

15 Years of Transformational Change in Global Cosmetics Regulation

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**HUMANE SOCIETY
INTERNATIONAL**

国际人道对待动物协会



OVERVIEW

Introduction to HSI

Cosmetics animal testing prohibitions: brief legislative history

Safety testing:

- Common tests for cosmetics
- Internationally accepted non-animal methods or approaches

Recent advances in safety assessment

- Integrated Testing Strategies (ITS)
- Integrated Approaches to Testing and Assessment (IATA) and Defined Approaches (DA)
- TT21C and the Adverse Outcome Pathways (AOP) framework
- OECD IATA projects for systemic effects

Frameworks that support non-animal safety assessment of cosmetics

- International Collaboration on Cosmetics Regulation (ICCR) Next Generation Risk Assessment (NGRA)
- The SEURAT workflow
- A new collaboration: Non-Animal Cosmetic Safety Assessment by 2023 (NACSA)

HSI is the leading international NGO working to advance non-animal safety testing and bioscience research worldwide.

Our goal: Expand the development and regulatory acceptance of innovative and effective alternative approaches while phasing out the use of animals in safety assessment and research.



- HSI is active on the ground in **60 countries**, including the Americas, Europe, India and South Korea
- Our Research & Toxicology Department brings together experts in eco/toxicology, regulatory science, biomedicine, law, etc.
- Working with research institutes, companies, government regulators, policy-makers and other stakeholders
- Work with the Organization for Economic Cooperation and Development (OECD) Test Guidelines program, and other national government advisory bodies on alternative methods and product safety

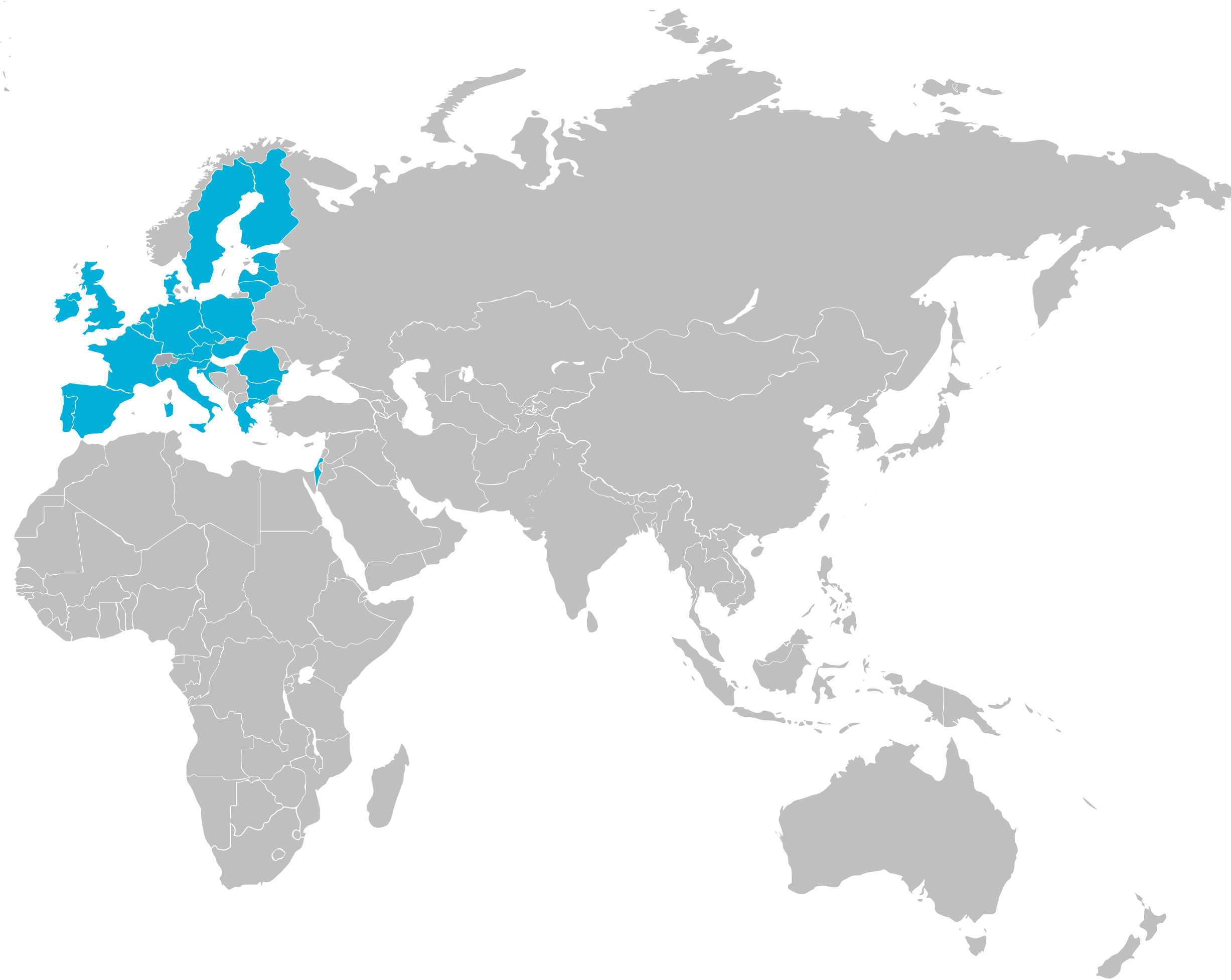


HUMANE SOCIETY
INTERNATIONAL

OVERVIEW

Cosmetics animal testing prohibitions: brief legislative history

LEGISLATIVE HISTORY



European Union: Regulation 1223/2009

2004

- Ban on animal testing of cosmetic products in the EU.
- Ban on the sale of cosmetic products and ingredients tested on animals outside of the EU where alternatives exist.

2009

- Ban on animal testing of cosmetic ingredients in the EU.
- Ban on the sale of cosmetic products and ingredients tested on animals for all but a few test areas (repeat dose toxicity, reproductive toxicity and toxicokinetics)

2013

- Ban on the sale of cosmetic products or ingredients tested on animals for the remaining test areas

Israel

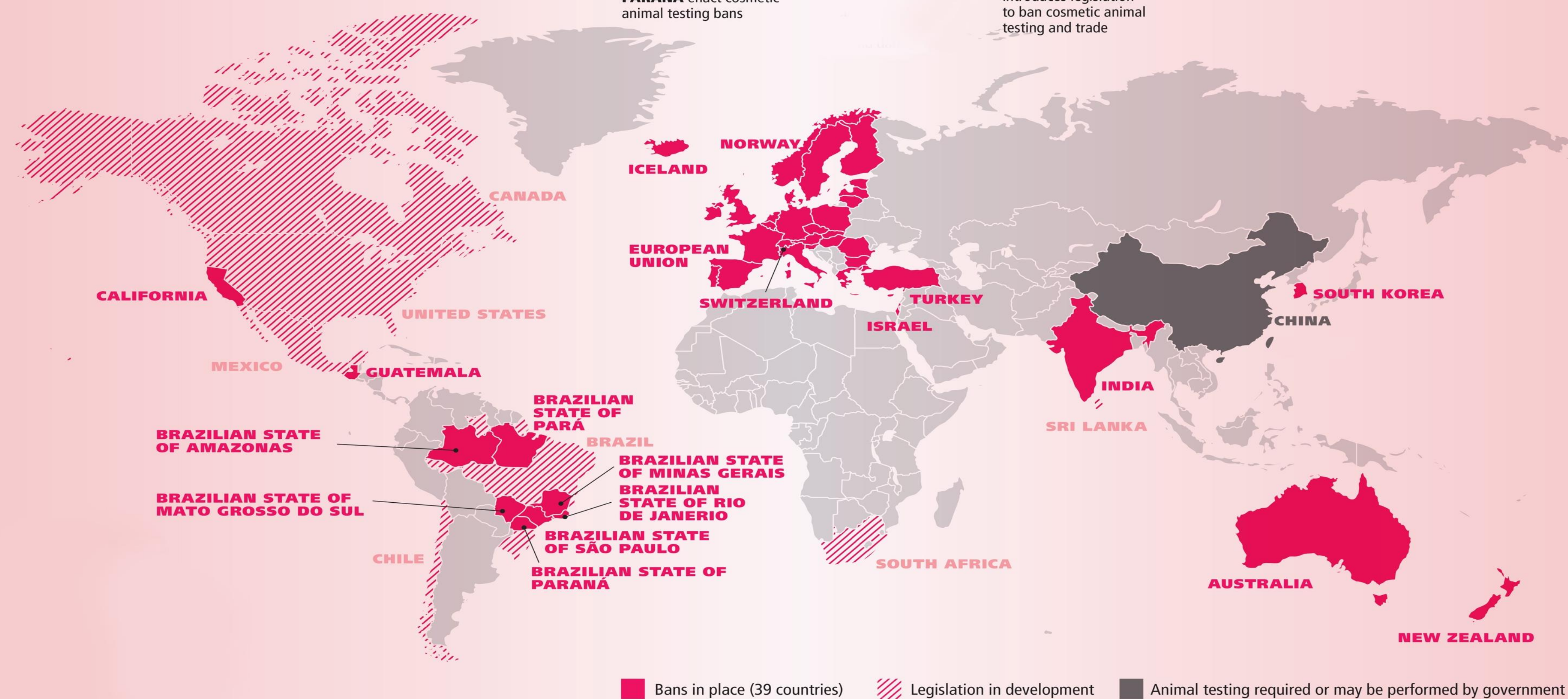
2007

Ban on the use of animals to test cosmetics

2010

Ban on the sale of animal-tested cosmetics

2012	2013	2014	2015	2016	2017	2018	2019
<p>Launch of global #BeCrueltyFree campaign</p>	<p>ISRAEL enacts ban on the sale of newly animal-tested cosmetics (in addition to previous testing ban)</p> <p>EUROPEAN UNION enacts sales ban (in addition to previous testing ban)</p> <p>NORWAY bans cosmetic animal testing and the sale of newly animal tested cosmetics.</p> <p>INDIA enacts cosmetic animal testing ban</p>	<p>BRAZILIAN STATES OF SAO PAULO and MATO GROSSO DO SUL enact cosmetic animal testing bans</p> <p>INDIA enacts import ban on newly animal-tested cosmetics</p> <p>CHINA ends mandatory animal testing for domestically manufactured non-special-use cosmetics</p>	<p>NEW ZEALAND bans cosmetic animal testing for finished products and ingredients intended exclusively for use in cosmetics</p> <p>SOUTH KOREA passes law to partially ban the manufacture and sale of newly animal tested cosmetic products and ingredients (where government-recognized, non-animal alternatives exist)</p> <p>BRAZILIAN STATES OF AMAZONAS and PARANÁ enact cosmetic animal testing bans</p>	<p>CHILE introduces legislation to ban cosmetic animal testing and the sale of newly animal tested cosmetics.</p> <p>TURKEY enacts ban on cosmetic animal testing and sales (where a validated alternative exists)</p> <p>CANADA reintroduces legislation to ban cosmetic animal testing, sales and data use</p>	<p>GUATEMALA enacts cosmetic animal testing ban</p> <p>UNITED STATES reintroduces legislation to ban cosmetic animal testing and sales</p> <p>SWITZERLAND enacts ban on the sale of newly animal-tested cosmetics</p> <p>BRAZILIAN STATE OF RIO DE JANEIRO bans cosmetic animal testing and the sale of newly animal tested cosmetics</p> <p>SOUTH AFRICA introduces legislation to ban cosmetic animal testing and trade</p>	<p>BRAZILIAN STATE OF MINAS GERAIS bans cosmetic animal testing</p> <p>SRI LANKA introduces general animal welfare bill including ban on cosmetic animal testing</p> <p>CALIFORNIA enacts ban on the sale of newly animal-tested cosmetics</p>	<p>AUSTRALIA bans the use of newly derived animal test data for cosmetics</p>




COSMETIC SAFETY TESTING

Safety testing:

- Common tests for cosmetics
- Internationally accepted non-animal methods or approaches

SAFETY TESTS: NEW COSMETIC INGREDIENTS

- 
- Acute systemic toxicity by oral and dermal routes
 - Local acute toxicity: skin and eye irritation and corrosion
 - Skin sensitization
 - Photo-induced toxicity and sensitization
 - Mutagenicity/genotoxicity
 - Toxicokinetics
 - Subchronic toxicity
 - Developmental/reproductive toxicity
 - Chronic toxicity/carcinogenicity

AVOIDING ANIMAL TESTING

ACUTE SYSTEMIC TOXICITY

SCCS NOTES OF GUIDANCE FOR THE TESTING OF COSMETIC INGREDIENTS AND THEIR SAFETY EVALUATION, 10TH REVISION (2018)

OECD Guidance Document 237: Guidance Document on Considerations for Waiving or Bridging of Mammalian Acute Toxicity Tests	2017
Collaborative Acute Toxicity Modeling Suite (CATMoS) US National Institute of Environmental Health Sciences	2018
OECD Guidance 194 on Grouping of Chemicals	2014
GHS additivity formula for estimating acute toxicity of mixtures	2017
OECD Guidance document 129 on cytotoxicity tests to estimate starting doses for acute oral toxicity tests	2010
3T3 Neutral Red Uptake for acute toxicity, non-toxic (European Commission JRC)(2013)	2013
OECD Test Guideline 428 Skin absorption in vitro	2004
OECD Test Guideline 432 3T3 Neutral Red Uptake Photo-toxicity Test	2004 China 2016



AVOIDING ANIMAL TESTING

ACUTE LOCAL SKIN/EYE

SCCS NOTES OF GUIDANCE FOR THE TESTING OF COSMETIC INGREDIENTS AND THEIR SAFETY EVALUATION, 10TH REVISION (2018)

OECD GD 203 on an Integrated Approach on Testing and Assessment (IATA) for Skin Corrosion and Irritation	2014
OECD TG 430 In Vitro Skin Corrosion: Transcutaneous Electrical Resistance Test Method (TER)	2015 China 2017
OECD TG 431 Skin corrosion using reconstructed human epidermis (EpiSkin™, EpiDerm™, SkinEthic™, and epiCS®)	2016
OECD TG 435 In Vitro Membrane Barrier Test Method for Skin Corrosion (Corrositex®)	2015
OECD TG 439 Skin irritation using reconstructed human epidermis (EpiSkin™, EpiDerm™, SkinEthic™, and LabCyte EPI-MODEL 24)	2015
OECD GD 263 on an Integrated Approach on Testing and Assessment (IATA) for Serious Eye Damage and Eye Irritation	2017
OECD TG 437 Bovine Corneal Opacity and Permeability (BCOP)	2017
OECD TG 438 Isolated Chicken Eye (ICE) Test Method	2018
OECD TG 460 Fluorescein Leakage (FL) Test Method for Identifying Ocular Corrosives and Severe Irritants	2017
OECD TG 491 Short Time Exposure (STE) in vitro method	2018 China 2019
OECD TG 492 Reconstructed Human Cornea-like Epithelium (RhCE) Test Method (e.g. EpiOcular™, SkinEthic™, LabCyte)	2018



AVOIDING ANIMAL TESTING

SKIN SENSITIZATION/MUTAGENICITY

SCCS NOTES OF GUIDANCE FOR THE TESTING OF COSMETIC INGREDIENTS AND THEIR SAFETY EVALUATION, 10TH REVISION (2018)

OECD GD 256 on the Reporting of Defined Approaches and Individual Information Sources to be Used within Integrated Approaches to Testing and Assessment (IATA) for Skin Sensitisation	2017
OECD TG 442C Direct Peptide Reactivity Assay (DPRA)	2015 China 2019
OECD TG 442D ARE-Nrf2 Luciferase Method (KeratinoSens™, LuSens™ assays)	2018
OECD TG 442E Activation of Dendritic Cells Test Method (h-CLAT, U-SENS™, IL-8 Luc assays)	2018
OECD TG 439 Skin irritation using reconstructed human epidermis (EpiSkin™, EpiDerm™, SkinEthic™, and LabCyte EPI-MODEL 24)	2015
OECD TG 429 Local Lymph Node Assay - LLNA	2018 China 2019
OECD TG 442A LLNA DA	2010
OECD TG 442B LLNA BrdU-ELIZA or -FCM	2018
Mutagenicity	
OECD TG 476 In Vitro Mammalian Cell Gene Mutation Test (HPRT, XPRT)	2015
OECD TG 473 In Vitro Chromosomal Aberration	2016
OECD TG 487 In Vitro Micronucleus	2010



RECENT ADVANCES IN SAFETY ASSESSMENT

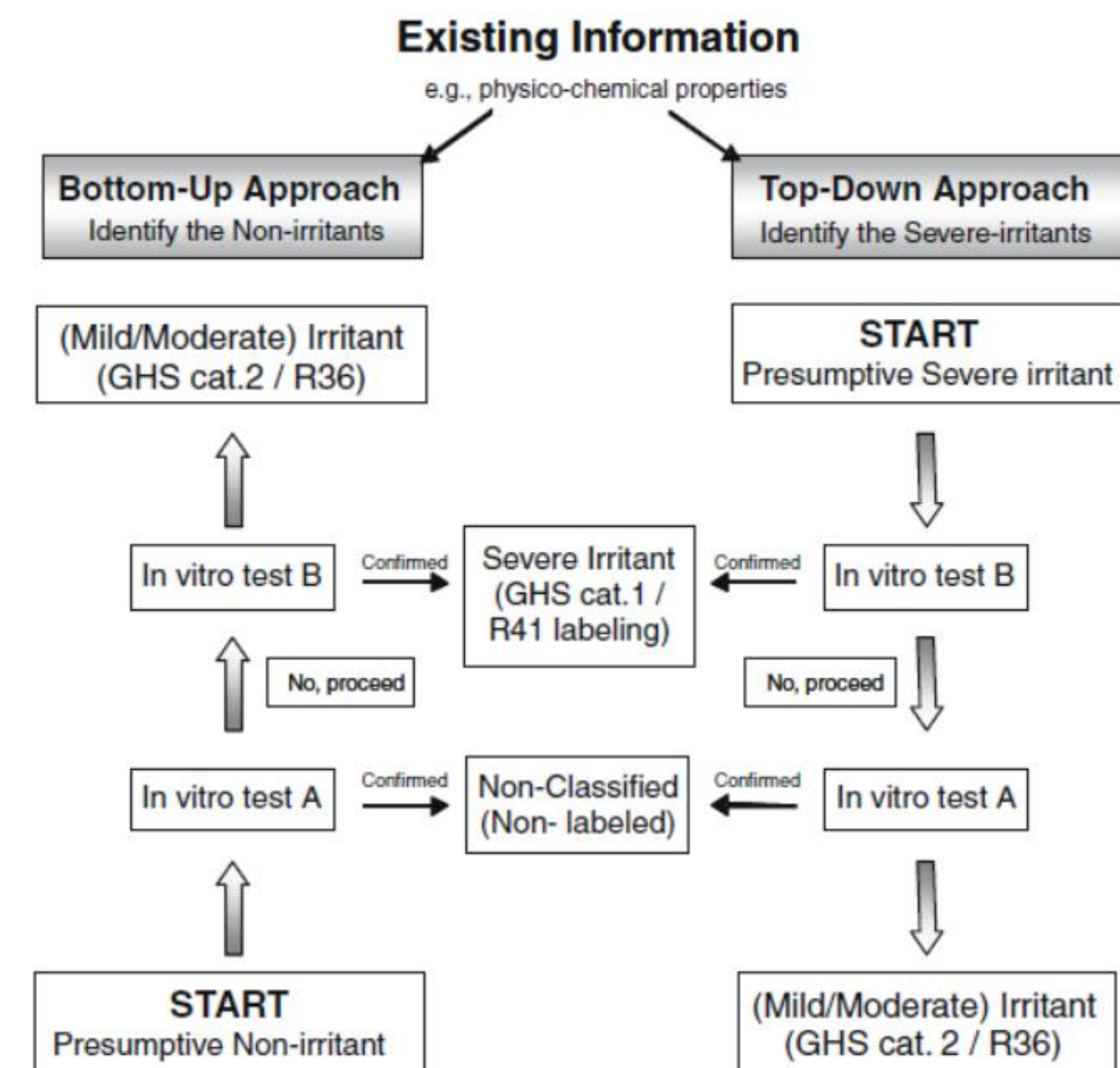
- Integrated testing strategies (ITS)
- Integrated Approaches to Testing and Assessment (IATA)
- Defined Approaches (DA)
- TT21C: using biological pathway information to predict safety
- Use of Adverse Outcome Pathways (AOPs)
- OECD IATA projects for systemic effects



INTEGRATED TESTING STRATEGIES

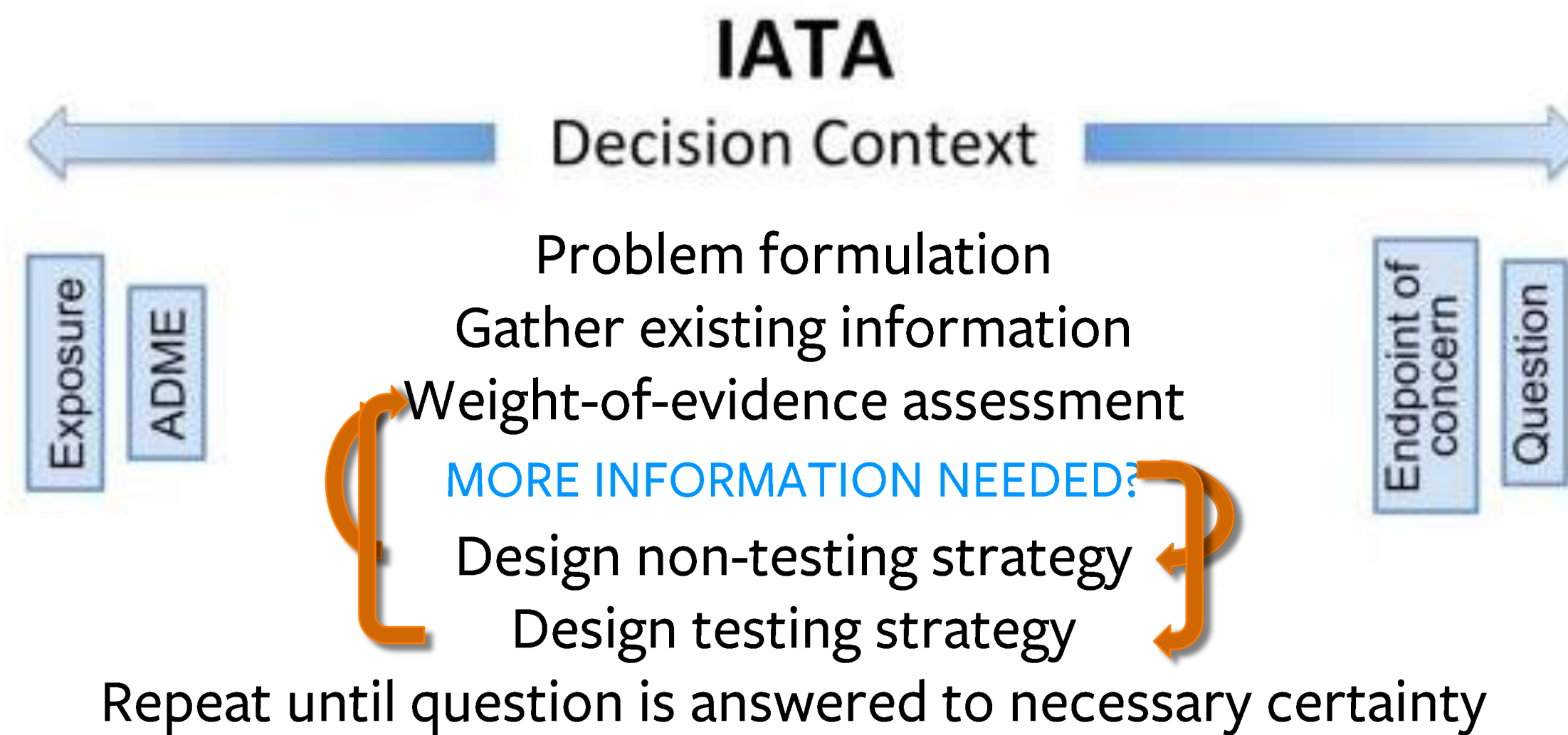
DATA GENERATION

- Combinations of tests to address specific endpoint or regulatory need (e.g. classification and labelling)
- Iterative, depends on existing and newly generated information

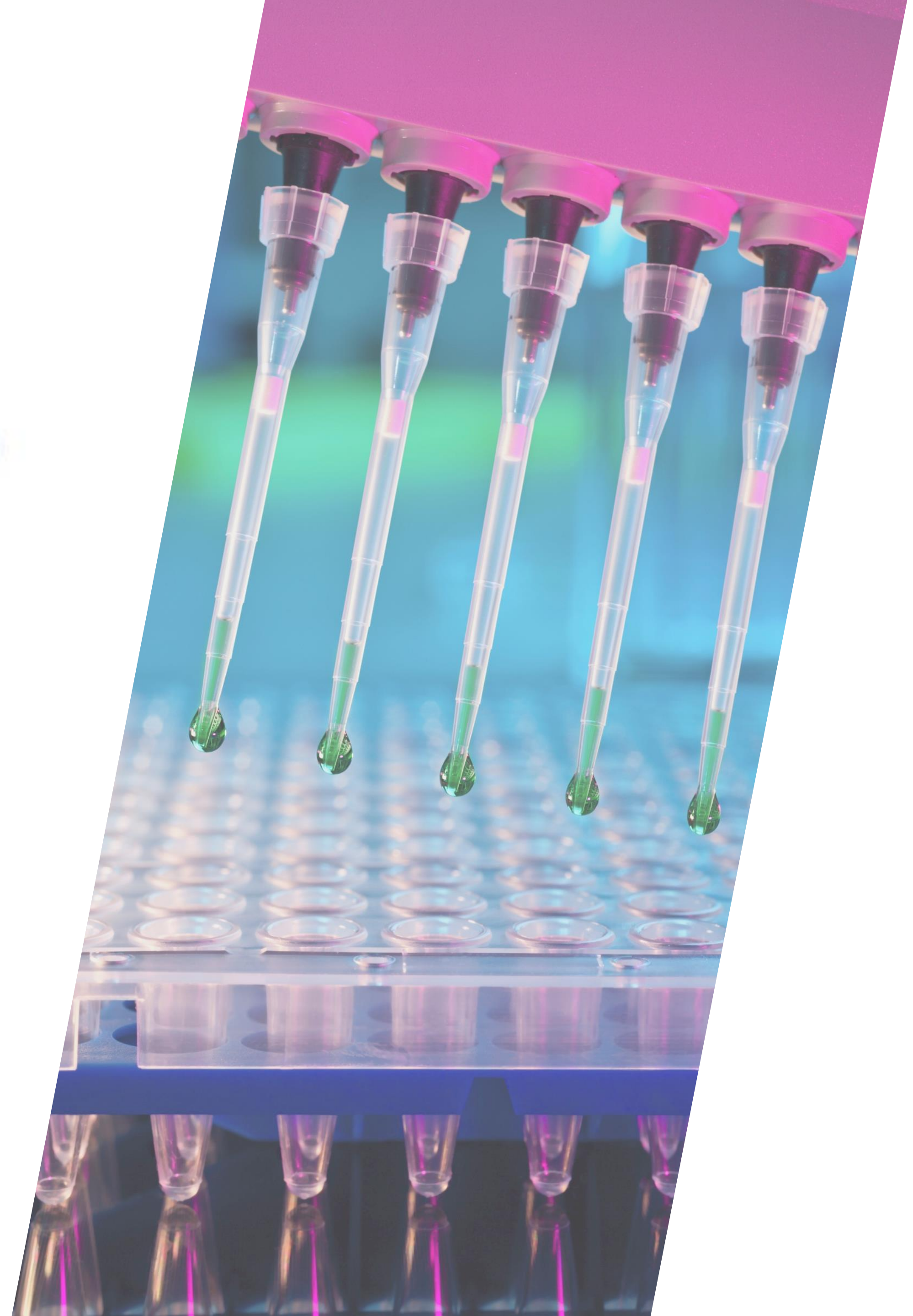


INTEGRATED APPROACHES TO TESTING AND ASSESSMENT

DECISION-MAKING



- Structured approach
- Integrates and weights all relevant data to
- Informs need for further targeted testing
- Optimizes data generation

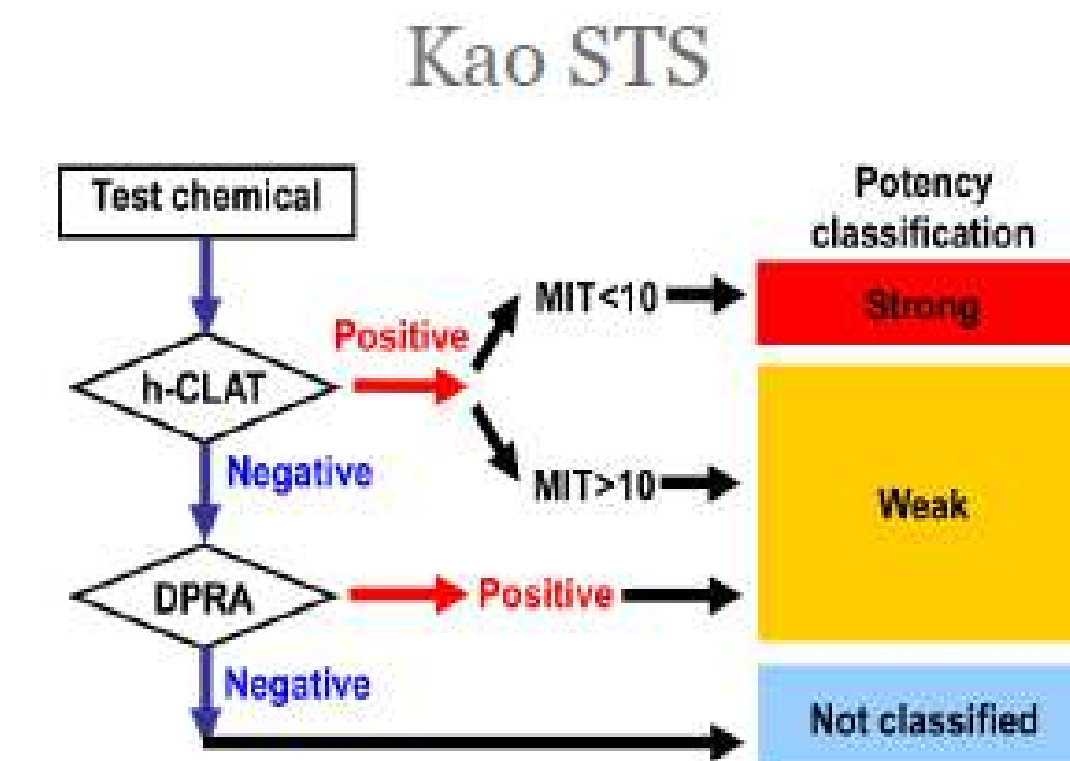
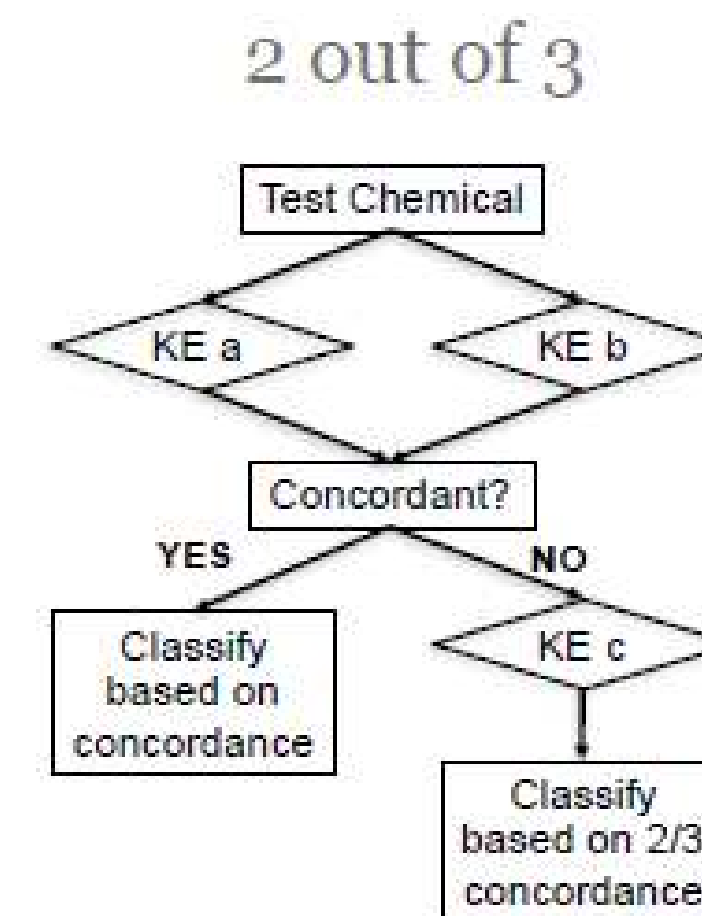


DEFINED APPROACHES TO TESTING AND ASSESSMENT

DECISION MAKING

- Special cases of IATA
- Fixed integrated testing strategy +
- Fixed prediction models & decision tree
- Provides regulatory consistency/certainty

2 DA for skin
sensitization

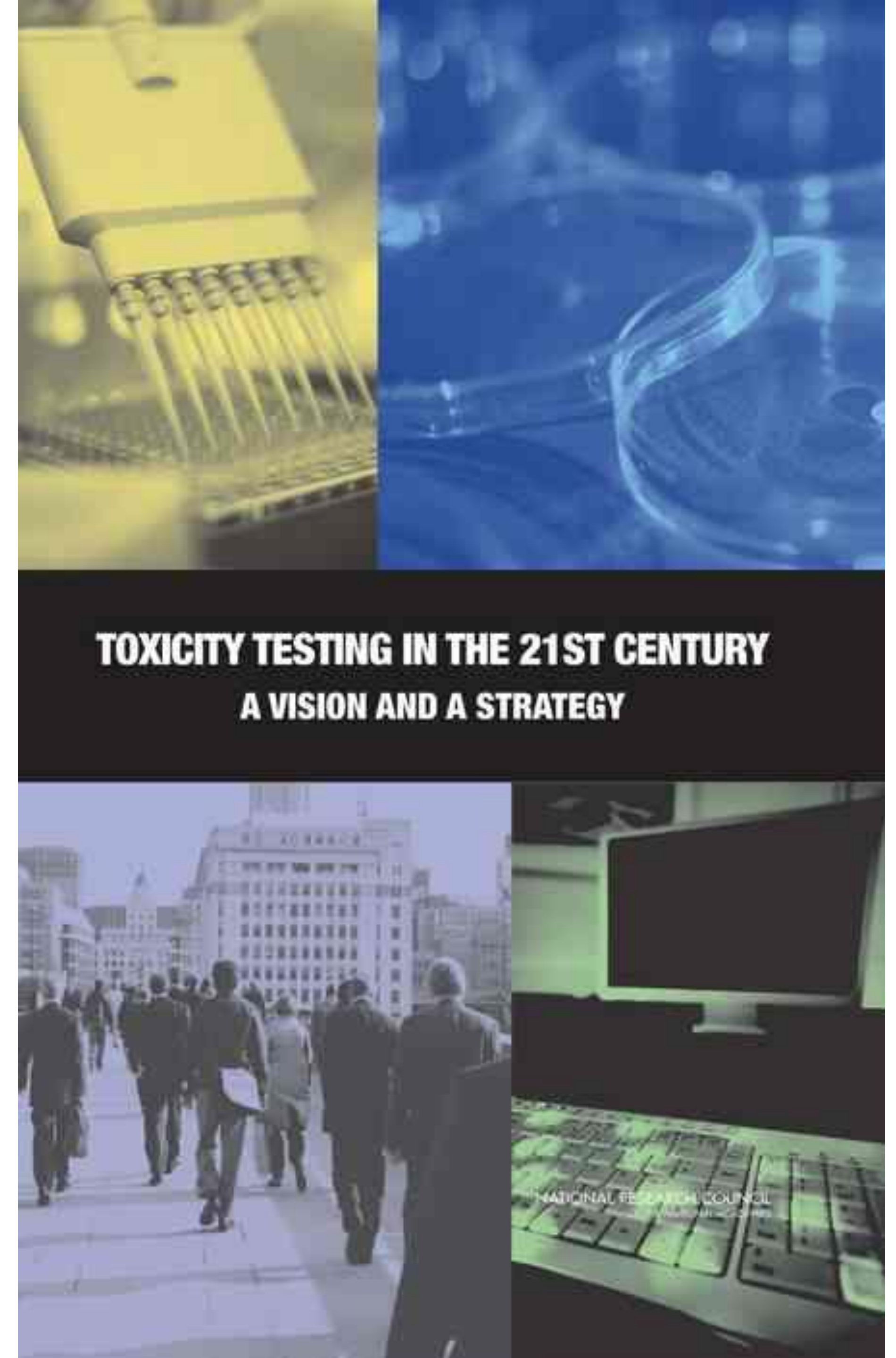


OECD Series on Testing and Assessment No. 255. 2016.
OECD Series on Testing and Assessment No. 256. 2016.

TOXICITY TESTING IN THE 21ST CENTURY (TT21C)

TRANSFORMING CHEMICAL SAFETY ASSESSMENT

- “Transform toxicity testing from a system based on whole-animal testing to one *founded primarily on in vitro methods* that evaluate changes in biologic processes using cells, cell lines, or cellular components, preferably of human origin”
- “The vision emphasizes the development of suites of predictive, high-throughput assays”
- “The mix of tests in the vision include tests that *assess critical mechanistic endpoints* involved in the *induction of overt toxic effects rather than the effects themselves.*”

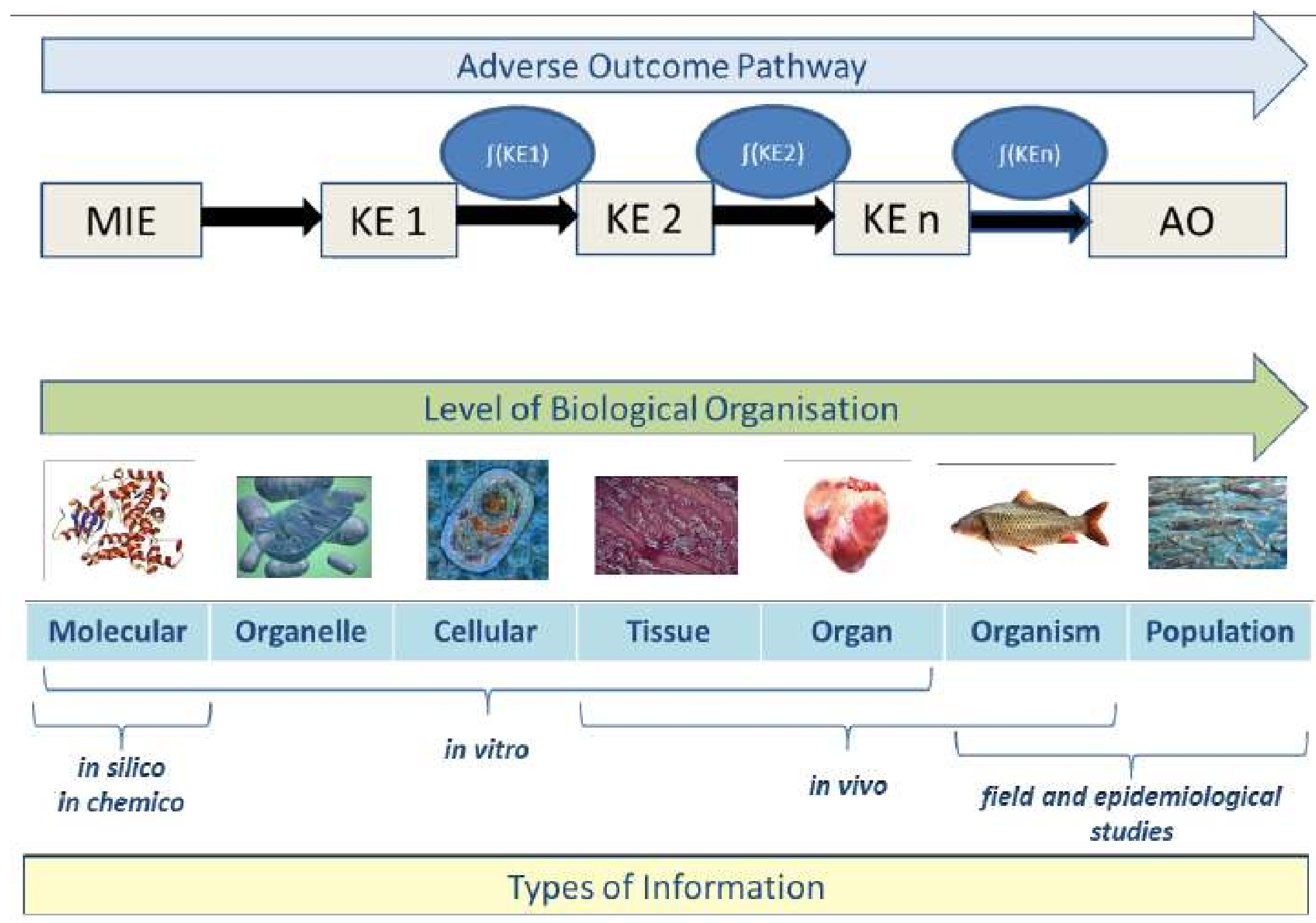


TOXICITY TESTING IN THE 21ST CENTURY A VISION AND A STRATEGY

NATIONAL RESEARCH COUNCIL
ON ENVIRONMENTAL HEALTH EFFECTS
NATIONAL ACADEMIES PRESS
WASHINGTON, DC 20540

ADVERSE OUTCOME PATHWAYS

DECISION SUPPORT

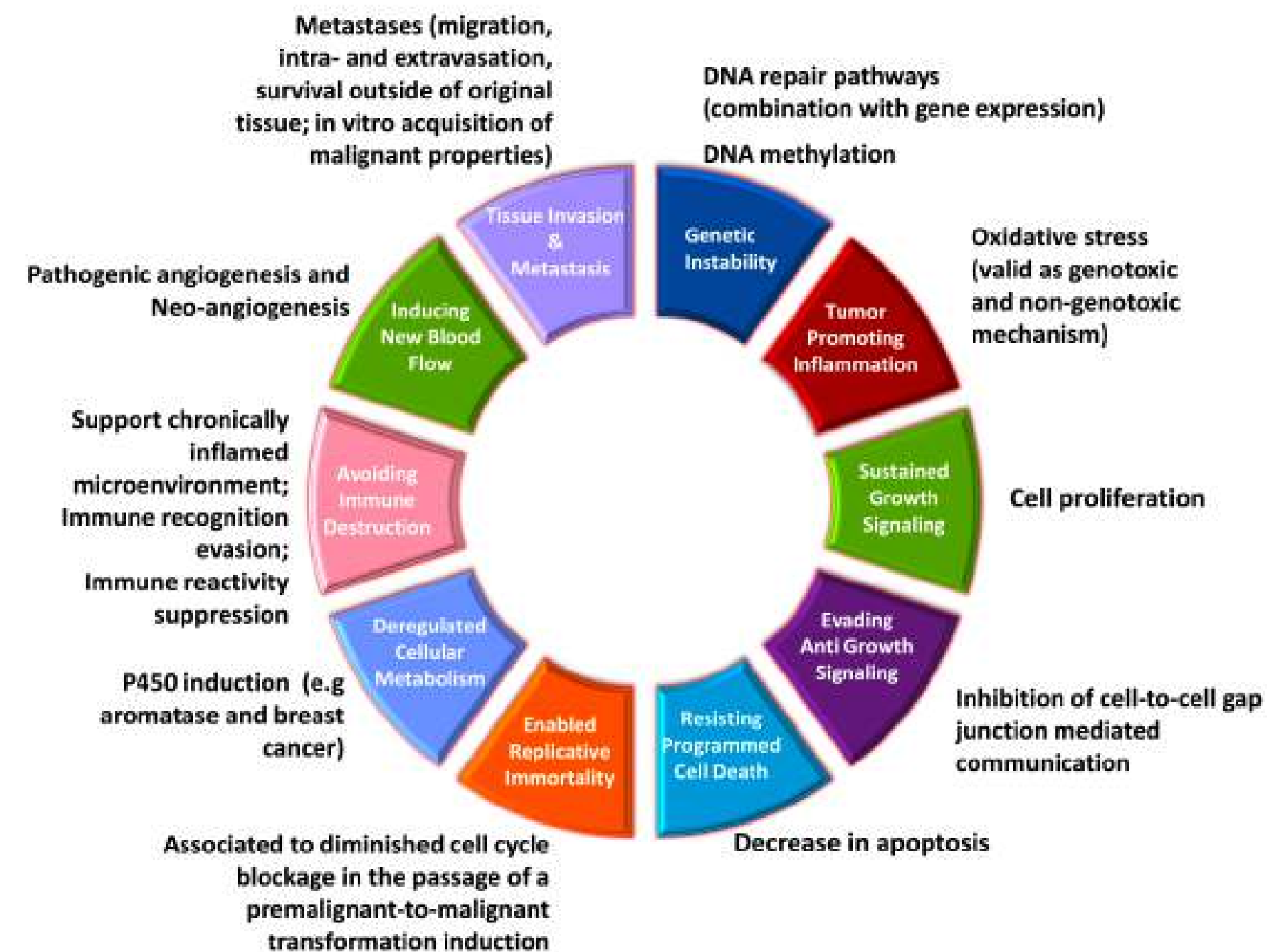


- Framework for organizing, relating and evaluating biological information
- Links upstream molecular and cellular events to downstream changes at the tissue, organ and organism and population levels
- Biology is described as a sequence of Key Events
- Key Event Relationships can include kinetic, quantitative information, feed-back loops
- Used to design ITS
- Supports IATA and WoE analyses
- Supports decision making using molecular information generated in vitro

NON-GENOTOXIC CARCINOGENICITY (NGTxC)

OECD EXPERT GROUP
PROJECT

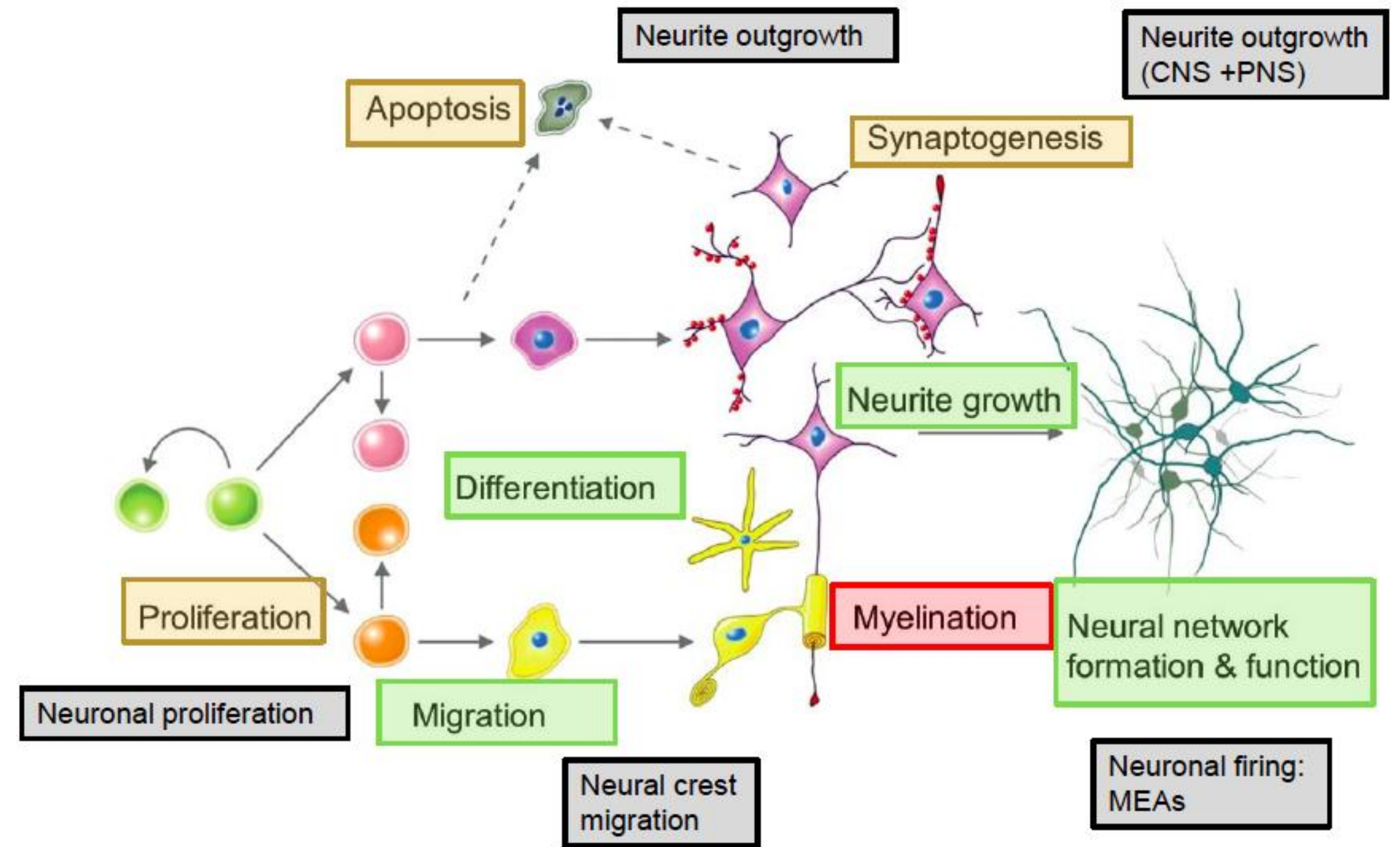
- Based on Hallmarks of Cancer
- Identify relevant mechanisms, MIEs, AOPs
- Identify appropriate in vitro methods
- Design IATA and DA to address regulatory needs



DEVELOPMENTAL NEUROTOXICITY

DECO EXPERT GROUP
PROJECT

- Based on pathways of neural development
- Identify relevant mechanisms, MIEs, AOPs
- Identify appropriate in vitro methods
- Focused on human biology
- Design IATA and DA to address regulatory needs



Aschner et al., 2017 & Mundy

DECISION FRAMEWORKS FOR COSMETICS

Frameworks that support non-animal safety assessment of cosmetics

- International Collaboration on Cosmetics Regulation (ICCR) Next Generation Risk Assessment (NGRA) decision framework
- The SEURAT workflow for chemical safety assessment
- A new collaboration: Non-Animal Cosmetic Safety Assessment by 2023 (NACSA)

INTERNATIONAL COOPERATION ON COSMETICS REGULATION (ICCR*) NEXT GENERATION RISK ASSESSMENT (NGRA)

NGRA DECISION PRINCIPLES

*Brazil, Canada, EU, Japan, US

Overarching

1. The overall goal is a human safety risk assessment
2. The assessment is exposure led
3. The assessment is hypothesis driven
4. The assessment is designed to prevent harm
(i.e. distinguish between adaptation and adversity)

Risk assessment process

5. Using a tiered and iterative approach
6. Appropriate appraisal of existing information
7. Using robust and relevant methods and strategies

Documenting risk assessments

8. The logic of the approach should be transparently and explicitly documented
9. Sources of uncertainty should be characterized and documented

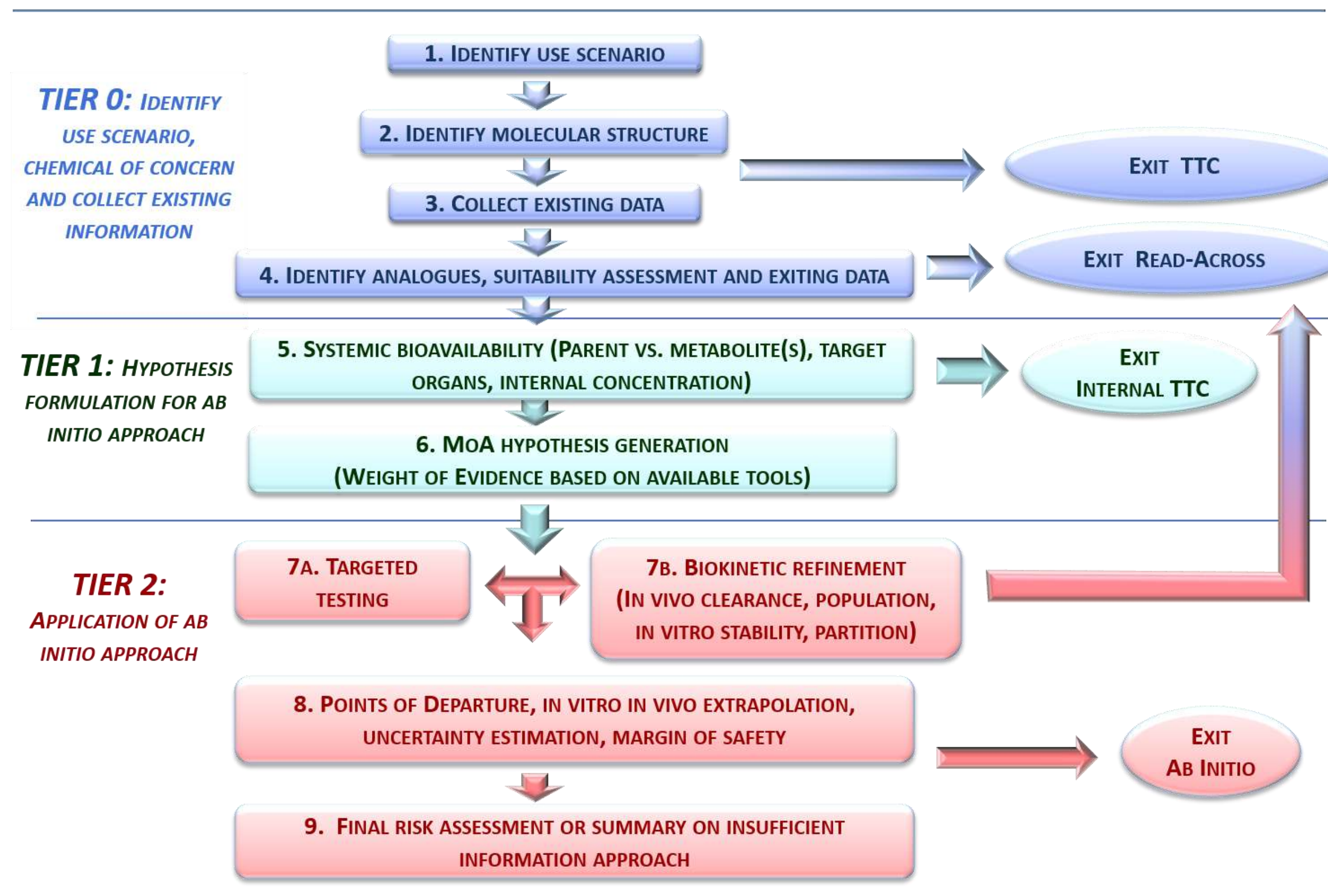
Report for International Cooperation on Cosmetics Regulation, Regulators & Industry Joint Working Group
(JWG): Integrated Strategies for Safety Assessment of Cosmetic Ingredients: Parts 1 & 2.



SEURAT WORKFLOW

DECISION FRAMEWORK

- Use of NAMs for cosmetic safety assessment
- Exposure-led
- Ingredient-based



SUMMARY

Since the first ban on animal testing of cosmetics in the EU passed in 2004:

- 39 countries now have testing and/or sales bans, with several more in consideration
- In vitro methods have blossomed, with more available every year
- There is a new way of thinking developing about chemical safety
 - Based on understanding biological pathways and
 - Measuring upstream molecular events
 - to identify safe exposure (vs toxicity)
- Several frameworks have been developed to support decision making with NAMs
 - International collaborations
 - International support (OECD)

More and better NAMs combined with evolved safety assessment processes leads to improved decisions regarding human safety

However, there is still a lot to be done....





COLLABORATION FOR *NON-ANIMAL* COSMETIC SAFETY ASSESSMENT (*NACSA*)

A new collaboration between Humane Society International, industry partners and other interested groups to help shape future cosmetics legislation and build decision-making infrastructure to support cosmetic safety assessment.

The project has 3 objectives:

- Global harmonization of non-animal cosmetic safety assessment legislation
- Sharing information on decision-making approaches without new animal testing
- Education and Training to build capacity for non-animal safety decisions within both the regulated and regulatory cosmetic communities

Partners: industry, regulators, methods developers, contract research organizations, consultants, NGOs

Target audiences: Regulators and industry assessors, including SMEs, safety and regulatory compliance consultants, academic researchers and students, informed consumers

EDUCATION AND TRAINING MODULES

DECISION-MAKING ELEMENTS

- Overview of exposure-led, non-animal risk assessment approaches
- Problem formulation
- Decision-making frameworks
 - Point-of-departure determination
 - Uncertainty characterization
 - Governance for traceability/transparency
- Risk assessment case studies



TOOLS & APPROACHES

- Exposure-led risk assessment
 - Determination of acceptable exposure limits
 - Scenario-based exposure calculations
- Predictive chemistry
 - (Q)SAR, read-across
- History of safe use
- Data generation (in vitro methods)
- Next-generation risk assessment approaches
 - Exposure (PBPK, free concentration, metabolism)
 - Tiered approach (in silico, in vitro)
 - Computational modeling

DELIVERY

Webinars, videos, 1-pagers, website, continuing education sessions, symposia, academic lectures & collaborations



- Partners in developing detailed plans
 - ▶ for capacity building and education, and ensuring globally harmonized legislation
- ▶ Interest in any or all of the 3 project elements
- ▶ Expertise with specific modules
- ▶ Broad range of stakeholders, groups and organisations, many ways to contribute!

CONTACT KWILLETT@HSI.ORG

THANK YOU!

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