Modernizing the Acute Toxicity ‘Six-Pack’ for U.S. EPA’s Office of Chemical Safety and Pollution Prevention (OCSPP)

MONIQUE PERRON, SC.D.

SENIOR SCIENCE ADVISOR

U.S. EPA/OCSPP/OPP

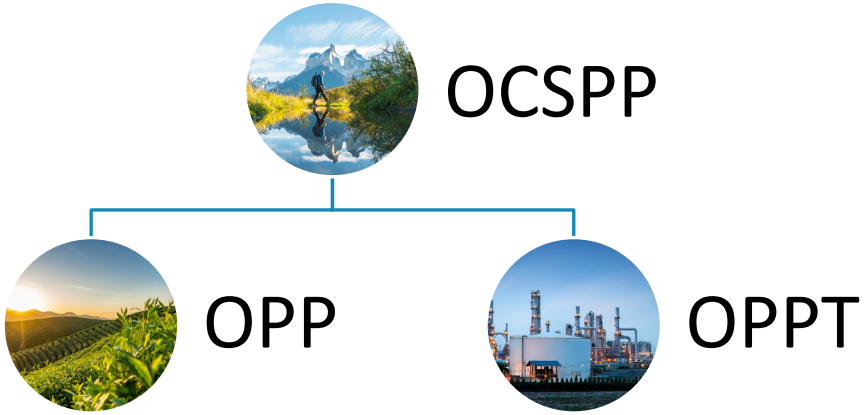
SACATM 2023

Disclaimer

This presentation has been reviewed and approved in accordance with U.S. Environmental Protection Agency policy.

Any mention of trade names, products, or services does not imply an endorsement by the U.S. Government or the United States Environmental Protection Agency. EPA does not endorse any commercial products, services, or enterprises.

Office of Chemical Safety and Pollution Prevention



- Office of Pesticide Programs
  - Regulates the manufacture and use of all pesticides and establishes maximum levels for pesticide residues in food.
  - 40 CFR Part 158 specifies the acute toxicology data requirements for active ingredients and pesticide products.

- Office of Pollution Prevention and Toxics
  - Regulates new chemicals and existing chemicals under the Toxic Substance Control Act (TSCA).
  - A baseline set of data is not required for new chemical notices under TSCA Section 5.

EPA NAMs Workplan

- Describes EPA's 5 objectives and strategies for development and implementation of new approach methods (NAMs)

OPP Implementation

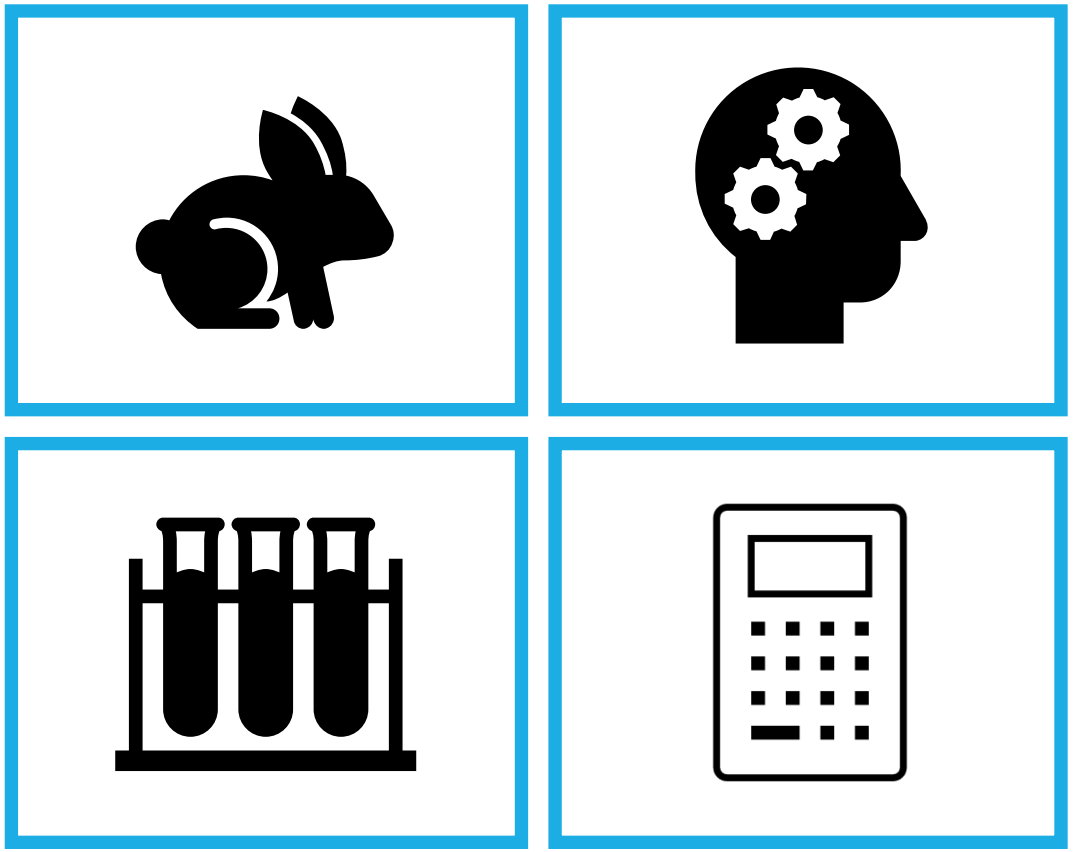
- Publication of multiple guidance documents which outline critical data needs to support regulatory decisions and opportunities to reduce or replace animal testing in certain circumstances.

OPPT Implementation

- Strategic plan was developed to incorporate NAMs which "provide information of equivalent or better scientific quality and relevance for assessing risks…" TSCA Section 4(h)(2)(A)

- OCSPP efforts to reduce and replace vertebrate animal testing are tied directly to the Agency's NAMs Workplan.
- Development and implementation of NAMs may be program and/or project specific.
  - Efforts on NAMs for replacement of the "six-pack" are relevant for both offices.

Current Efforts on Reduction and Replacement for Acute “Six-Pack”

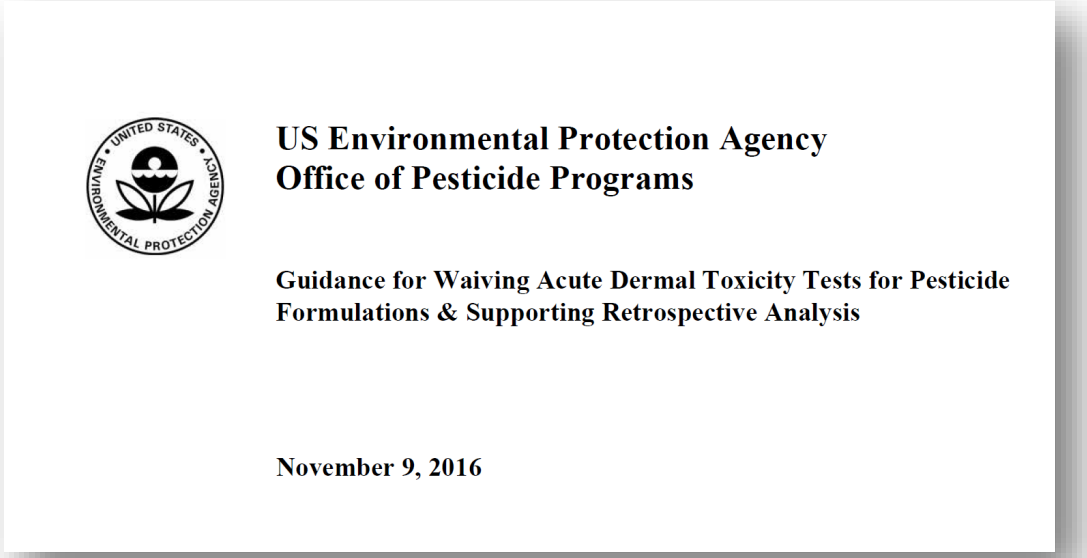


1. Acute Dermal
2. Acute Oral Toxicity
3. Acute Inhalation
4. Eye Irritation
5. Dermal Irritation
6. Dermal Sensitization

Acute Dermal Waiver Guidance

- 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

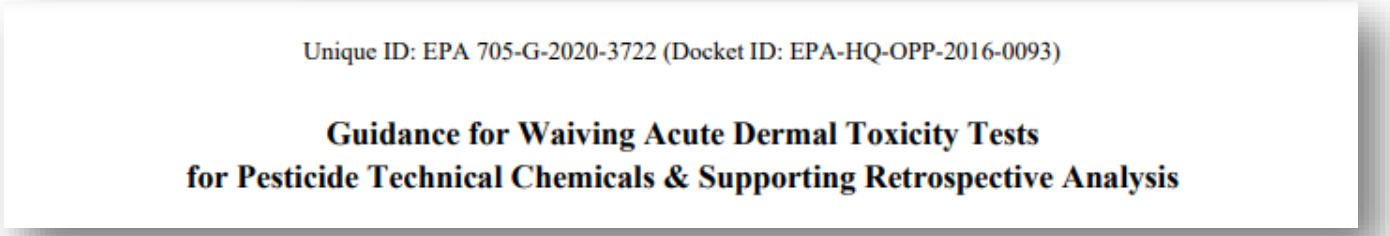
https://www.epa.gov/pesticide-registration/bridging-or-waiving-data-requirements



US Environmental Protection Agency
Office of Pesticide Programs

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

November 9, 2016

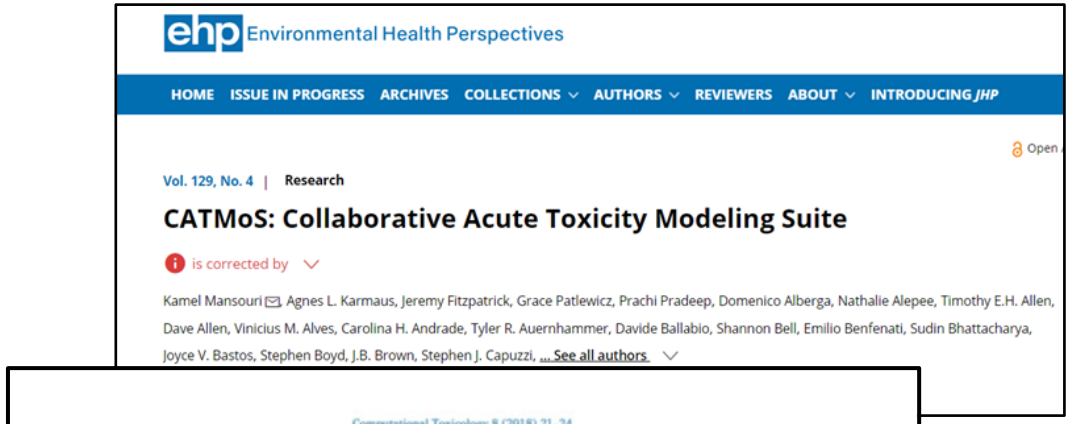


Unique ID: EPA 705-G-2020-3722 (Docket ID: EPA-HQ-OPP-2016-0093)

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

CATMoS: Collaborative Acute Toxicity Modeling Suite

- The U.S. Interagency Coordinating Committee on the Validation of Alternative Methods (ICCVAM) and over 30 international groups collaborated to develop *in silico* predictive models
- CATMoS is a quantitative structure-activity relationship (QSAR) model for predicting rat acute oral toxicity
- OPP is comparing CATMoS consensus model predictions with data from *in vivo* studies for almost 200 pesticides
- Promising results indicating the models can identify non-toxic chemicals (LD_{50} > 2000 mg/kg)
- Analysis and conclusions are planned for publication in near future



Acute Oral Toxicity – GHS Mixture Equation

- OPP initiated the "Mixtures Equation Pilot Program to Reduce Animal Testing" in 2016 to assess the utility of the GHS mixtures equation to predict the acute oral categories for formulated pesticides.
- Five companies submitted data through the pilot program; three companies submitted data directly to NICETAM.
  - 618 agrochemicals; 51 antimicrobial cleaning products
- Hamm et al. (2021) evaluated the concordance of the paired *in vivo* data and predicted LD_{50} values for both EPA and GHS classification.

Concordance Analysis

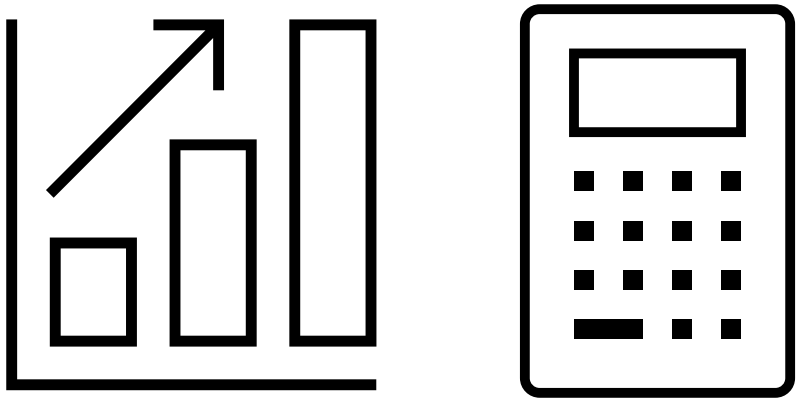
- Within-class concordance for EPA Toxicity Categories I-IV was 75%, 26%, 50%, and 87% respectively
- Majority of formulations (550/669) included in retrospective were classified as EPA Toxicity Category III or IV based on *in vivo* data
- Majority of predictions that differed from *in vivo* fell into range of *in vivo* LD50 > 2000 mg/kg (EPA Category III) but predicted LD50 > 5000 mg/kg (EPA Category IV)
- Most substances in the data set were LD50 > 500 mg/kg
  - Supplementary analysis combined all formulations with LD50 > 500 mg/kg
  - Improved concordance of predictions

Total for all classifications	Primary Approach			Supplementary Analysis (>500mg/kg)		
	Full	AMCP	Agrochem	Full	AMCP	Agrochem
EPA	55% (367/671)	84% (43/51)	52% (324/620)	82% (547/669)	100% (51/51)	80% (496/618)
GHS	72% (484/671)	98% (50/51)	70% (434/620)	NA	NA	NA

Lowest classification	Primary Approach (Cat IV or 5/NC)			Supplementary Analysis (>500 mg/kg)		
	Full	AMCP	Agrochem	Full	AMCP	Agrochem
EPA (Cat IV)	87% (138/157)	95% (38/40)	85% (99/117)	93% (514/550)	100% (51/51)	93% (463/496)
GHS (5/NC)	88% (337/381)	100% (49/49)	87% (288/332)	NA	NA	NA

GHS Prediction – Weight of Evidence

- Results indicate GHS equation is useful to predict toxicity of mixtures, especially in cases where expected toxicity is low
  - Lack of toxic formulations in this data set prevented thorough analysis of the utility of predicted LD_{50} values <500 mg/kg
- GHS Mixture equation prediction may also be useful in weight of evidence approach to assess acute oral toxicity of a pesticide
- OPP has received several waiver rationales for acute oral testing that have included predicted LD_{50} calculated using GHS mixture equation.
  - Often *in vivo* data on a related formulation included in the rationale



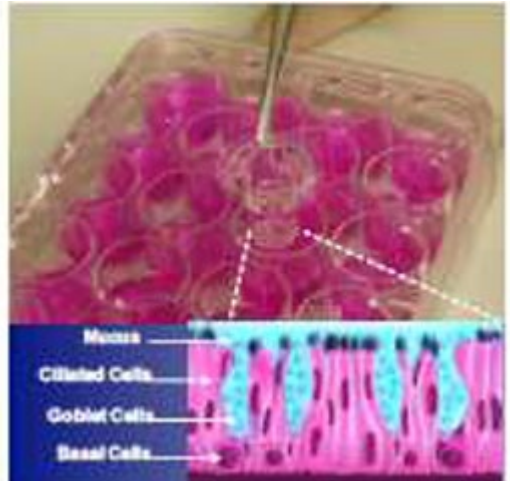
Acute Inhalation

- 2012 waiver guidance describes criteria to support waivers for acute inhalation toxicity:
  - Pesticide cannot be generated as a gas, vapor, or aerosol
  - Low volatility
  - Non-inhalable aerosol particle size
  - Test material is corrosive
- Possible to extend acute oral approaches to inhalation
  - Pilot for GHS mixtures equation for acute inhalation
  - In silico predictions
- Ongoing investigations using *in vitro* assays
- Collaborating on in depth review of species differences

Office of Pesticide Programs

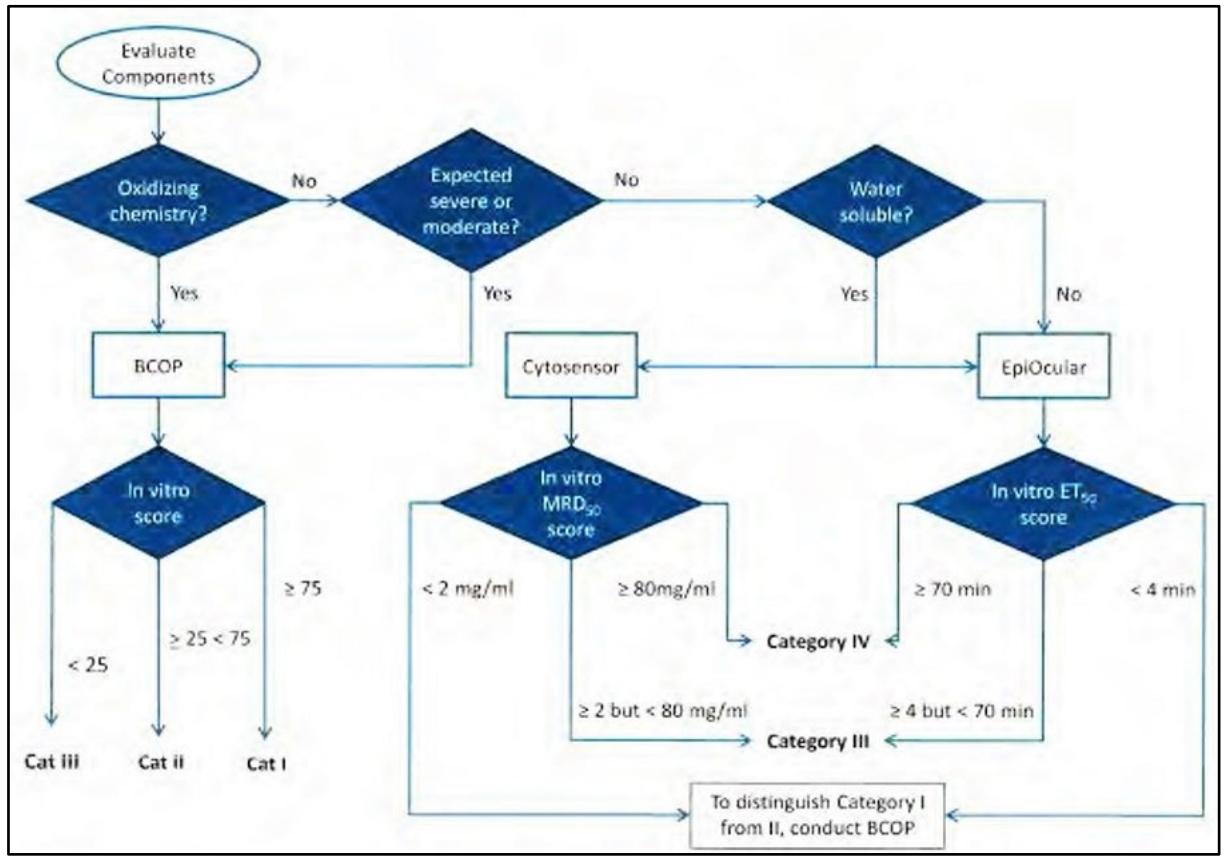
Guidance for Waiving or Bridging of Mammalian Acute Toxicity Tests for Pesticides and Pesticide Products (Acute Oral, Acute Dermal, Acute Inhalation, Primary Eye, Primary Dermal, and Dermal Sensitization)

March 1, 2012



Taken from Kirkland and Millard (2020)

Defined Approaches for Eye Irritation: OPP

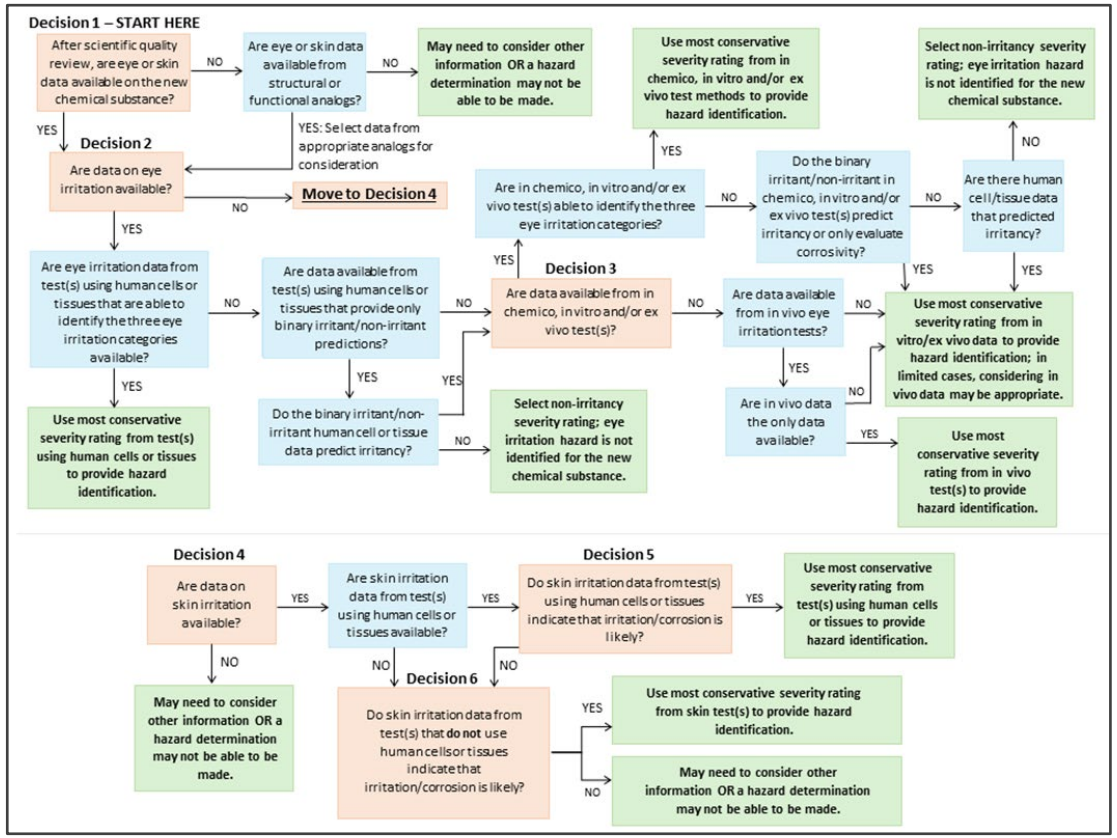


- Testing framework for assessing eye irritation potential of antimicrobial cleaning products using three *in vitro/ex vivo* assays.
  - Currently considered on case-by-case basis for other classes of pesticides
  - OPP currently receiving paired *in vivo* and *in vitro* data on agrochemical formulations
- Two defined approaches are presented in a manuscript submitted for publication co-authored by PETA, IIVS, NICEATM, and EPA for agrochemical formulations.
  - Compared performance of 2 defined approaches for 29 agrochemical formulations

Image: https://www.epa.gov/sites/default/files/2015-05/documents/eye_policy2015update.pdf

Draft Decision Framework for Eye Irritation: OPPT - New Chemicals Program (NCP)

- Submitters of a new chemical notice or exemption application required to report any existing, available data on human health or environmental hazards under Toxic Substances Control Act (TSCA) Section 5
- NCP may receive *in vitro/ex vivo* tests or *in vivo* tests or a combination for a Section 5 application
- Draft decision framework was developed to assess eye irritation hazard through prioritization of reproducible and human-relevant data on substance or analogue
  - Includes OECD approved test methods that identify three eye irritation categories and binary outcomes.
- Expected to be released for public comment
  - Intended to provide transparency for stakeholders and to improve consistency in hazard assessments



Efforts on NAMs for Skin Irritation

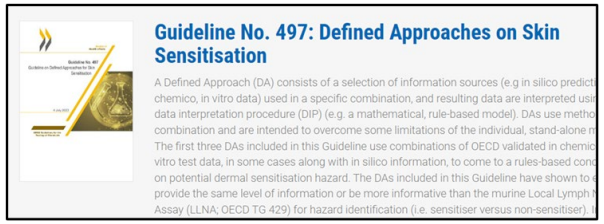
- Several *in vitro* methods for assessing dermal corrosion, dermal irritants or non-irritants are accepted by the OECD
  - OECD TG 430 – In Vitro Skin Corrosion: Transcutaneous Electrical Resistance Test Method (TER)
  - OECD TG 431 – In Vitro Skin Corrosion: Reconstructed Human Epidermis (RhE) Test Method
  - OECD TG 435 – In Vitro Membrane Barrier Test Method for Skin Corrosion
  - OECD TG 439 – In Vitro Skin Irritation: Reconstructed Human Epidermis Test Method
- Proposed testing strategies developed for pesticides using OECD TGs as well as consideration of additional assays to aid in identification of mild irritants
  - Manuscript prepared for submission
- OPPT New Chemicals Program is currently developing a decision framework to assess skin irritation hazard when multiple lines of evidence exist (NAMs and *in vivo* tests)

Efforts on NAMs for Dermal Sensitization

OECD TGs assess 3 key events in AOP
2015-2017

OCSPP Interim Science Policy
2018

Defined Approaches on Skin Sensitization OECD GD 497
2021



- OCSPP Draft Interim Science Policy applies to pesticide active ingredients, inerts, and single chemicals regulated under amended TSCA
  - Two defined approaches (DAs) currently accepted: “AOP 2 out of 3” and “KE 3/1 STS”
- OECD Guideline No. 497 adopted in June 2021
  - Includes “2 out of 3”, integrated testing strategy (ITSv1), and modified integrated testing strategy (ITSv2) DAs

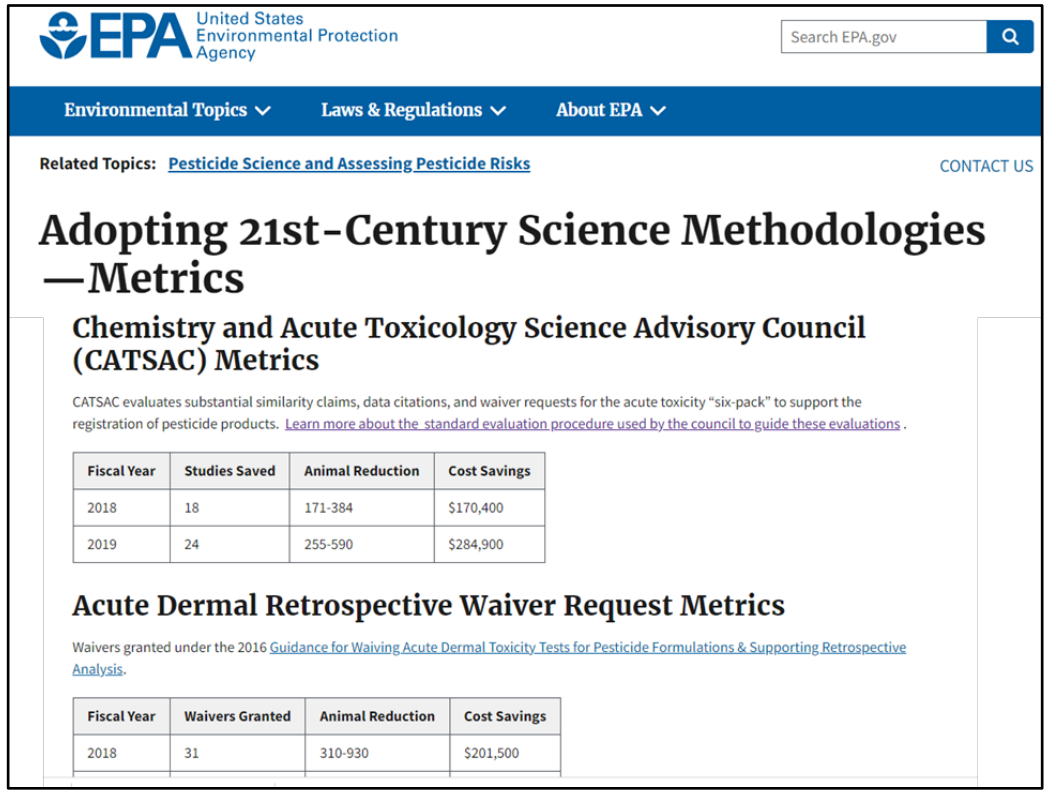
OCSPP NAMs Metrics

- OPP and OPPT are currently tracking submissions of alternative methods which replace *in vivo* data on pesticides and industrial chemicals
- Currently OPP metrics on animal reduction are published on the website
- Publication of OPPT metrics are in development
- NAMs represent a small portion of data submitted to OPP & OPPT for these toxicity endpoints
  - Both offices typically receive hundreds of applications/year

Non-animal Test Methods						
Fiscal Year	Eye Irritation Tests		Skin Irritation Tests		Skin Sensitization Tests	
	OPP	OPPT	OPP	OPPT	OPP	OPPT
2018	19	45	11	56	1	20
2019	12	40	7	49	0	19
2020	13	42	7	52	3	31
2021	32	39	28	54	12	23
2022	17	43	13	38	7	17
Total	**93**	**209**	**66**	**249**	**23**	**110**

https://www.epa.gov/pesticide-science-and-assessing-pesticide-risks/strategic-vision-adopting-new-approach-0

Additional NAMs Metrics



EPA United States Environmental Protection Agency

Search EPA.gov

Environmental Topics | Laws & Regulations | About EPA

Related Topics: Pesticide Science and Assessing Pesticide Risks

CONTACT US

Adopting 21st-Century Science Methodologies —Metrics

Chemistry and Acute Toxicology Science Advisory Council (CATSAC) Metrics

CATSAC evaluates substantial similarity claims, data citations, and waiver requests for the acute toxicity "six-pack" to support the registration of pesticide products. Learn more about the standard evaluation procedure used by the council to guide these evaluations.

Fiscal Year	Studies Saved	Animal Reduction	Cost Savings
2018	18	171-384	$170,400
2019	24	255-590	$284,900

Acute Dermal Retrospective Waiver Request Metrics

Waivers granted under the 2016 Guidance for Waiving Acute Dermal Toxicity Tests for Pesticide Formulations & Supporting Retrospective Analysis.

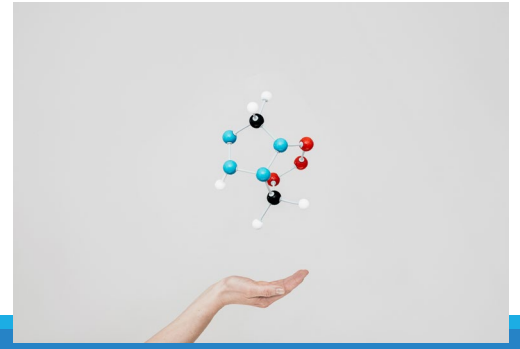
Fiscal Year	Waivers Granted	Animal Reduction	Cost Savings
2018	31	310-930	$201,500

- OPP aims to track metrics associated with each guidance document published to reduce or replace animal tests
- Data waivers granted and associated animal reduction reported annually through science advisory councils
- Chemistry and Acute Toxicology Science Advisory Council (CATSAC) grants waivers for ~20 acute toxicity studies per year.
- Since these waivers are not inclusive of all data waivers across the program, OPP is developing a comprehensive approach to accurately reflect the full scope of animal reduction.

https://www.epa.gov/pesticide-science-and-assessing-pesticide-risks/adopting-21st-century-science-methodologies-metrics

Challenges

- Providing policy/guidance documents to encourage submissions
- Consistency across OCSPP when possible
- International harmonization
- Coverage of relevant chemical space



Summary

- OPP has flexibility in data requirements that allows for consideration of waivers and alternative approaches
- OPPT has a statutory mandate to consider the availability of NAMs that are equal to or better than the animal study before requesting vertebrate animal testing and encourages the use of NAMs
- Both offices will continue to assess the progress and extent of adoption of NAMs yearly
- As new NAMs guidance documents are published, EPA will assess the progress and extent of adoption of these approaches over the years and evaluate any trends
- EPA is working with multiple national/international organizations and stakeholders on development and implementation of NAMs

Thank you!