Evaluation and Implementation of New Approach Methodologies for Evaluation of Pesticide Chemicals

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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 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

Modernizing Acute Toxicity "6 Pack"

- 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.

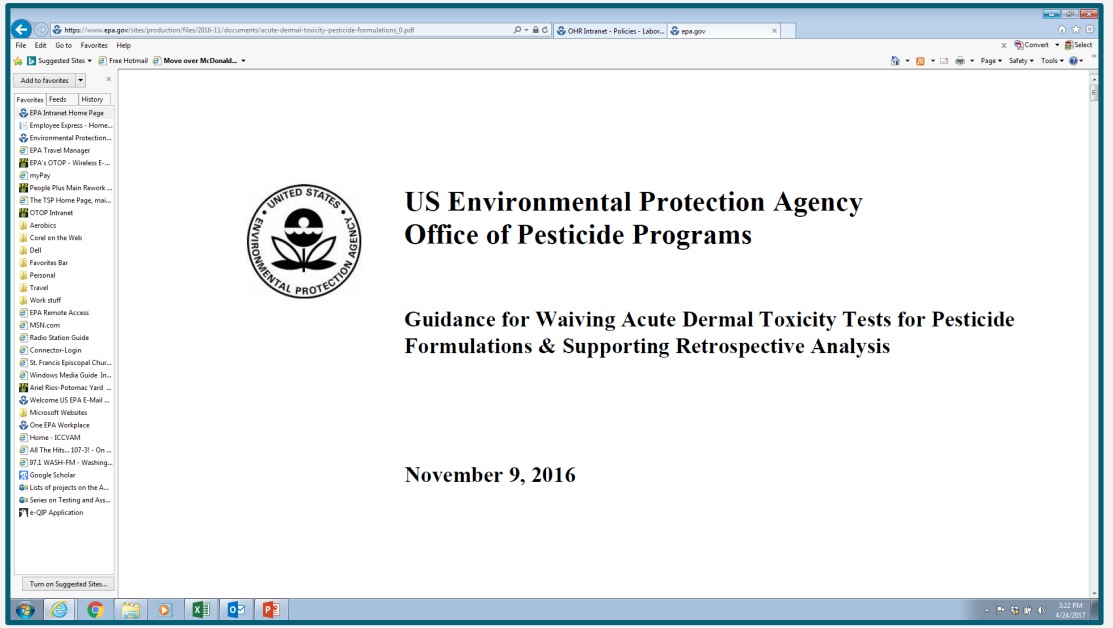
Skin Sensitization: Replacement of Laboratory Animal Testing

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, and Canada PMRA
- EPA is accepting these approaches under certain conditions described in the interim policy for active or inert ingredients

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 evaluating expansion of the dermal waiver guidance to include technical ingredients



Chemistry and Acute Toxicology Science Advisory Council (CATSAC)

- Reviews and provides guidance on bridging and waiving acute toxicity studies
- Representatives across OPP divisions
  - Chemists, toxicologists, regulatory scientists
- Applies guidance document on considerations for waiving or bridging mammalian acute toxicity tests (OECD 2016)

http://www.oecd.org/env/ehs/testing/mono%202016%2032.pdf

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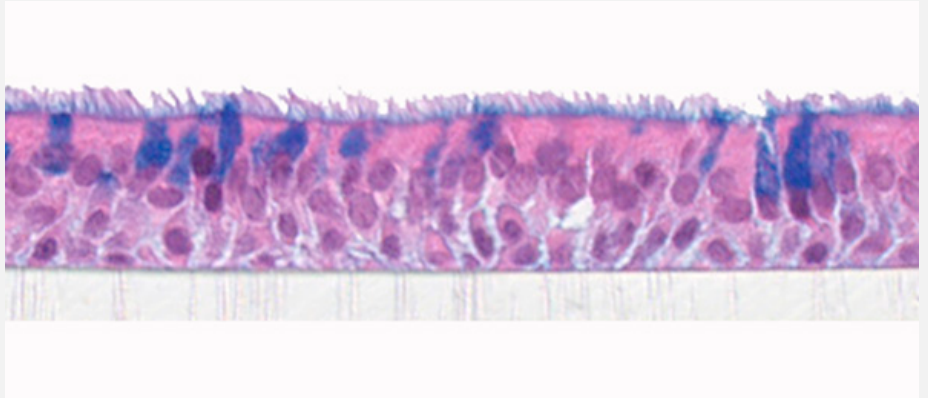
https://www.sciencedirect.com/science/article/pii/S0273230019302454

Summary of HASPOC Waivers December, 2011 through May 2018										
		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

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 >30 triple pack studies
- NICEATM/ILS has completed the analysis, manuscript being developed

Ecological Studies

Avian subacute/acute risk retrospective

- 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?
- In most cases (there are some exceptions) a robust avian acute risk assessment can be conducted without the sub-acute dietary studies.
  - Hilton et al. 2019, Regulatory Toxicology and Pharmacology, 105: 30-35
  - Policy finalized in February, 2020: https://www.epa.gov/sites/production/files/2020-02/documents/final-waiver-guidance-avian-sub-acute-dietary.pdf

Fish acute retrospective

- 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?
- >800 studies collected, dataset is completed & statistical analysis is on-going

ICCVAM Strategic Roadmap

- Connect end users with the developers of NAMs
- Foster use of efficient, flexible, and robust practices to establish confidence in new methods
- Encourage adoption and use of new methods and approaches by federal agencies and regulated industries

Thank you!