Efforts to Reduce Animal Testing at EPA

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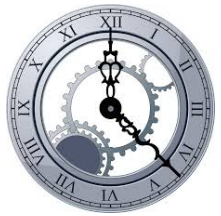
Some driving forces…..

Ethics & Animal Welfare

Efficiency



Public Health (Human Relevance, Improved science)

Expectations

Slide thanks to Warren Casey, Director, NIEHS-NICEATM

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

- In the 1990's, an ad hoc ICCVAM was established by the Director of the National Institute of Environmental Health Sciences (NIEHS) in September 1994 to develop a report responsive to requirements in the NIH Revitalization Act of 1993, Public Law 103-43.
- In 2000, Congress passed the ICCVAM Authorization Act and established ICCVAM as a permanent committee administrated by NIEHS
  - Comprised of 16 Federal regulatory and research agencies that require, use, generate, or disseminate toxicological and safety testing information.
  - ICCVAM facilitates the development, validation, and regulatory acceptance of test methods that replace, reduce, or refine the use of animals in testing.
  - NTP Interagency Center for the Evaluation of Alternative Toxicological Methods (NICEATM) of the NIEHS provides scientific and operational support for ICCVAM technical evaluations and related activities.

Agency for Toxic Substances and Disease Registry • Consumer Product Safety Commission • Department of Agriculture
Department of Defense • Department of Energy • Department of the Interior • Department of Transportation
Environmental Protection Agency • Food and Drug Administration • National Institute for Occupational Safety and Health
National Institutes of Health • National Cancer Institute • National Institute of Environmental Health Sciences
National Library of Medicine • Occupational Safety and Health Administration • National Institute of Standards & Technology

OPP's Strategic Vision

- After the NRC published its 2007 report on Toxicity Testing in the 21st Century: A Vision and a Strategy, OPP developed a *Strategic Vision for Adopting 21st Century Science Methodologies* (2008)
  - https://www.epa.gov/pesticide-science-and-assessing-pesticide-risks/strategic-vision-adopting-21st-century-science
  - *A broader suite of computer-aided methods to better predict potential hazards and exposures, and to focus testing on likely risks of concern;*
  - *Improved approaches to more traditional toxicity tests to minimize the number of animals used while expanding the amount of information obtained;*
  - *Improved understanding of toxicity pathways to allow development of non-animal tests that better predict how exposures relate to adverse effects;*
  - Improved diagnostic biomonitoring and surveillance methods to detect chemical exposures and identify causes of toxic effects;
  - A suite of spatial databases and geographic information tools, which will aid in developing more spatially explicit risk assessments that identify geographic areas of concern for both human health and ecological exposure.

2013 Guiding Principles for Data Needs for Pesticides

- Purpose: provide consistency in the identification of data needs, promote and optimize full use of existing knowledge, and focus on the critical data needed for risk assessment.
  - https://www.epa.gov/pesticide-registration/guiding-principles-data-requirements
  - "…ensure there is sufficient information to reliably support registration decisions that are protective of public health and the environment while avoiding the generation and evaluation of data that does not materially influence the scientific certainty of a regulatory decision…."
  - "…avoid unnecessary use of time and resources, data generation costs, and animal testing."
- Flexibility in implementing Part 158 data requirements (§158.30):
  - *Waivers* may be granted as permitted by 40 CFR Part 158.45;
  - Additional data beyond the 158 data requirements may be important to the risk management decision (§158.75), *alternative approaches* can be accepted, and other data can be used.

2016 OPP's Goal to Reduce Animal Testing

- Letter to Stakeholders on OPP's Goal to Reduce Animal Testing from Jack E. Housenger, Director.
  - https://www.regulations.gov/#!documentDetail;D=EPA-HQ-OPP-2016-0093-0003
  - Working in partnership with other governmental entities, industry and non-governmental organizations (NGOs) and need continued robust participation and support to achieve our mutual goal.
  - Activities fall under three main objectives
    - Critically evaluating which studies form the basis of OPP decisions;
    - Expanding acceptance of alternative methods and;
    - Reducing barriers such as challenges of data sharing among companies and international harmonization to adopting alternative methods in the U.S. and internationally.

USEPA Administrator Memo Prioritizing Efforts to 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.
- https://www.epa.gov/environmental-topics/administrator-memo-prioritizing-efforts-reduce-animal-testing-september-10-2019

EPA Administrator Memo Prioritizing Efforts to Reduce Animal Testing, September 10, 2019

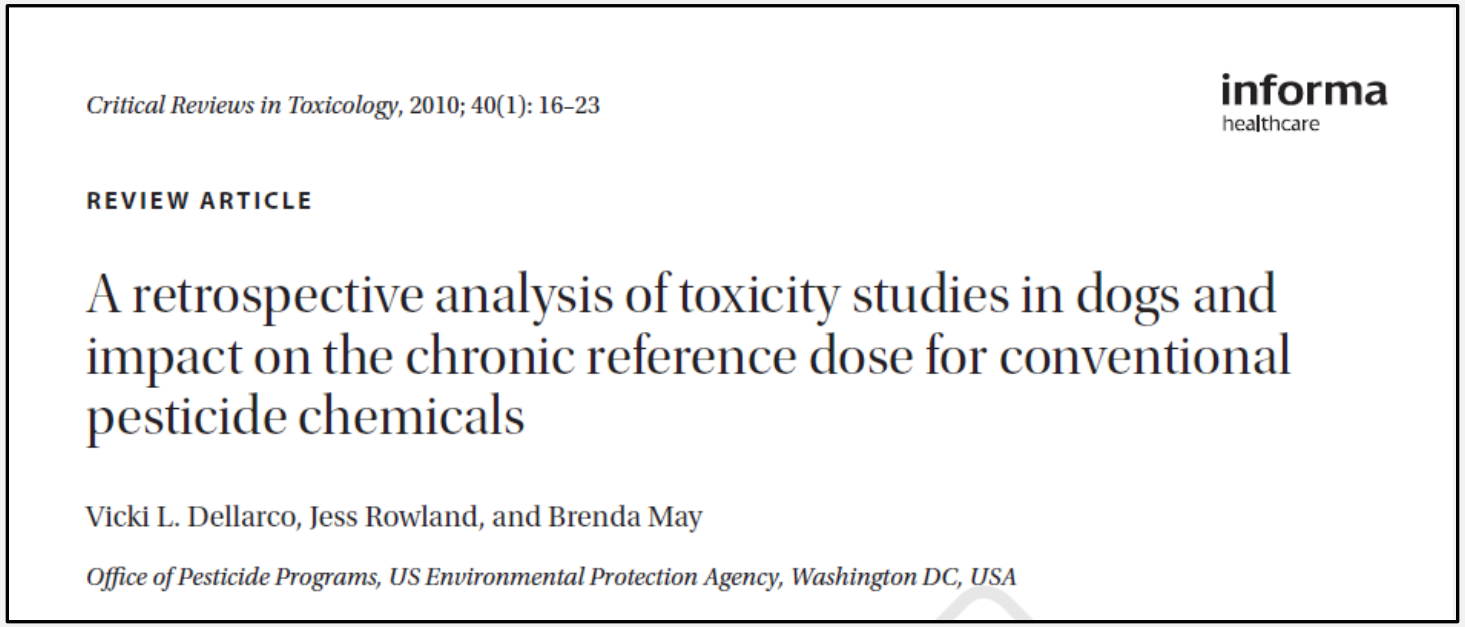
- This plan will include:
  - Validation to ensure that NAMs are equivalent to or better than the animal tests replaced;
  - Demonstration that NAMs are applicable for use in risk assessment and that new decision-making approaches are as protective of human health and the environment as existing approaches;
  - Recognition that statutory and regulatory requirements for animal testing currently exist and that a plan to adopt more flexible requirements should be developed;
  - Outreach to all stakeholders to incorporate their knowledge and address concerns; and
  - Establishment of baselines, measurements and reporting mechanisms to track the agency's progress.
- EPA will hold a joint annual conference on NAMs for presentations by leading scientists in the NAMs field, with the first conference to be held in 2019.
- https://www.epa.gov/environmental-topics/administrator-memo-prioritizing-efforts-reduce-animal-testing-september-10-2019

3 Rs: 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

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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

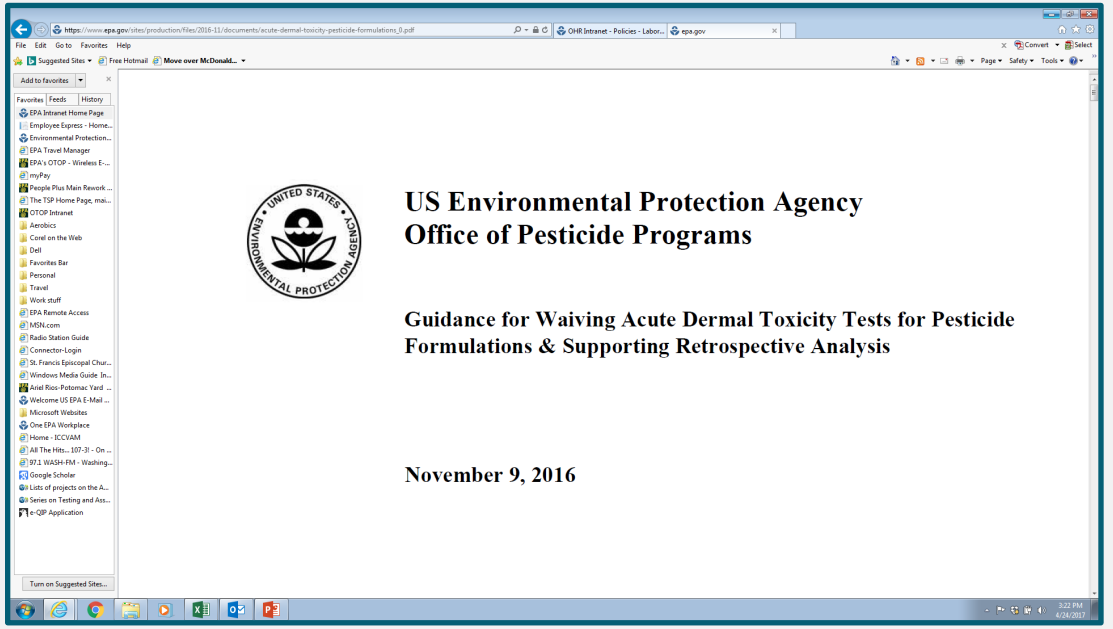
Waiving or Bridging Acute Toxicity Tests

- 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

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

- "…ensure there is sufficient information to reliably support registration decisions that are protective of public health and the environment while avoiding the generation and evaluation of data that does not materially influence the scientific certainty of a regulatory decision…."
- "It is important to only require data that adequately inform regulatory decision making and thereby avoid unnecessary use of time and resources, data generation costs, and animal testing."

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

- Document covers:
  - Subchronic Inhalation (870.3465),
  - Subchronic Dermal (870.3250),
  - Neurotoxicity screening batteries (870.6200; acute and subchronic neurotoxicity),
  - Immunotoxicity (870.7800)
- If a waiver can not 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.

Other Guideline Studies…..

- Although not specifically covered by the guidance, EPA has flexibility to waive other guideline studies…..
  - Less-frequent guideline studies considered by HASPOC
    - Developmental, reproductive, DNTs, chronic/carcinogenicity toxicity
    - Special studies (e.g., acute inhalation for fumigants, CCA studies)
    - Requests by registrants to conduct pharmacokinetic studies in lieu of toxicity study
  - The same basic principles apply
    - WOE based on exposure pattern, risk assessment, hazard profile, MOA, other members of the class, etc….

OPP's Hazard & Science Policy Council (HASPOC)

- HASPOC metrics are reported in the Annual PRIA Report
  - In FY'16, waivers were granted for 153 of 180 requests resulting in savings of about 44,000 animals and over $16 million in the cost of conducting the studies.
  - 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.

Summary of HASPOC Waivers December, 2011 through May 2018										
		Waiver Review Summary			Study Execution (Savings to the Registrant)				Study Report Review (Savings to EPA)	
Type of Study	OCSPP guideline	Waiver Requests	Waivers Granted	Required Studies	# animals/ study	Total # animals saved	Cost/ study	Total cost savings	Price to review study per contract	Total Cost Savings
Subchronic Inhalation	870.3465	296	233	63	80	18,640	$576,000	$134,208,000	$3,426	$798,258
Neurotoxicity (ACN and SCN)	870.6200	330	306	24	80	24,480	$211,550	$64,734,300	$6,441	$1,970,946
21/28-Day Dermal	870.3200	62	55	7	80	4,400	$114,100	$6,275,500	$3,426	$188,430
Developmental (rat and rabbit)	870.3700	44	39	5	80	3,120	$155,800	$6,076,200	$5,162	$201,318
DNT	870.6300	21	19	2	1,100	20,900	$771,600	$14,660,400	$10,326	$196,194
Subchronic dog	870.3150	15	13	2	32	416	$259,900	$3,378,700	$7,743	$100,659
Reproductive	870.3800	38	34	4	2,600	88,400	$432,000	$14,688,000	$12,354	$420,036
Immunotoxicity	870.7800	229	223	6	16	3,568	$71,200	$15,877,600	$8,075	$1,800,725
Chronic/Cancer	870.4300	25	23	2	480	11,040	$1,773,400	$40,788,200	$11,314	$260,222
Subchronic rat	870.3100	15	12	3	80	960	$173,000	$2,076,000	$7,743	$92,916
CTA	non-guideline	20	15	5	1800	27,000	$550,000	$8,250,000	$12,354	$185,310
Totals		1095	972	123		202,924		$311,012,900		$6,215,014

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
- National Toxicology Program (NTP) starting initiative to re-visioning the rodent cancer bioassay: https://ntp.niehs.nih.gov/ntp/about_ntp/bsc/2019/june/presentations/15casey_bsc_508.pdf
- Early stages of collaborative project to develop a waiver guidance for pesticides:
  - Project led by PETA-ISC with contributions from ORD, BASF, Corteva, Syngenta, OPP-HED
  - Society of Toxicology session held in March 2019
  - Case studies being developed

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
- Draft policy to reduce pesticide testing on birds released September 17, 2019. Accepting public comment until Nov. 1, 2019.

  https://www.epa.gov/pesticides/epa-releases-draft-policy-reduce-pesticide-testing-birds

Fish acute retrospective

- OPP ecological risk assessments use studies with warm freshwater fish, cold freshwater fish, and estuarine/marine fish to assess acute risks to fish.
- Science Question: Is there a consistently more sensitive fish across all compounds and can we reduce data sets to two or even one fish study?
- Collaboration with NIEHS NICEATM
- >800 studies collected, data extraction being done now

3 Rs: Replacing Laboratory Animal Studies with 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

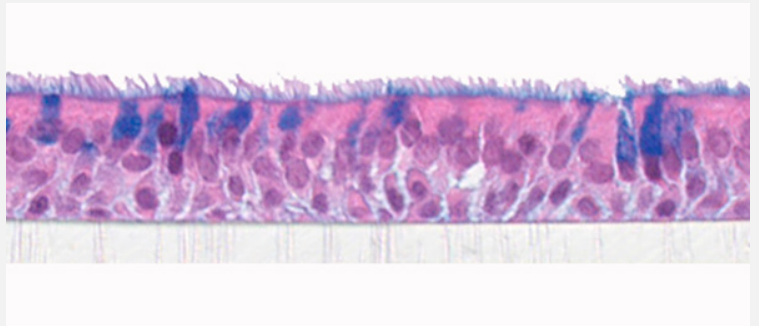
Skin Sensitization: Replacement of Laboratory Animal Testing

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 for identifying skin sensitization hazard in place of animal studies.
    - Multiple non-animal testing strategies - *in vitro, in chemico*, and *in silico* inputs demonstrate comparable or superior performance to the laboratory animal studies.
- The interim policy is the result of collaboration between ICCVAM, NICEATM, ECVAM, Canada PMRA

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 National Toxicology Program Interagency Center for the Evaluation of Alternative Toxicological Methods (NICEATM) 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
- Science questions: Is the *in vivo* study needed? Can the *in vitro* studies be used alone?
- Industry partners have provided >20 triple pack studies
- NICEATM/ILS has compiled the data and conducting the analysis


scientific tools
partnerships
share resources
promote health
computational tools
best science
cost effective
agency capacity
competitiveness
share expertise
National leadership
decision-making
technology transfer
regulatory science
sustainable
encourage adoption
quality
modernize toxicology
relevance
rigorous
NEW APPROACHES
efficient
transform understanding
collaboration
new information
improvements
overcome bottlenecks
risk management
validated tools
solutions
technology
specificity
working cooperatively
innovation
diverse partners
science
early identification
better predict
global adoption