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	2016	2017
Acute oral	870.1100	324	248	328	268	322	254
Acute dermal	870.1200	292	257	313	255	267	234
Acute inhalation	870.1300	264	217	248	254	270	246
Eye irritation	870.2400	291	261	273	251	263	239
Skin irritation	870.2500	270	254	268	258	259	238
Skin sensitization	870.2600	247	237	262	267	255	240

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, EFED & BPPD
  - With additional input from FEAD & PRD
- 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 (703-347-0109, jewell.shannon@epa.gov)
- Docket: EPA-HQ-OPP-2016-0093

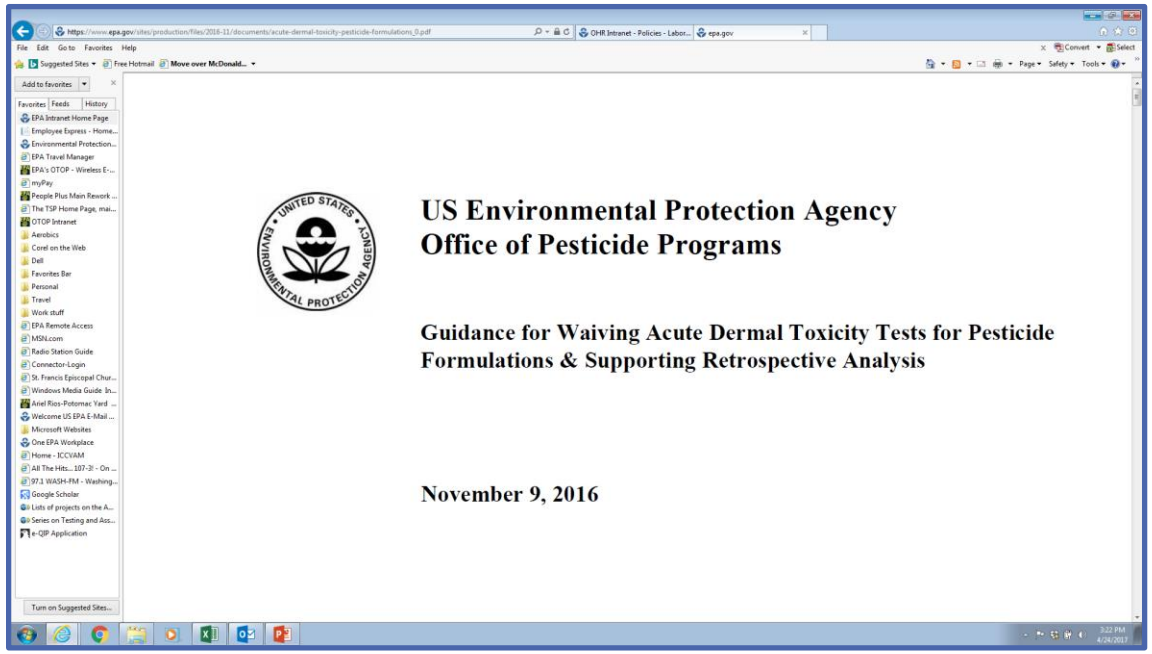
U.S. Federal Collaboration

- 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



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
- 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
  - NICEATM analysis indicated prospective in vitro testing needed
- Prospective testing to fill in the gaps:
  - Phase 1 will evaluate 6 formulations donated by industry (along with reference in vivo data) in BCOP, EpiOcular, NRR, PorCORA, ICE
  - Phase 2 will then test up to 40 additional formulations donated by industry
  - Co-chaired by PETA -ISC and NICEATM, with members from PCRM, EPA, PMRA, ECVAM, and Industry

International Cooperation on Alternative Test Methods (ICATM) – Skin Sensitization

- Representatives from: USA, EU, Japan, Korea, Canada, Brazil, China
  - Special WNT on SPSF, December 2017 in Italy as a follow up to October 2016 ICATM workshop
    - Multiple non-animal testing strategies - *in vitro, in chemico*, and *in silico* inputs demonstrate *comparable or superior performance* to the mouse LLNA.
    - An assessment framework for integrated non-animal approaches that could *serve as replacements* for the current animal test.
  - Agreement on framework for defined approaches for skin sensitization:
    - Casati et al. 2017. **Standardization of defined approaches for skin sensitization testing to support regulatory use and international adoption**: position of the International Cooperation on Alternative Test Methods. Arch Toxicol 92:611-617NAM should under go independent scientific review
  - Move forward on performance based testing (PBT) criteria for acceptance of future testing strategies.

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.

- The interim policy is the result of collaboration between
  - Interagency Coordinating Committee on the Validation of Alternative Methods (ICCVAM)
  - NTP Interagency Center for the Evaluation of Alternative Toxicological Methods (NICEATM)
  - European Union Reference Laboratory for Alternatives to Animal Testing (EURL ECVAM)
  - Health Canada (PMRA).

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

- EPA will begin accepting these approaches immediately under certain conditions described in the interim policy.
  - Existing OECD guidelines for determining hazard (only)
  - Approaches for combining results of 2 or 3 assays described in the draft, interim policy
  - 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
- Comments on the draft skin sensitization policy must be submitted to docket # EPA-HQ-OPP-2016-0093 at www.regulations.gov on or before June 9, 2018.

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.
  - Assembling a dataset to evaluate the ability of the GHS mixtures equation to predict the acute toxicity categories from oral and inhalation routes in formulation/product testing.
  - Have (so far) received submissions from: Syngenta, Dow Chemical, BASF, EcoLab, Control Solutions Inc., P&G
  - Pending the outcome of that analysis (to begin within the next few months), may be able to substantially reduce the use of animals.

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

Dermal Absorption Triple Pack

- Triple packs
  - Human *in vitro*, rat *in vitro,* and rat *in vivo* studies using similar protocols (e.g., same test material, doses)
  - Used by OPP to refine dermal assessments by adjusting for differences between in vitro and in vivo absorption as well as species differences
- NICEATM/ILS in process of compiling data from triple pack studies
  - assess possibility of using humanin vitro study only for risk assessment

Questions?

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