Advancing Eye Irritation Assessment with Non-Animal Methods for Industrial Chemicals: Progress at U.S. EPA

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U.S. Environmental Protection Agency
March 29, 2024

Disclaimer

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Overview

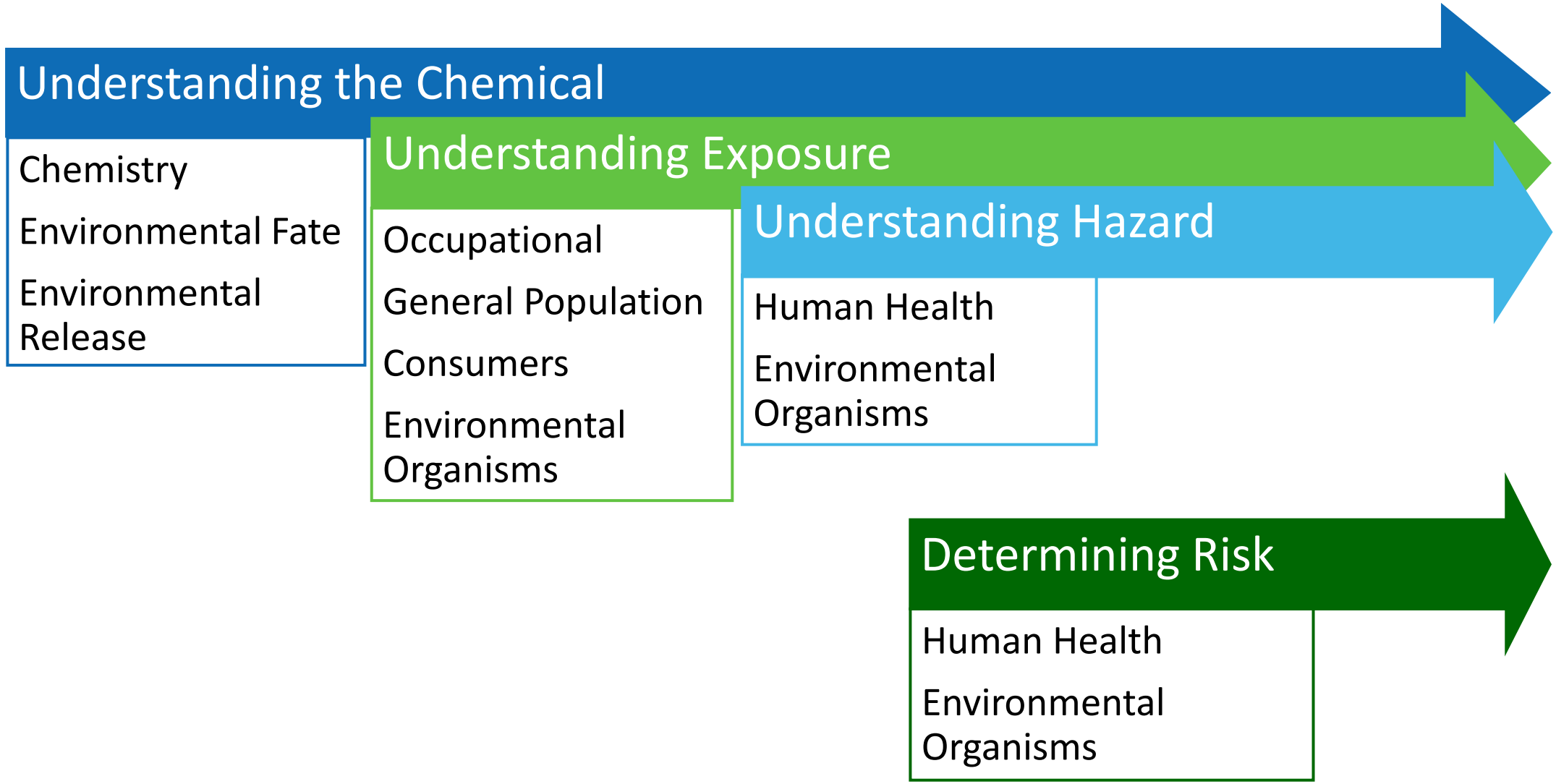
- Background
- Toxic Substances Control Act (TSCA) Section 4(h)
- Evaluating Eye Irritation and Corrosion in the TSCA New Chemicals Program
- Ongoing Efforts and Future Plans

Background

What Does the New Chemicals Program Do?

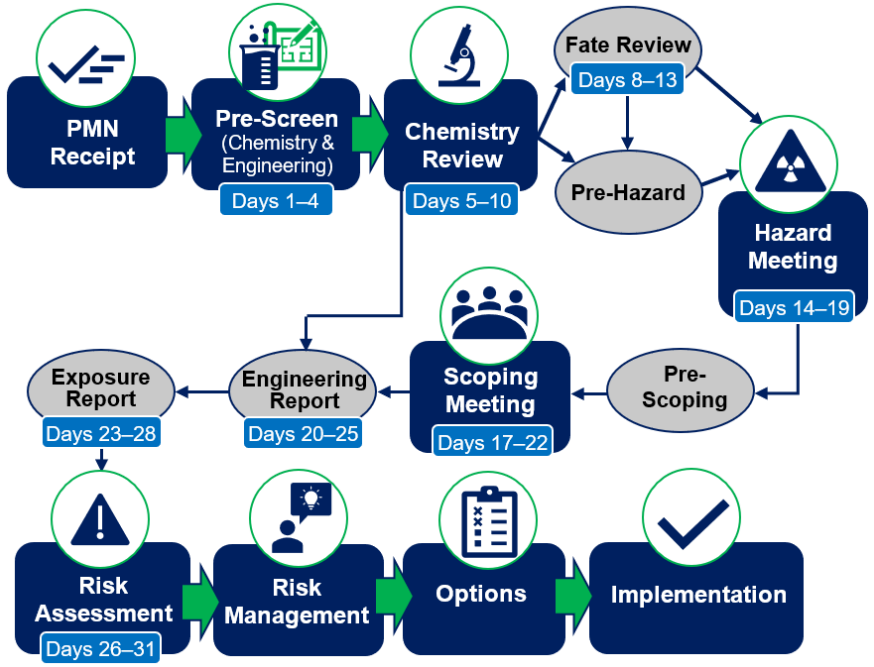
- EPA's New Chemicals Program serves as a "gatekeeper" role to help manage potential risk to human health and the environment from chemicals new to the marketplace
- The New Chemicals Division (NCD) is responsible for implementation of:
  - TSCA Section 5 - risk assessment and risk management of new chemical submissions
  - TSCA Section 8 (section 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

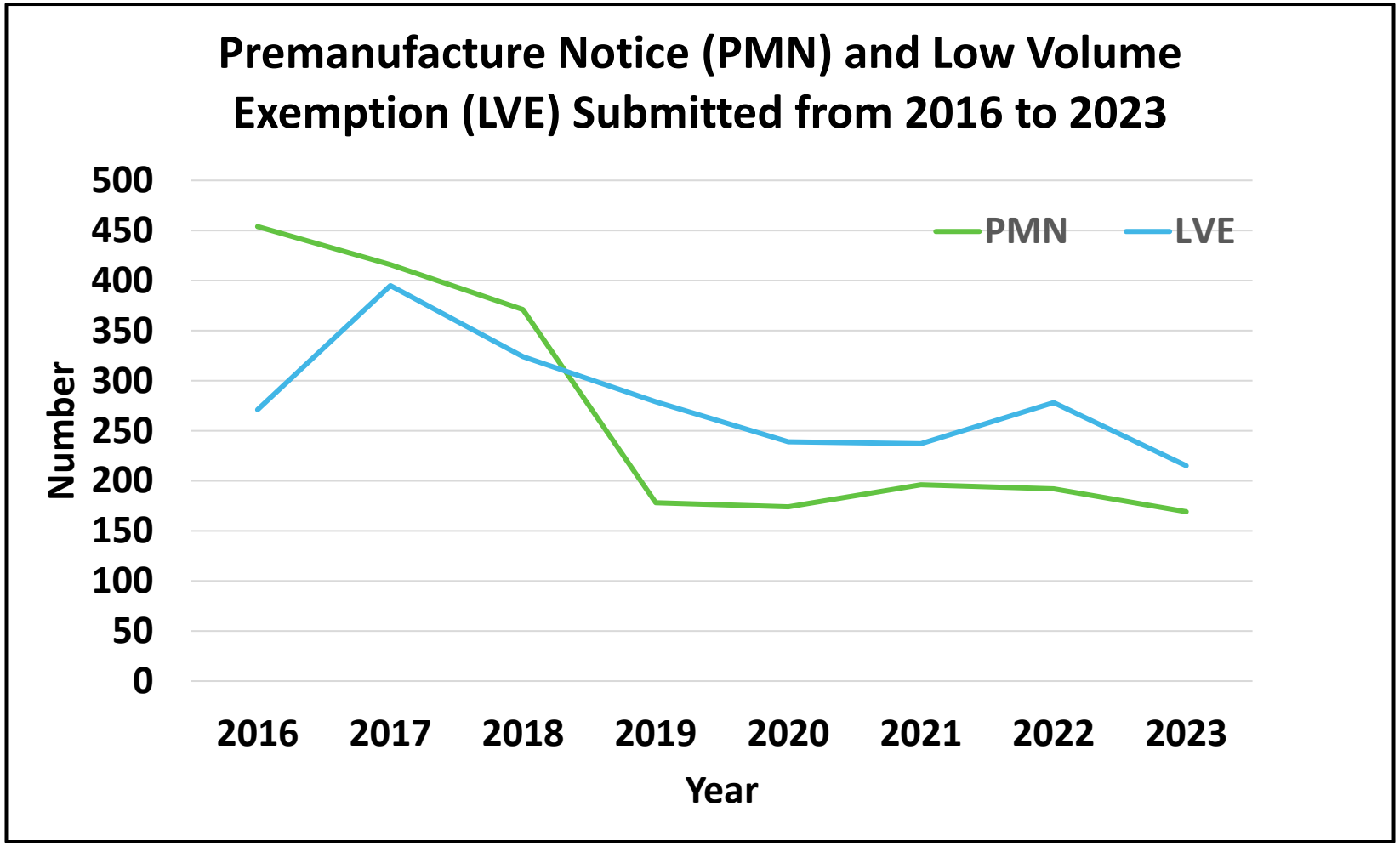


Risk Assessment/Management Review Process

- Section 5
  - Statutory deadlines
    - 90 days for standard Premanufacture Notices (PMN)
    - 30 days for Low Volume Exemptions (LVE) and other exemption categories
  - Submission requirements
    - "… such person submits to the Administrator, at least 90 days before such manufacture or processing, a notice, in accordance with subsection (d), of such person's intention to manufacture or process such substance…"
    - Submitters must provide all data in their possession or control related to health and environmental effects, but no further requirements are detailed including any specific requirements for data
    - Outcome: PMNs and LVEs are often submitted with no human health data



New Chemical Notice Submissions Since Lautenberg



Data taken from: TSCA New Chemical Statistics

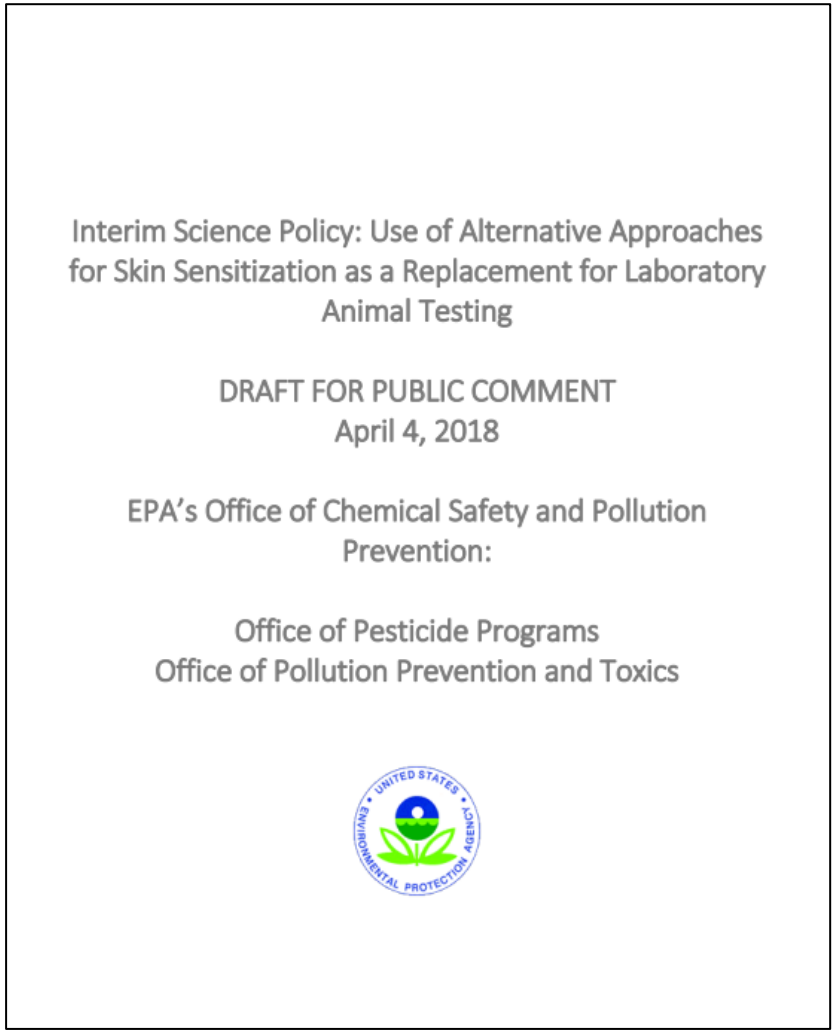
TSCA Section 4(h)

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…"

Current Efforts on Reduction and Replacement

- Eye irritation
  - OECD test guidelines (and other assays) available
  - New Chemicals Program (NCP) Eye Irritation Framework announced January 2024
- Skin irritation
  - OECD test guidelines (and other assays) available
  - NCP Skin Irritation Framework in development
- Skin sensitization
  - OECD test guidelines available
  - 2018 OCSPP policy
  - SARA/ICE implementation for point-of-departure identification
  - NCP Skin Sensitization Framework in development

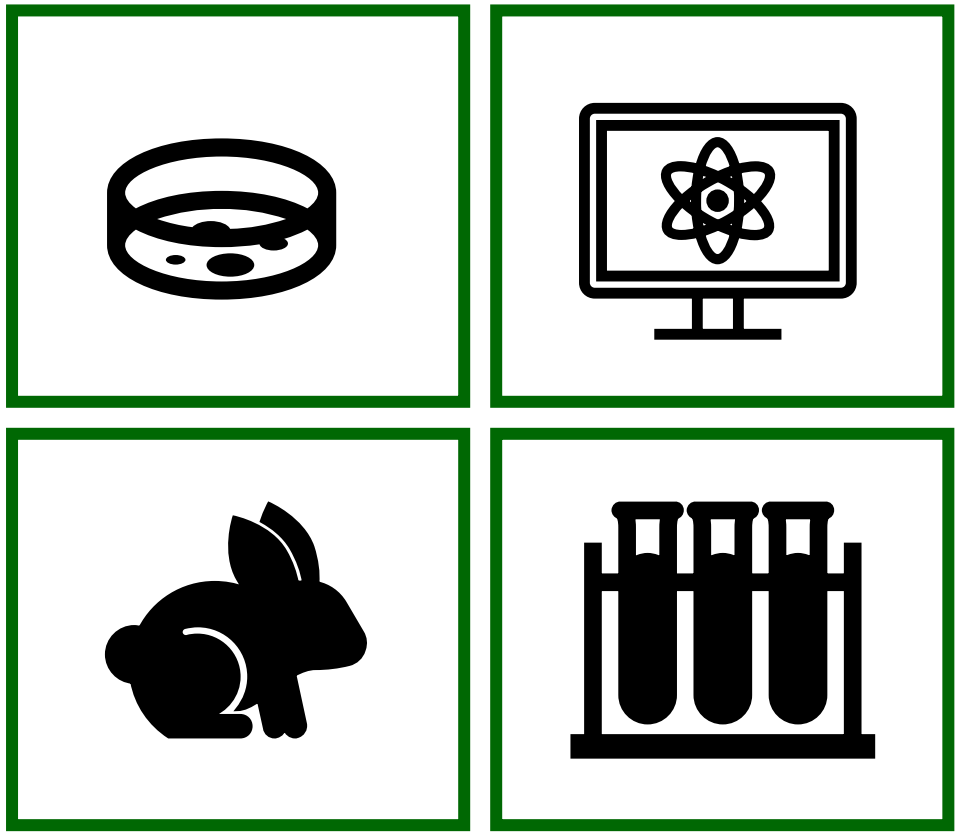

Interim Science Policy: Use of Alternative Approaches for Skin Sensitization as a Replacement for Laboratory Animal Testing

DRAFT FOR PUBLIC COMMENT
April 4, 2018

EPA's Office of Chemical Safety and Pollution Prevention:

Office of Pesticide Programs
Office of Pollution Prevention and Toxics

Also (older) New Approach Methods (NAMs)



- Read across
  - NCD makes extensive use of analogue data from both internal TSCA chemicals and all publicly available databases
  - Category assessments from other national and international hazard and risk assessment entities
  - 2010 TSCA New Chemicals Program Chemical Categories
  - Structural Alerts
- In silico tools
  - OncoLogic™
  - OECD QSAR Toolbox
    - Carcinogenesis
    - Skin sensitization
    - Respiratory sensitization

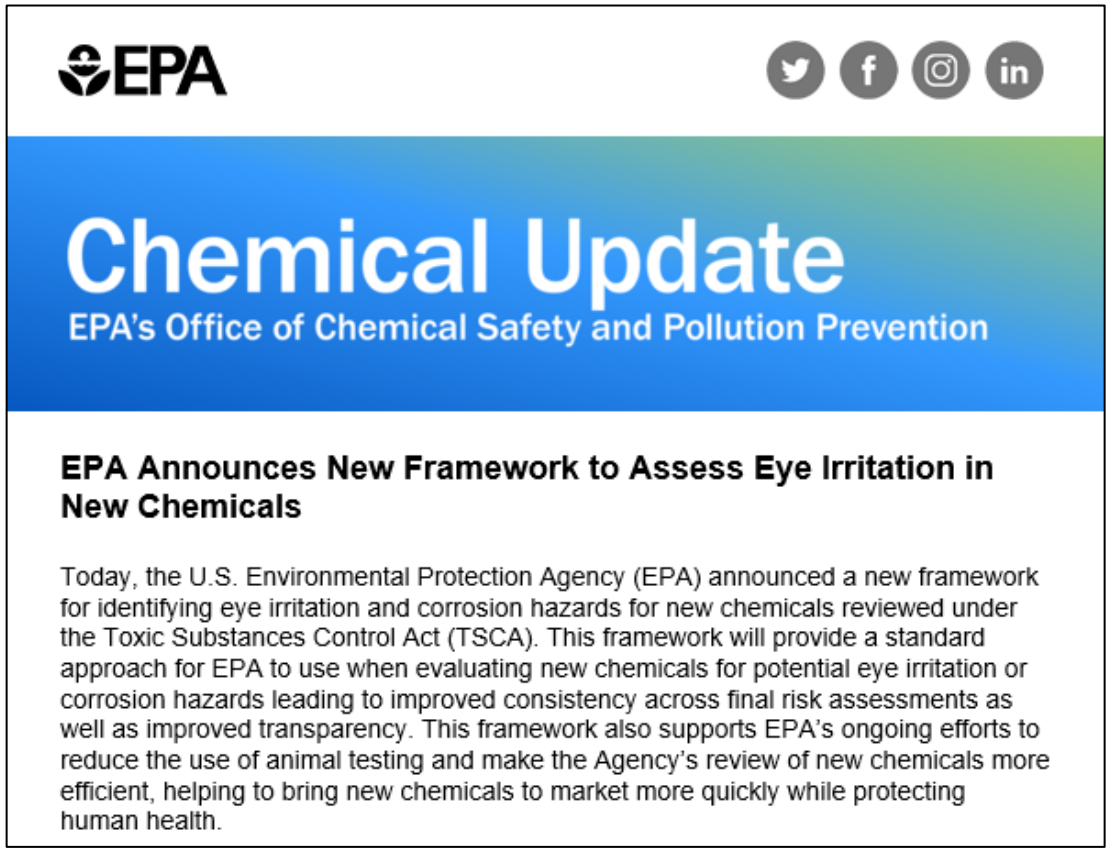
Evaluating Eye Irritation and Corrosion in the TSCA New Chemicals Program

Eye Irritation and New Chemicals

- Endpoint of concern
  - Eye irritation and corrosion hazards for occupational and consumer exposures assessed for every new chemical
  - Corrosion: Irreversible effect; potentially severe and life-altering/blinding
  - Hazard concern results in unquantified risk finding
  - Risk management
    - Workers: Personal protective eye equipment (e.g., goggles, faceshield)
    - Consumers: Cannot apply PPE; concentration limits placed on final formulations
  - Assessment important to all stakeholders
- Assessment
  - Regulatory decisions need to be based on best available science
  - New chemicals are new and therefore lack human information/case reports
  - In vivo OECD TG 405: Acute Eye Irritation/Corrosion (Draize rabbit eye test)
  - NAMs OECD TGs: Many! (437, 438, 460, 491, 492, 492B, 496)
  - Other methods: Cytosensor Microphysiometer, OptiSafe, Isolated/Enucleated Rabbit Eye, Neutral Red Release, Ex Vivo Eye Irritation Test, Porcine Opacity/Reversibility Assay

New Chemicals Program Decision Framework

- Goals
  - Prioritize use of the most reproducible, human-relevant scientific data for decision-making
  - Support EPA's mandate under TSCA to promote the development and implementation of alternative test methods and strategies that can provide information on chemical hazards without animal testing
  - Clear scientific direction for human health assessors leading to improved consistency across final new chemical risk assessments
  - Improve transparency to stakeholders regarding hazard identification of eye irritation and corrosion for new chemical submissions



EPA

Chemical Update

EPA's Office of Chemical Safety and Pollution Prevention

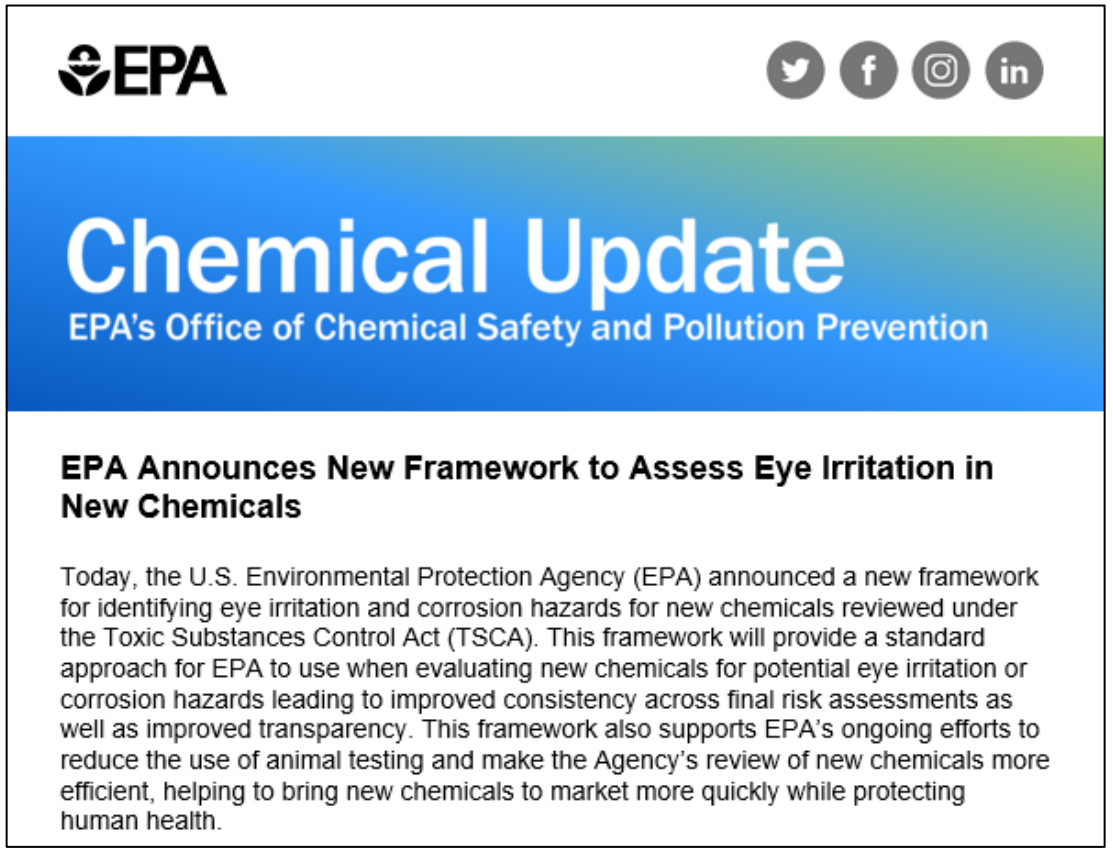
EPA Announces New Framework to Assess Eye Irritation in New Chemicals

Today, the U.S. Environmental Protection Agency (EPA) announced a new framework for identifying eye irritation and corrosion hazards for new chemicals reviewed under the Toxic Substances Control Act (TSCA). This framework will provide a standard approach for EPA to use when evaluating new chemicals for potential eye irritation or corrosion hazards leading to improved consistency across final risk assessments as well as improved transparency. This framework also supports EPA's ongoing efforts to reduce the use of animal testing and make the Agency's review of new chemicals more efficient, helping to bring new chemicals to market more quickly while protecting human health.

https://www.epa.gov/reviewing-new-chemicals-under-toxic-substances-control-act-tsca/framework-assess-eye-irritation-or

New Chemicals Program Decision Framework

- Goals
  - Prioritize use of the most reproducible, human-relevant scientific data for decision-making
- Strategy
  - Prioritize use of the most reproducible, human-relevant scientific data for decision-making
  - Use existing peer-reviewed publications and accepted guidance by international entities as foundation
  - Provide necessary flexibility to allow for assessment of often unique mix of new chemicals data and compliance with TSCA and OECD mutual acceptance of data system



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New Chemicals Program Decision Framework

- Strategy
  - Prioritize use of the most reproducible, human-relevant scientific data for decision-making
- Reproducible + human-relevant data
  - Historical standard: in vivo rabbit subject to inter/intraspecies variability, questionable exposure conditions and subjective assessment
  - Reproducibility for category 2 mild-moderate irritants is especially poor
  - In vitro, in chemico and ex vivo assays have demonstrated greater reproducibility and evaluate human-relevant endpoints

Tab. 1: Description of Draize Scoring Rules

Endpoint	Description	Range
Cornea	degree opacity and ulcerations	0-4
Iris	swelling, hyperaemia	0-2
Conjunctivae	redness, vessel discernibility	0-3
Chemosis	swelling, lids closed/open	0-4

Tab. 3: Conditional probability of Draize evaluations given a previous test result

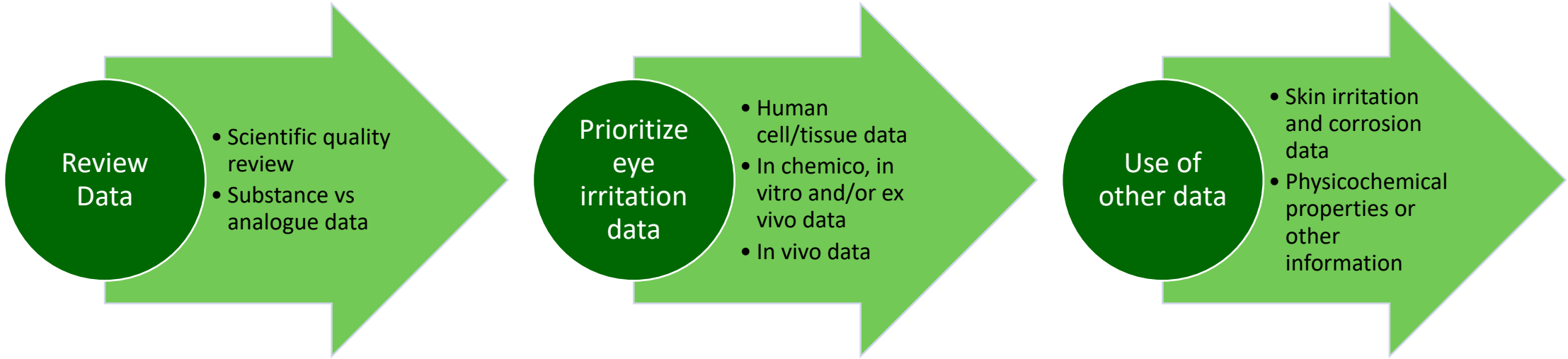
Substances filtered to those with at least two Draize studies and extractable eye irritation category in REACH registrations 2008-2014 (491 substances).

Prior Type	1	2A	2B	Non	Total
1	73%	16.1%	0.4%	10.4%	46
2A	4.2%	32.9%	3.5%	59.4%	138
2B	0.2%	4%	15.5%	80.2%	86
Non	1.1%	3.5%	1.5%	93.9%	400

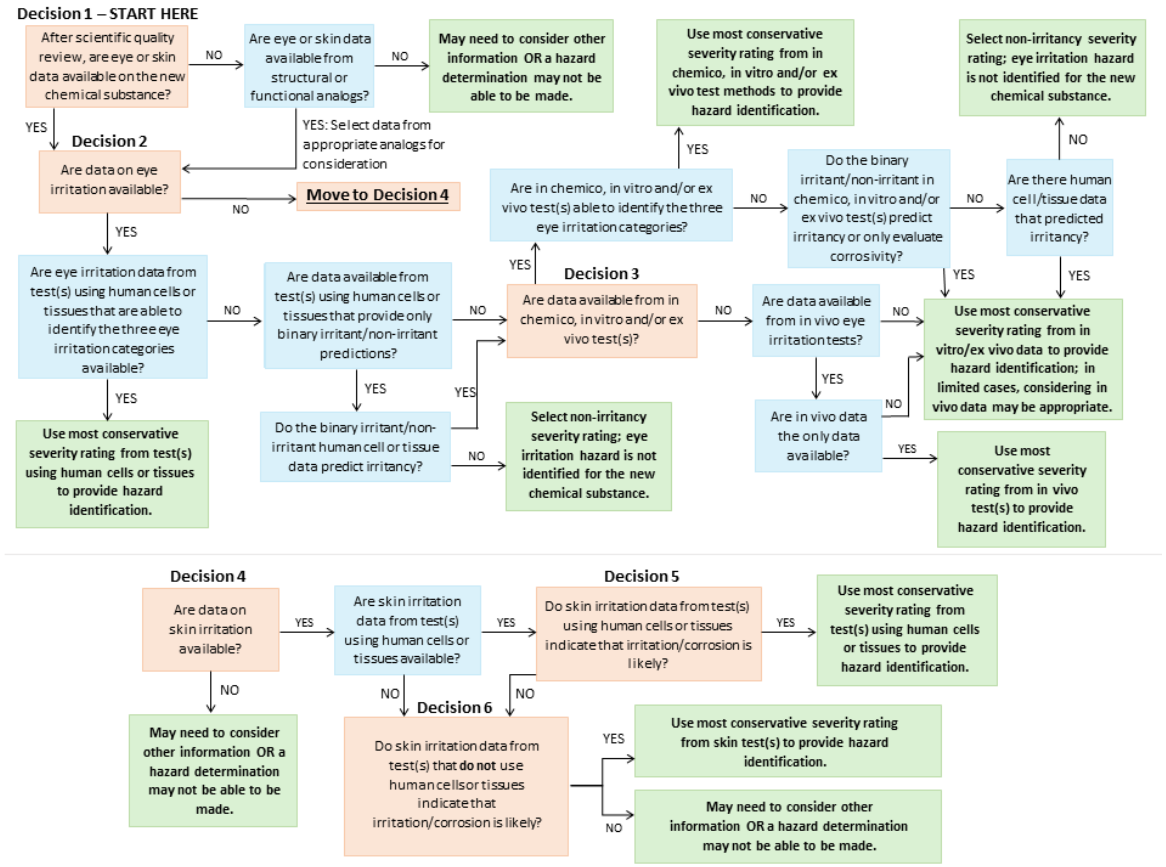
Luechtefeld et al., 2016; Clippinger et al., 2021

New Chemicals Program Decision Framework

- Approach
  - Prefer the use of methods that use human cells/tissues known to be sensitive, which carry a high degree of confidence when generating nonirritating predictions
  - To assess irritation or corrosion NCP prefers the use of methods that use human cells/tissues with the potential to assess the full range of severity and/or other reproducible and relevant in chemico, in vitro or ex vivo methods



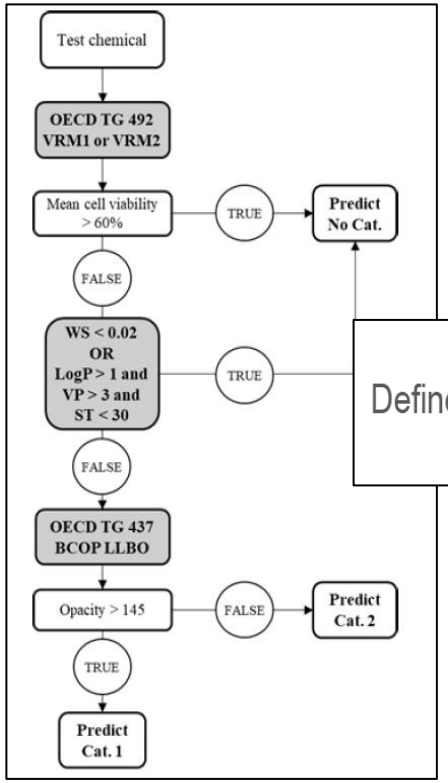
New Chemicals Program Decision Framework



- Scientific data quality review
- Main decision points
  - Are eye irritation/corrosion test data available for the new chemical substance or structural/functional analogues?
    - Are human cell/tissue eye irritation test data available?
    - Are in chemico, in vitro and/or ex vivo test data available?
    - Are in vivo data available?
  - In lieu of available eye irritation data, skin irritation data may be evaluated, or other information may be considered
- Framework only addresses prioritization of data; i.e., analogue selection, scientific review specifics, decision-making in complete absence of information is outside the document's scope

New Chemicals Program Decision Framework

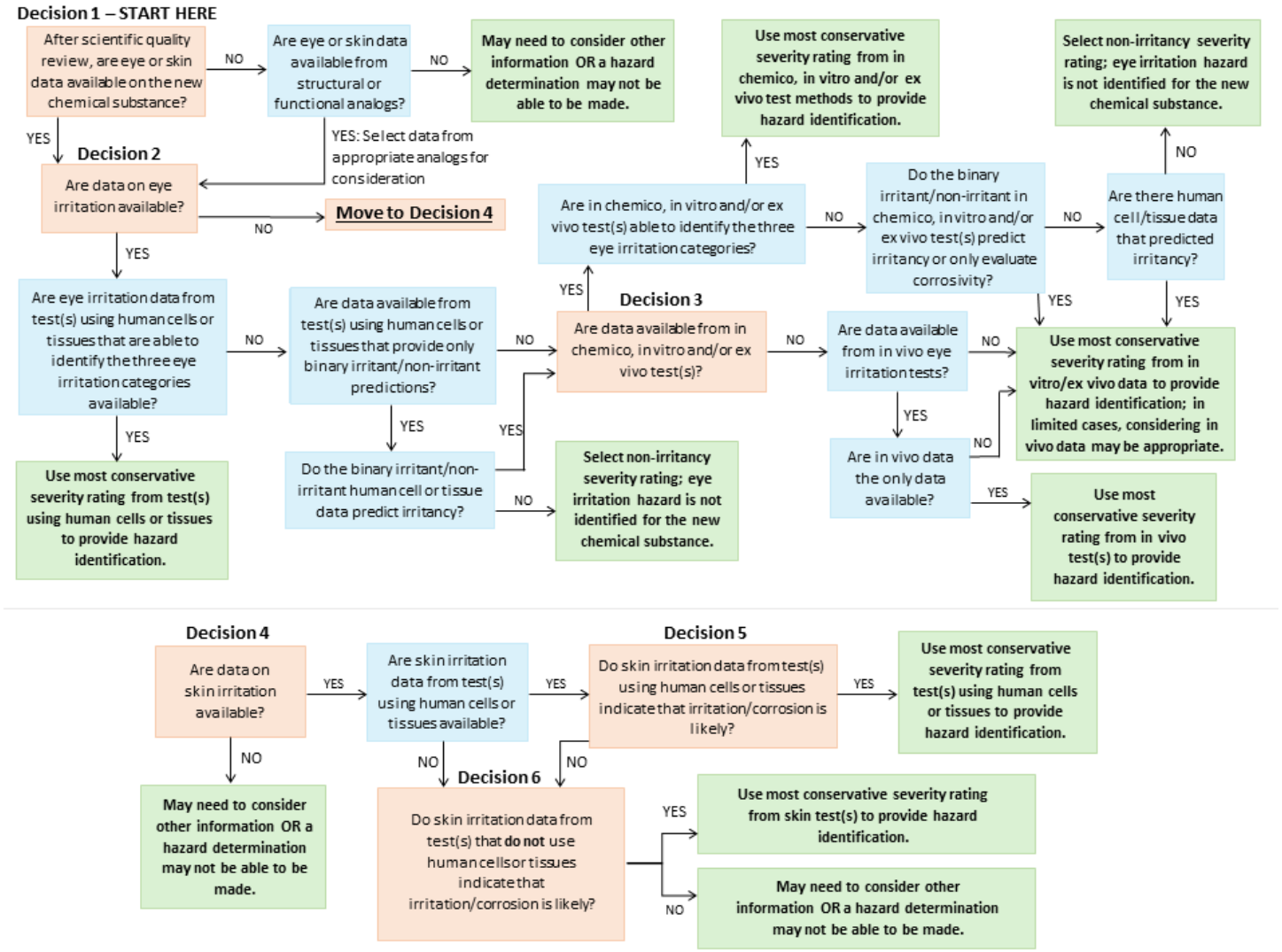
- Why not something simple like the OECD 467 Defined Approaches for Serious Eye Damage and Eye Irritation?
  - Recall:
    - Submitters must provide all data in their possession or control related to health and environmental effects, but no further requirements are detailed including any specific requirements for data
    - Outcome: Premanufacture notices are often submitted with no human health data
  - New Chemical sources data from historical Confidential Business Information (CBI) data, 8e submissions and other publicly available data such as ECHA Chemicals Database or risk assessments from other regulatory entities (e.g., OECD, Health Canada, etc.)
  - Result can be incomplete, mixed data sets and the framework needed to allow for these data



DAL - 1 option 2

Test Guideline No. 467
Defined Approaches for Serious Eye Damage and Eye Irritation

New Chemicals Program Decision Framework



Decision Framework: Case Example

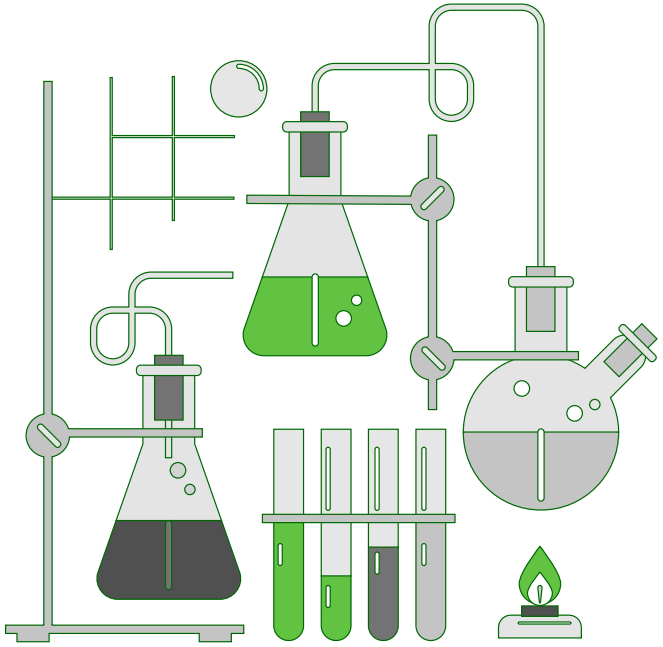
Chemical	Skin	Eye
NCS	None	None
NCS Analogue: Single good analogue identified but it lacks one functional group of the NCS. That functional group is represented in hydrolysis product and hydrolysis product analogues.	OECD 439: Reconstructed Human Epidermis Inconclusive: Either irritating or corrosive	OECD 438: Isolated Chicken Eye Inconclusive: No prediction can be made (Either irritating or corrosive)
Hydrolysis product	OECD 439: Reconstructed Human Epidermis – Inconclusive: Either irritating or corrosive OECD 431: In Vitro Skin Corrosion: Reconstructed Human Epidermis – not corrosive Final call: Irritating Open literature: Applied full strength to intact or abraded guinea-pig skin for 24 hr under occlusion, test substance was slightly irritating. Tested at 1% in petrolatum, it produced no irritation after a 48-hour closed patch test on human subjects.	OECD 492: Reconstructed Human Cornea-like Epithelium (RhCE) Inconclusive: Either irritating or corrosive ICCVAM Method: HET-CAM Test. Result unclear; ECHA called severe irritation (Could not easily match data in ECHA with any identified protocol version – there are several)
Hydrolysis product analogue	OECD 404: Irritating in rabbits	OECD 405: Nonirritating in rabbits
Hydrolysis product analogue	OECD 404: Irritating in rabbits	OECD 405: Nonirritating in rabbits
Hydrolysis product analogue	OECD 439: Reconstructed Human Epidermis – Inconclusive: Either irritating or corrosive OECD 431: In Vitro Skin Corrosion: Reconstructed Human Epidermis – not corrosive Final call: Irritating	OECD 437: Bovine Corneal Opacity and Permeability Test Inconclusive: No prediction can be made NGS In Vitro Eye Irritation Study in Human Corneal Epithelium (equivalent to OECD 492, SkinEthic model Not irritating Final call: Nonirritating

- New Chemical Substance
  - No eye irritation data provided for New Chemical Substance (NCS) (No data at all for any endpoint, actually)
  - Uncertain potential for enzymatic hydrolysis; will be very slow
- NCS analogue
  - A single good analogue identified but it lacked one functional group
  - ECHA NAMs eye irritation data: Irritating/Inconclusive
- Hydrolysis product
  - ECHA NAMs eye irritation data: Irritating/Inconclusive
- Hydrolysis product analogues
  - ECHA in vivo eye irritation data: Not irritating x2
  - ECHA NAMs eye irritation data: Not irritating
- All skin irritation data
  - Irritating or Irritating/Inconclusive
- Final hazard: Eye irritation

Recap: Take This Home

- TSCA New Chemicals Assessments
  - Around 500 new chemicals assessed yearly
  - Hazard and risk assessment generated for each new chemical submission
  - 30–90 day statutory timeline for which human health hazard and risk assessment is only allocated approximately 7 days
  - No data requirements: Hazard assessments are often not straightforward
- TSCA New Chemicals 4(h)
  - Encourage and facilitate the use of NAMs as required by law
  - NCP has incorporated and prioritized use of NAMs data for point-of-contact endpoints
  - Well-established NAMs exist for skin and eye irritation and skin sensitization
- NCP Framework for Hazard Identification of Eye Irritation and Corrosion
  - Every new chemical is evaluated for eye irritation and corrosion hazard
  - Prioritizes the most human-relevant and reproducible data for decision-making
  - Supports TSCA direction to promote NAMs, but also provides transparency to stakeholders and scientific direction to assessors to improve assessment consistency

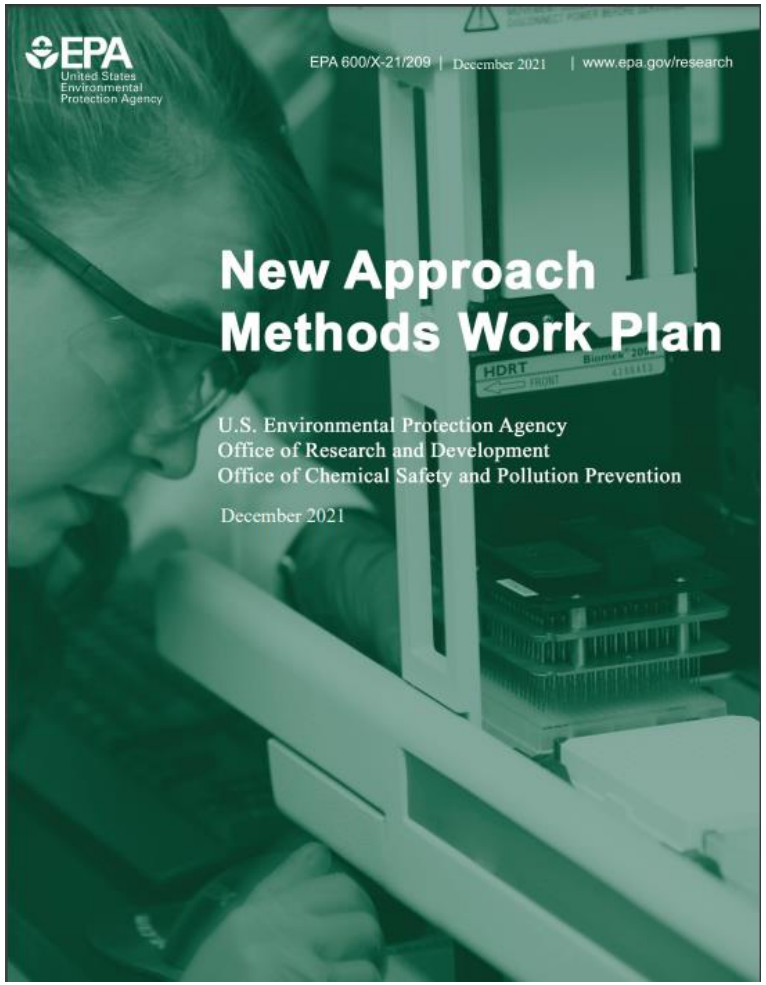
Ongoing Efforts



- Current framework activities
  - Initiated implementation
  - Ongoing:
    - Application of framework to cases
    - Review to ensure the framework is achieving stated goals with plans to iterate framework as necessary
    - Gathering data regarding outcomes of framework implementation and application
      - Interest in an eventual publication detailing outcomes and lessons learned to share information with stakeholders and risk assessment community

Future Plans

- Other eye irritation and NAMs efforts
  - Collaborate with Office of Pesticide Programs on eye irritation NAMs efforts to make use of all available advancements
  - Continue to build confidence in eye irritation and other NAMs within EPA and with external stakeholders
  - Promote development and acceptance of NAMs
  - Develop companion New Chemicals skin irritation and skin sensitization decision frameworks: target releases 2025, as resources allow



https://www.epa.gov/system/files/documents/2021-11/nams-work-plan_11_15_21_508-tagged.pdf

Acknowledgements

U.S. EPA

Shari Barash

Rachel Brunner

Iris Camacho

Jeff Gallagher

Anna Lowit

Lindsay O'Dell

Keith Salazar

Gino Scarano

Institute for In Vitro Sciences, Inc.

Hans Raabe

Inotiv

David Allen

Amber Daniel

NICEATM

Nicole Kleinstreuer

PETA Science Consortium International e.V.

Amy Clippinger

Anna van der Zalm

Thank you!

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