US EPA OPP regulatory perspective on acute inhalation toxicity testing

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Background: Pesticides

- EPA's Office of Pesticide Programs has developed a Strategic Direction for New Pesticide Testing and Assessment Approaches
  - http://www.epa.gov/pesticides/science/testing-assessment.html.
  - 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

- Guiding Principles for Data Requirements
  - 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.
  - http://www.epa.gov/pesticides/regulating/data-require-guide-principle.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…."
- "…avoid unnecessary use of time and resources, data generation costs, and animal testing."

Guiding Principles for Data Needs for Pesticides

- Promotes the full use of existing knowledge to focus on the data needed
- Provide consistency in the determination of toxicology data needs across OPP divisions
- Data needs decisions are typically case-by-case and consider all existing knowledge including the pesticides' physical–chemical properties, metabolism/pharmacokinetics, toxicological profile and exposure, available human information, as well as information on structural analogues.

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.

Guiding Principles for Data Needs for Pesticides

- Build efficiencies into the risk assessment process, while improving the scientific support for assessment
  - Focus on the integration & intersection of hazard with exposure
    - Who? How? What route? For what duration?
    - E.g., children vs. adults; dermal/oral/inhalation
  - Fewer studies submitted = Less resources spent
  - Improved focus on most important issues
  - Use of MOA/AOP to inform data needs

Modernizing the Acute Toxicity "6 Pack"

Guideline	Study Type	Food Use	Non-Food Use
870.1100	Acute oral toxicity – Rat	R	R
870.1200	Acute dermal toxicity – Rat /Rabbit	R	R
870.1300	Acute inhalation toxicity – Rat	R	R
870.2400	Primary eye irritation – Rabbit	R	R
870.2500	Primary dermal irritation – Rabbit	R	R
870.2600	Dermal sensitization – Guinea Pig	R	R

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

OECD Guidance Document for Waiving or Bridging Acute Toxicity Tests

- Waivers may be available:
  - If a test article exhibits low volatility, is not aerosolized, or otherwise made inhalable through heating, evaporation or other method.
  - If test articles are solids that are too large to be inhaled, do not easily crumble into inhalable particles or are aerosols with a certain particle size.
  - If a test article cannot be produced in an inhalable state (e.g., gas or vapor) to elicit toxic response under ideal conditions.
  - Test articles which are classified as GHS Category 1 or 2 for acute oral or dermal toxicity (test article would be classified as GHS Category 1 inhalation hazard in this instance).
- http://www.oecd.org/env/ehs/testing/mono%202016%2032.pdf

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 has formed Acute Toxicity Workgroup with representation across the program.
- Stakeholder group is meeting regularly to discuss progress, goals, & opportunities to work together
- If you are interested in joining the stakeholder group:
  - Contact Garland Waleko (703-308-8049, waleko.garland@epa.gov)
- Docket: EPA-HQ-OPP-2016-0093
- Good progress towards:
  - accepting alternative approaches is being made on skin sensitization
  - expanding acceptance for eye irritation.

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

ICCVAM Acute Toxicity Working Group

Sponsor Agencies: EPA, DoD

- Charge to the Workgroup:
  - Evaluate the usefulness of acute oral LD_{50} data for classifying dermal systemic hazard of potential toxicants such as pesticides, industrial chemicals, chemical warfare agents, and household chemicals
  - Evaluate *in vitro* and *in silico* approaches for predicting acute oral, dermal and/or inhalation systemic toxicity
  - Evaluate the usefulness of the GHS additivity formulas for classifying formulations and mixtures for acute systemic toxicity tests
  - Contribute to a scoping document that outlines the current requirements and testing needs for U.S. and international regulatory authorities
    - Manuscript in prep on US requirements
  - Develop a draft ICCVAM strategy and roadmap on using *in vitro* and *in silico* approaches to replace, reduce, and refine animal use in acute systemic toxicity testing

Developing database of acute toxicity data from pesticide products

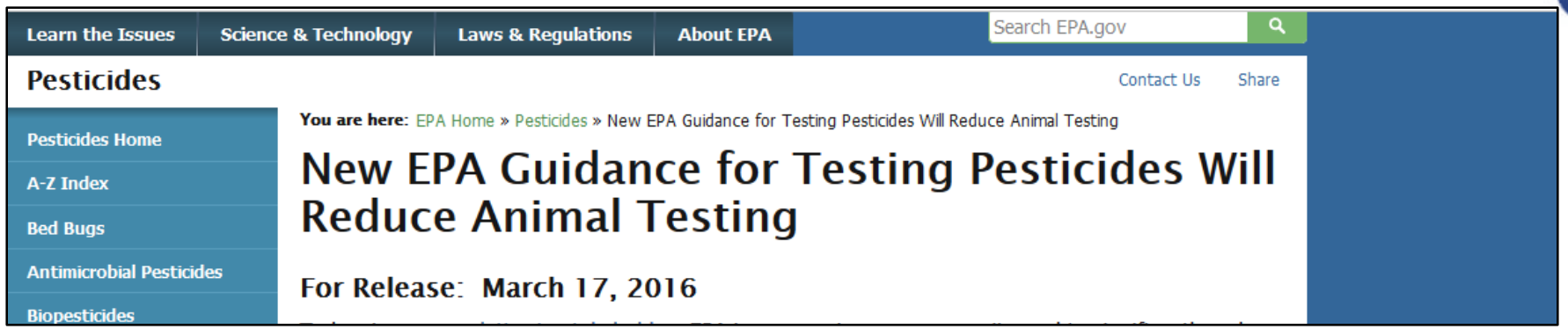
- Collaborative effort between EPA & NICEATM, as part of charge for ICCVAM Acute Toxicity Workgroup
- Purpose:
  - Assess variability within and across studies for comparing/evaluating to alternative approaches
  - Develop read across approaches
  - Assess GHS additivity equation
- Study protocol components: strain/species/dosing route/testing laboratory, sex, concentration/particle size
- Acute oral, dermal and inhalation toxicity data and skin sensitization have been extracted; data curation is still on-going
- Data extraction for skin/eye irritation in progress

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.

Acute Toxicity “6 Pack”

- 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



Draft for Public Comment

March 11, 2016

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

4.0 Waiver Guidance.

The agency believes this retrospective analysis fully supports a conclusion that waivers can be granted of acute dermal toxicity studies for formulations. The agency will be soliciting public comment on this draft policy. Registrants may begin submitting waiver requests through existing processes to respective OPP division.

https://www.epa.gov/pesticides/new-epa-guidance-testing-pesticides-will-reduce-animal-testing

Reducing Barriers to Adopting Alternative Methods

- We will soon be starting a voluntary pilot program 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.

Reducing Barriers to Adopting Alternative Methods

- GHS additivity formulas for classifying formulations and mixtures for the acute toxicity

The acute toxicity estimate (ATE) of ingredients should be considered as follows:

- Include ingredients present at 1% or greater with a known acute toxicity, which fall into any of the GHS acute toxicity categories.
- Ignore ingredients that are presumed not acutely toxic (e.g., water, sugar).
- Ignore ingredients if the oral limit test does not show acute toxicity at 2,000 mg/kg/body weight.

The ATE of the mixture is determined by calculation from the ATE values for all relevant ingredients according to the following formula below for Oral, Dermal or Inhalation Toxicity:

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

where:
C_i= concentration of ingredient i
n ingredients and i is running from 1 to n
ATE_i = Acute Toxicity Estimate of ingredient 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.

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

- Purpose: guidance on the weight of the evidence-based determination of data needs (e.g., risk assessment and waiver decisions).
- Document covers:
  - Subchronic Inhalation (870.3465),
  - Subchronic Dermal (870.3250),
  - Neurotoxicity screening batteries (870.6200; acute and subchronic neurotoxicity),
  - Immunotoxicity (870.7800)
- https://www.epa.gov/sites/production/files/2014-02/documents/part158-tox-data-requirement.pdf

From December 8, 2011 to August 4, 2016

Type of Study	Waivers Granted	Required Studies	Total # of Requests
Inhalation, subchronic	212	64	276
Neurotoxicity	158.5	21.5	180
Dermal	47	7	54
Developmental	34	9	43
DNT	12	2	14
Subchronic Dog	11	3	14
Reproductive	30	6	36
Immunotoxicity	202	16	218
Chronic/ Carcinogenicity	20	4	24
Subchronic Rat	9	2	11

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Questions?