Applying a NAMs Confidence Framework at the EPA

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US Environmental Protection Agency

Webinar Series on the Use of New Approach Methodologies (NAMs) in Risk Assessment

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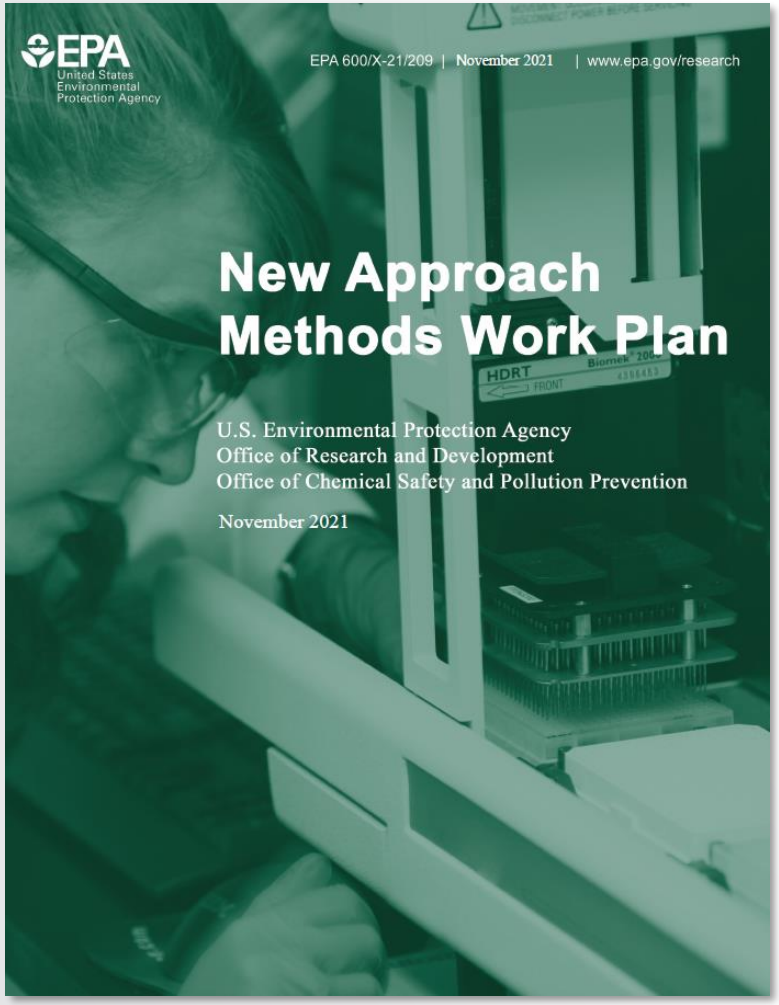
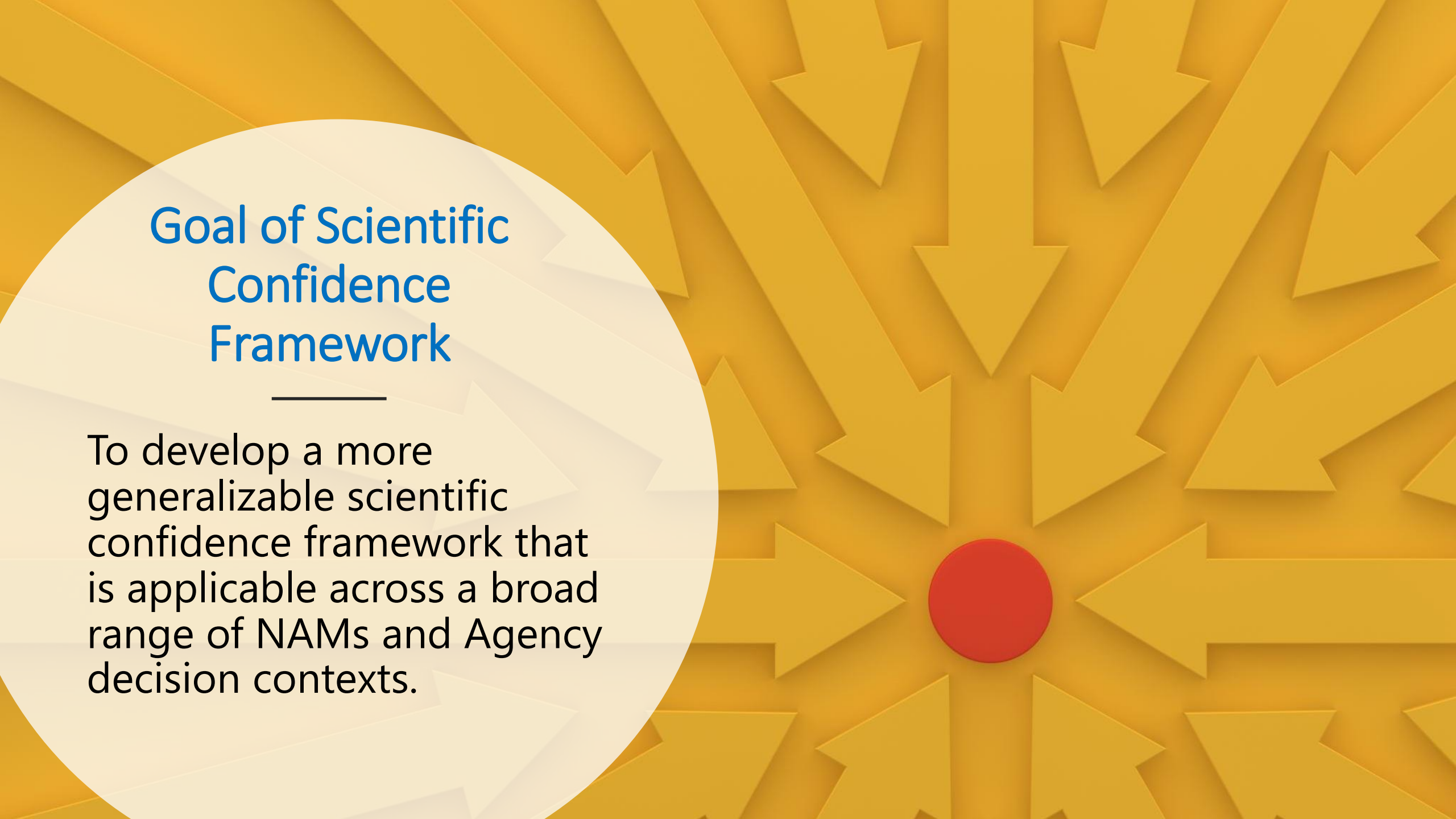
The release of the EPA NAM Work Plan provided clear objectives, strategies and deliverables



- Five objectives for achieving the reduction goals while ensuring that Agency decisions remain fully protective of human health and the environment
  - Evaluate regulatory flexibility
  - Develop baselines and metrics
  - **Establish scientific confidence** and demonstrate application
  - Develop NAMs to address information gaps
  - Engage and communicate with stakeholders
- Changes in 2021 updated work plan:
  - Modified timelines & deliverables through 2024; two case studies
  - Covered species now includes all vertebrate animals, consistent with TSCA
  - Pilot study to develop NAMs training courses for a broad range of stakeholders

Goal of Scientific Confidence Framework

To develop a more generalizable scientific confidence framework that is applicable across a broad range of NAMs and Agency decision contexts.



Initial Framing of Confidence Framework

- Many scientific resources emerging, tend to focus on a specific NAM type or applicability domain:
  - OECD guidance document on the validation of (Quantitative)Structure-Activity Relationships [(Q)SAR] models
  - OECD guidance document on good *in vitro* method practices (GIVIMP)
  - Casati, S., et al., *Standardisation of defined approaches for skin sensitisation testing to support regulatory use and international adoption: position of the International Cooperation on Alternative Test Methods.* Arch Toxicol, 2018. **92**(2): p. 611-617.
  - Patlewicz, G., et al., *Proposing a scientific confidence framework to help support the application of adverse outcome pathways for regulatory purposes.* Regul Toxicol Pharmacol, 2015. **71**(3): p. 463-77.
  - van der Zalm, A.J., et al., *A framework for establishing scientific confidence in new approach methodologies.* Arch Toxicol, 2022.
  - Etc!

What is a NAM?

- **NAMs include any technology, methodology, approach, or combination that provides information on chemical hazard and risk assessment while avoiding the use of animal testing.** Examples include *in silico, in vitro,* and *in chemico* approaches.
  - The definition of a NAM has expanded to include new approaches for assessing: hazard, dose response, toxicokinetics, and exposure.

- Use of NAMs allows the **Agency to meet its objective to reduce the reliance on vertebrate animals to test chemicals in evaluating the risks of chemicals, where scientifically justifiable**. The EPA has multiple statutory requirements and policy initiatives that prioritize reduction of animal testing (*e.g.*, the 2018 Toxic Substances Control Act (TSCA) Alternatives Strategic Plan, the Endocrine Disruptor Screening Program for the 21st Century, and the Office of Pesticides Program guidance on waiving acute toxicity studies).

Essential Elements of Framework

Graphic inspired by figure presented in van der Zalm *et al.* 2022.

Transparent

The technology, method, and/or analysis procedure associated with the NAM should be **transparently described and sufficiently detailed to enable independent review and evaluation.**

- Depending on the type of NAM, the description of the technology, methods, and analysis procedures should follow scientific best practices and applicable guidance, where available. The underlying principle, technology, and methods for the NAMs should be clearly documented and published in open-access journals or released to public access, made public via government repositories or accessible online servers, and/or summarized in public-facing regulatory or policy documents.
- For commercial NAMs, the computer code, models, or assay system should be available as a commercial service, product, or license.

Transparent

The technology, method, and/or analysis procedure associated with the NAM should be **transparently described and sufficiently detailed to enable independent review and evaluation.**

The NAM(s) should undergo an appropriate level of independent, external review necessary to raise confidence in the approach. Peer review and publication of a NAM's context-informed relevance, fitness-for-purpose, and/or technical characterization is encouraged.

If NAMs are subjected to an independent review, the results of the review should be made publicly available.

Reliable

The **reliability of the NAM** should be characterized, clearly described, and considered within the context of intended use.

REPRODUCIBLE

Report extent of reproducibility of results within* and across laboratories

Use best practices for the NAM type

*Depending on the decision context and the specific NAM being evaluated, reliability may be confined to intra-laboratory reproducibility.

Reliable

The **reliability of the NAM** should be characterized, clearly described, and considered within the context of intended use.

REPRODUCIBLE	APPROPRIATE CONTROLS
Report extent of reproducibility of results within* and across laboratories Use best practices for the NAM type	Positive and negative controls Document purity, stability, and solubility

Reliable

The **reliability of the NAM** should be characterized, clearly described, and considered within the context of intended use.

REPRODUCIBLE	APPROPRIATE CONTROLS	DOMAIN OF APPLICABILITY
Report extent of reproducibility of results within* and across laboratories Use best practices for the NAM type	Positive and negative controls Document purity, stability, and solubility	Chemical domain AND/OR Endpoint-specific domain May be defined by chemicals in the training or reference set

Chemical domain of applicability includes chemical structural features, chemical classes, and/or physical-chemical properties that can be confidently evaluated by the NAM as well as those structural features, classes, or physical-chemical properties that may not be confidently evaluated.

Endpoint-specific domain of applicability may include biological-, mechanistic-, temporal-, or process-specific constraints on the use of the NAM. For example, a NAM may be applicable to only certain species, potency classes, or exposure scenarios.

Reliable

The **reliability of the NAM** should be characterized, clearly described, and considered within the context of intended use.

REPRODUCIBLE	APPROPRIATE CONTROLS	DOMAIN OF APPLICABILITY	PUBLIC AVAILABILITY
Report extent of reproducibility of results within* and across laboratories Use best practices for the NAM type	Positive and negative controls Document purity, stability, and solubility	Chemical domain AND/OR Endpoint-specific domain May be defined by chemicals in the training or reference set	Reliability data should follow FAIR Guiding Principles for scientific data management and stewardship

Relevance

The **relevance of the NAM for the intended use should be described** to the extent possible**.**

Relevance to the endpoint being evaluated should be clearly described.

The mechanistic interpretability of the NAM and direct scientific linkage to the regulatory endpoint being assessed is desirable and reduces uncertainty in the applicability of NAM.

Uncertainty

Uncertainties relating to the NAM should be well-described.

a. Uncertainty refers to a lack of data or an incomplete understanding of NAM components, inputs, or outputs and their relationship to the regulatory decision. Uncertainty can be qualitative or quantitative. During evaluation, the uncertainties of the NAM should be described and reported relative to the chemical- and endpoint-specific domains of applicability.
b. Where appropriate, applicable uncertainties for the NAM should be presented relative to uncertainties associated with standard or traditional approaches that the NAM seeks to replace.
c. Depending on the NAM and its context of use, the acceptable level of uncertainty associated with the NAM may vary.

Process toEPA's 2024 Confidence Framework

Including (but not limited to) NAS report on variability and relevance of current laboratory mammalian toxicity tests and expectations for NAMs for use in human health risk assessment

Building Confidence Through Collaboration

Interagency Coordinating Committee for the Validation of Alternative Methods (ICCVAM)

International Collaborations

Physicians Committee for Responsible Medicine

PETA SCIence

THE HUMANE SOCIETY OF THE UNITED STATES

OECD

European Commission
JOINT RESEARCH CENTRE

Australian Government
Australian Pesticides and Veterinary Medicines Authority

Health Canada
Santé Canada

Building Confidence Through Transparency

United States Environmental Protection Agency

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EPA NAMs Conference

U.S. Environmental Protection Agency NAMs Conference: State of Science on Development and Use of NAMs for Chemical Safety Testing

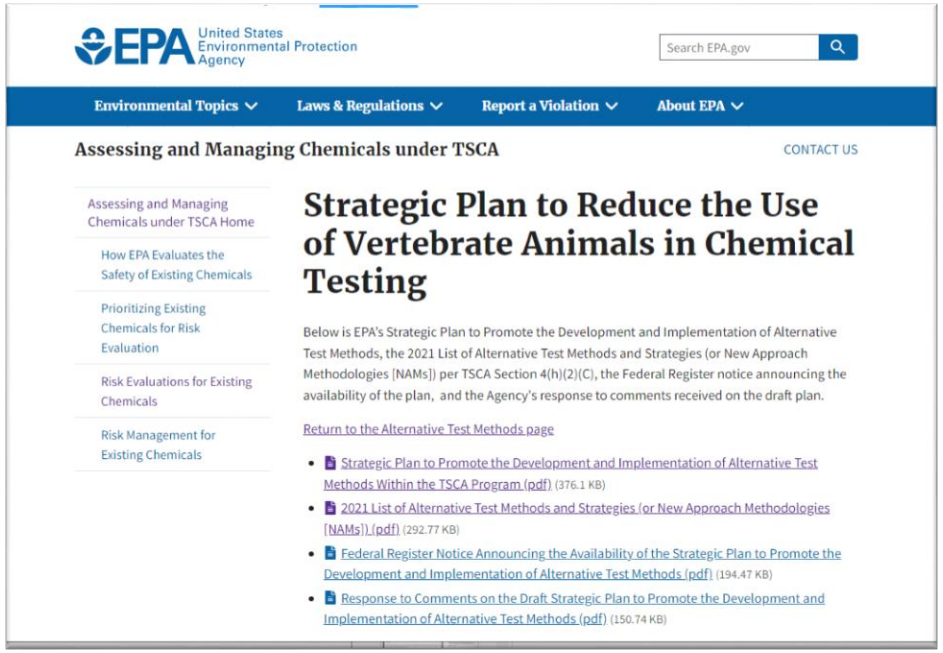
EPA hosted its 3rd NAMs Conference on October 12-13th, 2022. At the conference, attendees heard from representatives from EPA, other federal agencies, industry, universities, and international organizations on the state of the science on the development and use of NAMs for chemical safety testing. There were more than 600 participants for Day 1 and roughly 400 for Day 2, with approximately 50 in-person participants each day. Conference topics included:

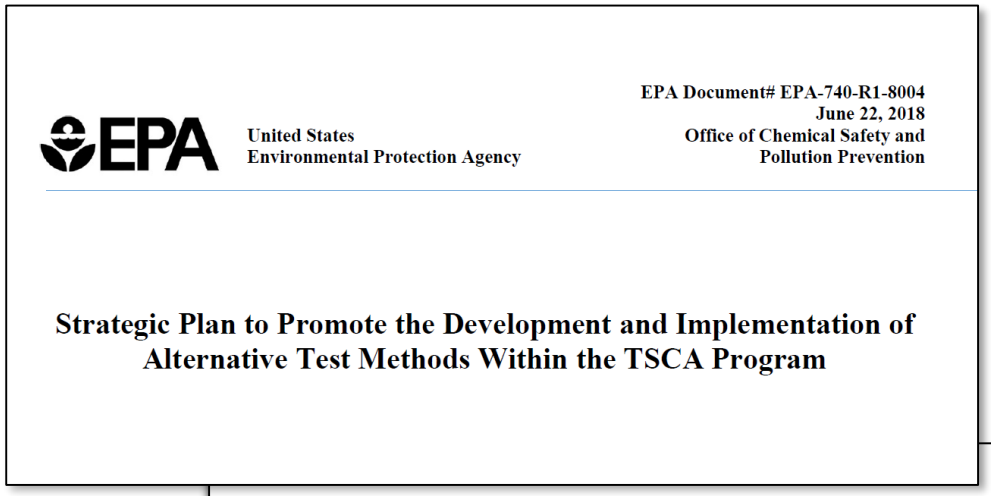
- Variability and Relevance of Traditional Toxicity Tests
- Evolution of Validation and Scientific Confidence Frameworks to Incorporate 21st Century Science
- Breakout groups discussing Variability of Traditional Toxicity Tests, Relevance of Traditional Toxicity Tests, and Feedback on EPA Scientific Confidence Framework

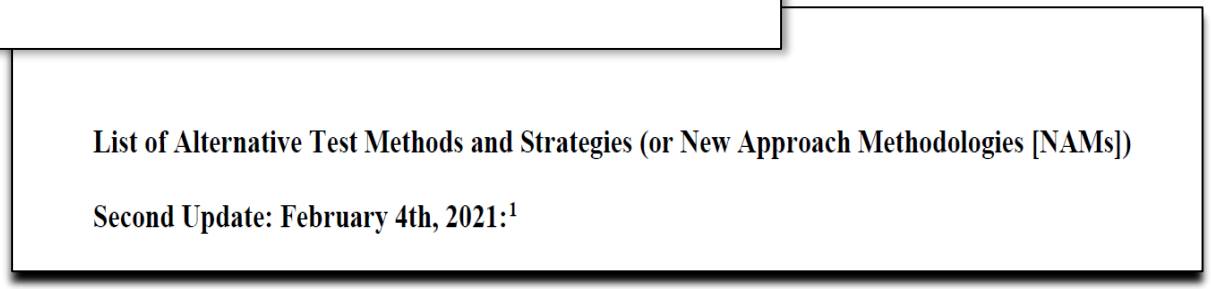
For questions, please contact us at NAM@epa.gov.

Fit-for-Purpose Application of NAMs at EPA

TSCA Strategic Plan







https://www.epa.gov/assessing-and-managing-chemicals-under-tsca/strategic-plan-reduce-use-vertebrate-animals-chemical

Pesticides Program

Waiver Guidances

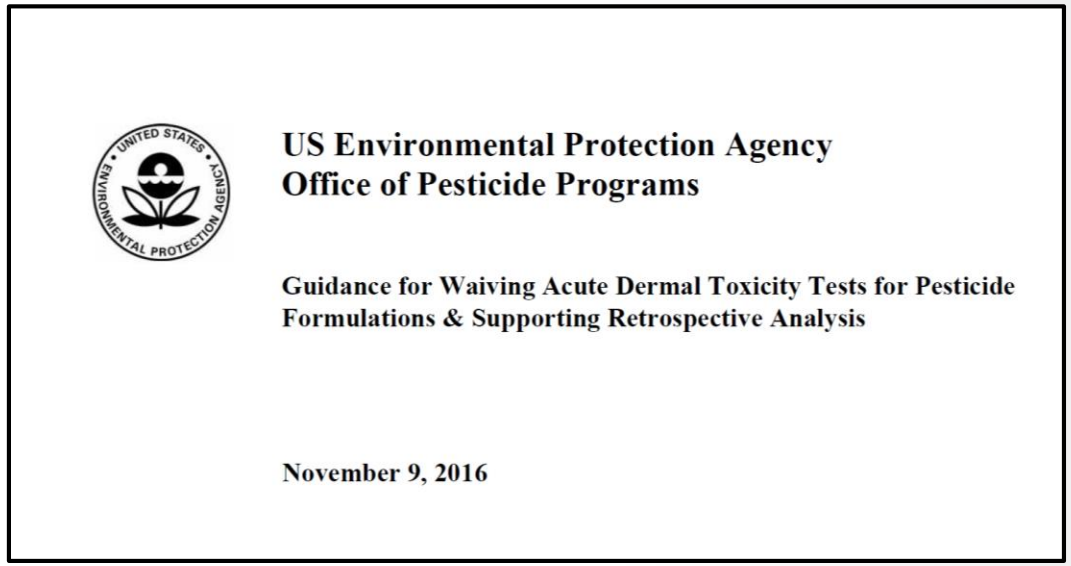
https://www.epa.gov/pesticide-science-and-assessing-pesticide-risks/strategic-vision-adopting-new-approach-1

Replacement Strategies

https://www.epa.gov/pesticide-science-and-assessing-pesticide-risks/strategic-vision-adopting-new-approach-2

Acute Dermal Pesticide Toxicity Testing

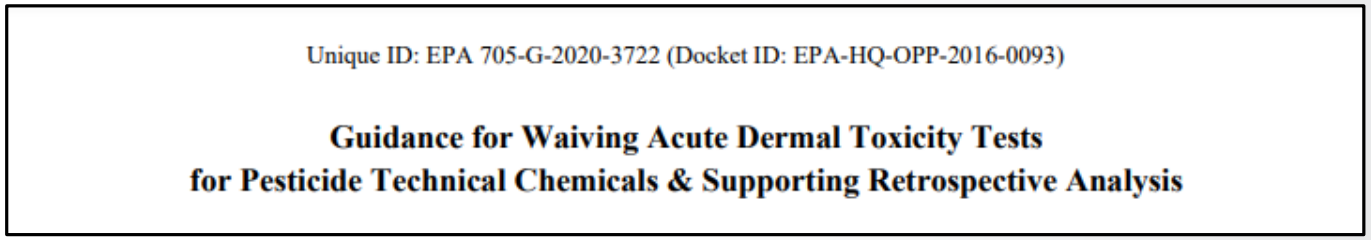
- Collaboration between EPA & NIEHS-NICEATM
- Analyzed the relative contribution of data from acute oral and dermal toxicity tests to pesticide hazard classification and labelling
  - Pesticide formulations, 2016
  - Active ingredients, 2020
- https://www.epa.gov/pesticide-registration/bridging-or-waiving-data-requirements



US Environmental Protection Agency
Office of Pesticide Programs

Guidance for Waiving Acute Dermal Toxicity Tests for Pesticide Formulations & Supporting Retrospective Analysis

November 9, 2016

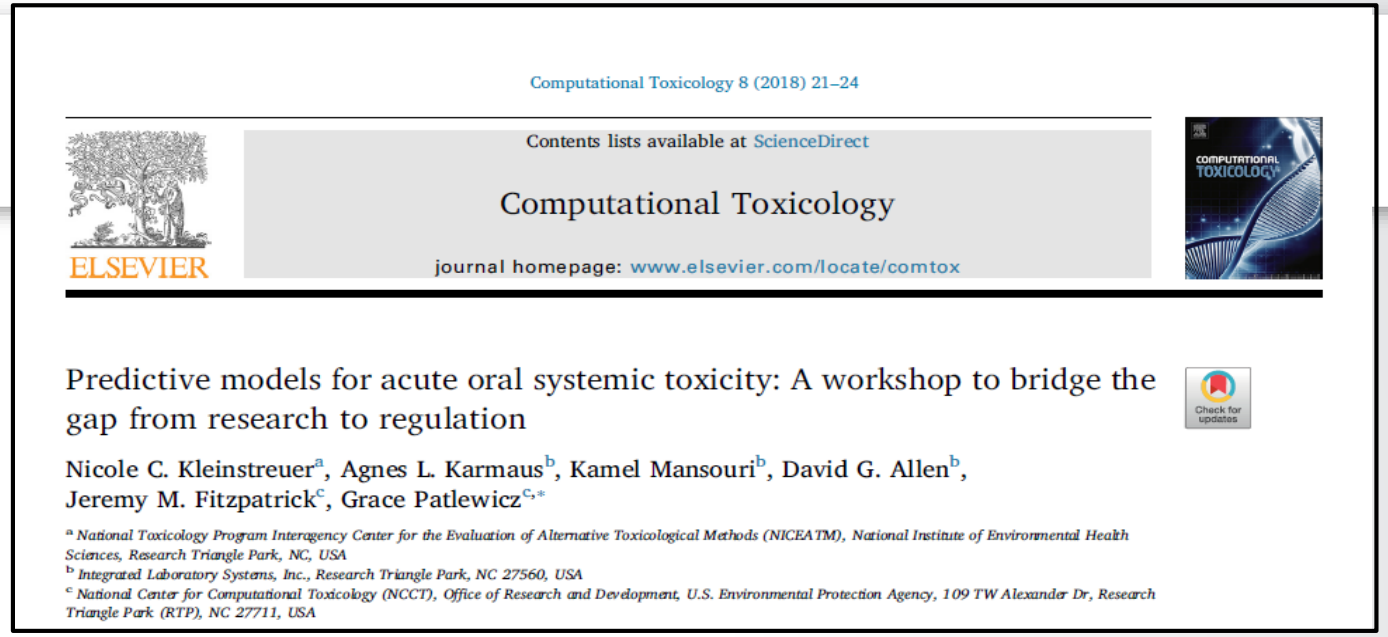


Unique ID: EPA 705-G-2020-3722 (Docket ID: EPA-HQ-OPP-2016-0093)

Guidance for Waiving Acute Dermal Toxicity Tests
for Pesticide Technical Chemicals & Supporting Retrospective Analysis

Acute Oral Pesticide Toxicity Testing

- CATMoS (Collaborative Acute Toxicity Modeling Suite)
  - Product of a 2018 ICCVAM workshop (>30 international groups)
  - In silico method that predicts rat acute oral LD50 based on chemical structure
  - Predictions include upper and lower CL determined from a variability analysis quantifying the uncertainty accompanying the experimental LD50 values.



Computational Toxicology 8 (2018) 21–24

Contents lists available at ScienceDirect

Computational Toxicology

journal homepage: www.elsevier.com/locate/comtox

Predictive models for acute oral systemic toxicity: A workshop to bridge the gap from research to regulation

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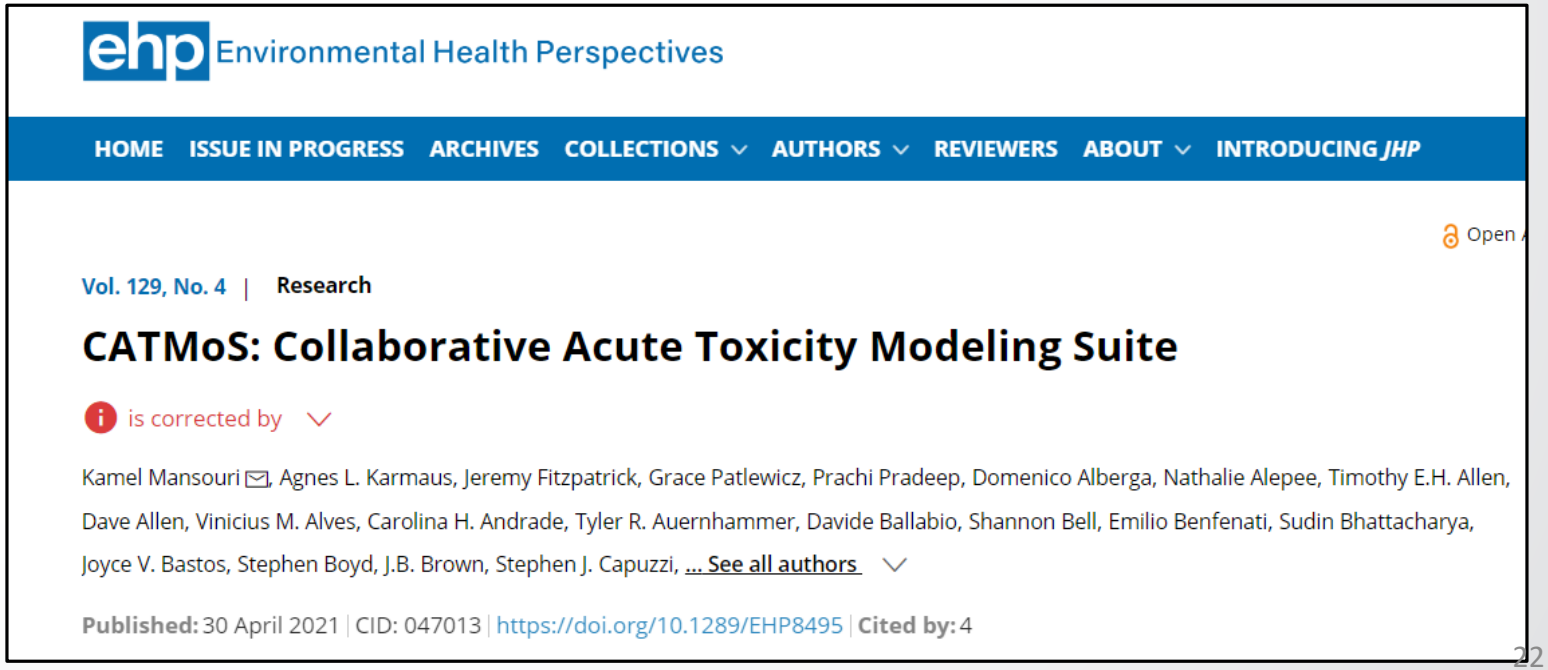

Environmental Health Perspectives

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CATMoS: Collaborative Acute Toxicity Modeling Suite

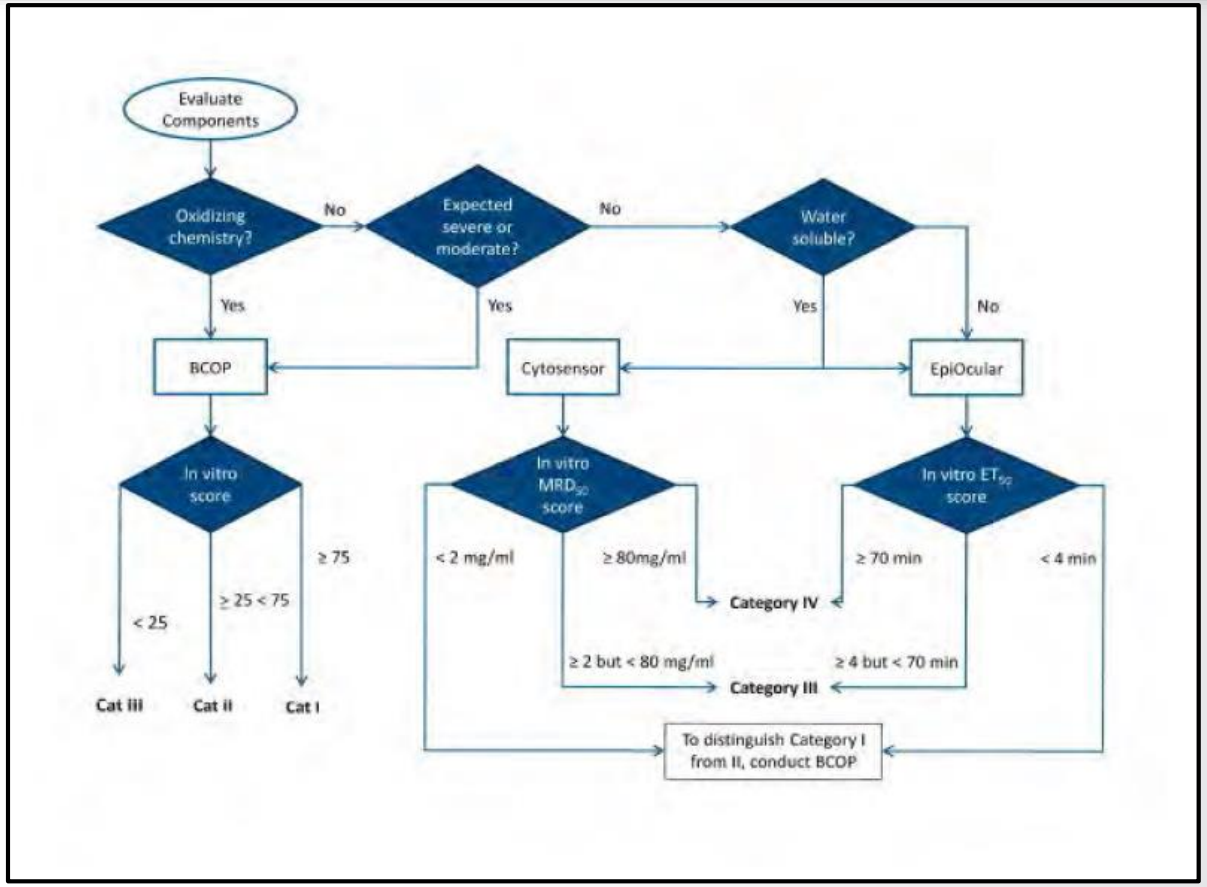
is corrected by

Kamel Mansouri, Agnes L. Karmaus, Jeremy Fitzpatrick, Grace Patlewicz, Prachi Pradeep, Domenico Alberga, Nathalie Alepee, Timothy E.H. Allen, Dave Allen, Vinicius M. Alves, Carolina H. Andrade, Tyler R. Auernhammer, Davide Ballabio, Shannon Bell, Emilio Benfenati, Sudin Bhattacharya, Joyce V. Bastos, Stephen Boyd, J.B. Brown, Stephen J. Capuzzi, ... See all authors

Published: 30 April 2021 | CID: 047013 | https://doi.org/10.1289/EHP8495 | **Cited by:** 4

Eye Irritation

- Testing framework for assessing eye irritation potential of EPA-registered antimicrobial cleaning products using three in vitro/ex vivo assays (non-animal tests):
  - *Bovine Corneal Opacity and Permeability assay (BCOP)*
  - *EpiOcular assay (EO)*
  - *Cytosensor Microphysiometer (CM) assay*
- The same testing approach is currently considered on a case-by-case basis for other classes of pesticides and pesticide products.
- https://www.epa.gov/sites/default/files/2015-05/documents/eye_policy2015update.pdf

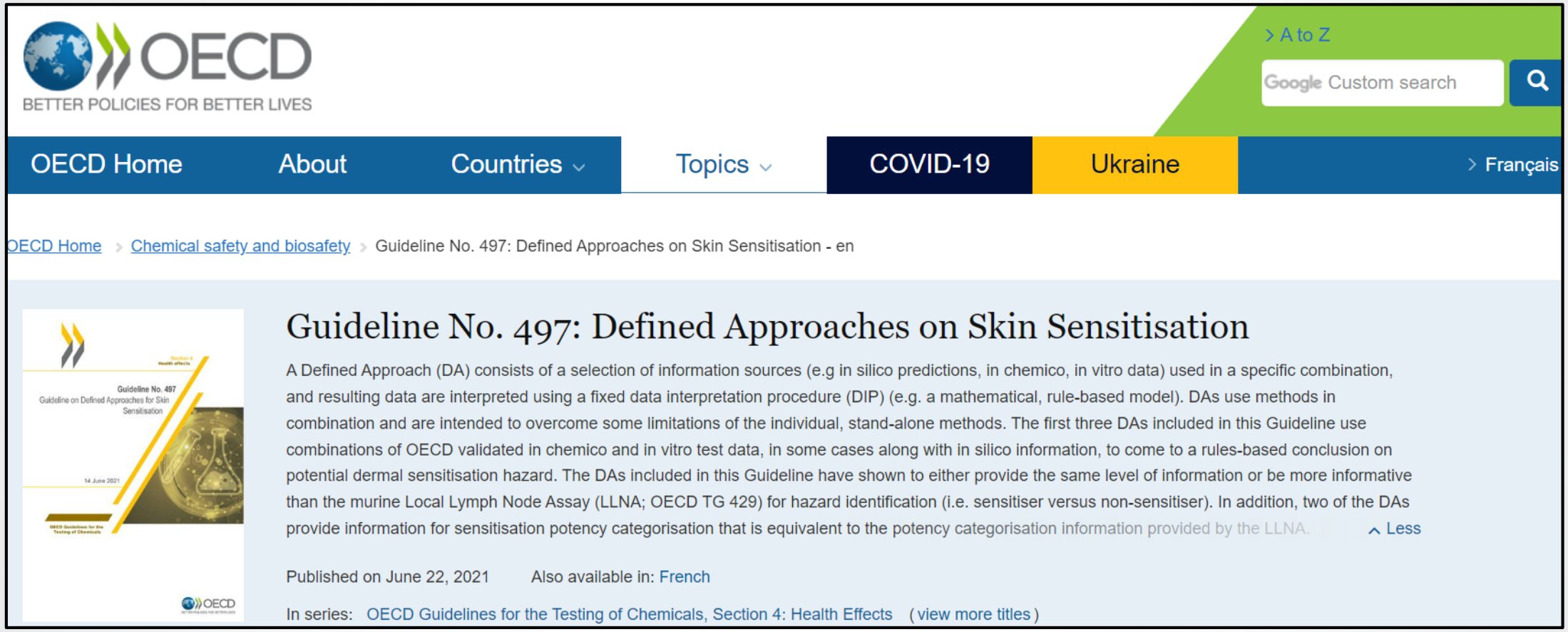


- Clippinger et al. Human-relevant approaches to assess eye corrosion/irritation potential of agrochemical formulations. Cutan Ocul Toxicol. 2021 Jun;40(2):145-167. doi: 10.1080/15569527.2021.1910291. PMID: 33830843.

2018 Draft Interim Science Policy: Use of Alternative Approaches for Skin Sensitization as a Replacement for Laboratory Animal Testing

- Joint policy between Office of Pesticide Programs (OPP) and Office of Pollution Prevention and Toxics (OPPT)
- Applies to pesticide active ingredients, inerts, and single chemicals regulated under amended TSCA
- Two DAs currently accepted: “AOP 2 out of 3” and “KE 3/1 STS”

Skin Sensitization



- https://www.oecd.org/chemicalsafety/guideline-no-497-defined-approaches-on-skin-sensitisation-b92879a4-en.htm

Expanding Coverage of Chemical Space for Skin Sensitization In Vitro Methods

- A significant number of chemicals used in the validation of non-animal test methods have been cosmetics ingredients
- US National Toxicology Program is supporting testing of other types of chemicals in three alternative test methods: DPRA, KeratinoSens, hCLAT
    - Expanded chemical space includes: pesticides, agrochemical formulations, dermal excipients, personal care product ingredients, “challenge” chemicals
- Chemical nominations from multiple agencies
    - EPA: Office of Pesticides, Office of Pollution Prevention and Toxics, Office of Research and Development
    - Consumer Product Safety Commission
    - Food and Drug Administration
    - NTP
- Testing of >200 chemicals has been completed

In Conclusion

- Building Confidence in the Use of NAMs to Make Progress in the 3Rs Requires:
  - ➢Collaboration across many sectors
  - ➢Transparency & use of peer review
  - ➢Learning by Doing → Application of Fit-for-Purpose Methods to Address Real-World Issues

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