

US EPA OPP Update – ICCVAM Public Forum

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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

- 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.



Hazard & Science Policy Council (HASPOC)

- In HASPOC, focus on the integration & intersection of hazard with exposure
- Implement the 3R's of animal testing: Replace, Reduce, Refine:
 - Reduce: Waivers for developmental, reproductive, DNT, chronic/carcinogenicity toxicity
 - Refine: Special protocol studies instead of standard guideline protocols (e.g., shorter duration, fewer animals, single gender, etc)
 - Refine: Pharmacokinetic studies in lieu of toxicity study
- In FY'16, waivers were granted for 153 of 180 requests resulting in savings of about 44,000 animals and over \$16 million in the cost of conducting the studies.
- In FY'17, waivers were granted for 70 of 78 requests resulting in savings of about 41,000 animals and approximately \$10.4 million in the cost of conducting the studies.

From December, 2011 to early April, 2018



Type of Study	Waivers Granted	Required Studies	Requests
Inhalation	229	65	294
Neurotoxicity	303	24	327
Dermal	55	8	63
Developmental	42	7	49
DNT	17	2	19
Subchronic Dog	13	3	16
Reproductive	32	6	38
Immunotoxicity	212	17	229
Chronic/ Carcinogenicity	26	2	28
Subchronic Rat	13	3	16
Total	942	137	1079



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.



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 the Acute Toxicity “6 Pack”

- 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



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



Addendum to Dermal Waiver Guidance

- EPA intends to expand the dermal waiver guidance to include technical ingredients (drafted and under review)
- Previous ecological risk assessment concerns about potential future need to assess acute dermal toxicity in wild mammals (e.g., threatened and endangered species) resolved:
 - Collaboration between ecological and human health risk assessors on their approaches used for human health
 - Adoption of a relative oral vs dermal absorption adjustment - adjust acute oral endpoints to an equivalent dermal dose endpoint



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.

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



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 PCRMA, EPA, PMRA, ECVAM, and Industry



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.
- 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)
- 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.



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 human *in vitro* study only for risk assessment



Ecotoxicology: New Projects

- Avian subacute/acute risk retrospective comparison project
 - Collaborative effort with PETA
- Fish acute lethal endpoint retrospective project
 - Collaborative effort with NICETAM
- Considering ideas for additional projects
 - Looking to partner with government and private stakeholders



Avian subacute/acute risk retrospective

- 40CFR Section 158 outlines two requirements for avian acute effects testing
 - Two single oral dose LD50 studies (quail or mallard and a songbird)
 - Two subacute dietary LC50 studies (quail and mallard)
- Risk assessments use both studies (most sensitive endpoint from each)
- Question: How often have subacute dietary risk quotients (RQs) quantitatively driven risk assessment conclusions?
- Focus on RQ's, which integrate toxicity and exposure, in new use assessments from 1998-2016
- Identify MOA
- Partnership with PETA-ISC



Avian subacute/acute risk retrospective cont'd

Preliminary results:

- 118 of 119 evaluated new use assessments (99% of cases) - subacute dietary approach not change risk conclusions already reached using oral dose-based RQ's
- For majority of unevaluated of cases, were represented by chemical analogs that were evaluated
- Unique modes of action that were not 'covered' may be a candidates for establishing a baseline set of studies (and RQ comparisons) for future use.
- Next Steps:
 - Peer-reviewed scientific journal publication (PETA lead, Agency coauthors)
 - Draft of internal policy instructions to risk assessors and risk managers

Fish acute retrospective

- 40CFR Section 158 outlines three requirements for fish acute effects testing
 - warm freshwater fish, cold freshwater fish, estuarine/marine fish
- Risk assessments use the most sensitive freshwater fish and the estuarine/marine fish
- Question: Is there a consistently more sensitive fish across all compounds and can we reduce data sets to two or even one fish study?
- Focus is comparative toxicity
 - Exposure estimates the same whether fresh or salt
 - Need to rely on study reviews rather than risk assessments
- Next steps, develop dataset & conduct analysis



Questions?