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.

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 January 26, 2017

Type of Study	Waivers Granted	Required Studies	Total # of Requests
Inhalation	222	66	288
Neurotoxicity	163.5	22.5	186
Dermal	50	7	57
Developmental	39	9	48
DNT	15	3	18
Subchronic Dog	11	3	14
Reproductive	32	6	38
Immunotoxicity	207	16	223
Chronic/ Carcinogenicity	24	4	28
Subchronic Rat	10	2	12

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.

Modernizing the Acute Toxicity "6 Pack"

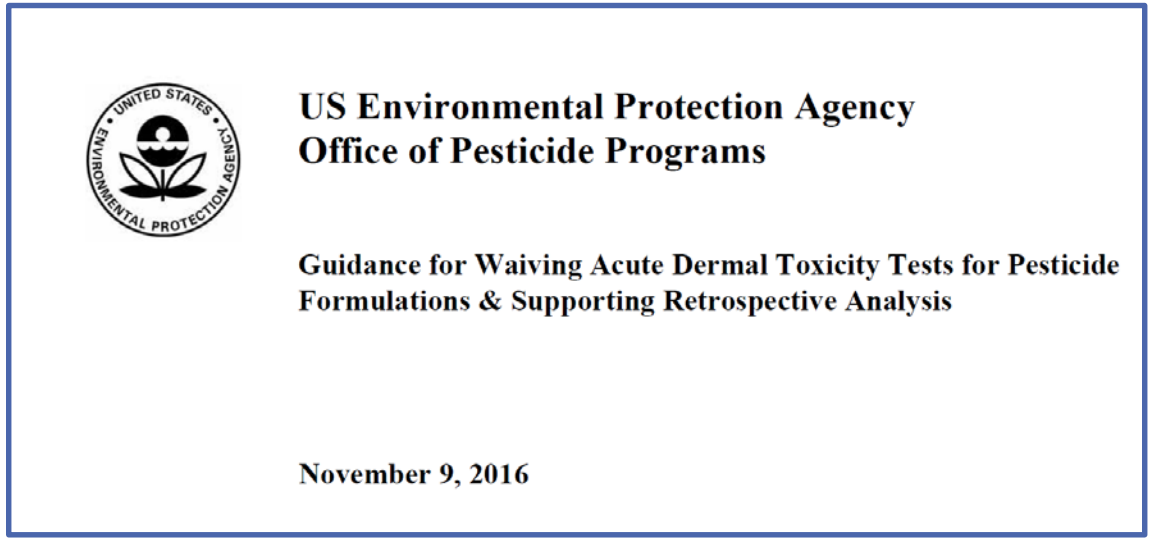
	Guideline	2012	2013	2014	2015
Acute oral	870.1100	324	248	328	268
Acute dermal	870.1200	292	257	313	255
Acute inhalation	870.1300	264	217	248	254
Eye irritation	870.2400	291	261	273	251
Skin irritation	870.2500	270	254	268	258
Skin sensitization	870.2600	247	237	262	267

Modernizing 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 (703-308-4776, 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
- Dermal waiver guidance finalized Nov 2016



US Environmental Protection Agency
Office of Pesticide Programs

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

November 9, 2016

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.

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

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

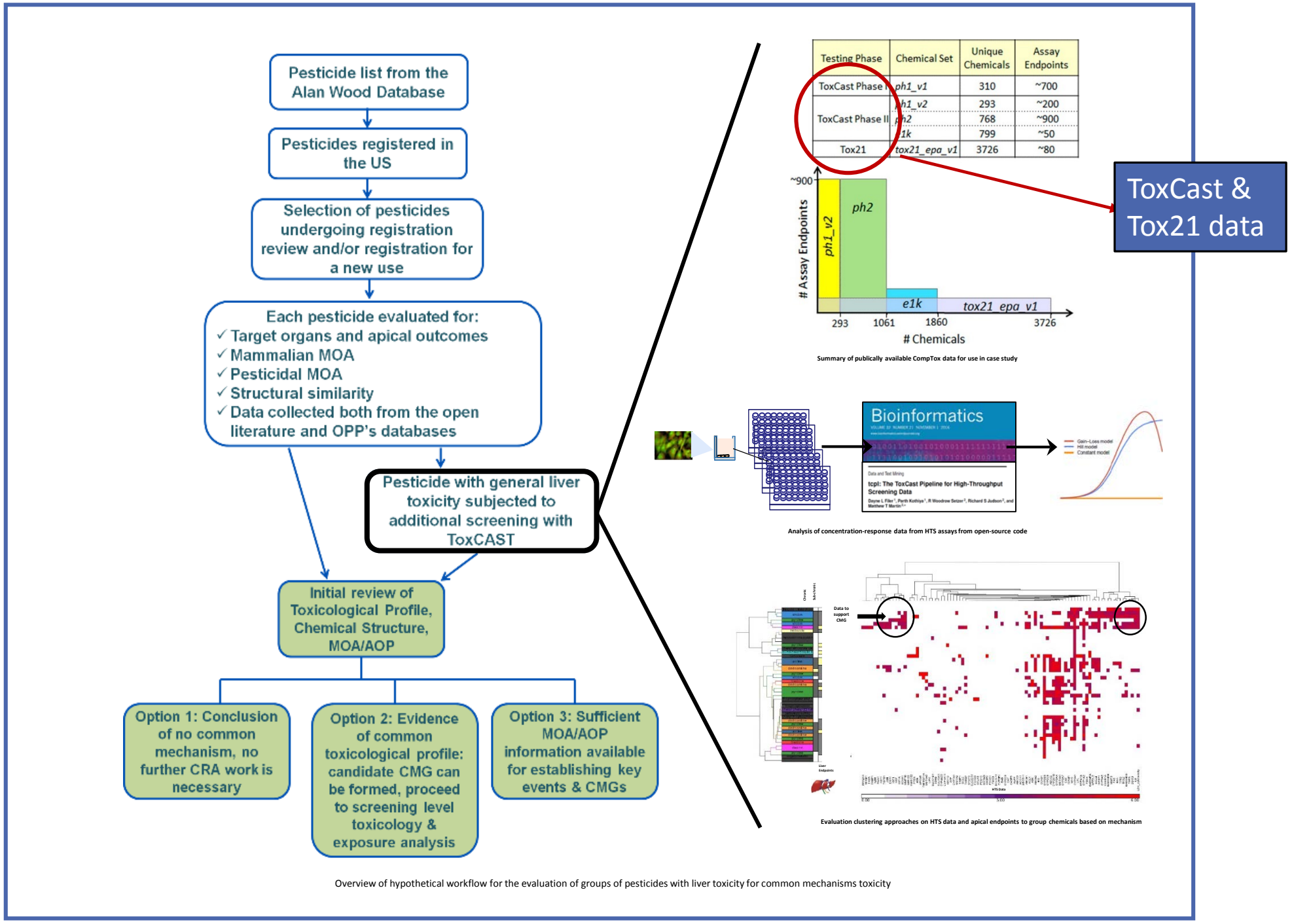
Alternative Assays: Eye Irritation

- 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

Cumulative Risk Screening Analysis

- Under the Food Quality Protection Act, EPA is required to take into account available evidence concerning the cumulative effects of pesticides and other substances that have a common mechanism of toxicity.
- Screening framework for CRAs has been developed to assist in screening pesticides for potential CMGs and conducting screening-level CRAs.
  - https://www.epa.gov/pesticide-science-and-assessing-pesticide-risks/pesticide-cumulative-risk-assessment-framework
- Begins with analysis of the toxicological knowledgebase to determine if the available evidence for a particular group of pesticides does or does not support common toxicological profiles—*and possible candidate common mechanism group*.
- ***Objective:*** Develop and evaluate an approach to use CompTox data to support the identification of candidate CMGs for the CRAs of pesticides

Develop a workflow to evaluate HTS assays and data analysis methods to identify candidate groups for screening level cumulative risk assessments



Overview of hypothetical workflow for the evaluation of groups of pesticides with liver toxicity for common mechanisms toxicity

Case Study: Use of ToxCast Data to Screen for Candidate CMGs

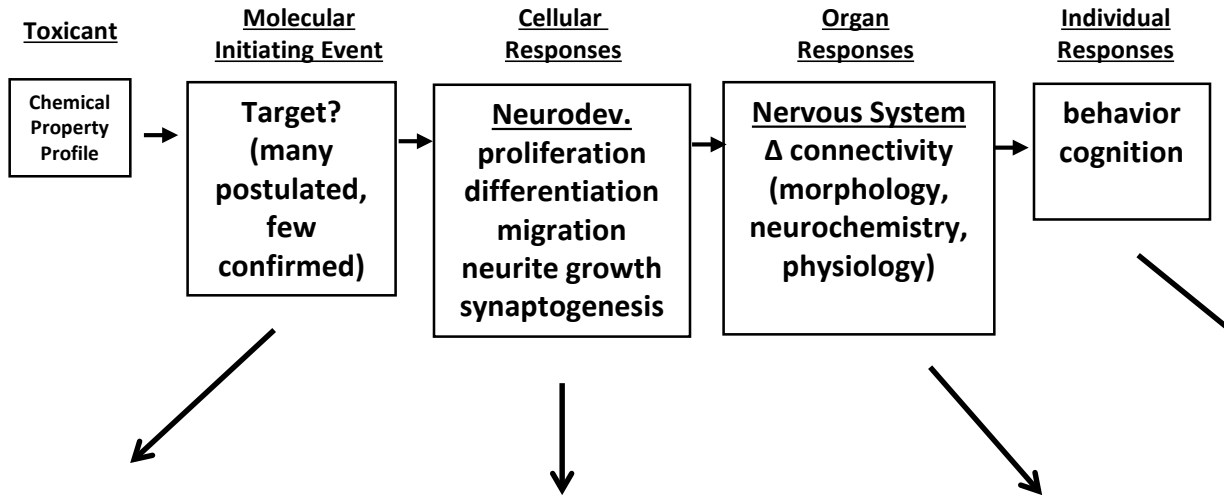
- Anticipated Case Study Products
  - *Evaluation of clustering approaches—On-going*
  - Application of approaches to several different groups of chemicals--FY17 (Q3/4)
  - Deeper analysis of a large group of chemicals--FY18 (Q2/3)

Alternative Battery for DNT

- On-going work at ORD-NHEERL to develop a screening battery for evaluating DNT
  - Rationale: Normal brain development depends upon coordinated expression of critical neurodevelopmental processes that are conserved across species and can be modeled in vitro and in small, non-mammalian organisms
  - Approach:
    - Identify key events in neurodevelopment at increasing levels of biology
    - Use model systems that recapitulate key neurodevelopmental processes
    - Apply new technologies for high-throughput assessment of endpoints at cell, tissue, and intact organism level
- *Case study with OPP to test set of pesticides in the battery*

Assays based on measuring key events in Adverse Outcome Pathways

Generic AOP for Developmental Neurotoxicity

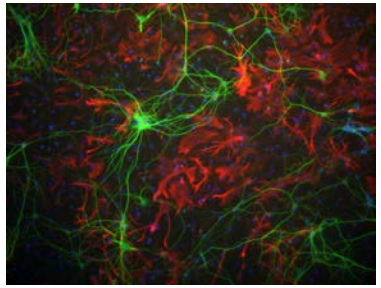


Target-based Screening
(known MIEs)

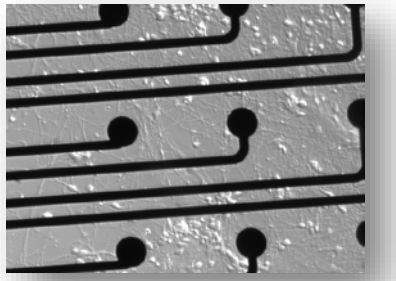
Phenotypic Screening in physiologically-relevant models
(MIE not assumed)

HTP Molecular assays (ToxCast)
ion channels
AChE
neurotransmitter receptors
growth factor receptors
transcription factors
kinases
…

Cell-based assay



Functional electrophysiology



Intact organism

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Questions?