ICCVAM Public Forum
U.S. Environmental Protection Agency
Office of Pesticide Programs

Monique Perron, Sc.D.
perron.monique@epa.gov
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USEPA Administrator Memo Prioritizing Efforts to Reduce Animal Testing, September 10, 2019

https://www.epa.gov/environmental-topics/administrator-memo-prioritizing-efforts-reduce-animal-testing-september-10-2019

- EPA will reduce its requests for, and our funding of, mammal studies by 30 percent by 2025
- EPA will eliminate all mammal study requests and funding by 2035. Any mammal studies requested or funded by the EPA after 2035 will require Administrator approval on a case-by-case basis.
- Form a working group of agency experts in this field who will provide a work plan within six months.
- EPA held the *First Annual Conference on the State of the Science on Development and Use of New Approach Methods (NAMs) for Chemical Safety Testing* on December 17, 2019
  - Conference report: https://www.epa.gov/chemical-research/conference-summary-state-science-development-and-use-new-approach-methods-chemical

Stakeholder Engagement is Extensive

- Industry:
  - Consortia (ACC, CropLife America, ILSI HESI)
  - Individual companies (Dow/Dupont/Corteva, BASF, Syngenta, Bayer, Clorox, P&G, etc)
  - Contract labs (e.g., Charles River, IIVS, MatTek, Epithelix, etc)
- Animal welfare groups:
  - People for the Ethical Treatment of Animals International Science Consortium (PETA-ISC)
  - Physicians Committee for Responsible Medicine (PCRM)
  - Humane Society US & Human Society International
- Other governments: California, Canada, Brazil, Australia, EU, etc.

International Activities

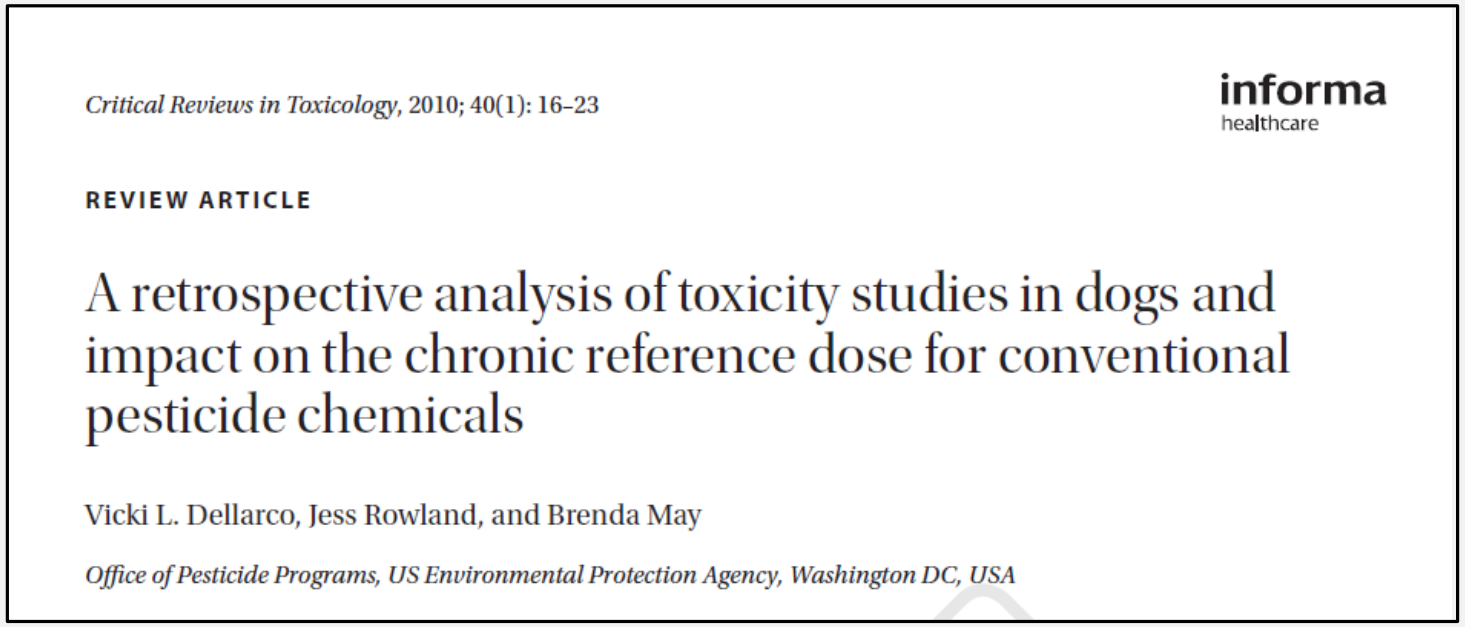
- ICATM: International Cooperation on Alternative Test Methods established in 2009 and includes US, European Union, Japan, Health Canada, Korea, Brazil, China
- OECD is developing numerous new guidance documents & study guidelines on alternatives:
  - QSAR & computational approaches
  - Endocrine disruption
  - Eye & skin irritation
  - Skin sensitization
  - Metabolism
  - Fish
  - Etc.…

Reducing Laboratory Animal Use

Reducing Animal Use

- OPP began its systematic evaluation of pesticide data requirements for human health in early 2000's leading to the elimination of the chronic study in dogs in the 40CFR in 2007

- Since then, animal reduction activities have accelerated substantially & expanded to ecotoxicology in 2018.



Critical Reviews in Toxicology, 2010; 40(1): 16–23

informa
healthcare

REVIEW ARTICLE

A retrospective analysis of toxicity studies in dogs and impact on the chronic reference dose for conventional pesticide chemicals

Vicki L. Dellarco, Jess Rowland, and Brenda May

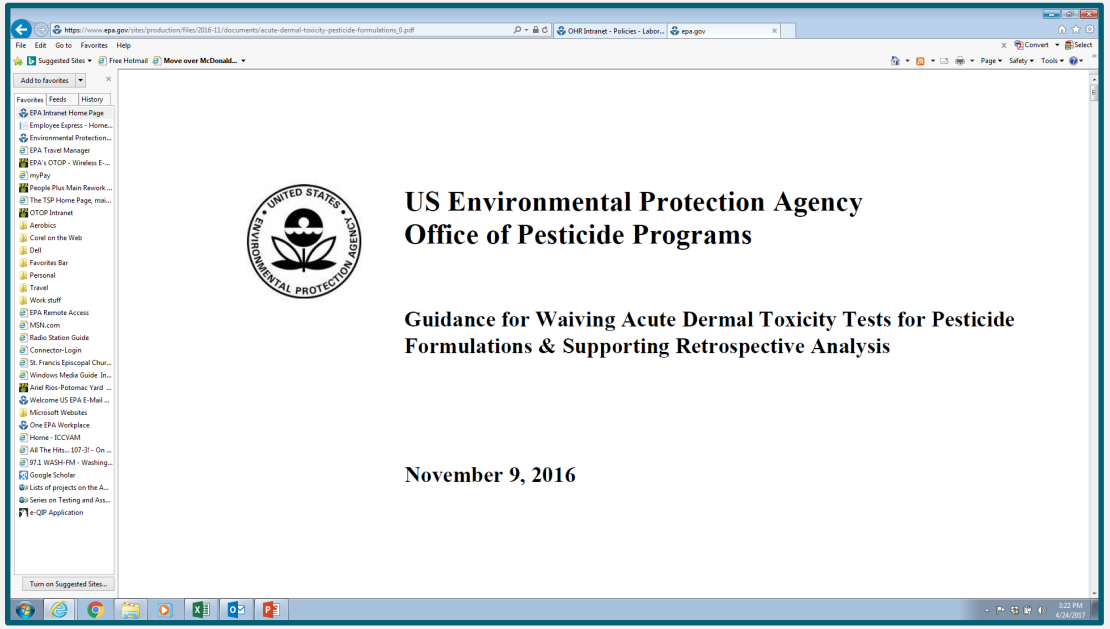
Office of Pesticide Programs, US Environmental Protection Agency, Washington DC, USA

Waiving or Bridging Acute Toxicity Tests

- OECD Guidance Document for Waiving or Bridging Acute Toxicity Tests
  - Co-authored by USEPA & Canada PMRA
  - Provides international guidance on waiving acute lethality studies for oral, dermal and inhalation
  - http://www.oecd.org/env/ehs/testing/mono%202016%2032.pdf
- Chemistry and Acute Toxicology Science Advisory Council established in 2016, new SOPs in 2017
  - Expand waiver opportunities for formulations
  - In FY19, 12 Submissions (6 accepted)
    - Number of animals saved = 258 minimum
    - Study costs saved = $287,000

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
- Collected acute lethality dermal and oral toxicity data from rat studies with pesticide formulations
- OPP is working to expand the dermal waiver guidance to include technical ingredients



Part 158 Toxicology Data Requirements: Guidance for Neurotoxicity Battery, Subchronic Inhalation, Subchronic Dermal and Immunotoxicity Studies

http://www.epa.gov/pesticides/regulating/part158-tox-data-requirement.pdf

- Build efficiencies into the risk assessment process
  - Fewer studies submitted = Less resources spent
  - Better focus on most important issues
- If a waiver cannot be granted, the document provides guidance on retaining a database uncertainty factor (UF_{DB}) is needed until the study is conducted and/or other information is used to fill the data gap
- Although not specifically covered by the guidance, EPA has flexibility to waive other studies
  - Same basic principles apply

WOE Approach Used by Hazard & Science Policy Council (HASPOC)

- Physical chemical properties
- Use & exposure pattern
- Hazard characterization:
  - Toxicity profile, information on MOA/AOP, other pesticides in the class
- Risk assessment implications

Resource Savings

- HASPOC metrics are reported in the Annual PRIA Report
  - In FY'17, waivers were granted for 70 of 78 requests resulting in savings of about 41,000 animals and approximately $10.4 million in the cost of conducting the studies.
  - In FY'18, waivers were granted for 62 of 71 requests resulting in savings of about 15,780 animals and approximately $8.9 million in the cost of conducting the studies.
  - In FY'19, waivers were granted for 65 of 78 requests resulting in savings of about 27,500 animals and approximately $9.4 million in the cost of conducting studies
- Craig et al. (2019): https://www.sciencedirect.com/science/article/pii/S0273230019302454

Carcinogenicity

- Two cancer bioassays (rat, mouse) are routinely conducted for conventional pesticides as required by many countries.
  - 480 animals/study, cost: ~$2 million
  - Many of these studies are not used in the risk assessment
- Human relevance of this study in question by the scientific community
- Rethinking Carcinogenicity Assessment for Agrochemicals Project (ReCAAP)
  - Early stages of collaborative project to develop a waiver guidance for pesticides
  - Project led by PETA-ISC with contributions from PMRA, ORD, BASF, Corteva, Syngenta, OPP-HED (APVMA has recently joined)
  - Society of Toxicology session held in March 2019
  - Retrospective case studies have been developed as part of the WOE development
  - Currently drafting additional case studies to test WOE reporting framework.

Avian subacute/acute risk retrospective

- OPP ecological risk assessments use both acute oral and sub-acute dietary studies to assess acute risks to birds (the endpoint that results in the highest risk quotient drives the risk conclusion)
- Science Question: Can we confidently assess acute risk for birds using a reduced suite of effects studies focusing on the single oral dose protocol?
  - How often have subacute dietary risk quotients (RQs) quantitatively driven risk assessment conclusions?
- Partnership with PETA-ISC
- Bottom line results are that 99% (118 of 119) of all subacute dietary studies for new use assessments did not change risk conclusions already reached using oral dose-based RQ's.
  - In most cases (there are some exceptions) a robust avian acute risk assessment can be conducted without the sub-acute dietary studies.
- Hilton, G.M., Odenkirchen, E., Panger, M., Waleko, G., Lowit, A., Clippinger, A.J. 2019, Regulatory Toxicology and Pharmacology, 105: 30-35, https://doi.org/10.1016/j.yrtph.2019.03.013
- Policy finalized in February, 2020
  - https://www.epa.gov/sites/production/files/2020-02/documents/final-waiver-guidance-avian-sub-acute-dietary.pdf

Replacing Laboratory Animal Studies with New Approach Methodologies (NAMs)

Expanding Acceptance of Alternative Methods

TEST	ALTERNATIVE TEST	OECD
Skin Irritation	Reconstructed Human Epidermis models	OECD TG 431
	Reconstructed Human Epidermis models	OECD TG 439
Eye Irritation	Bovine corneal opacity permeability (BCOP) test	OECD TG 437
	Transcutaneous Electrical Resistance Test Method (TER)	OECD TG 430
	Fluorescein Leakage	OECD TG 460
	Isolated chicken eye (ICE) test	OECD TG 438
	Reconstructed human Cornea-like Epithelium (RhCE)	OECD TG 492
Skin sensitization	Direct Peptide Reactivity Assay (DPRA)	OECD TG 442C
	Keratinosens assay	OECD TG 442D
	Human Cell Line Activation Test (h-CLAT)	OECD TG 442E

Eye Irritation

- Currently have a policy in place to accept eye irritation assays for antimicrobial cleaning products: https://www.epa.gov/pesticide-registration/alternate-testing-framework-classification-eye-irritation-potential-epa
- Effort to extend the use of alternative assays for other classes of pesticides
- Voluntary data collection effort for conventional pesticides
  - >200 pairs of in *vitro-in vivo* data provided by industry
- Prospective testing to fill in the gaps co-chaired by PETA-ISC and NICEATM, with members from PCRM, EPA, Canada PMRA, ECVAM, and Industry
- Currently, working on a draft manuscript on eye irritation AOP(s) and providing link between AOP(s) with available *in vitro* assays

Skin Sensitization

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

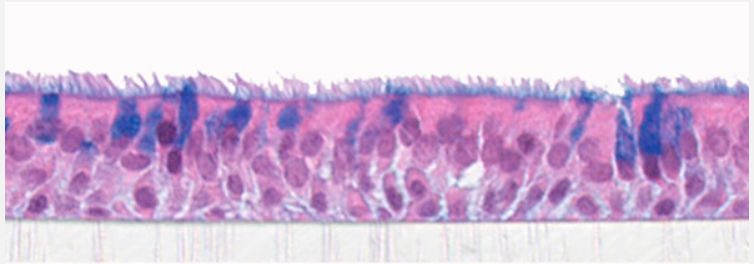
- Announced April 10, 2018 & describes the science that supports a policy to accept alternative (*in vitro, in silico, in chemico*) approaches
    - Multiple non-animal testing strategies - *in vitro, in chemico*, and *in silico* inputs demonstrate comparable or superior performance to the animal studies
- Interim policy is the result of collaboration between ICCVAM, NICEATM, ECVAM, Canada PMRA
- EPA is accepting these approaches under certain conditions described in the interim policy for active or inert ingredients (not formulations yet)
- On-going work at NTP to evaluate use of OECD guidelines on formulations/mixtures
    - Will revise policy in the future as appropriate

Isothiazolinones Risk Assessment

- 6 antimicrobial pesticides (biocides) that are positive skin sensitizers
  - Use as material preservative presents concern, as products containing these chemicals do not bear pesticide labels to communicate potential hazard to consumers
- Quantitative approach to assess potential skin sensitization by identifying induction and/or elicitation thresholds for each chemical to characterize risk from dermal exposure
- Approach extends previously used principles for assessing skin sensitization potential by using *in vitro* and *in chemico* assays and neural network-based defined approaches (DAs)
- First use of *in vitro* data to derive point of departure for pesticide risk assessment (draft risk assessments released May 14, 2020)
- https://www.regulations.gov/docket?D=EPA-HQ-OPP-2014-0159

Inhalation Risk Assessment

- Proposal for refining inhalation risk assessment using a 3D human airway epithelia reconstituted in vitro model initially presented to EPA in 2014 by Syngenta Crop Protection
- Agency recognized the value of the proposal for chlorothalonil, as well as other respiratory contact irritants and encouraged further development
- Collaborated with NICEATM and other EPA offices for review
- Convened FIFRA SAP meeting in December 4-7, 2018 to evaluate the proposed approach
  - First time a point of departure for risk assessment will be derived using in vitro data for a pesticide
  - Potential use for other contact irritants, as well as other chemicals that cause portal of entry effects in the respiratory tract
- SAP report released in April 2019
  - No panelists supported using the laboratory animal study



Dermal Absorption "Triple Packs"

- Human *in vitro*, rat *in vitro*, and rat *in vivo* studies using similar protocols (e.g., same test material, doses)
- Used to refine dermal assessments by adjusting for differences between *in vitro* and *in vivo* absorption as well as species differences
- To assess the feasibility of using only *in vitro* data to estimate the dermal absorption factor, a retrospective analysis of agrochemical triple pack reports was conducted between 2003 and 2019.
  - Collaborative effort with NICEATM, industry, Canada PMRA, CDPR, APVMA, Charles River Laboratory
- Current analysis shows that, in general, a DAF derived solely from *in vitro* data alone would be similar or more conservative than the triple pack DAF

Toxicokinetic Data

Utility of Toxicokinetic (TK) Data

- TK data support smarter testing strategies
  - Reduce & Replace: eliminate duplicative testing or unnecessary studies
  - Refine: lessen animal suffering by not testing at doses that cause overt toxicity
- Many potential uses, including:
  - *Dose selection*: avoid excessively toxic doses & characterization of doses closer to human relevant exposures
  - *Lifestage sensitivity*: Characterization of how metabolism & tissue dosimetry differs/changes among lifestages
  - *Animal to human extrapolation*: PBPK models for use in deriving Data Derived Extrapolation Factors (DDEFs)/Chemical Specific Adjustment Factors (CSAFs) and human derived points of departure

PBPK example: pyrethroids https://www.epa.gov/ingredients-used-pesticide-products/2019-evaluation-fqpa-safety-factor-pyrethroids

Upcoming events & activities

Upcoming SAB on NAMs for Chronic/Cancer Testing

- Upcoming Science Advisory Board on June 23-24, 2020 on "New Approach Methods and Reducing the Use of Laboratory Animals for Chronic and Carcinogenicity Testing"
- Topics organized around the 3Rs
  - Reduce: Rethinking Carcinogenicity Assessment for Agrochemicals Project (ReCAAP)
  - Replace:
    - Division of the National Toxicology Program (DNTP) of National Institute of Environmental Health Sciences (NIEHS): carcinogenicity initiative to develop efficient, fit for purpose approaches to characterize the potential for environmental exposures to cause or contribute to the development of cancer in humans
    - HESI to consider NAM-based approaches to replace chronic/carcinogenicity testing in mammals by use of omics-based points of departure
    - ORD case study to use NAMs on selected pesticides with established MOAs
  - Refine: use of kinetically derived maximum doses instead of traditional maximum tolerated dose

Upcoming FIFRA SAP on NAMs for Extrapolation: OP Case Study

- In September 2020, OPP plans to convene FIFRA SAP on "Use of New Approach Methodologies to Derive Extrapolation Factors and Evaluate Developmental Neurotoxicity for Human Health Risk Assessment"
  - *In vitro* data for 16 OPs to potentially reduce reliance on default risk assessment uncertainty factors in favor of more refined data-derived factors
  - ORD is working to develop a NAM for evaluating developmental neurotoxicity & utilizing *in vitro* to *in vivo* extrapolation methodologies
    - OPs are being used as a case study

Thank You!