US EPA OPP Initiative to Modernize the Acute "6-Pack" - Update to the PPDC

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Background: Pesticides

- EPA's Office of Pesticide Programs has developed a Strategic Direction for New Pesticide Testing and Assessment Approaches
  - 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.

Guiding Principles for Data Needs for Pesticides

- 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.

Submitted Acute 6-Pack Studies

	Guideline	2012	2013	2014	2015
Acute oral	870.1100	324	248	328	268
Acute dermal	870.1200	292	257	313	255
Acute inhalation	870.1300	264	217	248	254
Eye irritation	870.2400	291	261	273	251
Skin irritation	870.2500	270	254	268	258
Skin sensitization	870.2600	247	237	262	267

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.

Acute Toxicity “6 Pack” OPP workgroup

- OPP has formed Acute Toxicity Workgroup with representation across the program.
  - Made up of members from RD, AD, HED, & BPPD
  - With additional input from FEAD, PRD, & EFED
- Stakeholder group is meeting regularly to discuss progress, goals, & opportunities to work together
- If you are interested in joining the stakeholder group:
  - Contact Shannon Jewell (703-308-4776, jewell.shannon@epa.gov)
- Docket: EPA-HQ-OPP-2016-0093

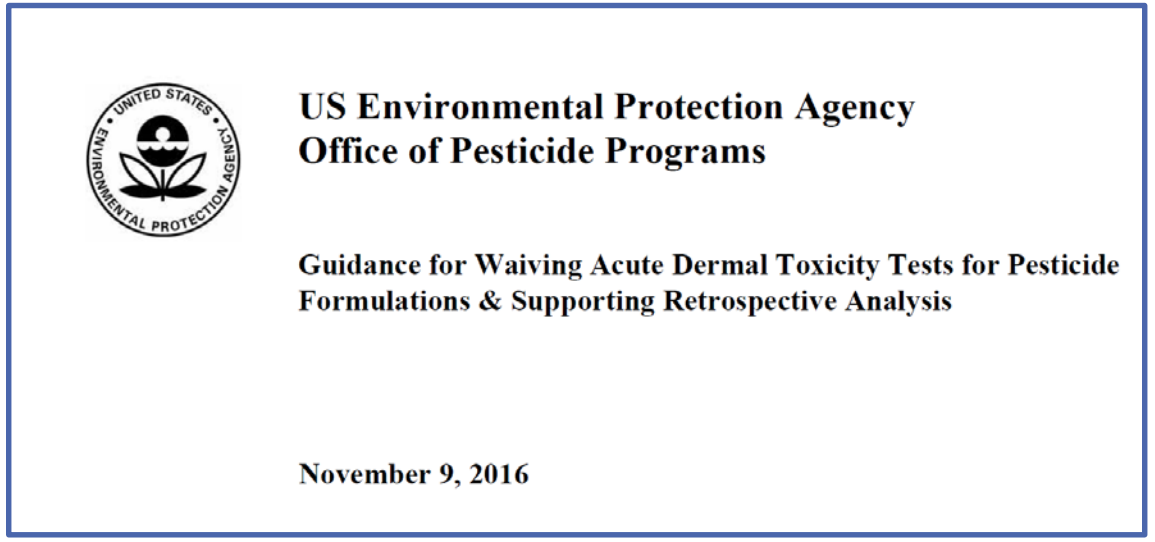
U.S. Federal Collaboration

- In 2000, Congress passed the ICCVAM Authorization Act and established Interagency Coordinating Committee on the Validation of Alternative Methods (ICCVAM)
  - Comprised of 17 Federal regulatory and research agencies that require, use, generate, or disseminate toxicological and safety testing information.
- 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

Acute Dermal Pesticide Formulation Toxicity Testing

- Collaboration between EPA & NIEHS-NICEATM
- Analyze 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



US Environmental Protection Agency
Office of Pesticide Programs

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

November 9, 2016

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

Alternative Assays: Eye Irritation

- Currently have a policy in place to accept eye irritation assays for antimicrobial cleaning products
- Interested in extending 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
- NICEATM is analyzing these new data in combination with the data from the antimicrobial cleaning product policy
  - Data entry is complete, analysis is on-going
  - Some prospective testing to fill in gaps may be needed

International Cooperation on Alternative Test Methods (ICATM)

- Representatives from: USA, EU, Japan, Korea, Canada, Brazil, China
  - First ever ICATM Workshop, October 4-5, 2016 in Ispra, Italy
  - On the international regulatory applicability and acceptance of alternative non-animal approaches
    - Identify the current regulatory requirements for skin sensitization in different regions by chemical sector (i.e. pesticides, cosmetics, pharmaceuticals, industrial chemicals, etc.);
  - More than >20 regulatory authorities were represented.
  - Identify what obstacles hamper the use of non-animal approaches in certain regulatory areas and regions;
  - Aim to achieve agreement on acceptance of skin sensitization IATAs;
    - Consider the ICCVAM IATA and others submitted to OECD
  - Define a set of performance based criteria for acceptance of future testing strategies.

International Cooperation on Alternative Test Methods (ICATM)

- Multiple non-animal testing strategies incorporating *in vitro, in chemico*, and *in silico* inputs demonstrate *comparable or superior performance* to the LLNA.
- A planned product of the ICATM workshop is the development of an assessment framework for integrated non-animal approaches that could *serve as replacements* for the current animal test, the LLNA.
- Publications in the scientific literature and white papers are likely to be developed based on the outcomes of the workshop.
  - SPSF already submitted to OECD---jointly sponsored by US, Canada, EU
- NTP conducting prospective testing for 3 different assays to fill in gaps for chemical sector & formulations/mixtures

Reducing Barriers to Adopting Alternative Methods

- Process For Establishing & Implementing Alternative Approaches To Traditional *In Vivo* Acute Toxicity Studies
  - https://www.epa.gov/sites/production/files/2016-03/documents/final_alternative_test_method_guidance_2-4-16.pdf
- This document describes a transparent, stepwise process for evaluating and implementing alternative methods of testing for acute oral, dermal, inhalation toxicity, along with skin and eye irritation and skin sensitization.

Reducing Barriers to Adopting Alternative Methods

- Voluntary pilot program underway where registrants may send the *in vivo* acute lethality study for *oral* and *inhalation* formulation/product testing as currently required and simultaneously submit the calculations using the GHS dose additive mixtures equation.
  - Hope to rapidly collect a dataset evaluating the ability of the GHS mixtures equation to predict the acute toxicity categories from oral and inhalation routes in formulation/product testing.
  - Pending the outcome of that analysis, may be able to substantially reduce the use of animals.

$$\frac{100}{ATE_{mix}} = \sum_{\eta} \frac{C_i}{ATE_i}$$

Reducing Barriers to Adopting Alternative Methods

- Exploring options for adopting GHS categories for the hazard portion of the pesticide label.
  - Currently, OECD is developing guidelines for alternative assays (i.e., *in vitro*) using the GHS categories but not US EPA toxicity categories.
  - Creating such a crosswalk from GHS to USEPA categories can be accomplished for some *in vitro* assays but has shown to be a significant challenge for others.
  - Possible that may have to go through rulemaking proceedings to change how the hazard labeling is conducted.
  - Issues are complex---plan to begin engaging stakeholders on these issues in the coming weeks and months – see separate GHS PPDC update

Charge to the PPDC

In light of the significant resources required to write such a large, broadly applicable rule & ultimately the resources to implement such a rule, what are science and policy steps should EPA consider before we prepare for a move to GHS?

Questions?