HOW ARE HUMAN HEALTH SYSTEMIC EFFECTS COVERED WHEN ANIMAL TESTING IS NOT ALLOWED?

A Perspective from the Scientific Committee on Consumer Safety (SCCS)

Prof. Qasim Chaudhry
University of Chester, UK
Chair of the SCCS

The Scientific Committee on Consumer Safety

Independent Committee of the Commission:

- scientific advice on the safety of non-food consumer products (cosmetics, personal-care products, textiles, toys…..)
- broad expertise (chemistry, toxicology, medicine, dermatology, exposure assessment, risk assessment, NAMs…..)
- transparent, evidence-based, free access, stakeholders' views
- detailed guidance
- stringent safety oversight

- safety of the EU consumer
- credibility boost for the EU cosmetics for safety & reliability

Safe Ingredients for Safe Products

European Commission

Quantitative Risk Assessment, not hazard-based classification or categorisation

Physicochemical nature, toxicological hazard, consumer exposure

Likelihood of harmful effects at the intended level of use in consumer products

→ CALCULATION OF SAFE USE LEVEL

- The Cosmetic Regulation (EC) No 1223/2009 is the first EU regulatory framework to have completely banned animal testing & marketing of cosmetic products tested on animals since March 2013, **making the use of NAMs imperative**;
- Data from animal studies can still be used to support safety of a cosmetic ingredient, if the tests had been carried out before 11 March 2013, or to meet requirements of a different (non-cosmetic) regulation;

SCCS' Experience with NAMs

'Validated' vs 'Valid'

- Generally, data are only accepted from validated NAMs carried out in accordance with the OECD Guidelines, but the SCCS also considers well documented scientifically-justified methods that may not have been officially validated yet on a case-by-case basis;
- The SCCS Notes of Guidance give a detailed view on each available NAM (including those that are under various stages of development/validation);
- A single NAM is unlikely to provide sufficient evidence for safety assessment – a combination of NAMs is generally necessary;
- A structured framework is essential for putting together the data from different NAMs;
- The key point of interest for the SCCS is how NAMs data are put together for use in risk assessment.

Available NAMs

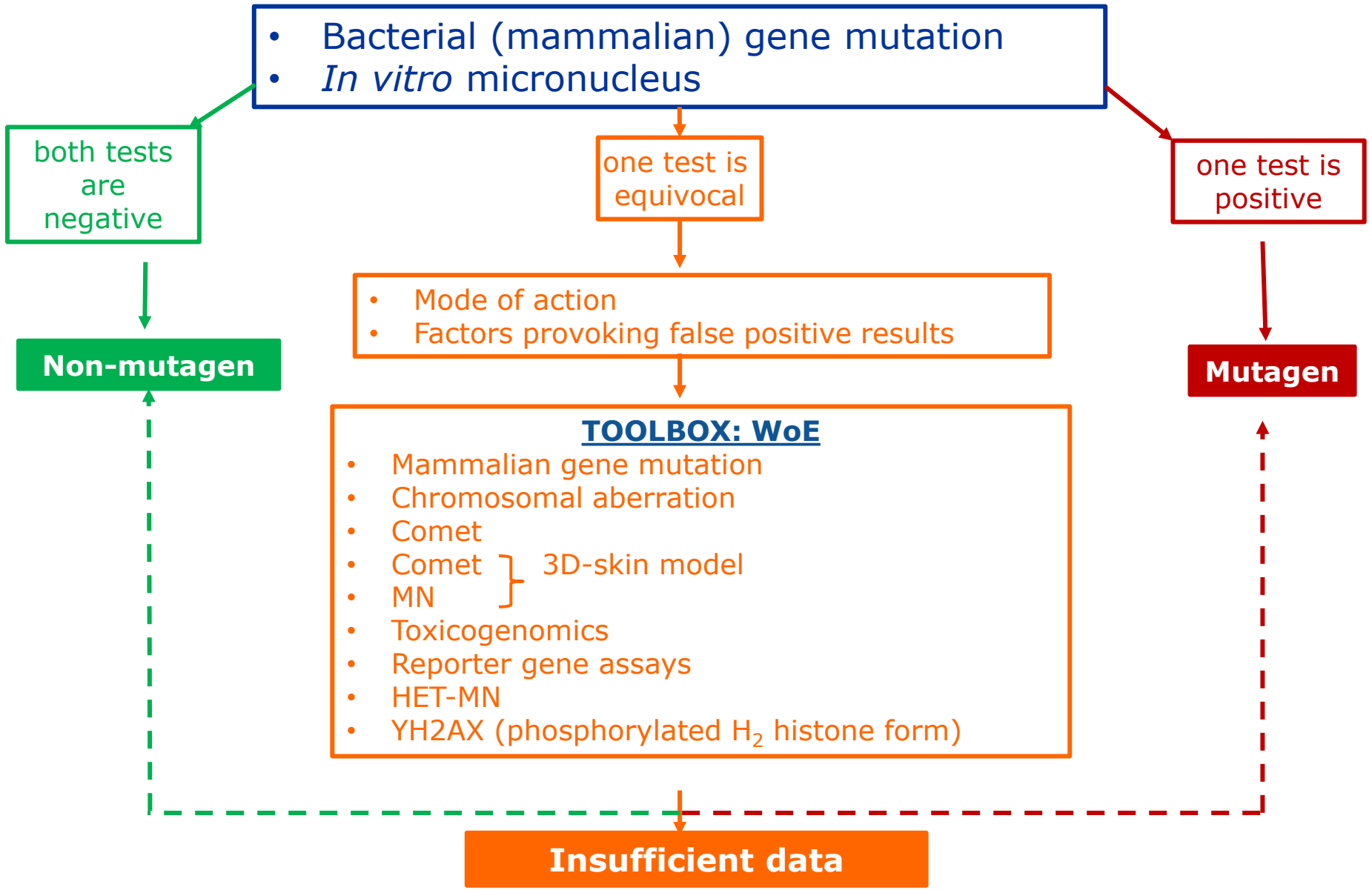
Toxicological endpoint	*In silico* models/ read-across	Validated *in vitro* tests
Acute Toxicity	☑	☑
Skin corrosion/irritation	☑	☑
Skin sensitisation	☑	☑
Phototoxicity	☑	☑
Toxicokinetics	☑	☑A ☒DME
Repeated dose toxicity/ chronic toxicity	☑	☒
Reproductive & developmental toxicity	☑	☒
Mutagenicity/genotoxicity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

Building a Credible Picture from Pieces of Evidence

Can NAMs data alone give a risk assessor the same level of confidence as the data from a traditional in vivo test?

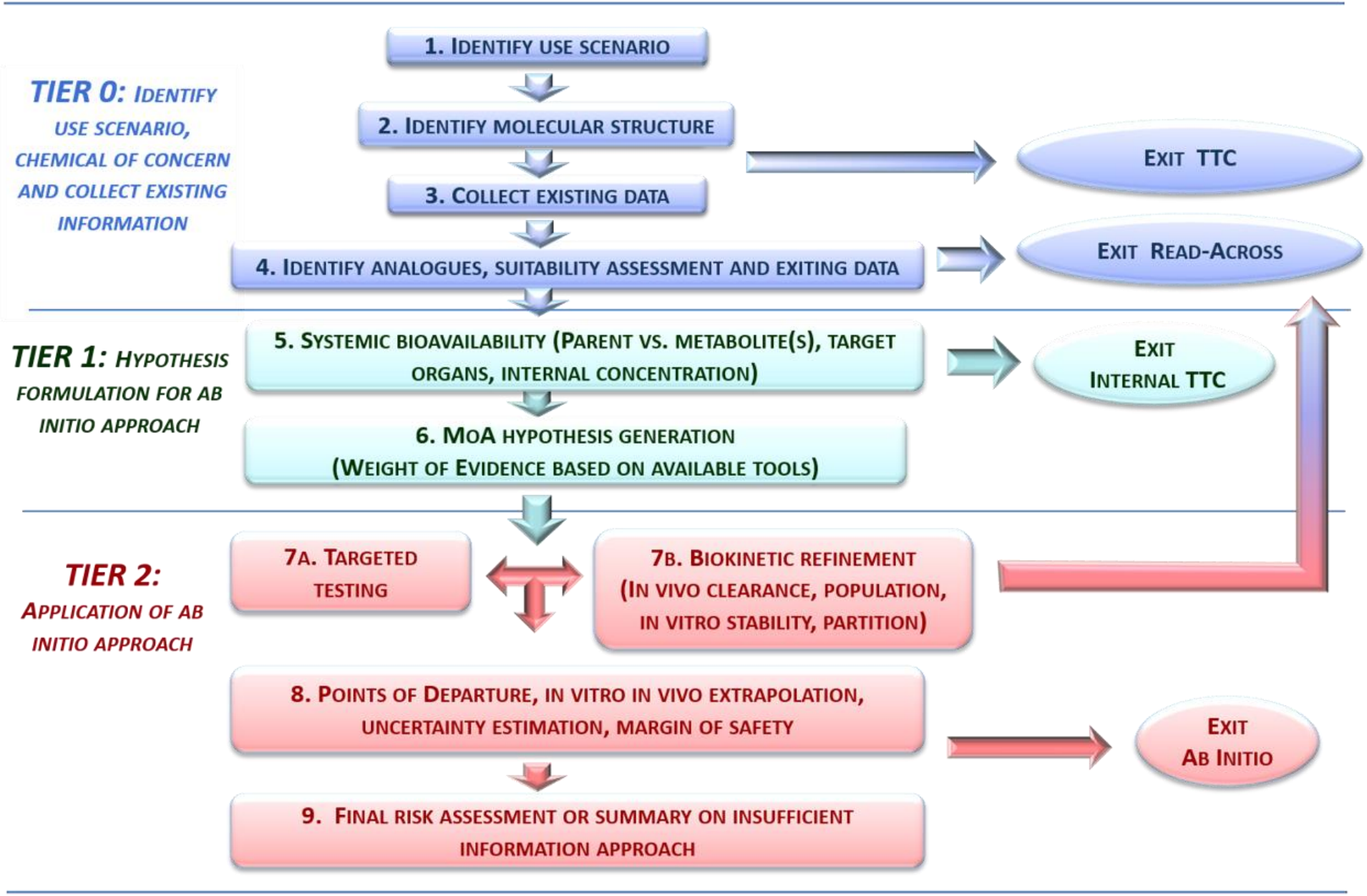
- The answer seems to have gradually moved over the years from 'unlikely' to 'may be' to 'potentially' and 'yes' for some endpoints, such as:
  - skin irritation/corrosion, skin sensitisation, phototoxicity, mutagenicity/genotoxicity, endocrine activity, 'A' of ADME, and partially for acute toxicity and carcinogenicity.
  - more complex endpoints are still a difficult challenge, such as sub-chronic/chronic repeated dose toxicity, reproductive/developmental toxicity, non-genotoxic carcinogenicity, endocrine disruption.

A TOOLBOX STRATEGY FOR GENOTOXICITY



Building a Credible Picture from Pieces of Evidence

- A few structured frameworks exist (such as Defined Approaches for skin sensitisation) – but generally limited to where MoA and key molecular events are known;
- *In silico* models and read-across are very useful when conducted properly and used in conjunction with other sources of data in a weight of evidence. However, unlike validated *in vitro* methods, they do not carry an 'official' validation tag.
- A few reliable *in silico* platforms are available for reliable prediction of chemical toxicity, but a harmonised framework for their selection, use, and interpretation of results is lagging behind;
- The SCCS is also watching the developments of new ideas under NGRA, which proposes risk assessment based on *ab initio* approach that combines *in silico* modelling/ read-across, MoA, systemic bioavailability/ biokinetics, targeted *in vitro* testing, and the plausibility for manifestation of toxicological effects through in vitro/in vivo extrapolation.



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

Other Ideas under Development

- 3D in vitro cellular/organoid models (skin, GIT, lung, liver);
- Skin Sensitisation Quantitative Risk Assessment (QRA) - exposure-based approach to determine safe use levels of fragrance ingredients in different consumer products based on chemical, cellular, and molecular understanding of skin sensitisation;
- Inhalation threshold of toxicological concern (iTTC);
- Internal TTC – TCC approach applied to systemically available levels of a substance;

Summary

- The EU regulatory ban on animal testing has posed a real challenge to risk assessment of cosmetics – limiting the 3Rs options to only 1R (Replacement) – and heavy reliance on NAMs;
- Currently available NAMs mostly cover local endpoints. Gradual progress has been made on some systemic endpoints;
- Need for development and validation of structured frameworks for putting together data from different NAMs into weight of evidence for use in risk assessment;
- Discussion is needed on what sort of 'validation' is needed for NAMs acceptance for regulatory risk assessments.

Thank you for your attention