It is a NAMS world: Evaluating Personal Care Product Ingredient Safety without Animals

GETA of Northern California: Spring Symposium

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US and EU Regulatory Requirements for Safety Substantiation

US Regulatory Framework

- There is no pre-market approval by the US FDA on cosmetic products or ingredients.
- Safety substantiation is the **responsibility of the product manufacturer,** and has been since the enactment of the FD&C Act.
- In 2022 MoCRA (the modernization of cosmetics regulation act) provided the first update to the FD&C Act since 1938.
- With MoCRA, safety substantiation was addressed: A responsible person for a cosmetic product shall ensure, and maintain records supporting, that there **is adequate substantiation of safety of such cosmetic product**.
    - "adequate substantiation": tests, studies, research, etc…**considered among experts** sufficient to evaluate safety
    - "Safe": the product, including any ingredient thereof, is **not injurious** to users under prescribed conditions of use or under conditions that are customary or usual.

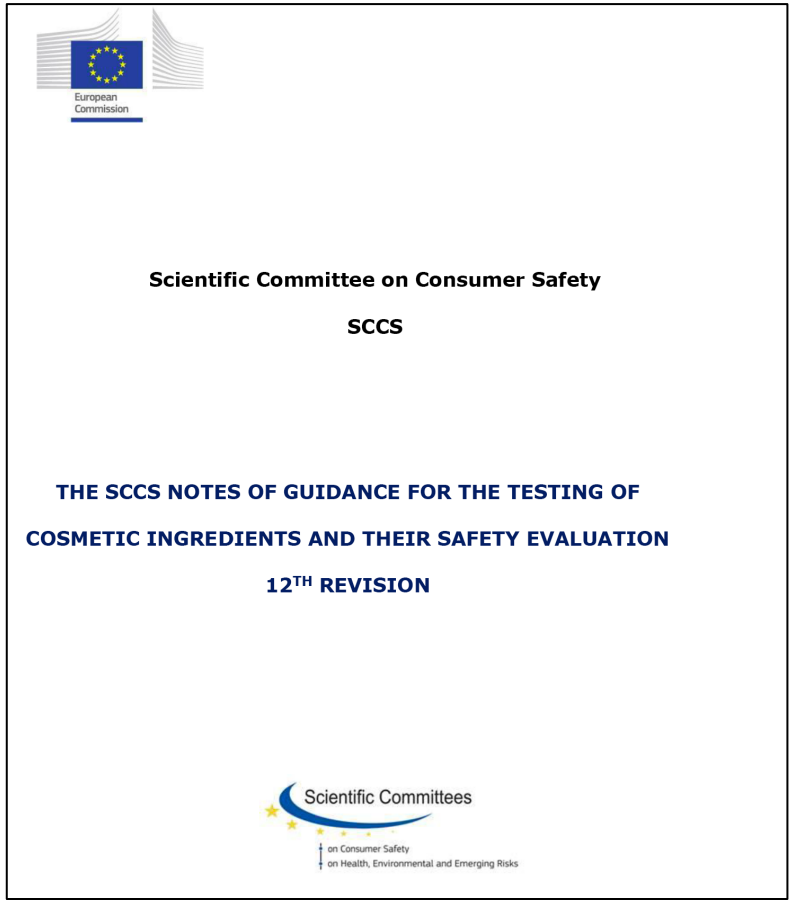
EU Regulatory Framework

- For consumers, regulation of cosmetics falls under the Cosmetics Regulation in the EU.
- Key provisions of this regulation:
    - The safety of finished cosmetic **products can be assessed based on the safety of ingredient they contain**.
    - To demonstrate safety, a cosmetics product safety report (CPSR), must be developed **prior to market**.
    - The CPSR must be done by "a person in possession of a diploma or other evidence of formal qualifications…"
    - The sections to be addressed in the CPSR are dictated in the directive. This includes a focus on **local toxicity** (i.e., irritation) skin sensitization, photo-induced toxicity. "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."

Best Practices for Cosmetic Ingredient Safety Assessment

Considering the US and EU:

- US has no government issued guidance at this time.
- The EU has the Scientific Committee on Consumer Safety Notes of Guidance, last updated in 2023.



A full toxicological profile is required for a proper safety assessment

Recall a CPSR must include: local toxicity (i.e., irritation) skin sensitization, photo-induced toxicity. “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.”

A safety assessor must consider and address the following:

- ✓ Skin irritation/corrosion
- ✓ Eye irritation/corrosion
- ✓ Skin sensitization
- ✓ Photo-induced toxicity
- ✓ Repeated dose toxicity
- ✓ Reproductive/development toxicity
- ✓ Mutagenicity
- ✓ Carcinogenicity

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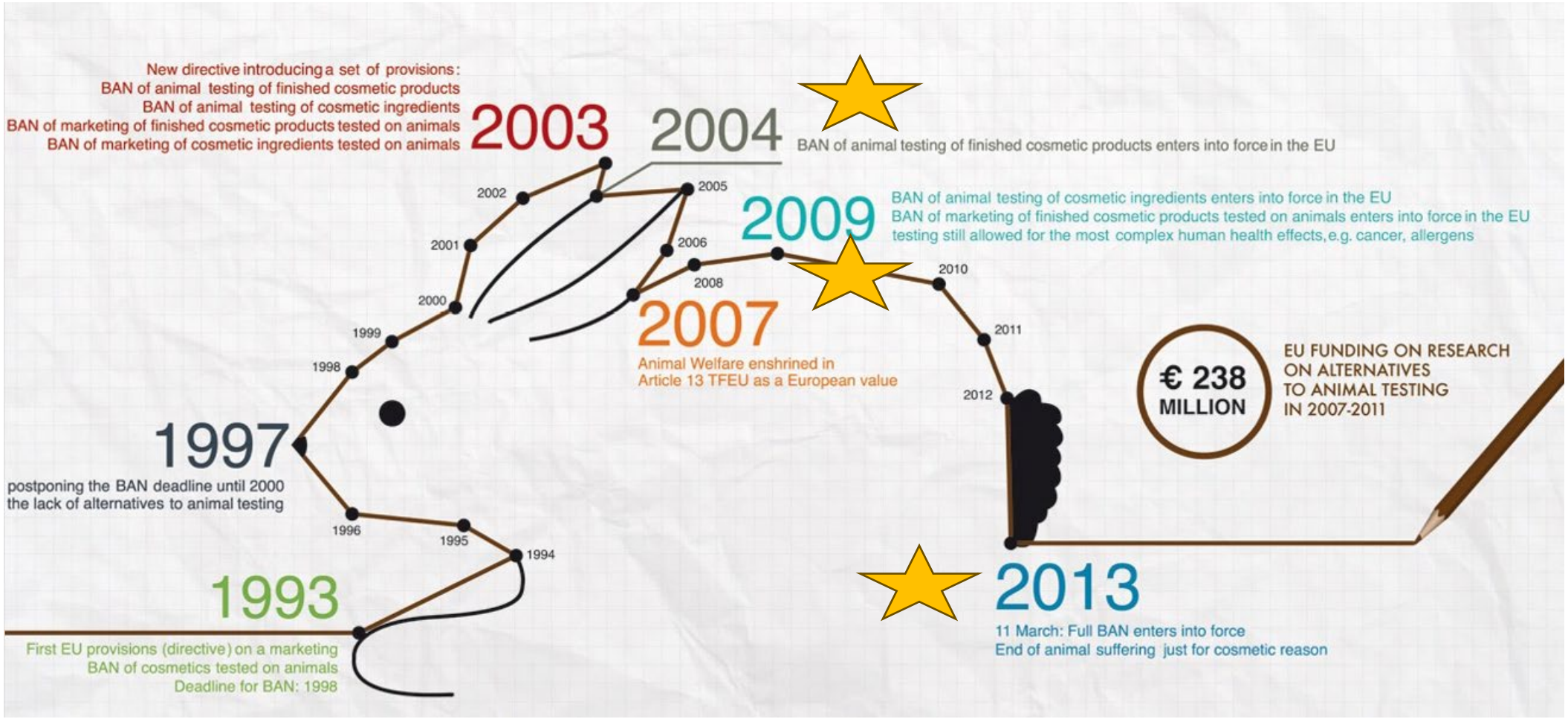
‘Historical’ Safety Assessment Approaches

Endpoint	Example Assay (traditional animal used)	Traditional Safety Approach
Skin corrosion/skin irritation	Draize skin irritation/corrosion test (rabbit)	Compare concentration of use to concentration that causes irritation. Evaluate at the product level.
Serious eye damage/eye irritation	Draize eye test (rabbit)	Compare concentration of use to concentration that causes irritation. Evaluate at the product level.
Skin sensitization	Local lymph node assay (LLNA) (mouse) Guinea Pig Maximization Test (GPMT)	Define a No Expected Sensitization Induction Level (NESIL; in µg/cm^2) convert to acceptable exposure dose with safety factors compare to estimated consumer exposure level
Repeated dose toxicity	28 or 90-day repeated dose study (rodent)	Define a point of departure (mg/kg/day); if from oral study convert to systemic dose dermal exposure; compare to estimated exposure and determine adequacy of MoS

Note: “In light of the animal testing ban for cosmetic ingredients, data on acute toxicity is not mandatory for assessing the safety of cosmetic ingredients for consumer use. A WoE approach may be sufficient - such as justified conclusions from chemical grouping/read-across, (Q)SAR, *in vitro* studies, or when accessible, repeated dose toxicity studies.” (SCCS, 2023)

EU Banned All Animal Tests for Cosmetic Ingredients by 2013

Regulatory requirements and ethical considerations

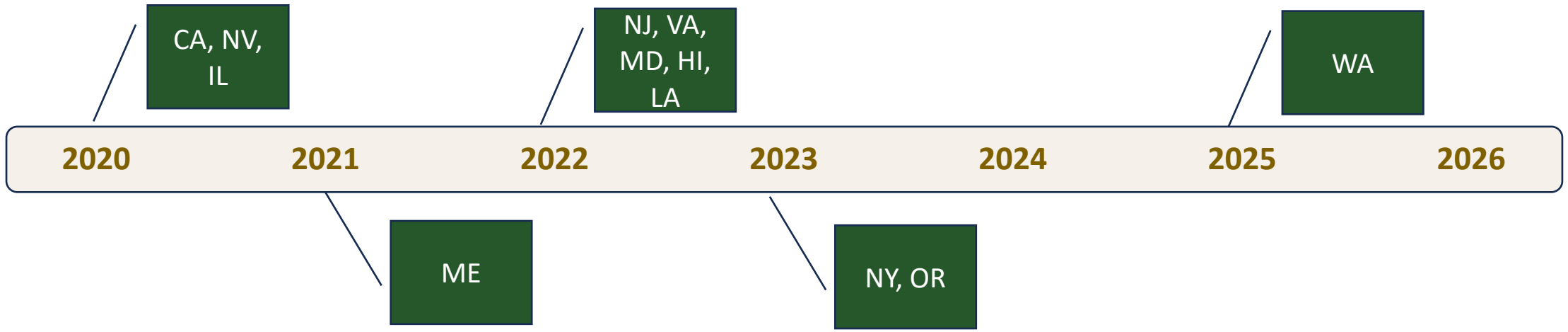


Source: https://single-market-economy.ec.europa.eu/sectors/cosmetics/ban-animal-testing_en

12 states have banned animal testing on cosmetic products and/or ingredients in the U.S.

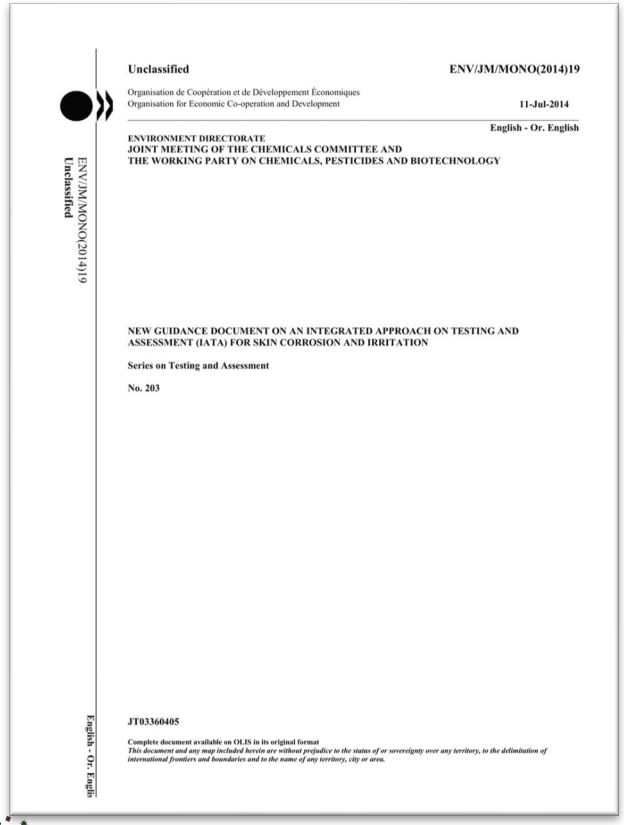
No federal animal testing ban.

- MoCRA included a “sense of the Senate” statement that animal testing should not be used, but there is no statutory requirement
- As of April 2026, twelve U.S. states have banned the sale of any cosmetic product if the manufacturer knew or reasonably should have known that the product or its ingredients were tested on animals after the law’s cutoff date.



Rethinking ‘Historical’ Safety Assessment Approaches

Endpoint	Example Assay (traditional animal used)	Status of In Vitro Replacement
Skin corrosion/skin irritation	~~Draize skin irritation/corrosion test (rabbit)~~	Replacements available see OECD GD 203 Integrated Approach for Testing and Assessment (IATA) for skin corrosion and irritation (2014)
Serious eye damage/eye irritation	~~Draize eye test (rabbit)~~	Replacements available see OECD defined approach for serious eye damage and eye irritation (Guideline number 467; 2025) and OECD GD IATA 263


Unclassified ENV/JM/MONO(2014)19

Organisation de Coopération et de Développement Économiques
Organisation for Economic Co-operation and Development

11-Jul-2014

English - Or. English

ENVIRONMENT DIRECTORATE
JOINT MEETING OF THE CHEMICALS COMMITTEE AND
THE WORKING PARTY ON CHEMICALS, PESTICIDES AND BIOTECHNOLOGY

ENV/JM/MONO(2014)19
Unclassified

NEW GUIDANCE DOCUMENT ON AN INTEGRATED APPROACH ON TESTING AND ASSESSMENT (IATA) FOR SKIN CORROSION AND IRRITATION

Series on Testing and Assessment

No. 203

JT03360405

Complete document available on OLIS in its original format
This document and any map included herein are without prejudice to the status of or sovereignty over any territory, to the delimitation of international frontiers and boundaries and to the name of any territory, city or area.

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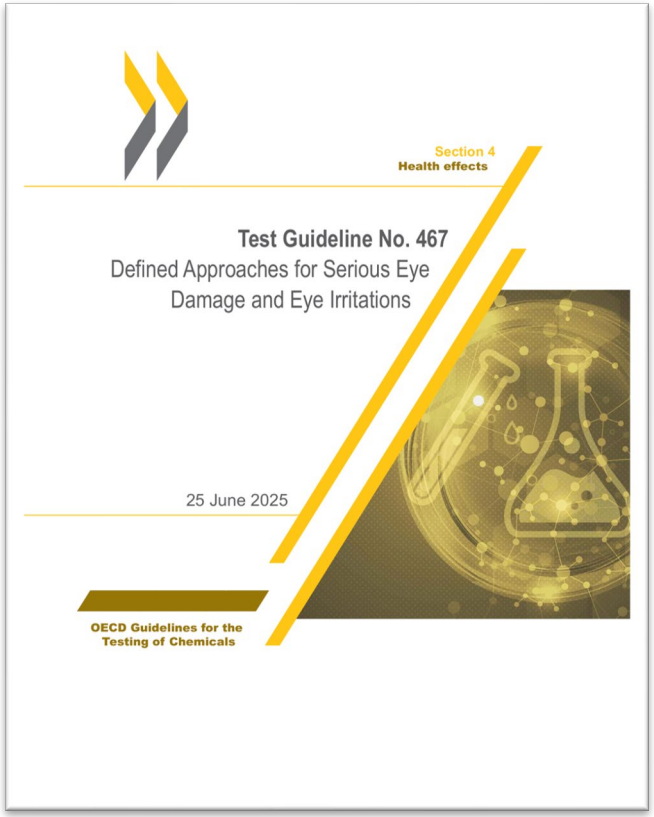
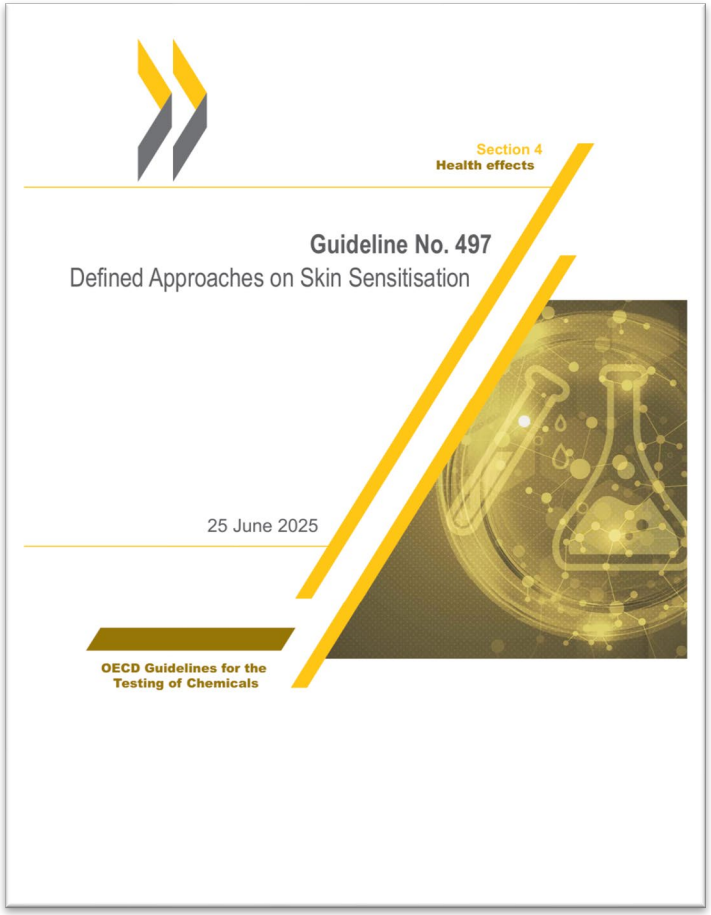
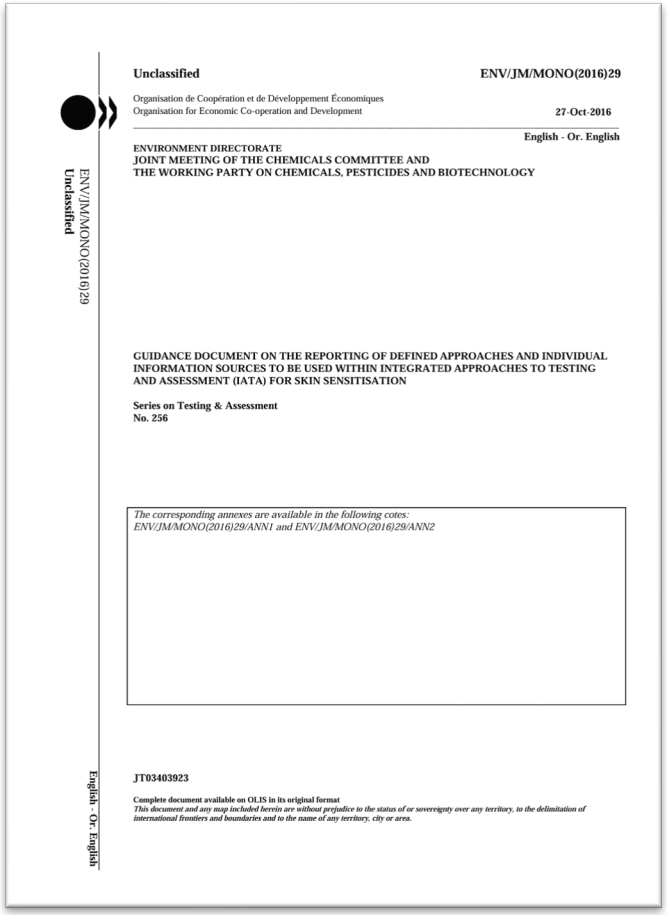


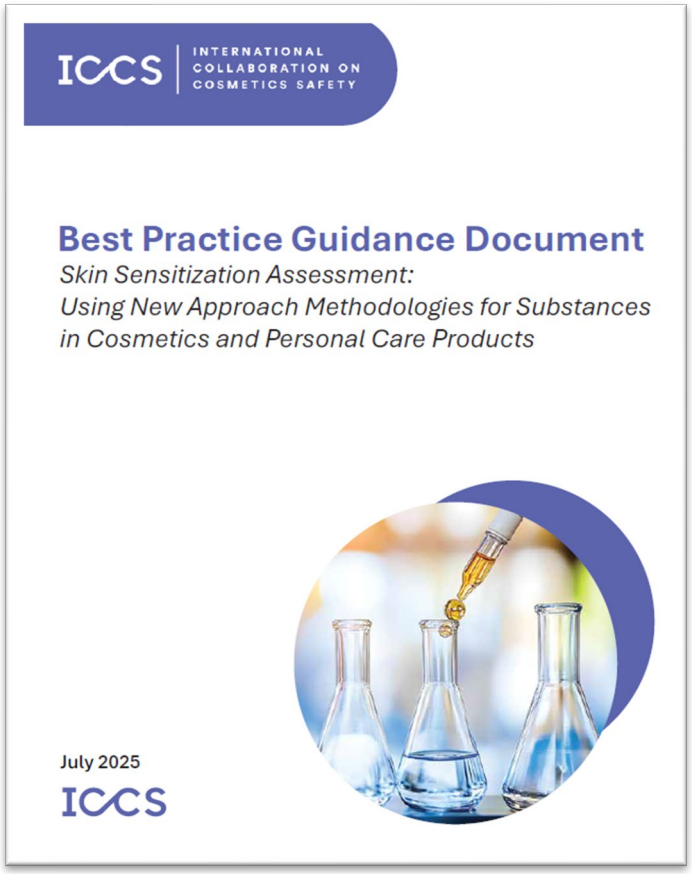
Rethinking ‘Historical’ Safety Assessment Approaches

Endpoint	Example Assay (traditional animal used)	Status of In Vitro Replacement
Skin sensitization	~~Local lymph node assay (LLNA) (mouse)~~ ~~Guinea Pig Maximization Test (GPMT)~~	Replacements available, see OECD defined approaches for skin sensitization (guideline number 497; 2025) and OECD GD 256 on reporting of DAs to be used within IATA



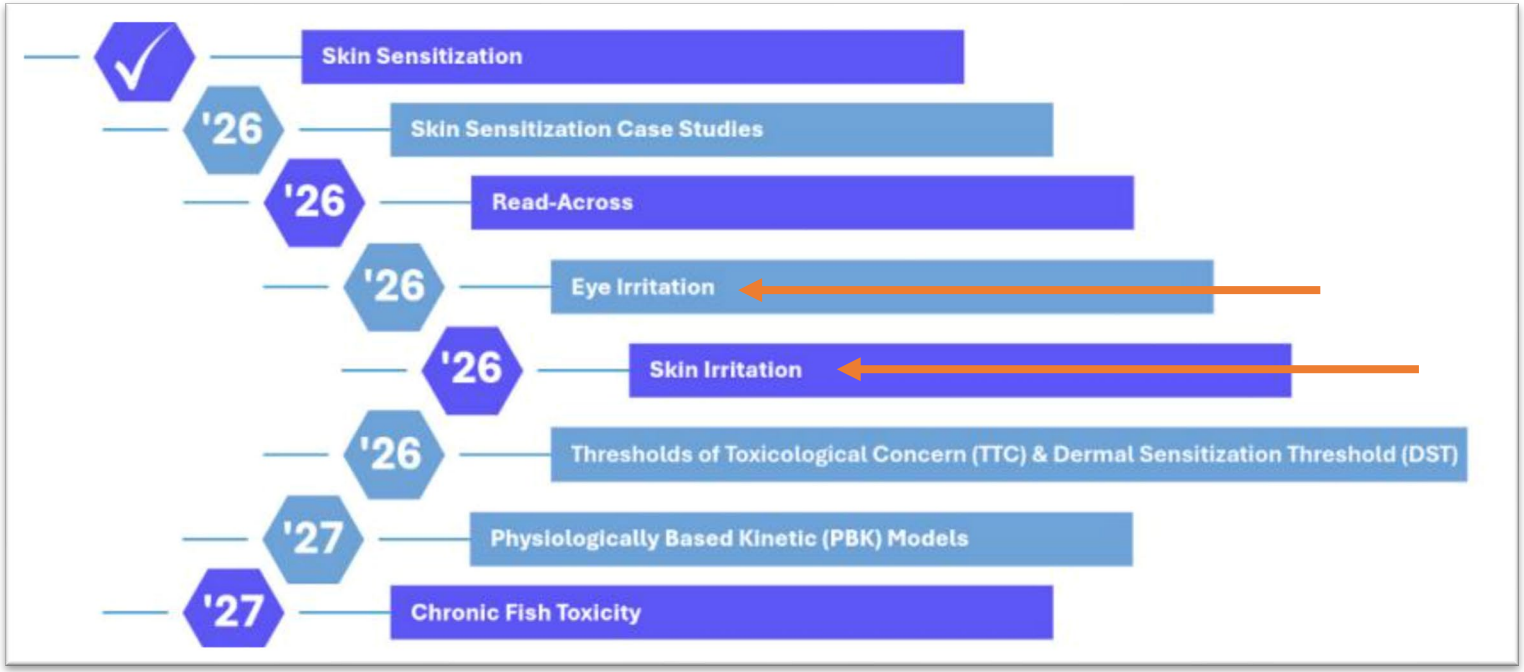


Additional Resources for Local Toxicity & Skin Sensitization



Source: https://www.iccs-cosmetics.org/education/best-practice-guidance/bpg-skin-sensitization-assessment-using-new-approach-methods

Anticipated Best Practice Guidance Documents from ICCS



Source: https://mailchi.mp/iccs-cosmetics/iccs-newsletter-issued-april-16-6750619

How do we think about systemic safety without animals?

Systemic Safety Assessment: Historical Approach

Use the Margin of Safety Approach

- Systemic poi[illegible]
- Derived fr[illegible]eated-d[illegible]nimal study
- Often fro[illegible]posure s[illegible]ies; need to do route conversio[illegible]most o[illegible]done [illegible] assumptions around bi[illegible]ailability ([illegible]ue from SCCS = 50%)
- In units of [illegible]g/day

$$\frac{POD_{sys}}{SED} = MoS$$

- Adequate magnitude of margin of safety dictated by uncertainties
- Often 100 (10 for animal to human; 10 for interindividual variability)
- May be more or less depending on data being used for POD

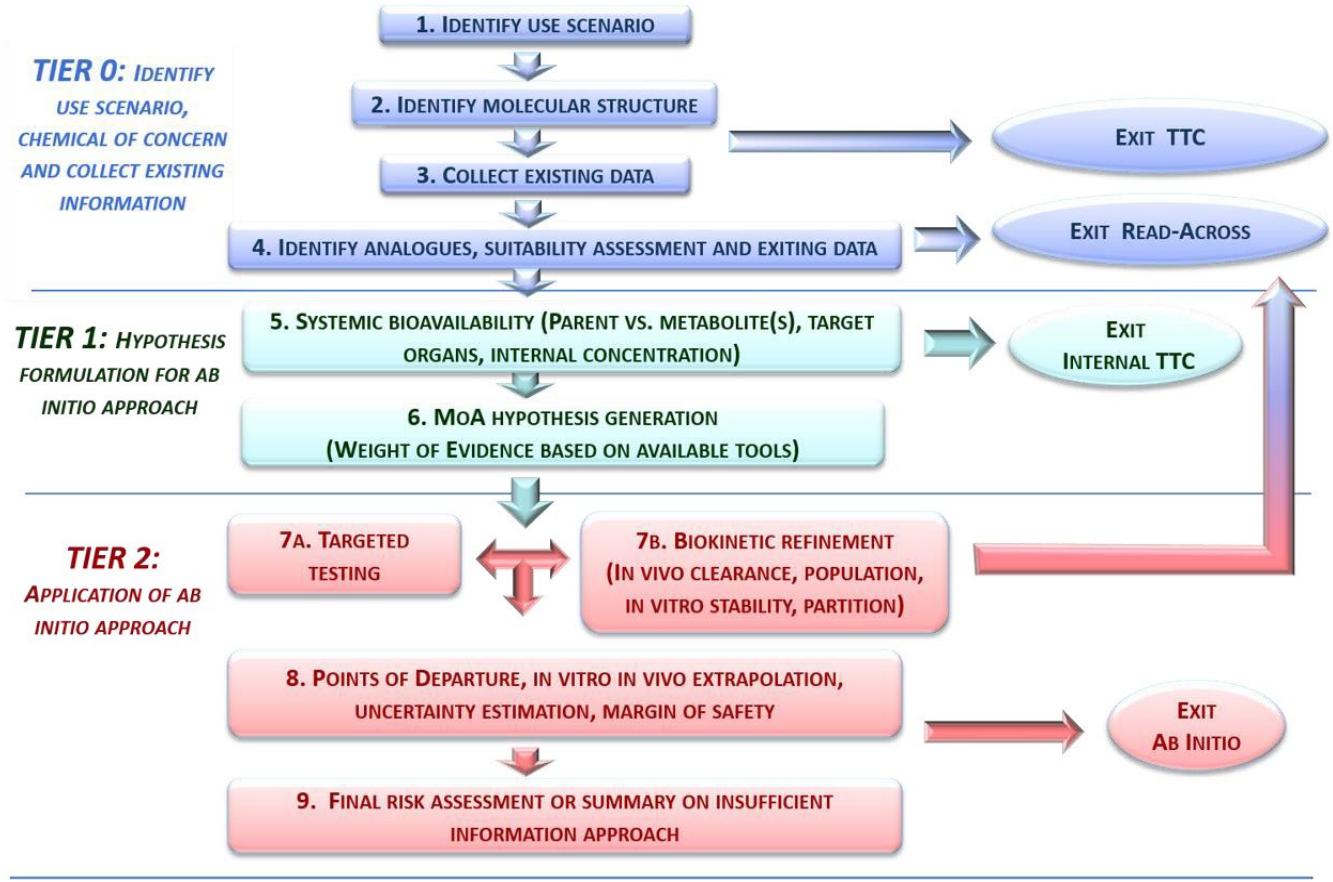
- Systemic Exposure Dose
- Based on concentration of ingredient in the formula and data on use amounts for product type (many defaults provided by SCCS)
- In units of mg/kg/day

Moving to Next Generation Risk Assessment

Next Generation Risk Assessment

- Process developed by International Cooperation on Cosmetics Regulation (ICCR) industry in late 2010s.
- Human relevant, exposure-led, hypothesis-driven risk assessment approach that integrates **in silico, in chemico, and in vitro approaches** to assure safety without the use of animal testing."
- Designed to prevent harm, not predict adversity
- Tiered and iterative process, requires assessment of all available information, characterization of uncertainty and robust methods with transparent documentation (see Dent et al., 2018)
- Incorporated into the 12th edition of the Scientific Committee on Consumer Safety Notes of Guidance

NGRA Framework



Source: Berggren et al. 2017 doi: https://doi.org/10.1016/j.comtox.2017.10.001.

NGRA Requires a Multidisciplinary 'Toolbox' approach

Initial Screening/Data Evaluation

- **TTC** — Threshold of Toxicological Concern
- **Read-Across** — Analog and Category data
- **In silico** — QSAR, Structural Alerts

Exposure Characterization

- **PBK Modeling** — Internal Concentrations
- **Metabolism Characterization** — Identify critical metabolites

Bioactivity characterization

- **HTTr** — High throughput transcriptomics
- **Cellular Stress Panels**
- **In vitro pharma profiling**

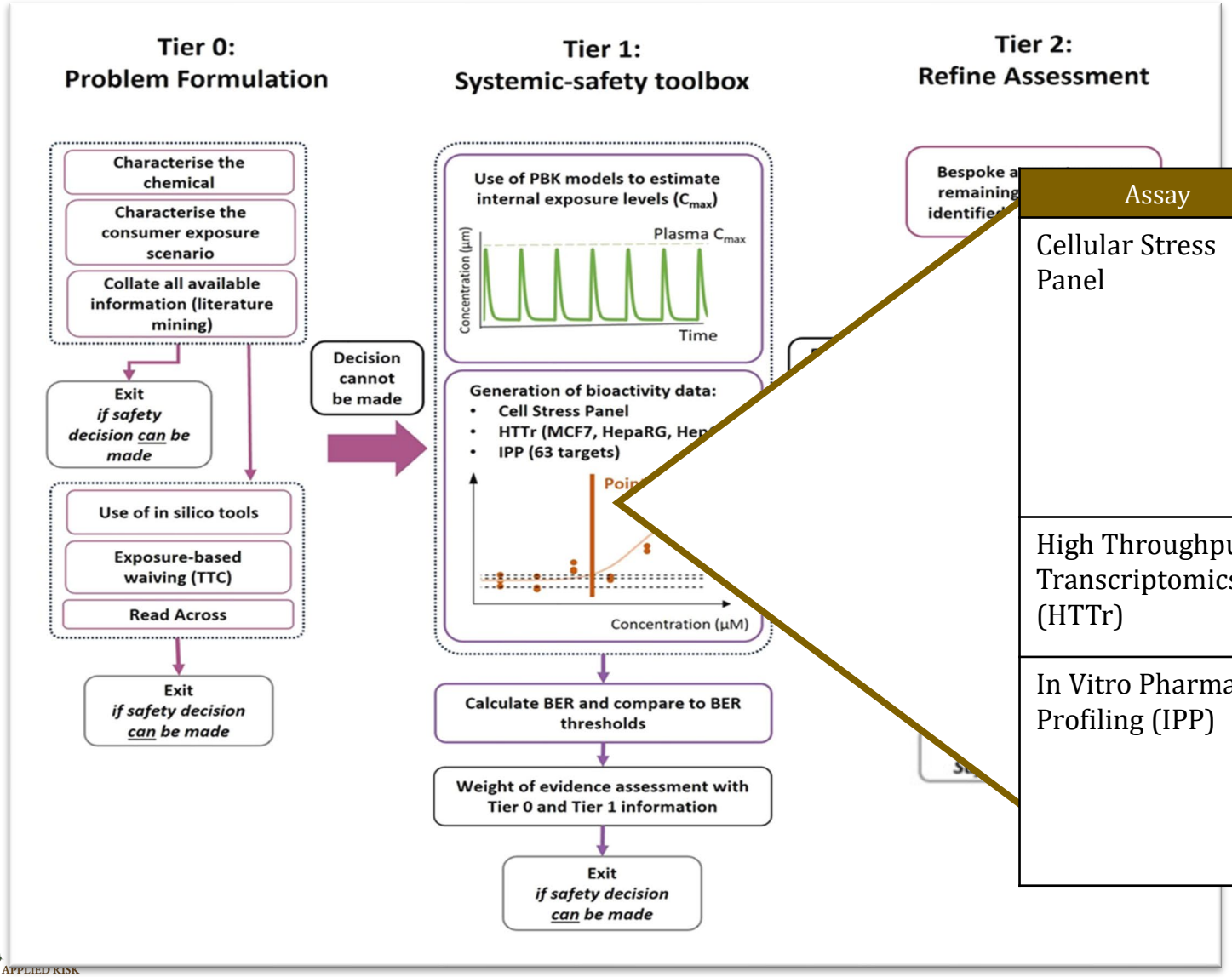
Targeted Testing

- **CALUX, ER/AR Assays** — Receptor-specific signaling
- **DART Assays** — ReproTracker, DevTox
- **Organ on Chip/MPS** — Tissue specific endpoints

Integration into a Risk Decision

- **IVIVE** — Bridges in vitro POD to in vivo POD
- **Bioactivity Exposure Ratio** — Decision metric; similar to MoS

NGRA in Practice: Putting the Pieces Together



Assay	Biological Space Covered	Why include it
Cellular Stress Panel	A panel of biomarkers across ~10 conserved cell stress pathways (oxidative stress, ER stress, DNA damage, mitochondrial toxicity, metal stress, inflammation, etc.) in human cells	Detects cellular distress regardless of upstream cause
High Throughput Transcriptomics (HTTr)	Whole transcriptome across multiple cell types	Hypothesis-free detection of any transcriptionally regulated pathway
In Vitro Pharma Profiling (IPP)	Binding/activity against ~50–80 receptors, enzymes, ion channels, and transporters with known links to *in vivo* adverse effects	Catches off-target effects missed by stress and transcriptomic readouts

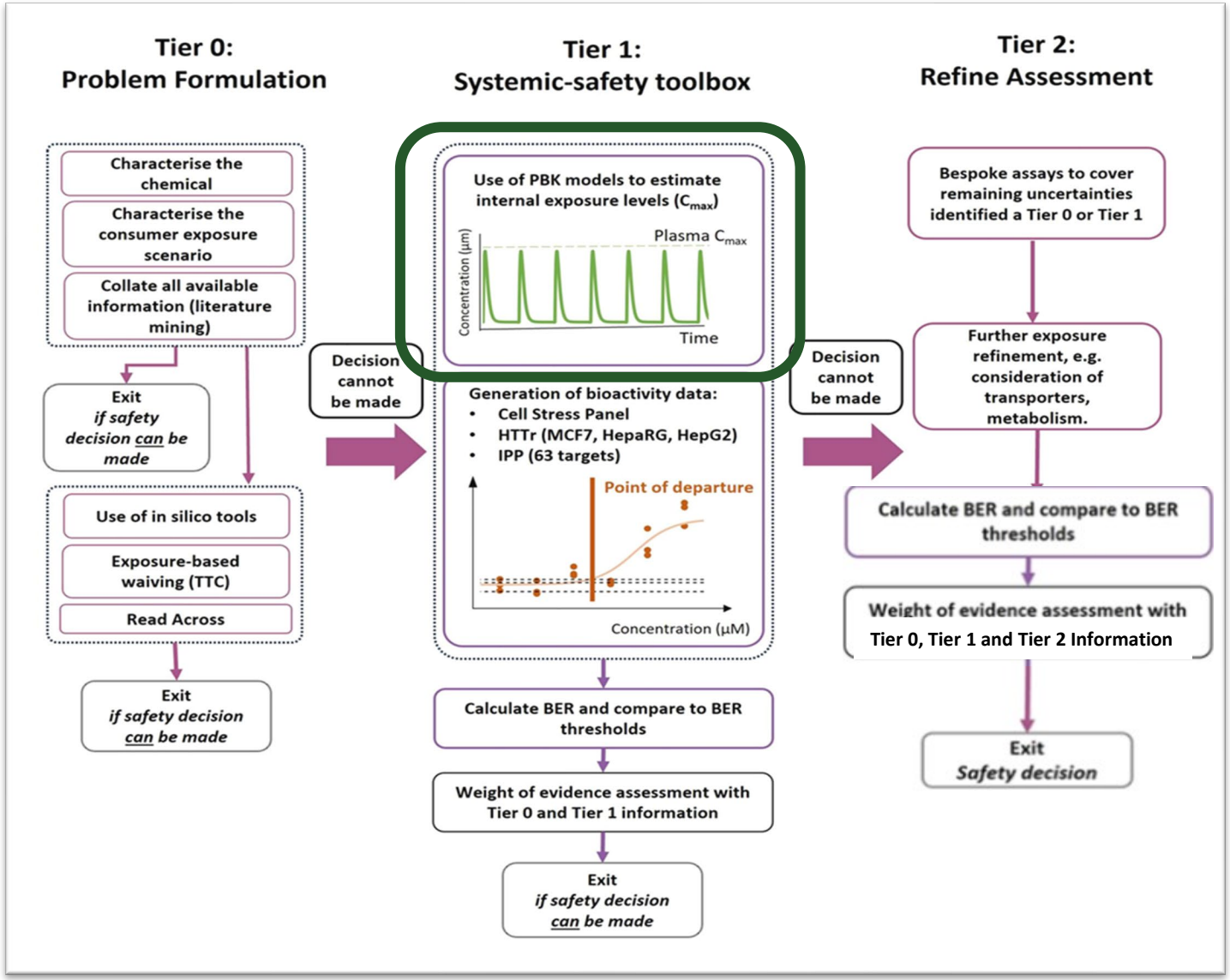
Source: Modified from Cable et al. 2025 https://doi.org/10.1093/toxsci/kfae159

NGRA in Practice: Identifying the Point(s) of Departure

Assay	Biological Space Covered	PoD Output
Cellular Stress Panel	A panel of biomarkers across ~10 conserved cell stress pathways (oxidative stress, ER stress, DNA damage, mitochondrial toxicity, metal stress, inflammation, etc.) in human cells	Lowest concentration at which any stress pathway is perturbed (~tens of PoDs per chemical, integrated to a global PoD)
High Throughput Transcriptomics (HTTr)	Whole transcriptome across multiple cell types	Lowest concentration producing a coordinated transcriptomic response (gene- or pathway-level BMD)
In Vitro Pharma Profiling (IPP)	Binding/activity against ~50–80 receptors, enzymes, ion channels, and transporters with known links to in vivo adverse effects	Lowest EC50/IC50 across all targets — flags potential off-target pharmacology

The minimum PoD across the three assays can be taken as a protective bioactivity PoD for use in quantitative risk assessment.

NGRA in Practice: Estimation of Internal Exposure



PBK Levels of Refinement based on data inputs

- Level 1: *in silico* only
- Level 2: *in silico* and *in vitro*
- Level 3: *in silico, in vitro* and clinical data

Source: Modified from Cable et al. 2025 https://doi.org/10.1093/toxsci/kfae159

Systemic Safety Assessment: Bioactivity Exposure Ratio

Analogous to the Margin of Safety Approach

- NAM-based point of departure from toolbox
- In units of µM

$$BER = \frac{POD_{NAM}}{C_{int}}$$

- Bioactivity exposure ratio
- Magnitude of ratio for adequacy still an area open to debate
- In Unilever papers, defined based on level of refinement of PBK model

  L1: 110, L2: 11, L3: 2.5

- Estimated internal concentration from PBK modeling
- In units of µM

Is the current testing approach protective enough?

Multiple research streams converge that NGRA is highly protective

Study	Chemicals Tested	Assays Used to ID PoD_{NAM}	Headline Finding Re: Protectiveness	Data Stream
Middleton et al. *2022 · Toxicol Sci* *189(1):124–147*	10 chemicals across 24 exposure scenarios (5 high-risk, 19 low-risk)	HTTr (TempO-Seq whole transcriptome; HepG2, HepaRG, MCF-7); CSP (HepG2); IPP	**100% protectiveness for high-risk scenarios (5/5) at a BER threshold of 11 (PBK level L2)**, with 69% utility (9/13 low-risk correctly identified). Pilot study that established the CSP + HTTr + IPP toolbox and the BER threshold framework — formed the basis for subsequent evaluations.	Cosmetics
Cable et al. *2025 · Toxicol Sci* *204(1):79–95*	38 chemicals 70 exposure scenarios (46 high-risk, 24 low-risk)	HTTr (TempO-Seq whole transcriptome; HepG2, HepaRG, MCF-7); CSP (HepG2); IPP	**93–98% protectiveness depending on PBK parameterization when using BER**. Of 25 chemicals with data, **nearly all had a minimum NAM PoD that was more conservative, i.e. lower, than the minimum traditional PoD.**	Cosmetics
Paul Friedman et al. *2020 · Toxicol Sci* *173(1):202–225*	448 chemicals ToxCast HTS + httk reverse dosimetry	ToxCast/Tox21 HTS (~1000+ assay endpoints; AC50 across cancer cell lines, reporter genes, biochemical targets); httk reverse dosimetry for IVIVE	**89% of $POD_{NAM,95}$ values were below $POD_{traditional}$**. For the remaining chemicals, the two PoDs were typically within a factor of 10 of each other.	EPA / APCRA
Paul Friedman et al. *2025 · Toxicol Sci* *205(1):74–96*	200 chemicals prospective; 20 selected for follow-up	2025 expansion adds HepaRG HTTr + targeted bioactivity flags (endocrine, neurological, immunosuppression)	Prospective expansion of APCRA combining broad-profiling and targeted NAMs; evaluated PODNAM as both protective AND predictive of PODtraditional for data-poor chemicals. Demonstrated combined use in a tiered NBA workflow.	EPA / APCRA
Chen et al. *2020 · ALTEX* *37(4):623–638*	42 ATSDR Superfund priority chemicals (iPSC-derived cells + HUVECs; 5 cell types)	High-content imaging across 5 human cell types — iPSC hepatocytes, neurons, cardiomyocytes, endothelial cells + HUVECs; cytotoxicity + functional phenotypes (48 endpoints)	When all five cell types are combined: only ~25% of in vitro PODs exceeded the in vivo value, and those within 10-fold. Single cell types alone were insufficient — multi-tissue coverage was essential for protectiveness.	Texas A&M

Where the Field is Heading: Extensions & Open Questions

ACTIVE EXTENSIONS

Where the toolbox is growing

Tier 2 hypothesis-driven testing

Tier 1 case studies cover broad systemic toxicity. Where Tier 1 flags uncertainty, Tier 2 layers in MoA-specific NAMs to interrogate known or plausible mechanisms.

Targeted DART toolbox

The Cable/Middleton toolbox is being extended for developmental and reproductive toxicity using hiPSC-based assays (ReproTracker, devTOX quickPredict) plus DART-relevant IPP targets — same BER framework, additional biological coverage.

Rajagopal et al. 2022 (Front Toxicol 4:838466); Jamalpoor et al. 2022 (Birth Defects Res 114:1210); Mueller et al. 2025 (Front Toxicol 7:1602065)

OPEN QUESTIONS

Where consensus is still building

What does an inadequate BER actually mean?

A bioactivity hit is not the same as an adverse outcome. How do we interpret a BER flag with respect to adversity and biology?

How do we define an adequate BER threshold?

Current thresholds depend on PBK refinement level. Harmonization is still under discussion.

What is the best suite of tools?

Different research groups have approached the question with different tools, how will we know what approach is best?

How do we handle difficult-to-test substances?

Complex mixtures, UVCBs, poorly soluble materials, and naturals don't fit neatly into single-chemical NAM workflows.

How do we capture biological & exposure variability?

Susceptible populations, life-stage differences, and inter-individual variability remain active areas of methods development.

Summary & Conclusions

01

Personal Care Product Safety Assessment Must Move Forward without Animals

Due to both regulatory and consumer pressures combined with ethical concerns animal testing for cosmetics and personal care products is no longer an option in most jurisdictions

02

Tools are available to begin this process now

For local endpoints, methods are well developed and being used today. For systemic endpoints, a weight of evidence approach is needed and science is demonstrating the safety profile of potential approaches

03

Multidisciplinary, weight of evidence approaches are needed to confirm safety of new ingredients

To successfully transition to non-animal testing an integrated approach applying a toolbox of methods to demonstrate safety is the best way forward.

APPLIED RISK & TOXICOLOGY

Thank You

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