US EPA Perspectives on GHS SCHC Fall Meeting

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Background: GHS

- GHS was adopted by the UN in 2003; the seventh revision was finalized in 2017.
- GHS is international approach to hazard communication, promoting standard criteria for classifying chemicals according to their health, physical, and environmental hazards.
- For EPA, 40 CFR 156.62 (Toxicity Category) & 156.70 (Precautionary Statements for Human Hazards) are prescriptive and do not allow for flexibility.
- Rule-making would be required in order to harmonize with GHS.

Background: EPA's Review of GHS

- EPA's Office of Pesticide Programs published a white paper for public comment entitled "The Globally Harmonized System of Classification and Labelling of Chemicals (GHS) Implementation Planning Issues for the Office of Pesticide Programs" in 2004.
- The paper presented two basic options for implementation: establishing a separate approval process or integrating GHS label changes into ongoing registration and re-registration actions. The paper also sought comments on the possible benefits of instituting a pilot project for GHS implementation, and what educational and outreach activities would be most effective.
- Public comments focused on implementation issues and the question of why EPA was proceeding with GHS. Commenters questioned harmonization solely for harmonization's sake and stated that deviations from current system to include new symbols would create confusion, among other issues.
- Stakeholder public meetings were held in October 2006 to address public comments and provide additional education on the benefits of GHS implementation for pesticide products.
- From 2007-2009, EPA continued to address stakeholder concerns, added GHS information and sample labeling changes to the website, and met internally to discuss implementation.

Background: Toxicity Testing in the 21st Century

- 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

- 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.

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 '6 Pack' Tests

Waivers may be available

- 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

- SimClinic – now Chemistry and Acute Toxicology Science Advisory Council (CATSAC)

Modernizing Acute Toxicity "6 Pack"

- 2016 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 to adopting alternative methods in the U.S. and internationally;
      - commits OPP to exploring GHS hazard categories for product labeling and GHS mixtures equation for formulations

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 on acute toxicity 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

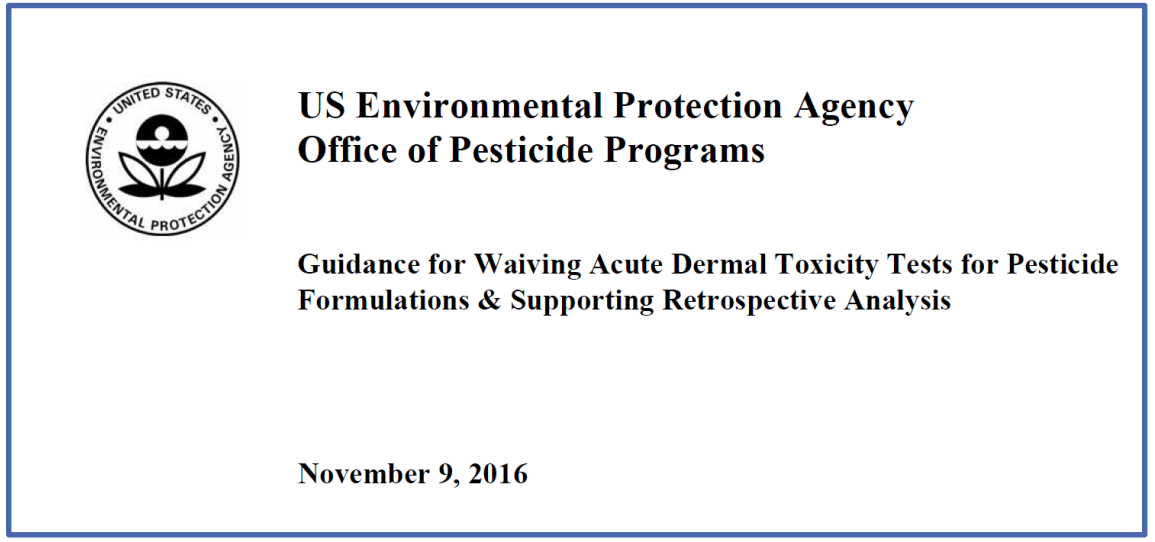
ICCVAM Acute Toxicity Working Group

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 – pilot currently underway
  - 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

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
- Alterative OECD eye irritation assays utilize GHS classification

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 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 – GHS

- Exploring options for utilizing 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 rulemaking proceedings would be needed to change how the hazard labeling is conducted.
  - Issues are complex---began engaging stakeholders on these issues in the in early 2017

Reducing Barriers to Adopting Alternative Methods- Benefits of GHS

- Facilitates international trade –reduces costs of compliance with different international standards and non-tariff barriers to trade
- Streamlines U.S. regulations and increases international regulatory harmonization
  - Federal partners (OSHA, DOT) and European countries utilizing GHS
  - Canada, Australia, Brazil, Thailand, and Vietnam are currently implementing in some sectors as well
- Facilitates adoption of new scientific alternatives and new OECD test guidelines

Reducing Barriers to Adopting Alternative Methods—GHS Implementation Considerations

- Not all of OPP's regulatory framework is tied to the classification category alone, some programmatic requirements are based on the signal word.
- Changing the signal word on product labeling including the loss of the "CAUTION" signal word could impact:
  - Worker Protection Standard requirements
  - Pesticide container and containment standards
  - Applicator training manuals and exams under the Certification regulations
- School Integrated Pest Management– varies by state and/or by school district
  - Pesticide product selection can also be based on classification categories or signal word

OPP Criteria, Signal Words, Symbol, and Hazard Statements	GHS Criteria, Signal Words, Pictograms and Hazard Statements
ACUTE ORAL TOXICITY: **Category I** LD_{50} ≤ 50 mg/kg DANGER Skull and Crossbones Fatal if swallowed **Category II** LD_{50} > 50 mg/kg ≤ 500 mg/kg WARNING No symbol May be fatal if swallowed **Category III** LD_{50} > 500 mg/kg ≤ 5000 mg/kg CAUTION No symbol Harmful if swallowed **Category IV** LD_{50} > 5000 mg/kg CAUTION or no signal word No symbol No hazard statement required; registrant may choose to use Category III statement	**ACUTE ORAL TOXICITY:** **Category 1** LD_{50} ≤ 5 mg/kg ***and*** **Category 2** LD_{50} > 5 mg/kg ≤ 50 mg/kg DANGER Skull and Crossbones in diamond Fatal if swallowed **Category 3** LD_{50} > 50 mg/kg ≤ 300 mg/kg DANGER Skull and Crossbones in diamond Toxic if swallowed **Category 4** LD_{50} > 300 mg/kg ≤ 2000 mg/kg WARNING Exclamation point in diamond Harmful if swallowed **Category 5** LD_{50}> 2000 mg/kg ≤ 5000 mg/kg (See Note (*e)* to GHS Table 3.1.1.) WARNING No symbol May be harmful if swallowed [LD_{50} > 5000 mg/kg not classified; no specified label elements]

Reducing Barriers to Adopting Alternative Methods—GHS Implementation Considerations

- Stakeholder outreach & support
- Staff training & education
- Resource demands
- SmartLabel integration
- Submission process & timing for review
- Next Steps
  - Completion of GHS Mixtures Equation Pilot analysis

GHS Stakeholder Meetings

- First stakeholder meeting was held in June 2016, follow up meeting held in August 2016
- Focusing on GHS Mixtures Equation Pilot – clarifications on pilot and addressing concerns regarding submission requests
- Goal is to continue making progress on alternative methods and discuss ways to create flexibility in OPP's regulatory framework to allow for GHS categorization, while maintaining current programmatic efforts tied to the acute toxicity framework

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Questions?