly cover local endpoints, but progress is being made for some systemic endpoints.
- Frameworks are also being developed for incorporating NAMs in the form of weight of evidence for risk assessment;
- Most dossiers evaluated by the SCCS so far have relied on the use of historic animal data. However, data from NAMs has started to increasingly appear in more recent dossiers.

Thank you for your attention