Setting the Stage: Identifying Hazard and Risk for the Dermal Sensitization Endpoint in the New Chemicals Program Under Toxic Substances Control Act (TSCA)

Louis Scarano
New Chemicals Division (NCD)
Office of Pollution Prevention and Toxics (OPPT)
Office of Chemical Safety and Pollution Prevention (OCSPP)
U.S. Environmental Protection Agency
January 30, 2024

Overview

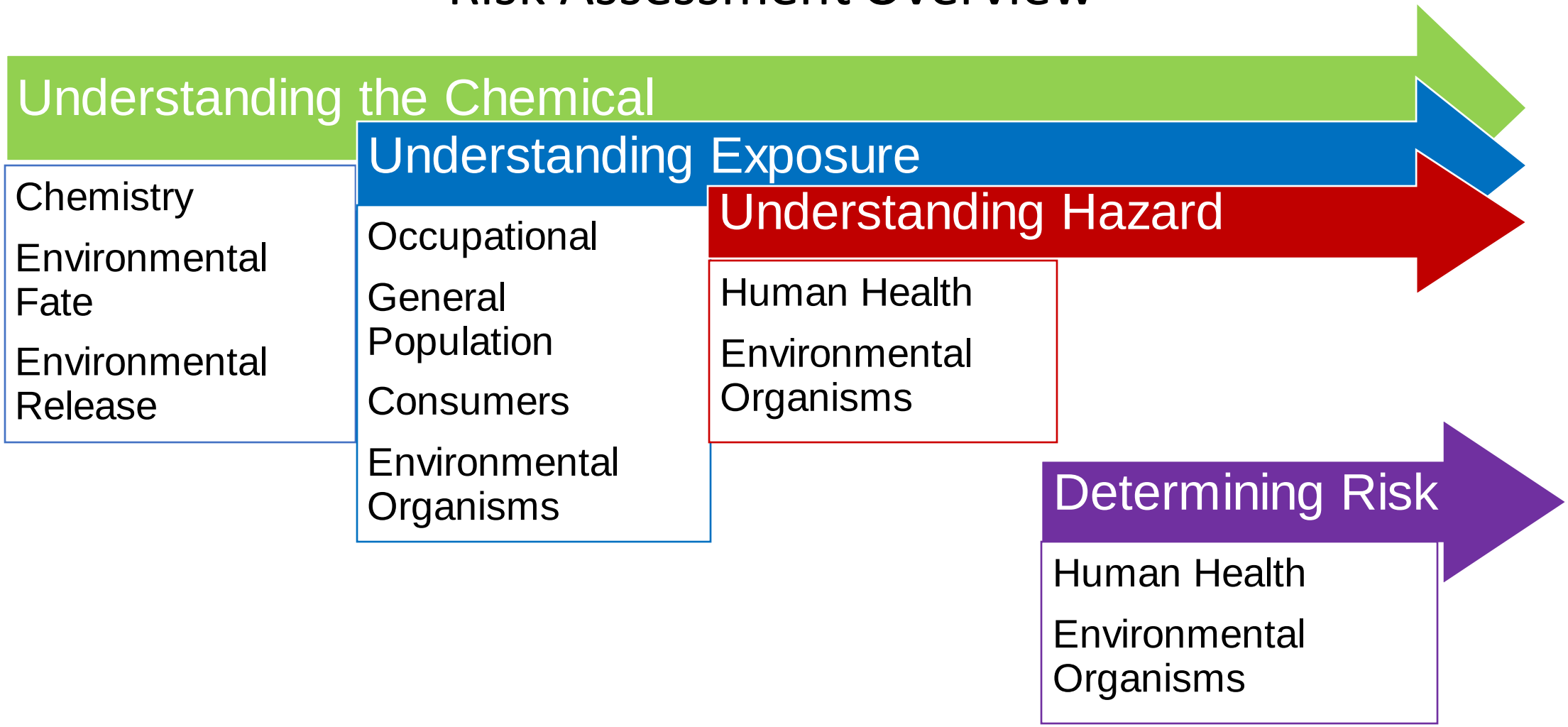
- Background
- TSCA Section 4(h)
- Evaluating Dermal Skin Sensitization in the TSCA New Chemicals Program
- Moving to the SARA-ICE Model
- Next Steps

Background

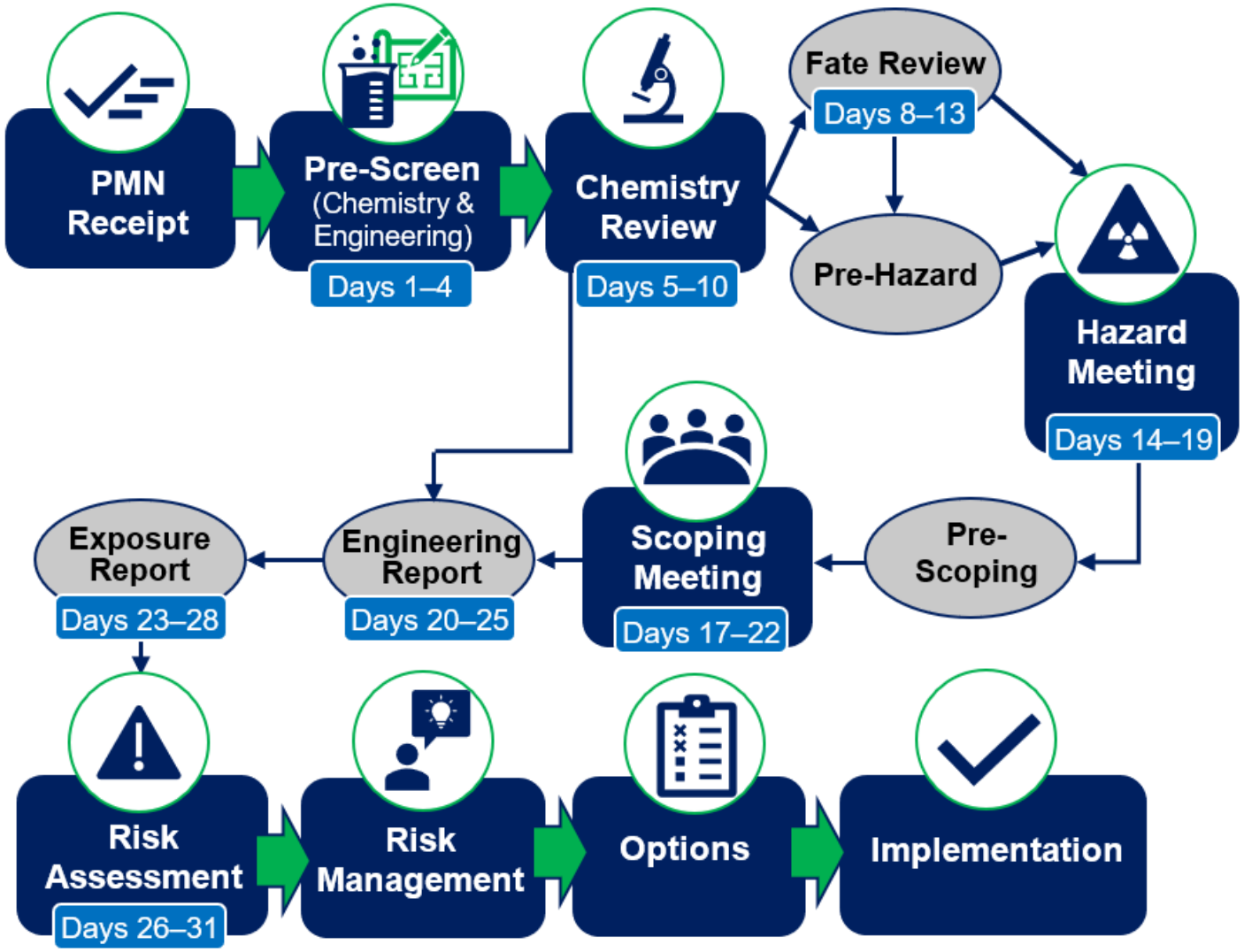
What Does The New Chemicals Program Do?

- EPA's New Chemicals Program serves as a "gatekeeper" role to help manage potential risk to human health and the environment from chemicals new to the marketplace.
- The New Chemicals Division (NCD) is responsible for implementation of:
  - TSCA Section 5 - risk assessment and risk management of new chemical submissions
  - TSCA Section 8 (sections related to chemical inventory) - maintenance and update of an Inventory of Chemicals in commerce
    - Any chemical that is not on the TSCA Inventory is considered a "new" chemical substance.
    - The Inventory contains >86,500 chemicals, of which >42,200 are active.

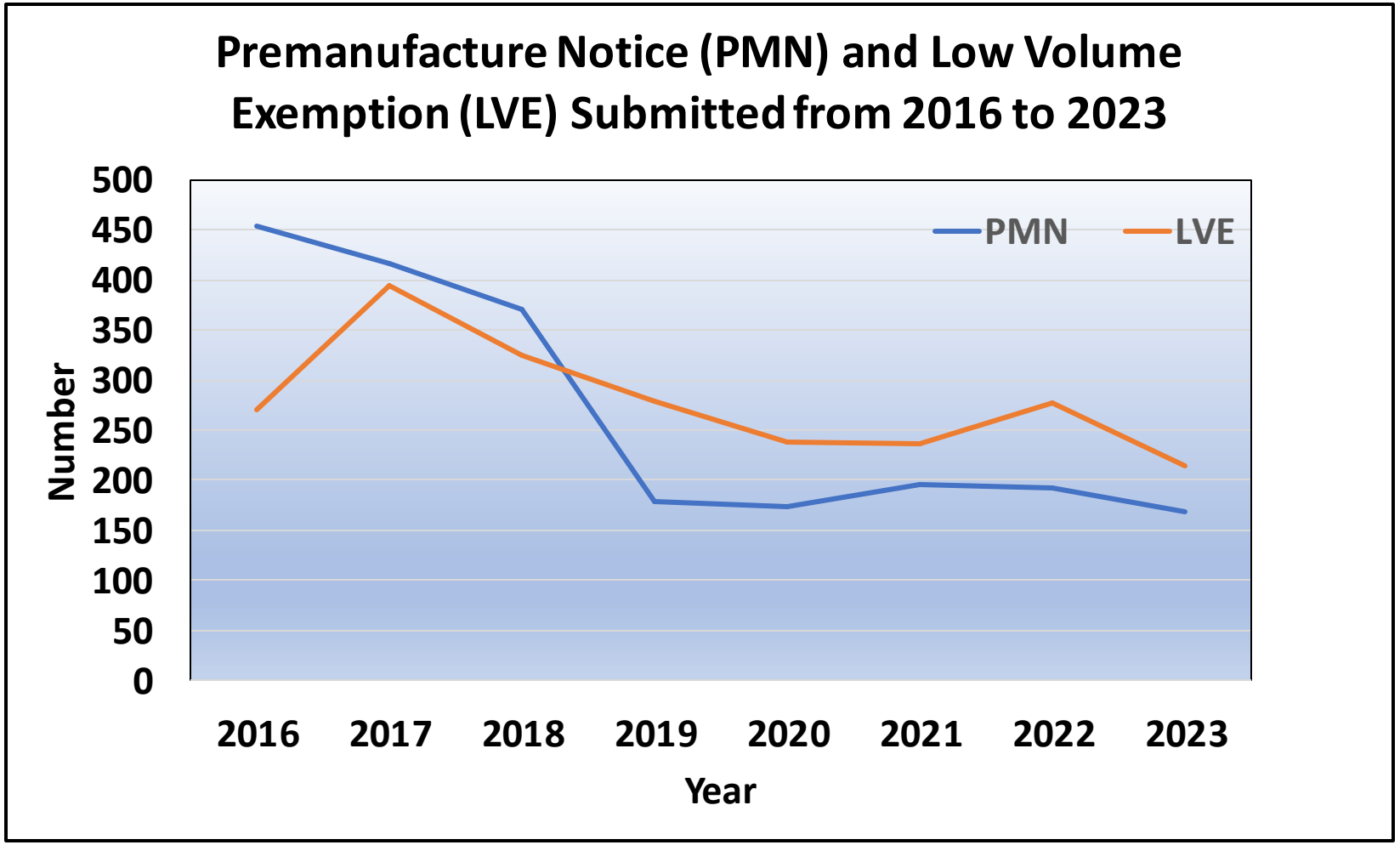
Risk Assessment Overview



Background: NCD Risk Assessment / Management review process



New Chemical Notice Submissions Since Lautenberg



Data taken from: [TSCA New Chemical Statistics]

Number of Fragrance Notices Received

Type of Notice	Approximate Number	
	Total from 1979 to December 2023	Total Since Lautenberg (2016-2023)
Low Volume Exemption (LVE)	128	22
Premanufacture Notice (PMN)	599	45
Significant New Use Notice (SNUN) or Test Market Exemption Applications (TMEA)	2	0
TOTAL	729	67
Fragrance intermediates	75	3
GRAND TOTAL	804	70*

*~30 of these are still active

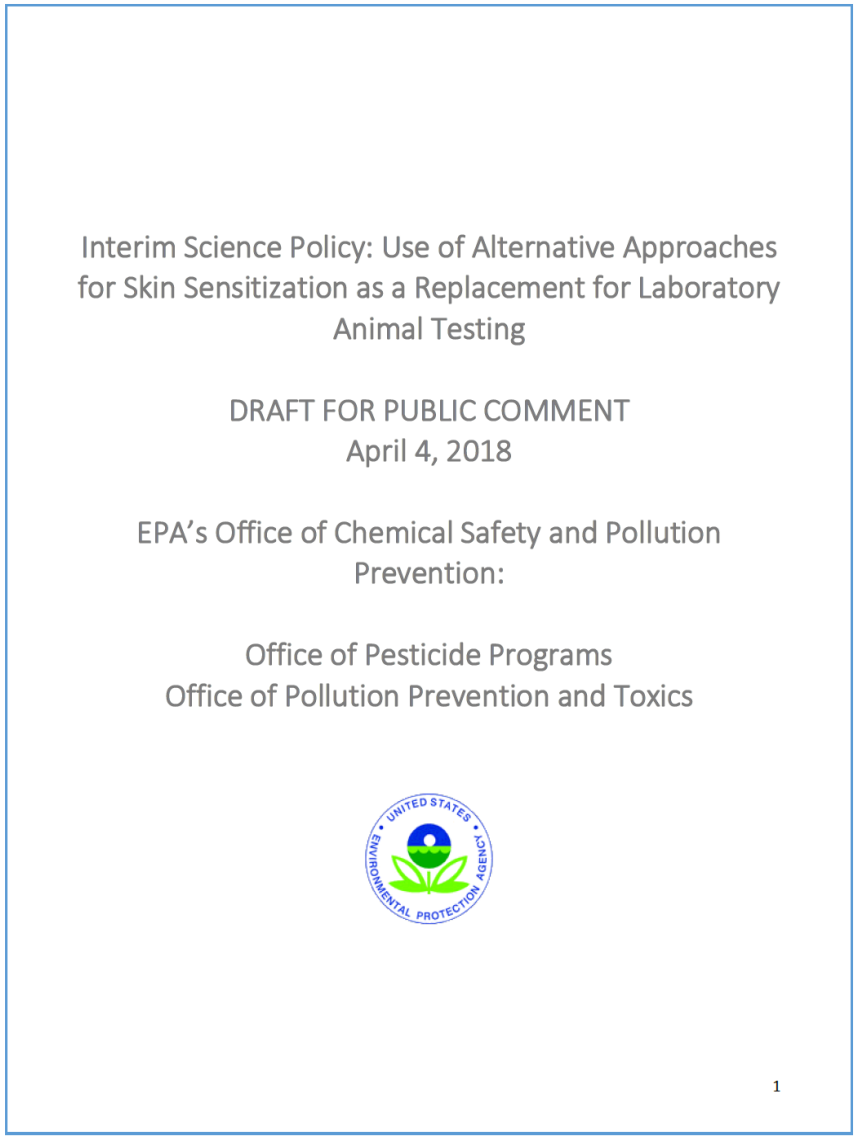
Numbers from Mona Singh, Industrial Chemistry Branch

TSCA Section 4(h)

Reduction of Vertebrate Testing and TSCA

- In 2016, TSCA was amended by the Frank R. Lautenberg Chemical Safety for the 21st Century Act.
  - Added Section 4(h) entitled *Reduction of Testing on Vertebrates*
  - Prior to requesting testing using vertebrates:
    - Consider reasonably available existing information, and
    - Encourage and facilitate (Section 4(h)(1)(B)(i):
      - "Scientifically valid test methods and strategies that reduce or replace use of vertebrate animals while *providing information of equivalent or better scientific quality and relevance* that will support regulatory decisions…"

Evaluating Dermal Skin Sensitization in the TSCA New Chemicals Program

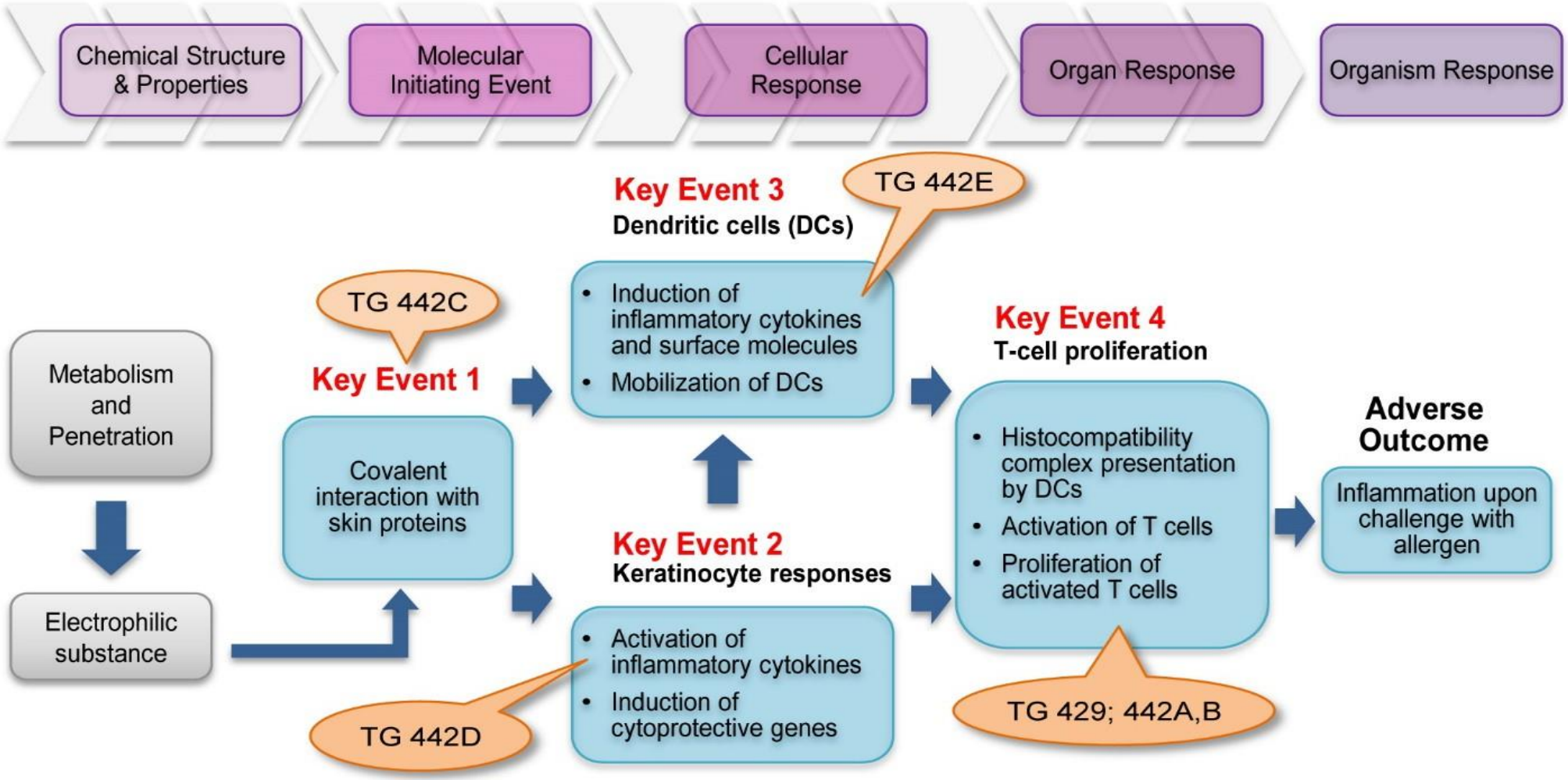


Skin Sensitization: Replacement of Laboratory Animal Testing

- Announced April 10, 2018, this document described the science that supports a policy to accept alternative (*in silico, in chemico,* and *in vitro*) approaches for identifying skin sensitization hazard in place of animal studies.
    - Multiple non-animal testing strategies (*in silico, in chemico* and *in vitro)* demonstrate comparable or superior performance to one of the most widely used laboratory animal studies for this endpoint, the local lymph node assay (LLNA).
- The draft interim policy was the result of collaboration among a number of entities working on alternative methodologies, including ICCVAM, NICEATM, ECVAM, and Canada PMRA
- This is a joint policy for use by EPA OPP and OPPT

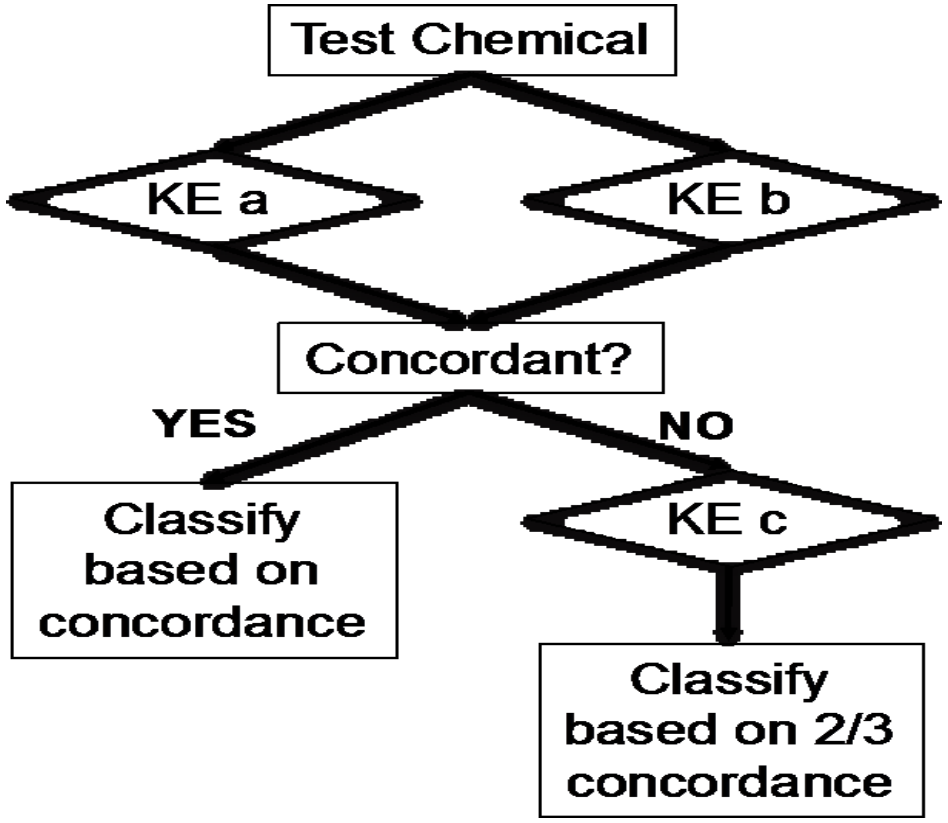
Adverse Outcome Pathway (AOP)

(adapted from Strickland et al., 2018)

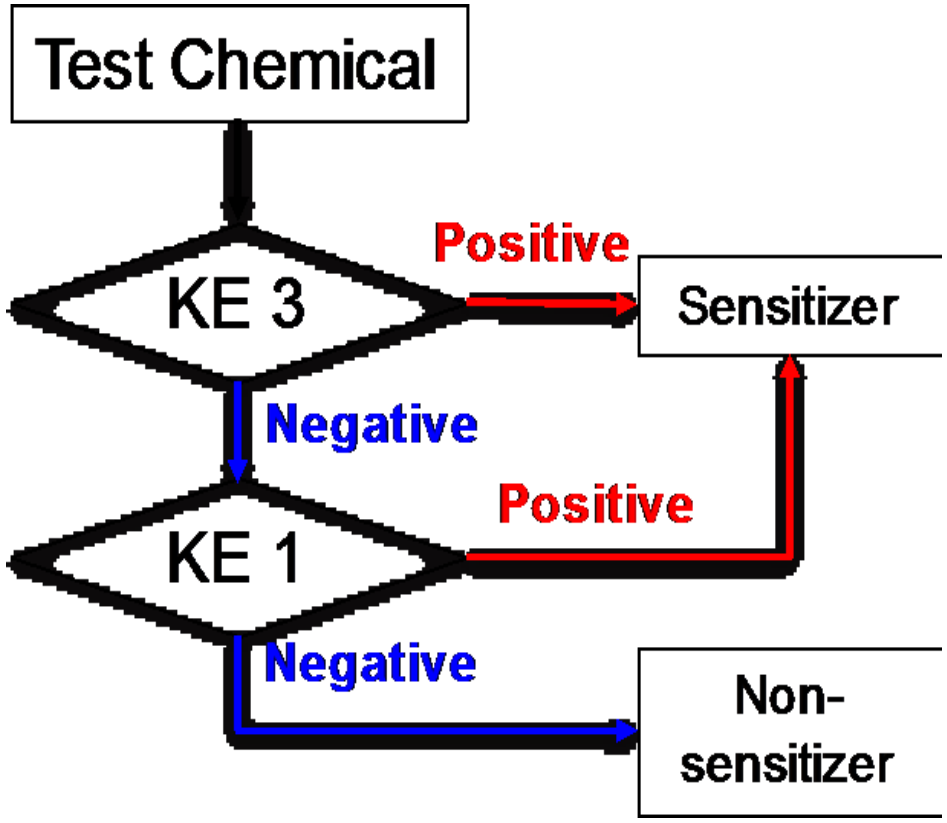


The Two Defined Approaches (DAs) in the 2018 OCSPP Policy

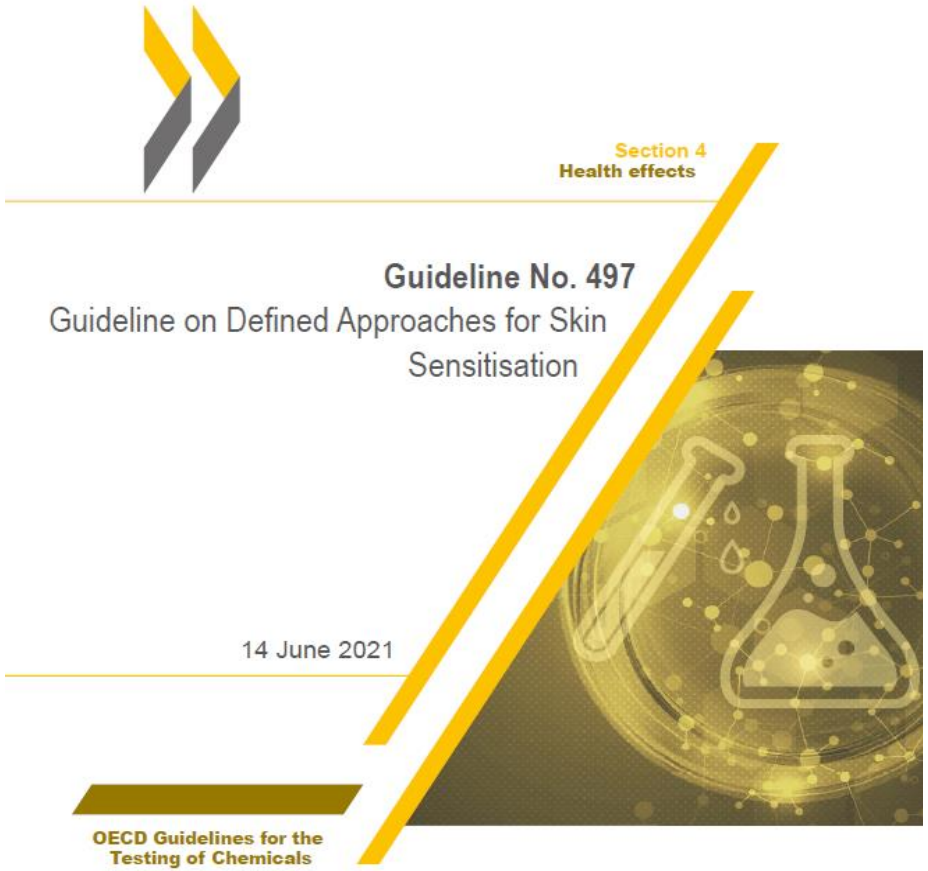
"Two out of Three"



Key Event 3/1 Sequential Testing Strategy



OECD Guideline on Defined Approaches for Skin Sensitization (GD 497, 2021)



DAs for Hazard ID:

- "2 out of 3"

DAs for Potency Categorization:

- Integrated Testing Strategy (ITS) v1
- ITS v2

Current EPA NCD Approach

1. If chemical specific and/or analogue data are available:
   a) LLNA or guinea pig data are available for the PMN substance, then those chemical specific data are used to establish the GHS category.
   b) If *in vitro* data are available for 2 or more key events, then those chemical specific data are used to establish the GHS category in accordance with OECD GD 497.
2. If no chemical specific and/or analogue data are available, the OECD toolbox evaluation is used:
   a) If positive, then assume potential skin sensitizer (Category 1/1a)
   b) If negative, then assume it's not a potential skin sensitizer (Unclassified)

Challenge: Some PMN substances need a more refined approach to derive a point of departure for quantification of human health hazard and risk.

Slide from Lowit, 2023

Moving to the SARA-ICE Model

Current List of Available DAs for Potency

Defined Approaches	Input	Output	Species
ITSv1/ITSv2	DPRA, h-CLAT, KeratinoSens, DEREK/OECD Toolbox	Potency Sub-category (GHS)	Human
STS	h-CLAT, DPRA	Potency Sub- category (GHS)	Human
BN-ITS3	DPRA, h-CLAT, KeratinoSens, TIMES-SS, bioavailability (solubility at pH 7, Log D at pH 7, plasma protein binding, fraction ionized)	pEC3 (Point of Departure)	Mouse
Shiseido ANN	DPRA, h-CLAT, KeratinoSens/LuSens	EC3 (Point of Departure)	Mouse
2of3 Regression	Combination of: DPRA, kDPRA, h-CLAT, KeratinoSens/LuSens, Vapor Pressure	pEC3 (Point of Departure)	Mouse
SARA-ICE	***Any combination of: HPPT, LLNA, DPRA, kinetic DPRA, KeratinoSens, h-CLAT, U-SENS***	***ED01 (Point of Departure)***	***Human***

Slide from Lowit, 2023

Why is EPA Interested the SARA-ICE Model? (1 of 2)

SARA-ICE is a robust model that provides the most human-relevant prediction. It has multiple advantages for use in regulatory risk assessment.

- Predicted outcome:
  - The other "Defined Approaches" estimate the LLNA EC3--a mouse outcome
  - The SARA-ICE model derives a human-based Effective Dose 01 (ED01), a dose at which 1% of the population would expect to be sensitized in a human predictive patch test
- Because SARA-ICE predicts a human outcome, it's use obviates need for the inter-species factor
  - In other words, the 10X for inter-species factor would not be applied
- SARA-ICE provides a probability distribution that accounts for population variability
  - Thus, when using this option, the intra-species factor could be reduced

Slide from Lowit, 2023

Why is EPA Interested the SARA-ICE Model? (2 of 2)

- It is a flexible model
  - Allows for the input from multiple data sources/data streams: LLNA, DPRA, kDRPA, KeratinoSens, h-CLAT, U-SENS
  - Most robust approach: *In vitro*, guideline studies for each of 3 key events
  - However, the model can accommodate partial data inputs/data streams
    - Increases predicted uncertainty
- SARA-ICE model will be publicly accessible in early 2024 and eventually housed on the ICE platform (https://ice.ntp.niehs.nih.gov/)

Slide from Lowit, 2023

SARA-ICE Evaluation for Addition to DASS Guideline 497

- Added to OECD Workplan in 2022 as Project 4.154
  - U.S. and U.K. are co-leads
    - NIEHS is co-leading; several other U.S. federal agencies are also participating
- Under evaluation by OECD for addition to Guideline for Defined Approaches for Skin Sensitization (DASS)
  - Will be evaluated using established reference classifications and any additional reference data
  - Will add capability for POD assessment and QRA to existing guideline
  - Publication of updated guideline is tentatively set for 2025
- Model outcomes
  - Hazard (yes/no)
  - GHS classification of skin sensitizers: Category 1A, 1B, and “not classified”
  - Human-relevant point of departure (POD) for quantitative risk assessment

Adapted Slide from Lowit, 2023

Next Steps and Challenges (Today)

Let's get in the details:

- Understanding SARA/ICE:
  - Emily Reinke (Inotiv/contractor to NICEATM) and Joe Reynolds (Unilever)will present the model
  - Multiple presentations from external stakeholder
  - Discussion
  - Challenges: There are several methods available to identify a point of departure (POD) to quantify hazard for risk assessment purposes for the dermal sensitization endpoint. Please provide individual input on EPA's proposal to use SARA/ICE for this purpose. Considerations may include:
    1. Are there other methods/models that have been (or are being) evaluated by the OECD for the same purpose?
    2. What are the strengths and limitations of SARA/ICE?
    3. The SARA/ICE can use the following information: in vitro inputs (DPRA, kDPRA, KeratinoSens™, h-CLAT, USens™) and in vivo inputs (HPPT, LLNA). Given this list, which of these data already exist for fragrance chemicals?
    4. What resources or training will be needed to make the SARA/ICE model accessible and implementable?

Next Steps and Challenges (Starting Tomorrow…)

- Consider the individual input and discussion from this Workshop
- Train NCD staff on the use of SARA/ICE
- Conduct a pilot/case studies with fragrance cases

Acknowledgements

EPA:
Shari Barash (Acting Division Director, New Chemicals Division)
Jeff Gallagher (Acting Branch Chief, New Chemicals Division)
Anna Lowit (Senior Science Advisor, Office of Pollution Prevention and Toxics)
Keith Salazar (Senior Toxicologist, New Chemicals Division)
Mona Singh (Chemist, New Chemicals Division)

InoTiv (contractor to NICEATM):
Emily Reinke

Questions

Contact information:

scarano.louis@epa.gov

202.564.2851