



Waiving Studies for Human Risk Assessment of Pesticides at USEPA

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Risk21 Summit

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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

National Academy of Science (NAS) report “Toxicity Testing in the 21st Century”



- 2007: National Academy of Science (NAS) report *Toxicity Testing in the 21st Century* provided a vision and strategy for transforming toxicity testing and estimated a 15-20 year timeframe for the vision to begin to be realized.
 - Move away from traditional laboratory animal studies to *in vitro*, *in chemico* and computational approaches that are more human/species relevant, more predictive, and more efficient (faster, cheaper).
 - Fast paced advancements in biotechnology, computational chemistry, and related fields, as well as the unprecedented collaborations across governments, NGOs, industry and academia are [allowing this transformation to unfold much sooner than expected](#).

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>

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

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Waiving or Bridging Acute Toxicity Tests

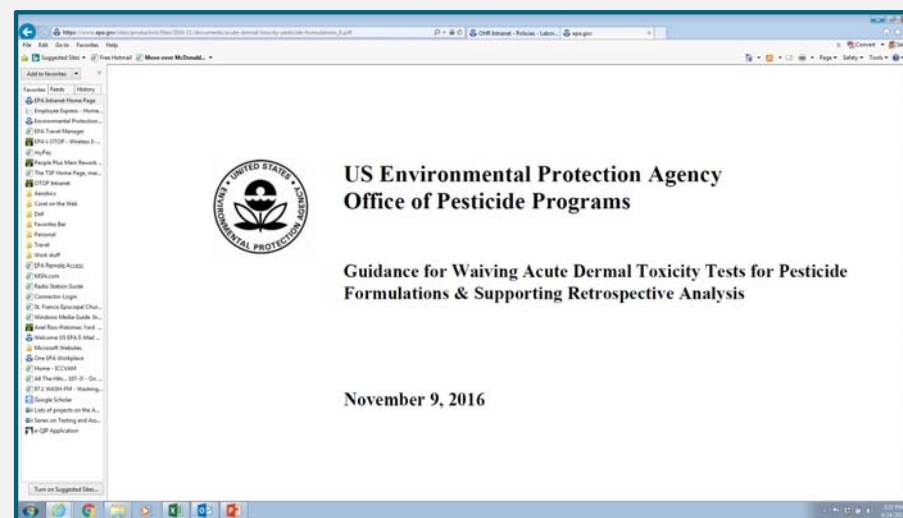


- OECD Guidance Document for Waiving or Bridging Acute Toxicity Tests
 - Co-authored by USEPA & Canada PMRA
 - Provides international guidance on waiving acute lethality studies for oral, dermal and inhalation
 - <http://www.oecd.org/env/ehs/testing/mono%202016%2032.pdf>
- Chemistry and Acute Toxicology 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.....



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- 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....

WOE Approach Used by HASPOC



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

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.

Regulatory Toxicology and Pharmacology 108 (2019) 104481



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



Reducing the need for animal testing while increasing efficiency in a pesticide regulatory setting: Lessons from the EPA Office of Pesticide Programs' Hazard and Science Policy Council



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<https://www.sciencedirect.com/science/article/pii/S0273230019302454>

Summary of HASPOC Waivers December, 2011 through May 2018

Type of Study	OCSP guideline	Waiver Review Summary			Study Execution (Savings to the Registrant)				Study Report Review (Savings to EPA)	
		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

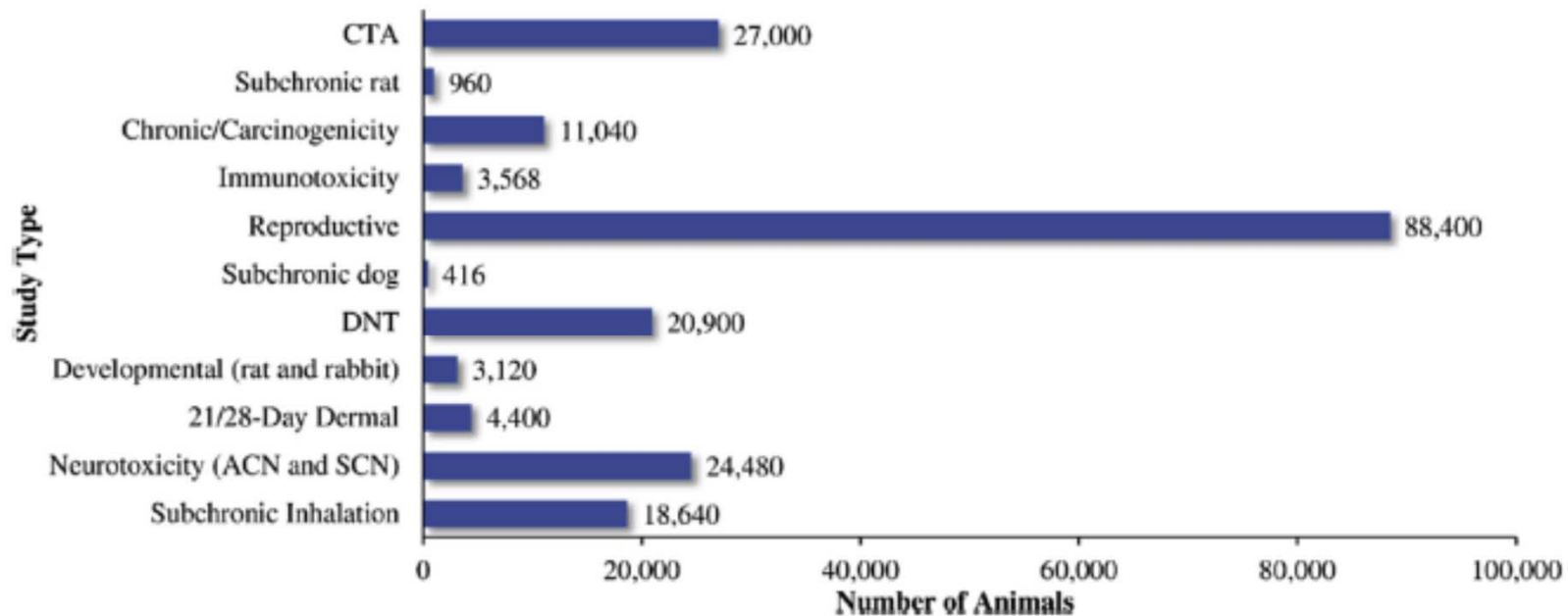
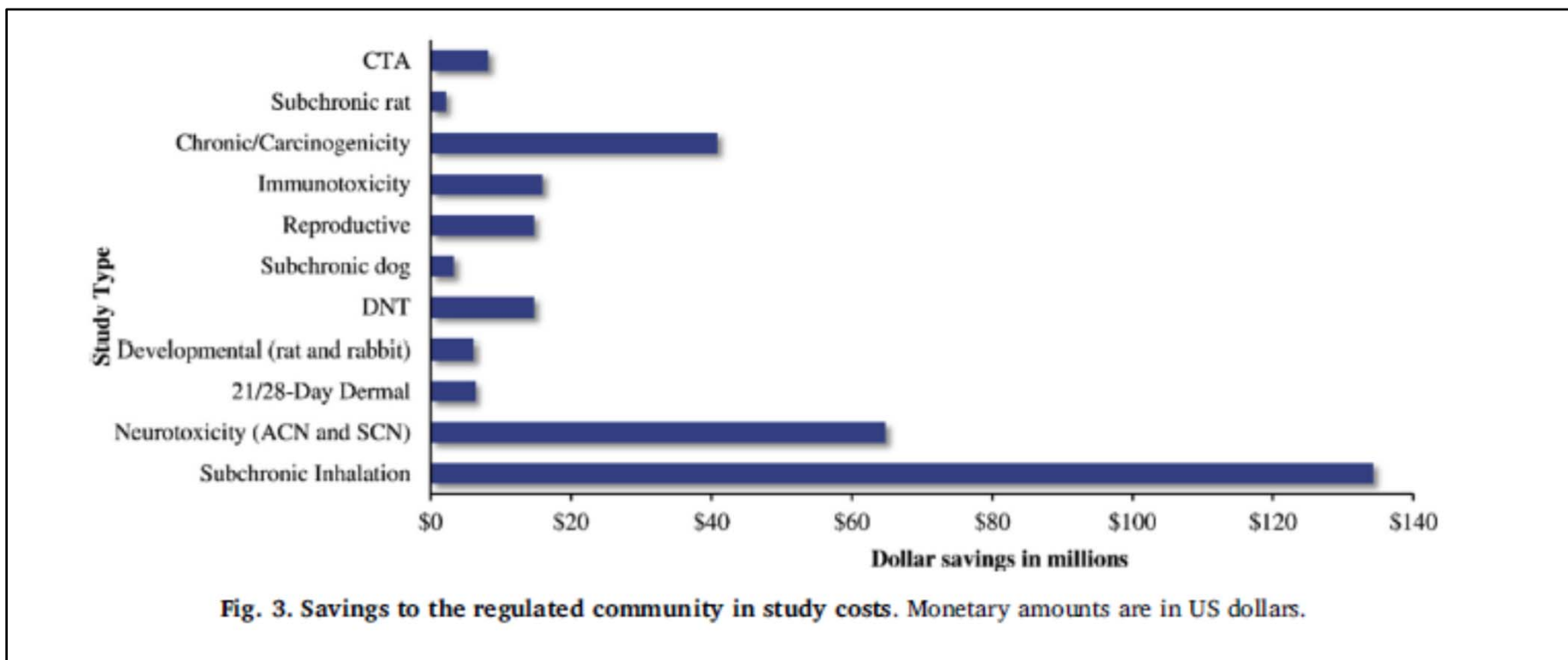


Fig. 2. Number of animals saved based on the type of studies recommended to be waived by HASPOC.



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

