Animal-Free Safety Assessment Education and Training Program

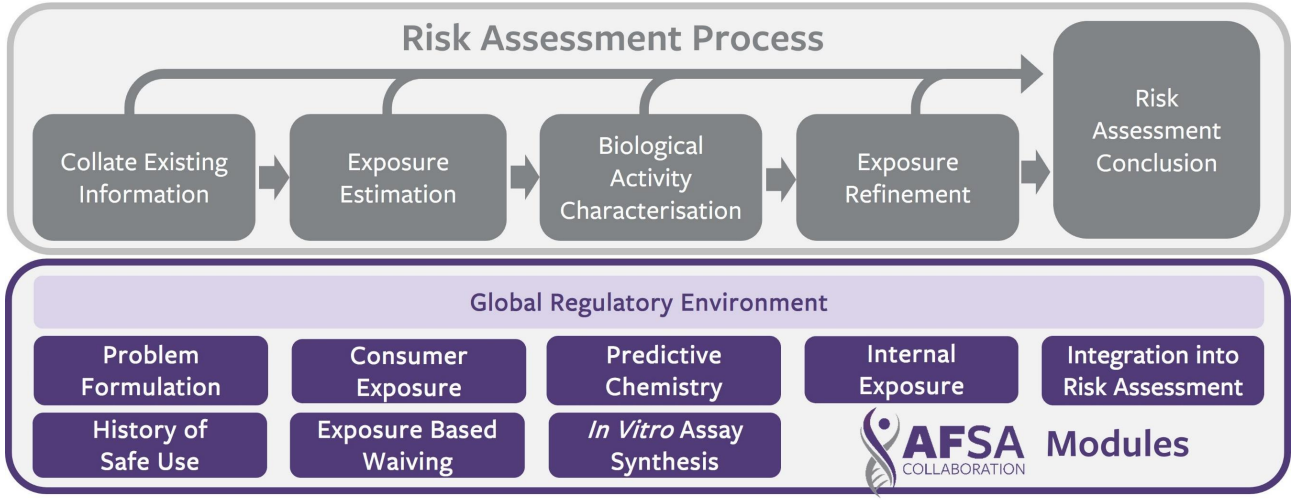
Global Regulatory Landscape

10 May 2022
11:00 am GMT/6:00 am EDT

Welcome and Introduction
Catherine Willett, Humane Society International

Global Cosmetics Regulatory Landscape
Jay Ingram, Delphic HSE

Slido Quiz and Q&A



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Overview: AFSA Cosmetics Education and Training

Catherine Willett
Humane Society International

10 May 2022

The Animal-Free Safety Assessment Collaboration

The HSI-coordinated **Animal-Free Safety Assessment** (**AFSA) Collaboration** works to accelerate global adoption of a modern, species-relevant approach to safety assessment that will better protect people and our planet, and hasten the replacement of animal testing

COSMETICS

CHEMICALS

BIOLOGICALS

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The Animal-Free Safety Assessment Collaboration

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COSMETICS

AFSA Education and Training in Next Generation Risk Assessment

CHEMICALS

BIOLOGICALS

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AFSA Cosmetics E&T

A Global Training Program in Non-Animal Risk Assessment

Scope

- Safety assessment of cosmetics and cosmetic ingredients without new animal data
- Covers all aspects of the process
  - Consumer exposure, external and internal
  - Acute local effects to systemic repeat effects
  - Information integration to make a risk decision
- Focus on *understanding* the information generated from the tools and *how to use* this information vs. how to perform or build the individual methods

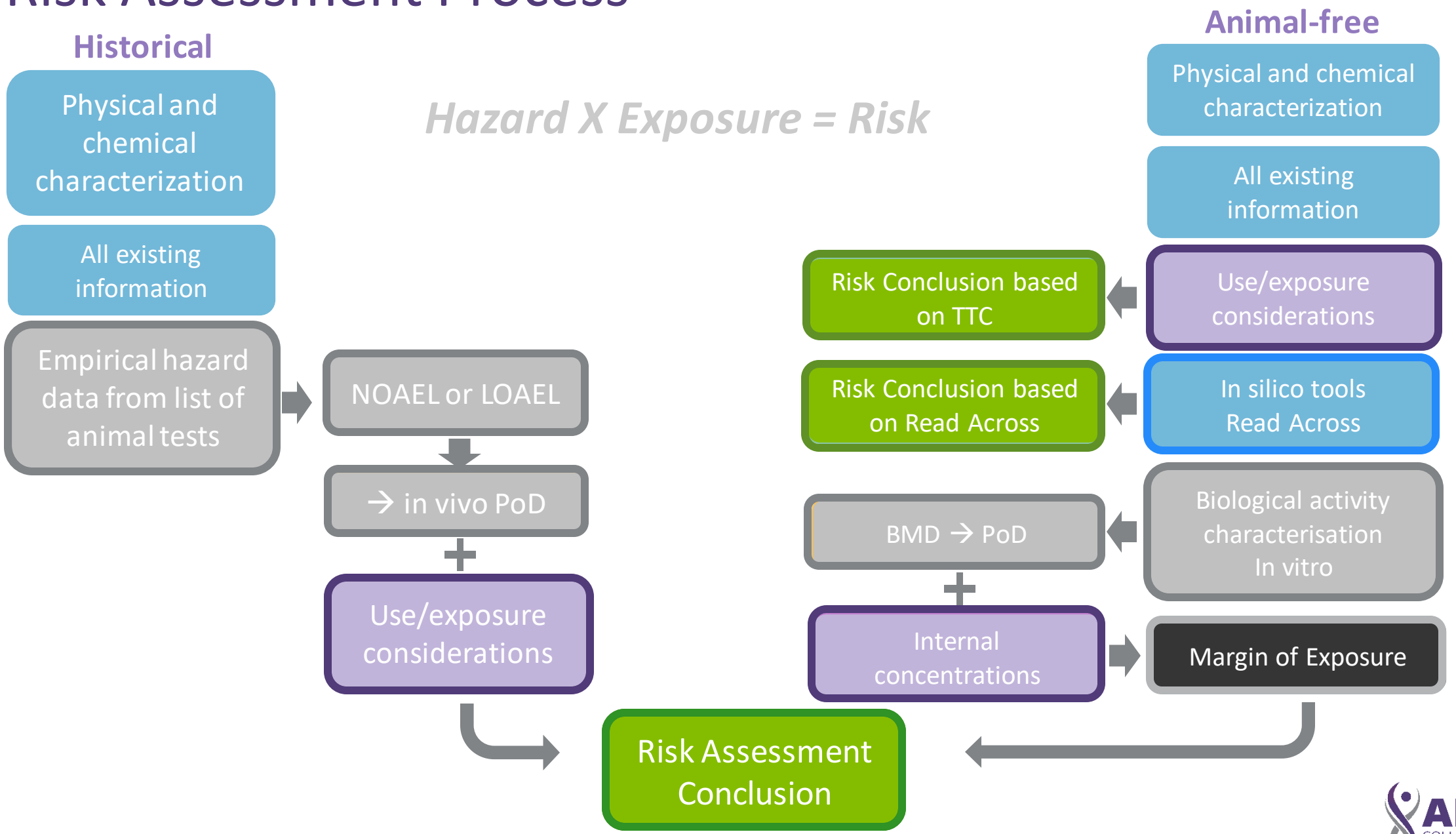
AFSA Cosmetics E&T

A Global Training Program in Non-Animal Risk Assessment

Purpose

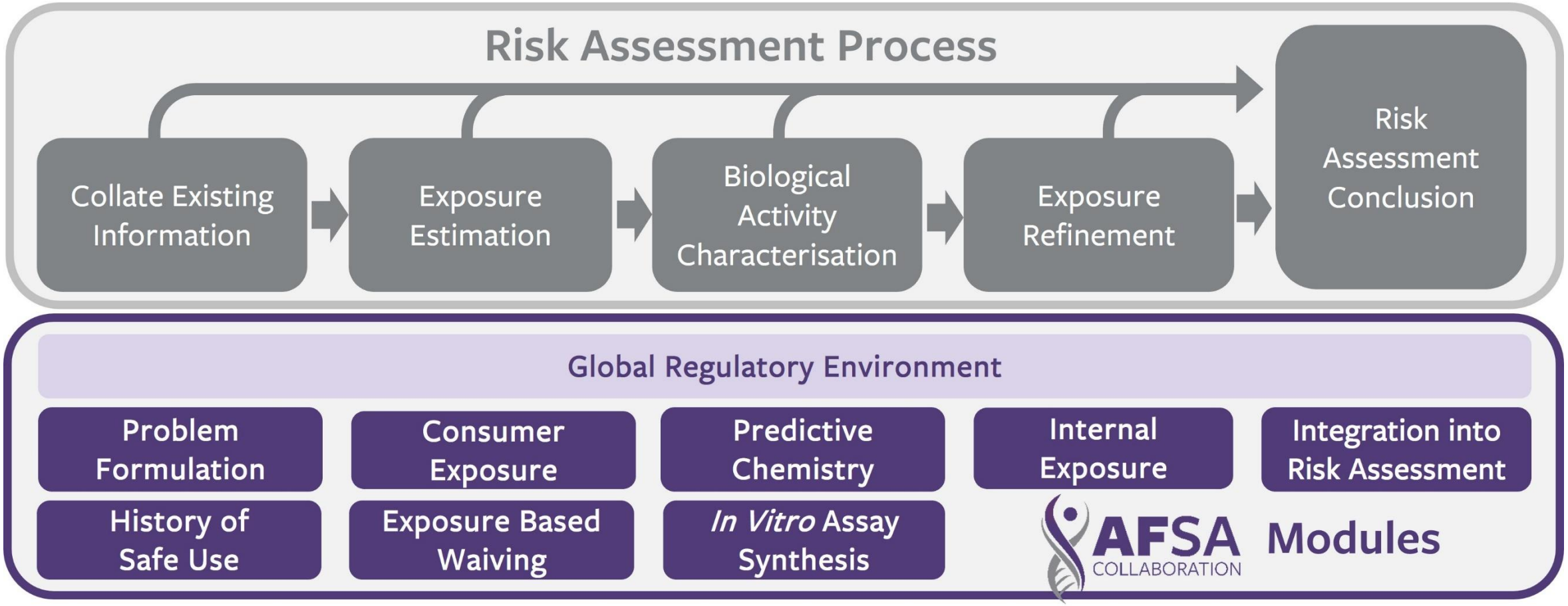
- Address the needs of regulatory & regulated communities as well as other stakeholders involved in risk assessment of products
- Support regional capacity-building to achieve long-term acceptance & implementation of non-animal approaches to safety assessment

Risk Assessment Process

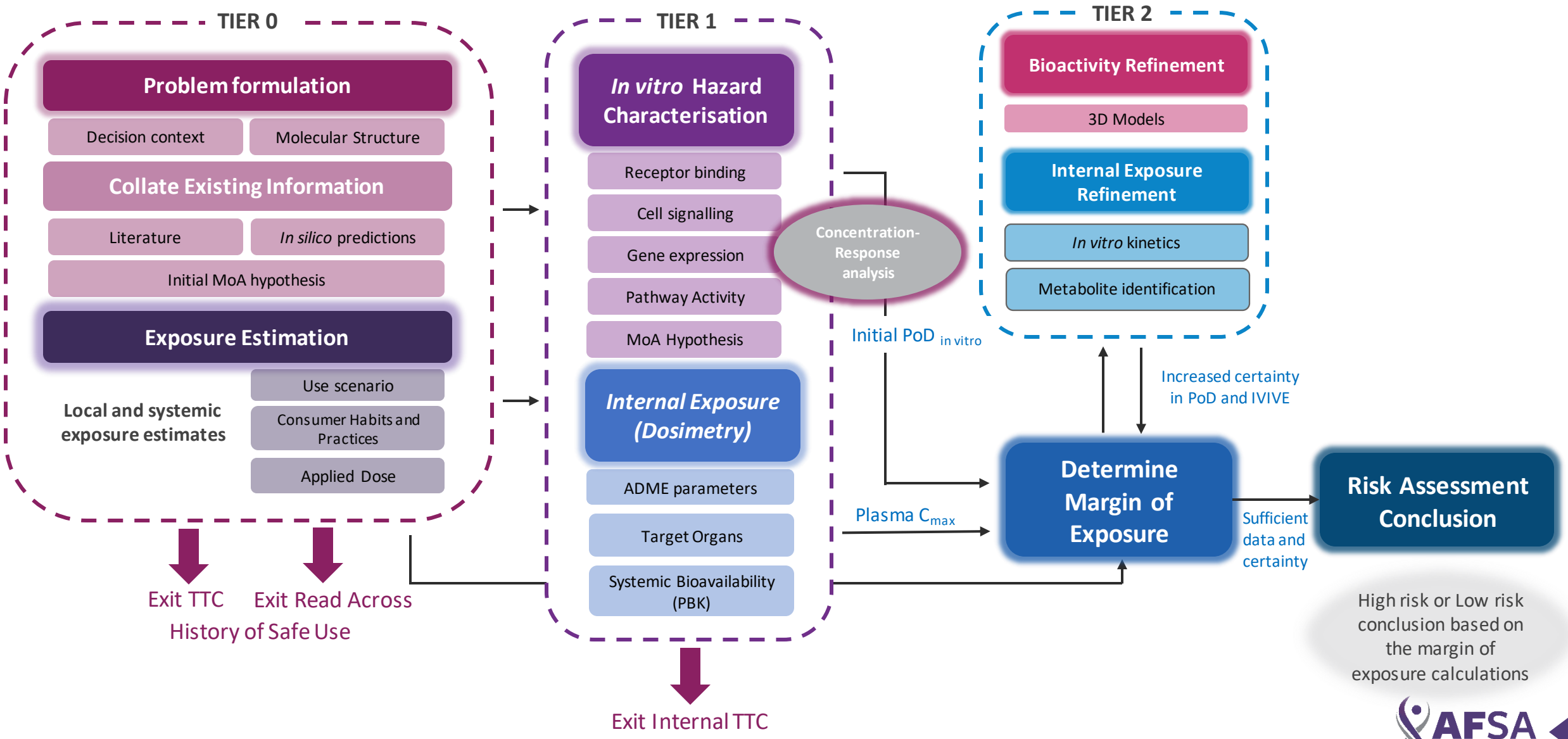


AFSA Cosmetics E&T

Covering Risk Assessment from start to finish



Next Generation Risk Assessment (NGRA) Framework



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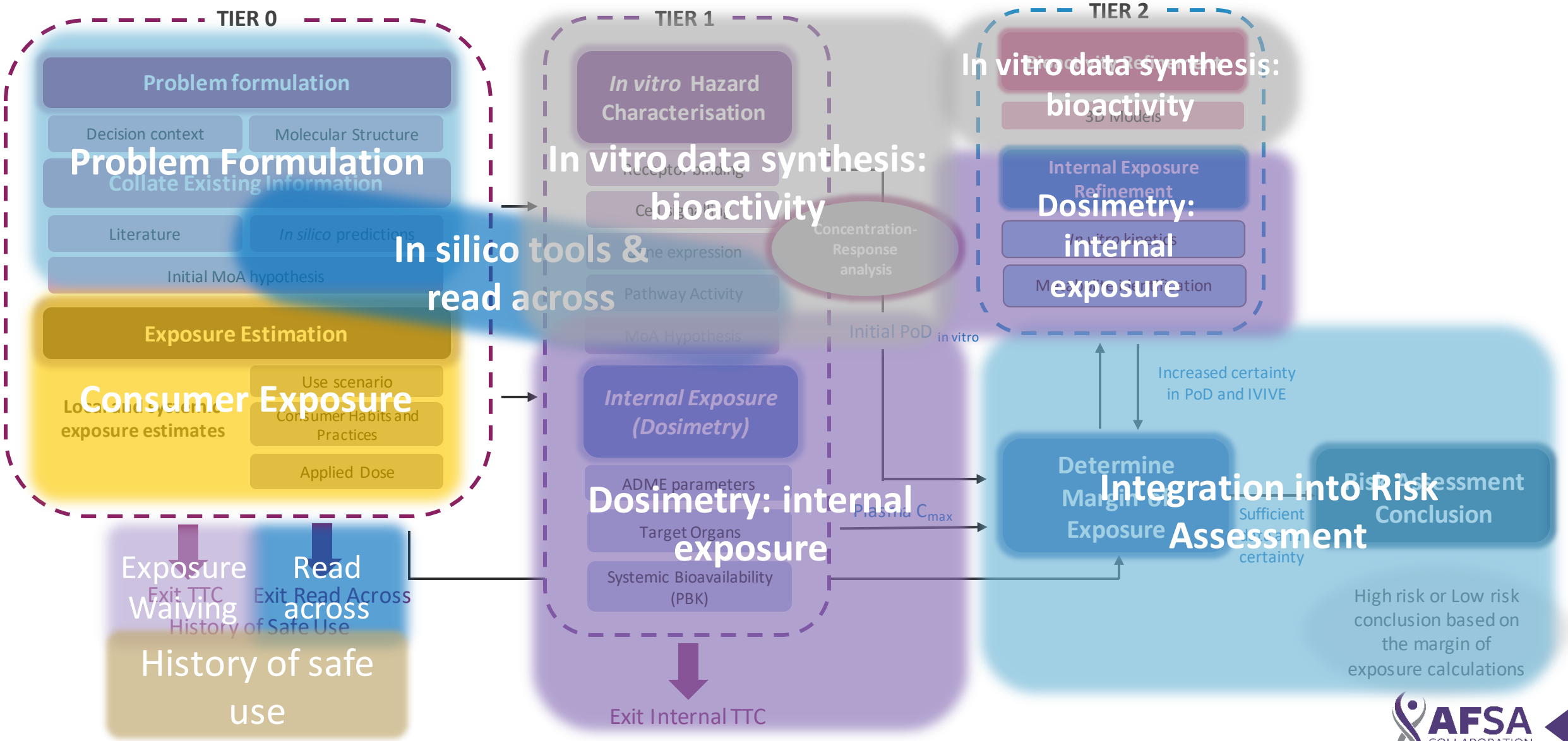
Next Generation Risk Assessment (NGRA) Framework



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Cosmetics Workstream Partners

HUMANE SOCIETY INTERNATIONAL

THE HUMANE SOCIETY OF THE UNITED STATES

Unilever

L'ORÉAL

P&G

Firmenich

AVON

iff

Givaudan

symrise

LUSH

Delphic HSE
SAFETY & REGULATORY SOLUTIONS

Lhasa Limited

IIVS
Institute for In Vitro Sciences

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Hermine Dika Nguea	L'Oreal
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AFSA – Module 9: Global Cosmetics Regulatory Landscape

Jay Ingram

Delphic HSE

10 May 2022

Overview

1. Historical Context
2. Current Regulatory Landscape
3. Regulatory Spotlight
4. Similarities & Differences
5. Complications in Implementation
6. Future Opportunities & Solutions

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Learning Objectives

By the end of this module, students should be able to:

- → Outline the historical context of the regulatory landscape
- → Identify countries and regions with cosmetic testing and sales bans
- → Compare and contrast differing styles and pieces of legislation
- → Explain complications that can arise in development & implementation of legislation
- → Describe opportunities and solutions made possible through the use of AFSA principles

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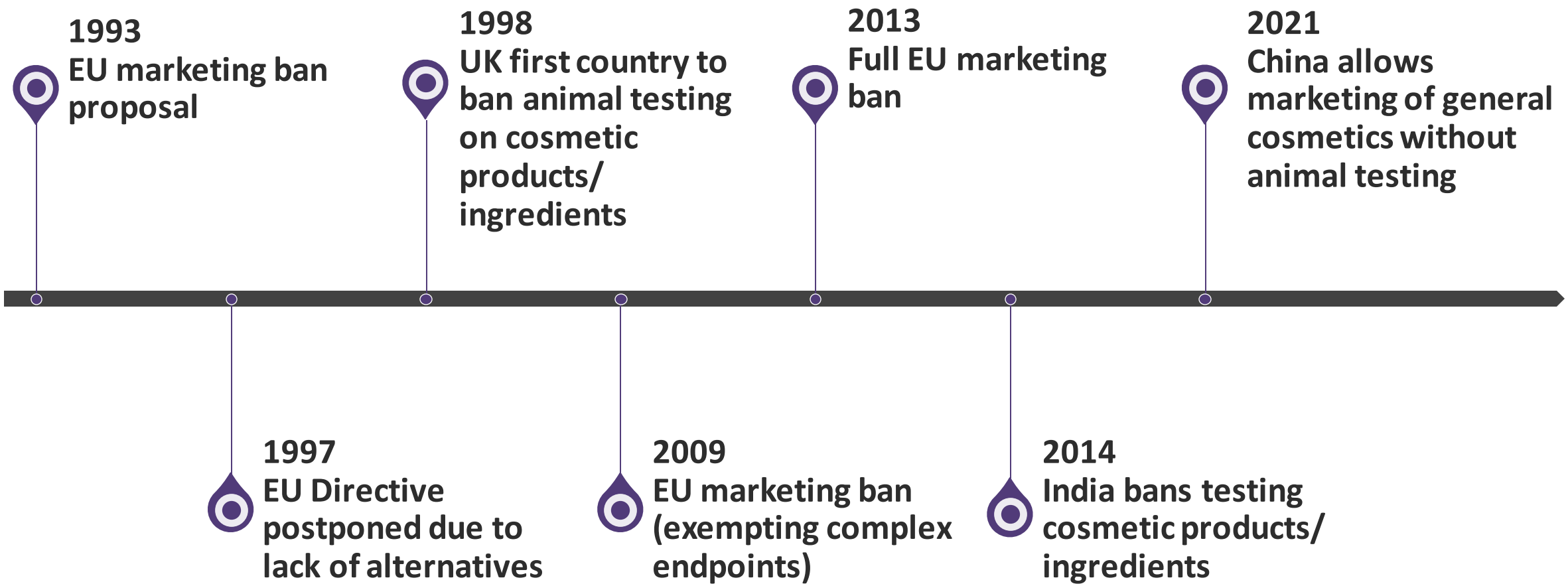
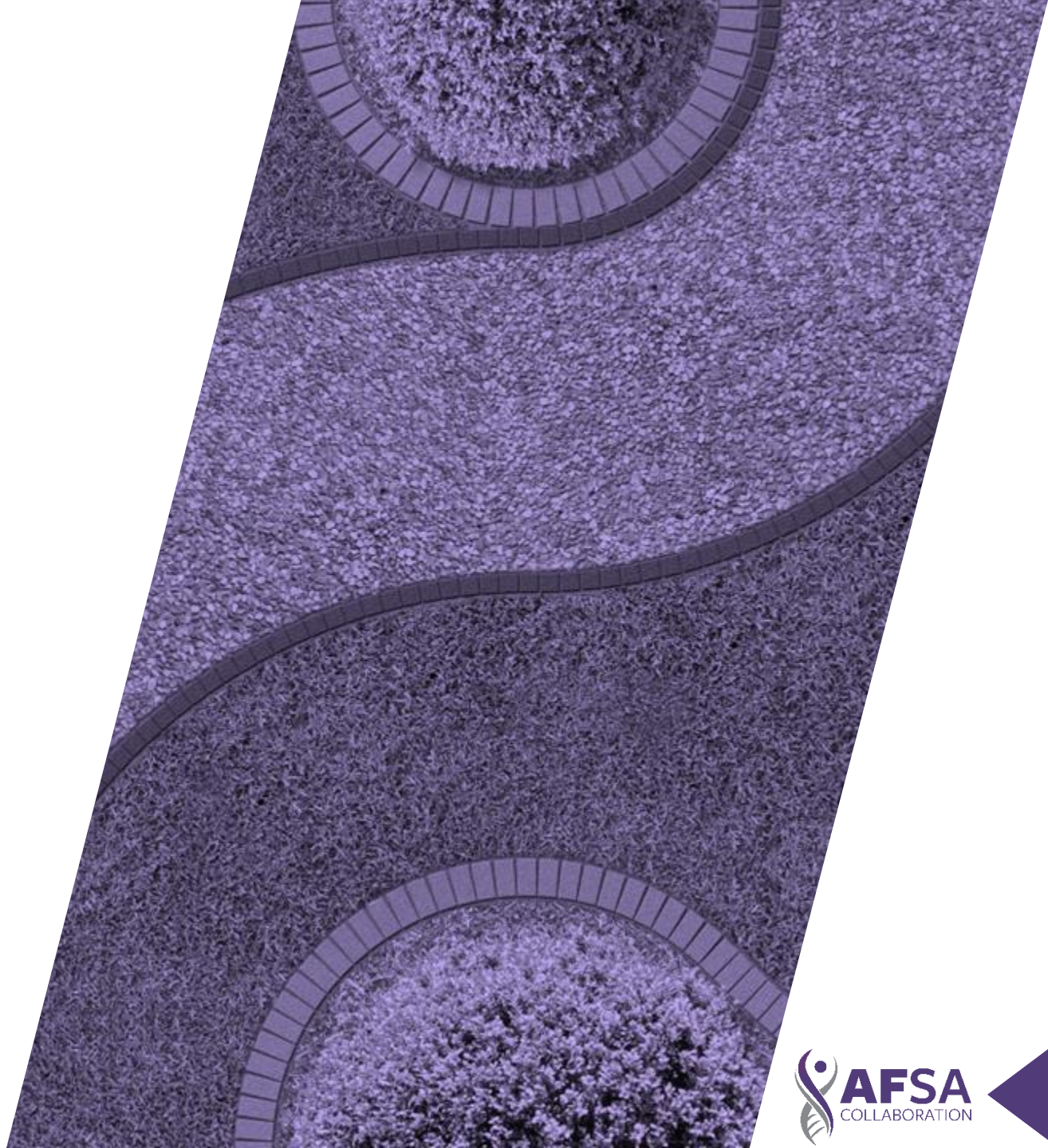
Historical Context

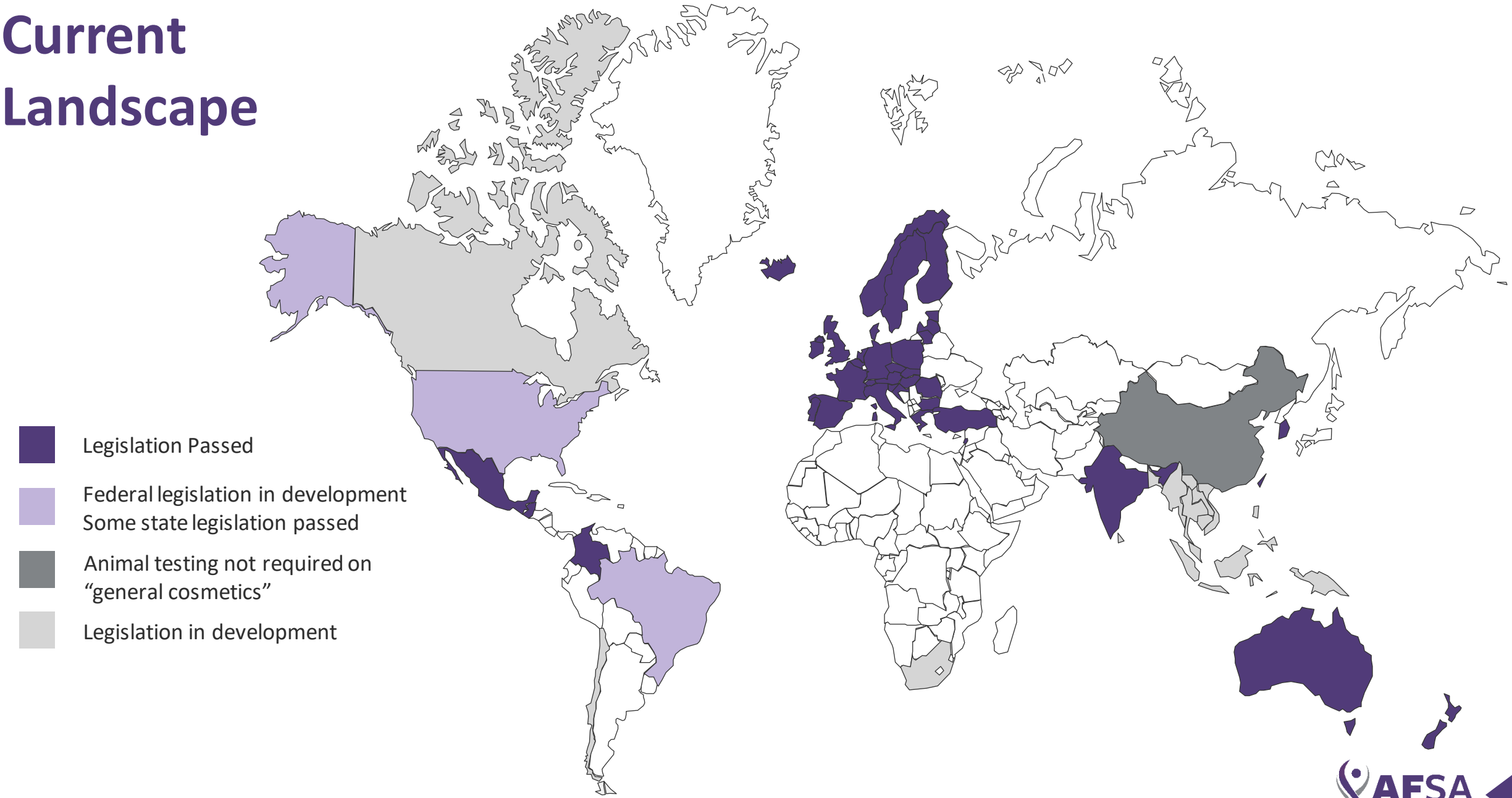
Historical Context



Current Regulatory Landscape



Current Landscape



Modified from: hsi.org/issues/be-cruelty-free/

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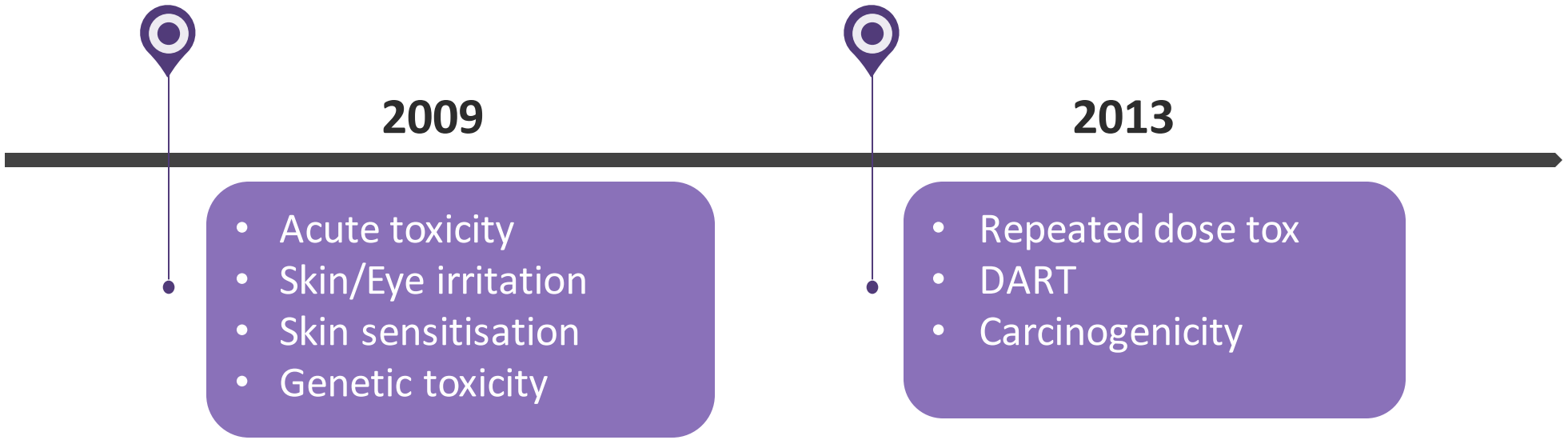
Regulatory Spotlight

European Union

EC 1223/2009

- All Cosmetics
- Finished Product & Ingredients
- Prohibits animal testing "…in order to meet the requirements of this Regulation"
- Staged prohibition:



China

Cosmetics Supervision and Administration Regulation

- Not an animal testing ban
- Allows for avoidance of animal testing for “General Cosmetic Products”
- Proof of GMP required
- Animal testing needed for
  - Child/infant products
  - New cosmetic products
- General vs. Special

- Special
- Hair Dyes/Perming
- Spot Treatments
- Sunscreens

India

Cosmetics Rules

November 2014

- First Asian Country to ban animal testing of cosmetics
- Rule 135-B: No cosmetic that has been tested on animals shall be **imported** into the country
- Rule 148-C: No person shall use any animal for testing of cosmetics
  - ✓ Products & ingredients

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Korea

Cosmetics Act

Passed: 2015

Into force: 2018

- Finished products & ingredients
- Excludes preservatives, UV filters, pigments
- Only applies where alternative methods approved by MFDS
  - ✓ Only non-complex endpoints & skin sensitisation

Australia

Industrial Chemicals Act 2019

In place July 2022

- New ingredients used exclusively in cosmetics cannot use animal testing to prove safety
- Not applicable for ingredients that may have industrial use
- Aligns w/ EU approach & exemptions
- Animal testing on on approval of Executive Director

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New Zealand

It is illegal to:

- *"Place on the market, cosmetic products where the final formulation...has been the subject of animal testing"*

- *"Place on the market, cosmetic products containing ingredients or combinations of ingredients which...have been subject to animal testing"*

Mexico

Animal test ban for cosmetics

September 2021

- Prohibits manufacture, import & marketing of cosmetics containing ingredients that have been tested on animals
- 2 year transition period to replace animal testing with
- *"alternative methods to assess safety & efficacy of cosmetic products"*
- Product must be labelled to indicate no animal test has taken place

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Turkey

July 2015
Animal testing
restricted

Jan 2016
Animal testing
prohibited

- Finished products & Ingredients
- Exemptions
- If an ingredient is in widespread use & cannot be replaced
- Specific human health concern
- Fulfilling regulation(s) of other countries/purposes
- TMMDA published Guidelines on Alternative Test Methods

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Israel

2007

Banned animal testing on cosmetic (and other) products manufactured in Israel

2013

Banned animal testing on cosmetic products imported to Israel

- No specific ban on ingredient testing
- regulatory practices broadly mirror EU
- EU is the most significant export market of Israeli made cosmetics

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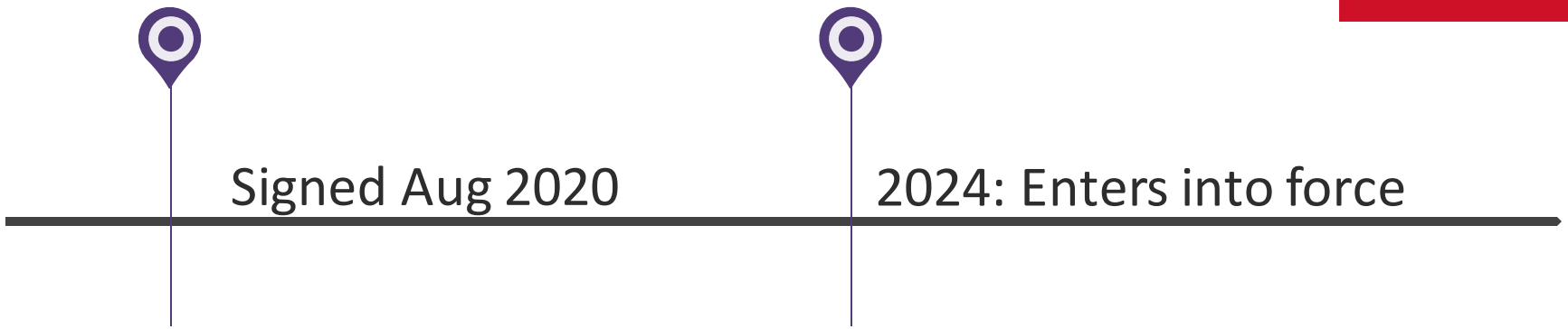
Columbia

Law 2047



- Bans import, manufacture & sale of cosmetics & ingredients tested on animals
- Exemptions consistent with EU

State-level Laws

USA

California

- First state implementing ban 2019

Nevada

- June 2019

Illinois

- September 2019

Virginia & Maryland

- Effective July 2022

Brazil

- Some animal tests abolished by CONCEA
- 10 states prohibit animal testing
- States represent >70% Brazil's national cosmetic industry
- Attempt by Rio de Janeiro to prohibit sale of cosmetics tested on animals in other Brazilian States

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Regulatory Comparison

EC 1223/2009

- All Cosmetics
- Finished Product & Ingredients
- Prohibits animal testing "…in order to meet the requirements of this Regulation"

CSAR

- Not a ban!
- General Cosmetics (Excludes e.g. hair dyes, hair perming products, spot removal, sunscreens)
- Animal tests required for:
- Infant/child products
- New cosmetic ingredients
- Proof of GMP required

Cosmetics Act

- All Cosmetics
- Finished Product & Ingredients
- Excludes: preservatives, UV filters & pigments
- Only where alternative methods approved by MFDS

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Similarities & Differences

Similarities

- Finished product & ingredients
- Exemptions
  - Testing required under other regulations
  - To address specific human safety concern

Differences

- Definition of cosmetic
- “Special Cosmetics” - China
- “Only where validated alternatives available” – South Korea
- State Level legislation – Brazil & USA
- Imported v. Local - NZ

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Complications in Implementation

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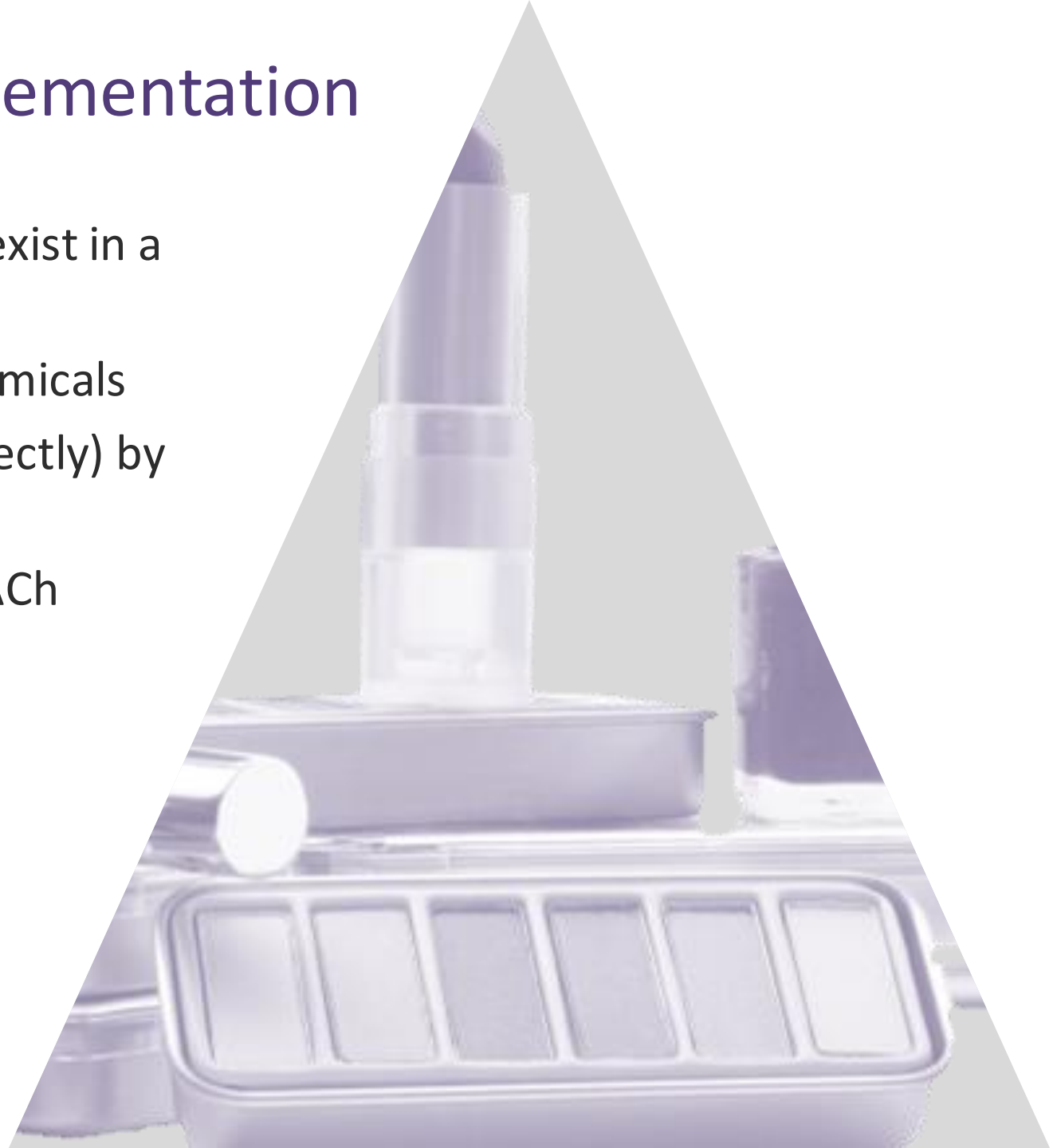
Complications in Implementation

Cosmetics regulation does not exist in a bubble

- → Cosmetics made up of chemicals
- → Impacted (directly or indirectly) by other pieces of Legislation
  - REACh/K-REACh/UK REACh
  - GHS/CLP
  - Borderline products

Many animal test bans exempt testing for other regulatory purposes



REACh

- Information requirements based on tonnage
- Relate to specific single-endpoint animal tests
  - → Read-across & in silico predictions can be used
    - only applicable within the bounds of answering the single-endpoint question
  - → Info requirements are collection of hazard data – not exposure
    - Exposure/risk assessed within CSA
      - Only certain substances will be subject to CSA
        - One trigger is hazard classification (more in CLP section)

REACh

Inflexible: explicit lists of test requirements

REACH	OECD TG	Average # animals/test
Annex VII: 1 - 10 tonnes/yr		
Skin irritation/corrosion in vitro	GD 203, 430, 431, 435, 439	
Eye irritation/corrosion in vitro	GD 263, 437, 438, 460, 491, 492,	
Skin sensitization in vitro	GD 256, 442C, 442D,442E (429, 406)	(LLNA 16 mice, GPMT 32 Guinea pigs)
Acute phototoxicity	432	
Gene mutation - in vitro (Ames)	471	
Acute systemic toxicity – oral	420, 423, 425	7, 6 - 12, 4-15 rats
Annex VIII: 10 - 100 tonnes/yr		
Skin irritation/corrosion in vivo	404	1-3 rabbits
Eye irritation/corrosion in vivo	405	1-3 rabbits
gene mutation - in vitro	476, 473, 487	
Acute systemic toxicity – inhalation	403	20 rats
Acute systemic toxicity – dermal	402	20 rats, rabbits or Guinea pigs
Repeat dose (28 day) toxicity - oral	407	40 rats
Repeat dose (28 day) toxicity – inhalation	412	40 rats
Repeat dose (28 day) toxicity – dermal	410	40 rats, rabbits or Guinea pigs
Reproductive/developmental screen	421, 422	675 rats
Short-term toxicity on fish	203	60 fish

REACH	OECD TG	Average # animals/test
Annex IX: 100 - 10000 tonnes/yr		
Mutagenicity – mouse micronucleus	474	50 rodents
Mutagenicity – chromosomal aberration in vivo	475	50 rats or hamsters
Mutagenicity – unscheduled DNA synthesis in vivo	486	12 rats
Mutagenicity – sister chromatid exchange in vivo		30 - 50 rodents
Mutagenicity – rodent dominant lethal	478	500 rodents (adults only)
Subchronic (90 day) toxicity - oral	408	80 rats
Subchronic (90 day) toxicity – inhalation	413	80 rats
Subchronic (90 day) toxcity - dermal	411	
Subchronic (90 day) toxicity – non-rodent	409	32 dogs
Prenatal developmetnal toxicity	414	80 rats or rabbits (pregnant females only)
Reproductive toxicity in 2 generations	416	2,600 rats
Long-term toxcity on fish	204	50 fish
Early life stage - fish	210	360 fish
Short-term fish embryo and sac-fry	212	180 fish
Fish Juvenile growth test	215	288 - 480 fish
Bioaccumulaton in aquatic species - fish	305	12 fish
Annex X: >1000 tonnes/yr		
Carcinogenicity/chronic toxicity – rodent	453	400 rats
Carcinogenicity – rodent	451	400 mice
Developmental toxicity – non-rodent	414	660 rabbits
Avian oral toxicity	205	
Reproductive toxcity - birds	206	approx. 400 birds

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REACh

"aims to improve the protection of human health and the environment through the better and earlier identification of the intrinsic properties of chemical substances"

- More appropriate to discuss "improving the protection of human health & the environment through the better understanding of the **risk** to human health & the environment posed by chemical substances"
  - Information requirements could be framed to address risk
  - Data gaps could be filled using NAMs rather than relying on animal tests to satisfy a "tick box" approach

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GHS/CLP

- Classifications based on single-endpoint animal test

- Classifications hazard-based
  → GHS does not consider exposure

- Purpose is communication of hazards throughout supply chain
  → Occupational
  → Accidental Release
  → Transport
  → Consumer
  → Environment

- In vitro methods available for non-complex endpoints

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Complications in Implementation

- ECHA Non-animal approaches report 2017*:

  "In spite of very active ongoing research in the area of non-animal approaches, approaches capable of replacing animal testing for complex endpoints are not yet available….nature of such future approaches cannot be established yet"

  "…may not provide the same level of information on the toxicity of substances as the current animal studies…dose/concentration-response relationship and adverse effects"

  "…need to be clarified how to make use of the evidence from new non-animal approaches that do not directly inform on adversity or specific toxicities for classification under the CLP Regulation"

*edited & highlighted for this presentation

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Complications in Implementation

Banning ≠ Acceptance

- Lack of familiarity
- Uncertainty & low degree of confidence in application
- Multi-faceted nature extends beyond traditional toxicology
- Validation requirements

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Future Opportunities & Solutions

Future Opportunities & Solutions

Understanding of uncertainty

Traditional v. Modern approaches

Building confidence through engagement & education

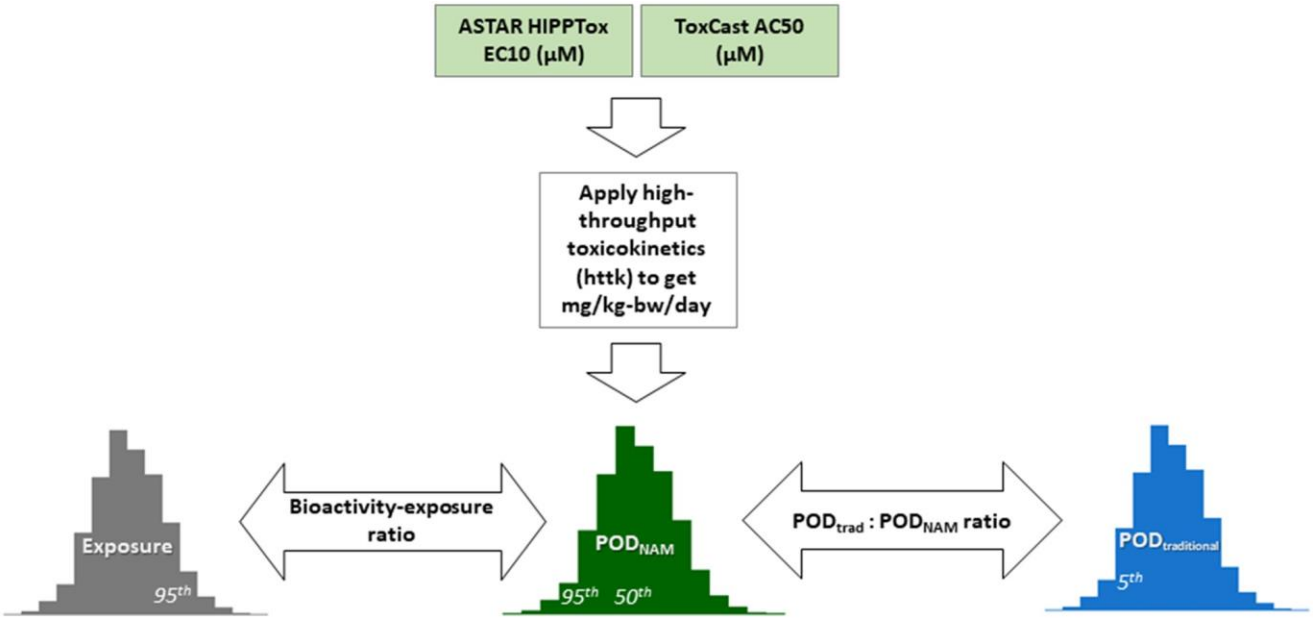
AFSA Education & Training Programme

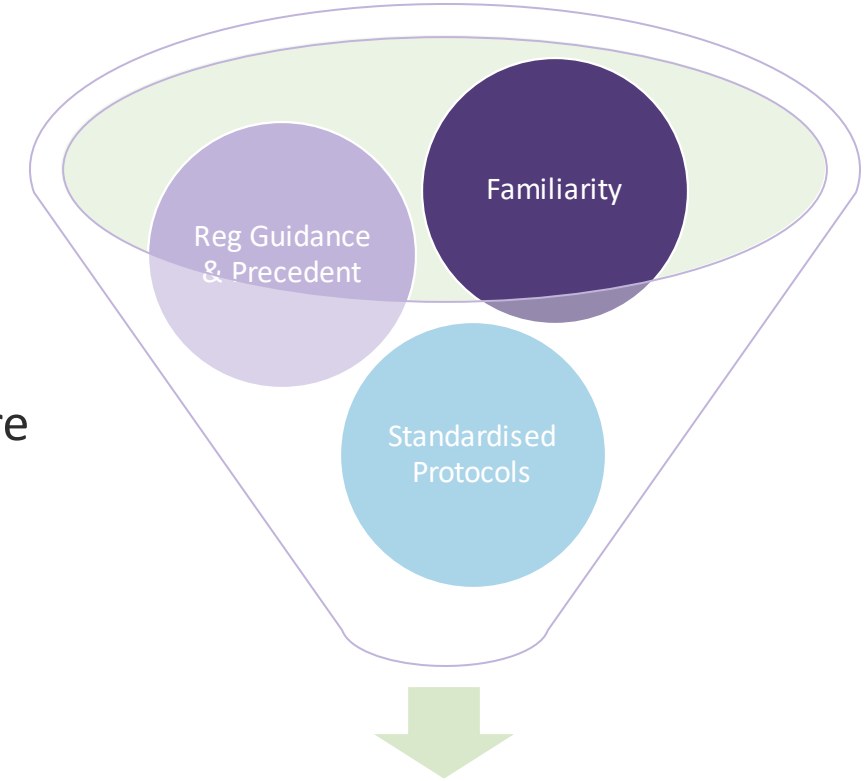
Holistic legislative frameworks

Science-based & Exposure-led

Understanding of Uncertainty

- Comfort in uncertainty of animal models built over time
- Inherent uncertainty mitigated by “safety factors”
- Validation is not a contributing factor to confidence
- NAMs frequently provide more conservative points of departure than traditional methods (Friedman et al. (2020)





Friedman et al., Toxicol Sci, Volume 173, Issue 1, January 2020, Pages 202–225, https://doi.org/10.1093/toxsci/kfz201

Toxicological Sciences

Utility of In Vitro Bioactivity as a Lower Bound Estimate of In Vivo Adverse Effect Levels and in Risk-Based Prioritization

Katie Paul Friedman, Matthew Gagne, Lit-Hsin Loo, Panagiotis Karamertzanis, Tatiana Netzeva, Tomasz Sobanski, Jill Franzosa, Ann Richard, Ryan Lougee, Andrea Gissi, Jia-Ying Joey Lee, Michelle Angrish, Jean-Lou Dorne, Stiven Foster, Kathleen Raffaele, Tina Bahadori, Maureen Gwinn, Jason Lambert, Maurice Whelan, Mike Rasenberg, Tara Barton-Maclaren, Russell S Thomas ✉

Toxicological Sciences, kfz201, https://doi.org/10.1093/toxsci/kfz201
Published: 18 September 2019 **Article history** ▾

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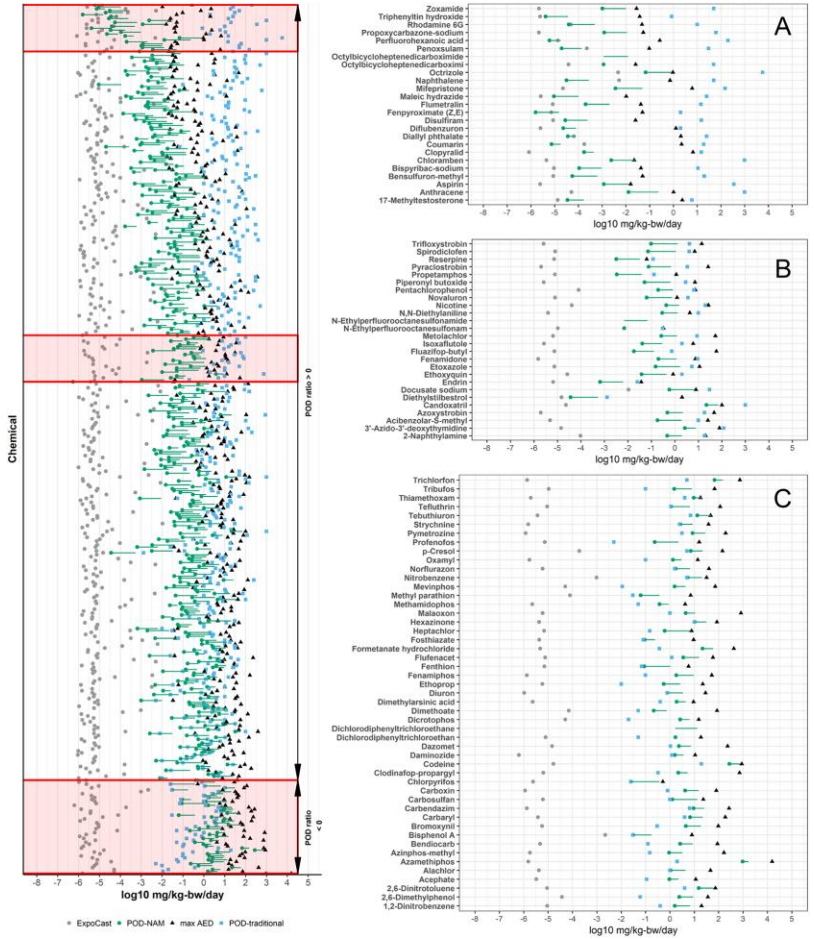
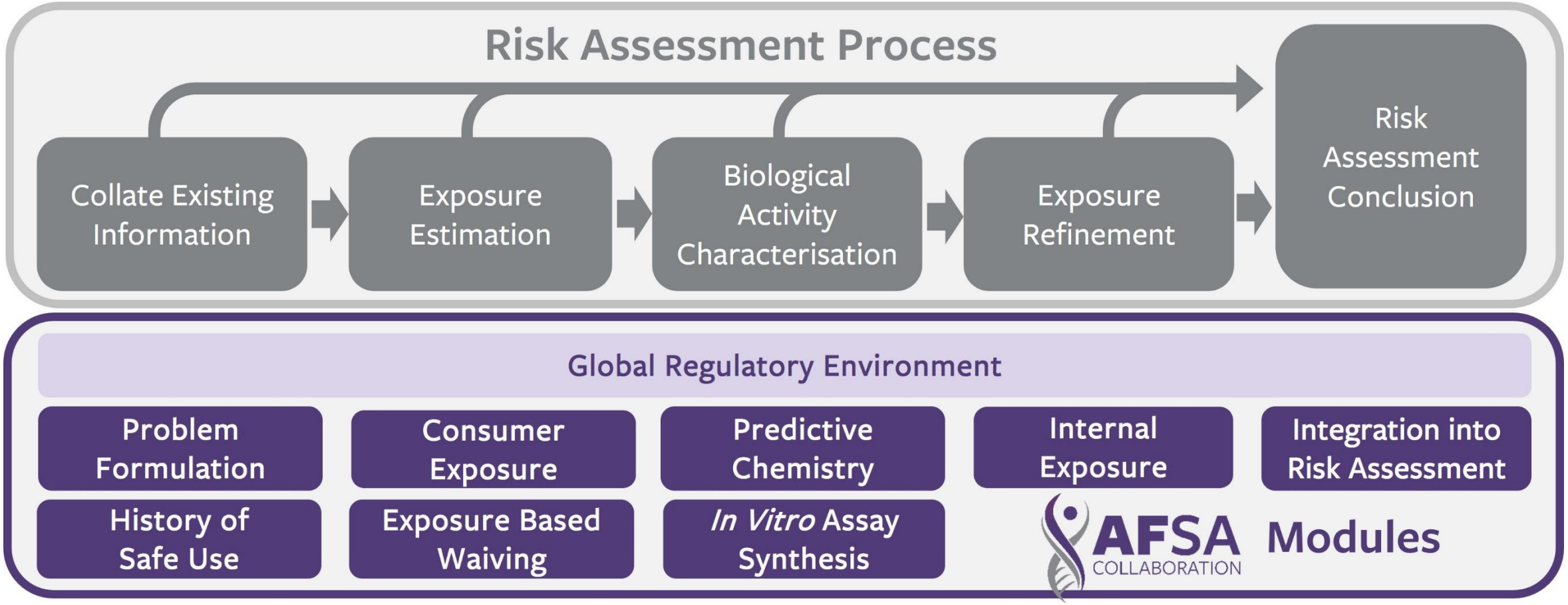
Accelerating the Pace of Chemical Risk Assessment (APCRA)

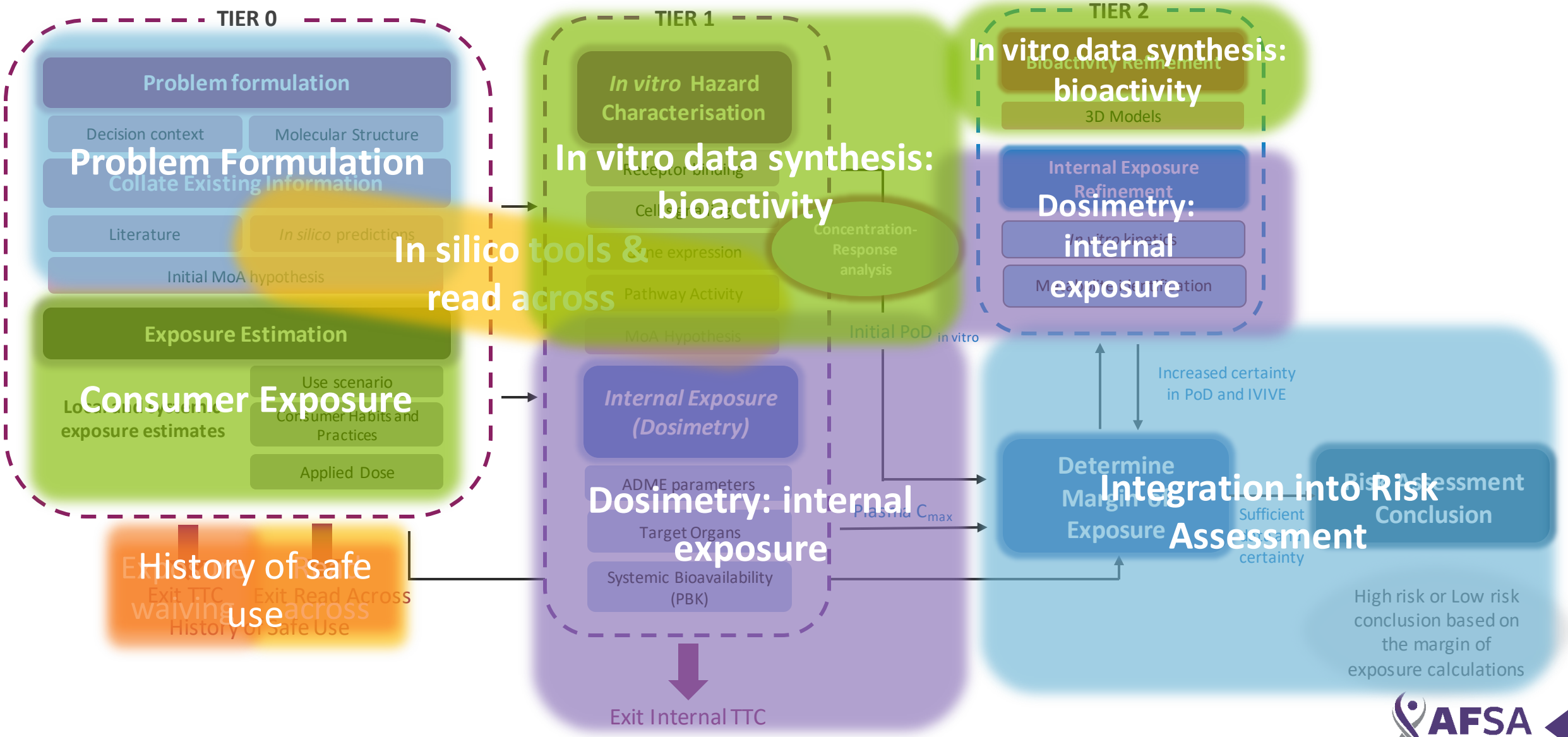


- Of the 448 substances, 90% had a $POD_{Bioactivity}$ that was less than the $POD_{Traditional}$ value with a median $log10_{POD}$ ratio of 2 (100-fold).
- The bioactivity POD served as a protective metric relative to traditional toxicological endpoints

Building Confidence through Engagement & Education



Building Confidence through Engagement & Education



Building Confidence through Engagement & Education

Accelerating the Pace of Chemical Risk Assessment (APCRA):

An International Governmental Collaborative Initiative

Australia: Australian Industrial Chemicals Introduction Scheme (AICIS)

Canada: Health Canada

European Union: ECHA, EFSA, JRC, INERIS, RIVM

Japan: Ministry of the Environment

South Korea: Ministry of the Environment, Ministry of Health, Welfare and Labour

Singapore: A*STAR

Taiwan: SAHTECH (Taiwan)

United States: EPA, Cal EPA, NTP, CPSC

- Common understanding of current state of the science applications of New Approach Methods (NAMs), including the regulatory context.
- Increased understanding of realistic benchmarks for performance of NAMs in different regulatory contexts.
- Determine mechanisms to enhance data sharing capabilities.
- Increase engagement and commitment to development and sharing of case studies of mutual interest.
- Increased cross-Agency collaboration to strategically address barriers and limitations of use of NAMs in a regulatory context.

https://www.epa.gov/chemical-research/accelerating-pace-chemical-risk-assessment-apcra

Building Confidence through Engagement & Education

CTPA NAMs Workshop March 2022

- UK Cosmetics Trade Association
- Included Industry, Regulators, Academics, & NGOs
- Need to avoid 2-tier accessibility to NAMs technology & capability
  - ✓ Gov't guidance needs to be clear & applicable to all
- Potential for x-governmental awareness & acceptance
- Require Constructive Dialogue vs. Rejection of Methods
  - ✓ "Safe space for experimental leveraging of methods

JUST DO IT!

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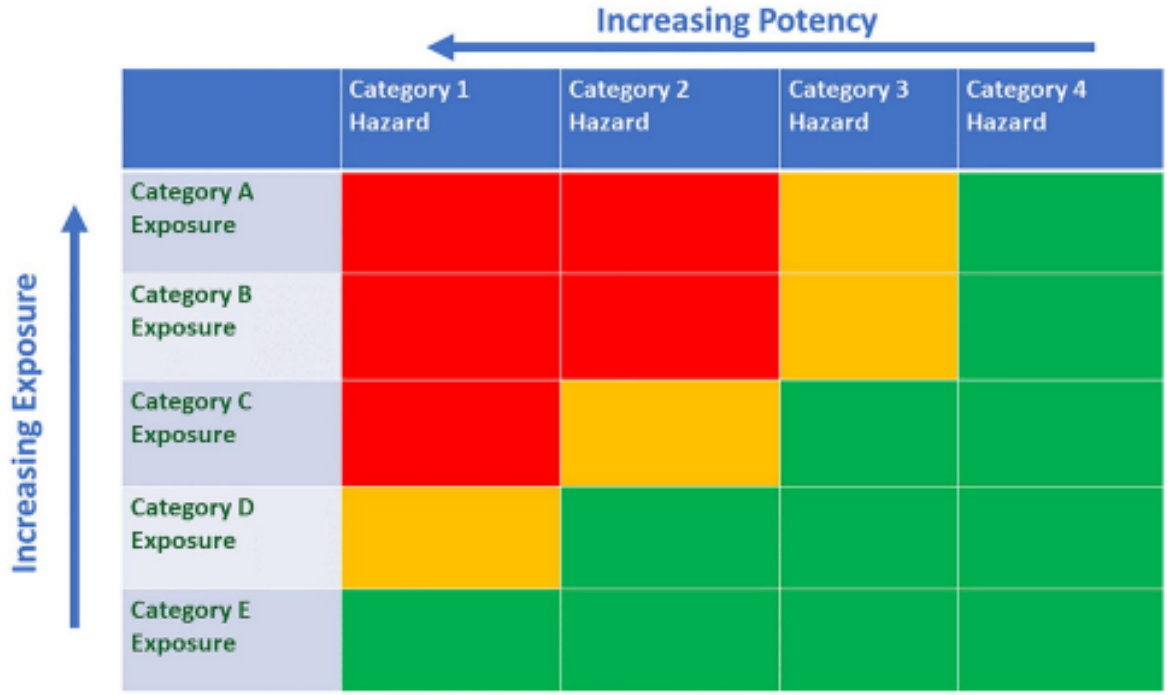
Holistic Legislative Frameworks

- "REACH (EC 1907/2006) aims to improve the protection of human health and the environment through the better and earlier identification of the intrinsic properties of chemical substances"
- NAMs offer *Protection not Prediction*
- Impactful regulation must be:
  - → Exposure-led
  - → Human relevant
  - → Hypothesis driven



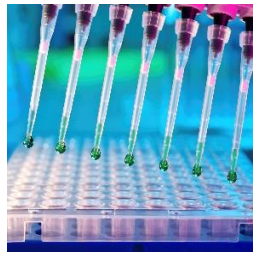
Ball et al. (2022) Archives of Toxicology. 96:743-766

US Toxic Substances Control Act

2016 update

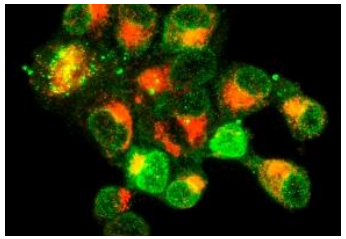
SECTION 4. TESTING OF CHEMICAL SUBSTANCES AND MIXTURES.

"IN GENERAL —The Administrator shall reduce and replace, to the extent practicable, scientifically justified, and consistent with the policies of this title, the use of vertebrate animals in the testing of chemical substances or mixtures under this title"



The Administrator shall "prioritize and…carry out performance assessment, validation, and translational studies to accelerate the development of scientifically valid test methods and strategies that reduce, refine, or replace the use of vertebrate animals…"

"Any person developing information for submission…shall first attempt to develop the information by means of an alternative test method or strategy…"



US Toxic Substances Control Act

2016 update

- **SECTION 4. TESTING OF CHEMICAL SUBSTANCES AND MIXTURES.**

- "…develop a strategic plan to promote the development and implementation of alternative test methods and strategies to reduce, refine, or replace vertebrate animal testing and provide information of equivalent or better scientific quality and relevance for assessing risks of injury to health or the environment…"

EPA United States Environmental Protection Agency

EPA Document# EPA-740-R1-8004
June 22, 2018
Office of Chemical Safety and Pollution Prevention

Strategic Plan to Promote the Development and Implementation of Alternative Test Methods Within the TSCA Program

Principles

→ Multi-office collaboration
→ public-private partnerships
→ Meeting needs of regulators and end-users

Approach

→ ID knowledge gaps
→ Relevance: fit for purpose and use
→ Reliability: performance-based criteria (Casati et al. (2017)
→ Integrated: AOP, IATA, Defined Approaches

Implementation

→ TSCA oversight team
→ Communication, Training, Outreach, Collaboration

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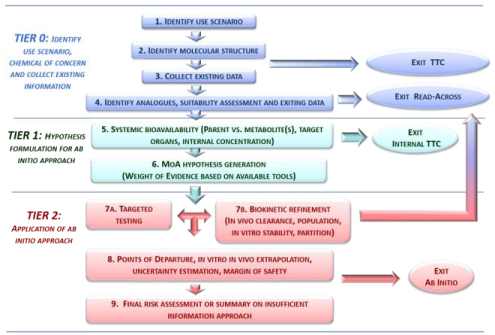
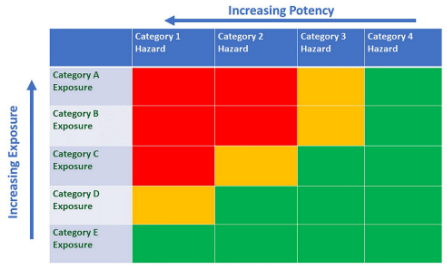
Flexible: Safety requirements without specific lists of required tests

TSCA 2016 update





- Risk-based decisions
- prioritization and chemical evaluation are risk, not hazard based, for both new and for existing chemicals

- Requirement for tiered screening and testing
- When requesting any new information, the EPA must employ a tiered screening and testing process, including :
  - reasonably available existing information
  - scientifically valid test methods and strategies not using vertebrate animals
  - chemical grouping
  - the formation of industry consortia

Existing chemicals: prioritization

- EPA has one year to establish a risk-based screening process to determine whether existing chemicals are low or high priority

Summary and Conclusion

- Long history of animal testing ban legislation
- Regulations established & evolving globally
- Many similarities, yet regional variations exist
  - → Caveats, Exemptions, Product Type Exclusions
- Complications impacting development & implementation
  - → Banning Animal Testing ≠ Acceptance of NAMs
  - → Uncertainty in NAMs fueling low confidence
- Opportunities & solutions
  - → AFSA Collaboration building confidence through education
  - → Use confidence to construct holistic policy accepting & promoting NAMs

We value your feedback! As the AFSA Collaboration works to complete its free Master Class on Animal-Free Cosmetic Safety Assessment, we would appreciate your input on what we've developed so far and presented via this webinar preview series. Please take our FEEDBACK SURVEY

Thank You !

Abbreviations

- AFSA: Animal Free Safety Assessment Collaboration
- APCRA: Accelerating Pace of Chemical Risk Assessment
- CLP: Classification, Labelling, & Packaging regulation (EU)
- CONCEA: National Council for Control of Animal Experiments (Brazil)
- CSAR: Cosmetic Supervision & Administration Regulation (China)
- EC 1223/2009: European Cosmetics Regulation
- GMP: Good Manufacturing Practice
- HSI: Humane Society International
- LRSS: Long Range Science Strategy (Cosmetics Europe)
- MFDS: Ministry of Food & Drug Safety (Korea)
- NAMs: Novel Approach/Non-Animal Methodologies
- NGRA: Next Generation Risk Assessment
- REACh: Registration, Evaluation, Authorisation of Chemicals
- TMMDA: Turkish Medicines & Medical Devices Agency

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