Toxicology for the 21st Century/New Integrated Testing Strategies Workgroup

Presentation to the PPDC, Session #5

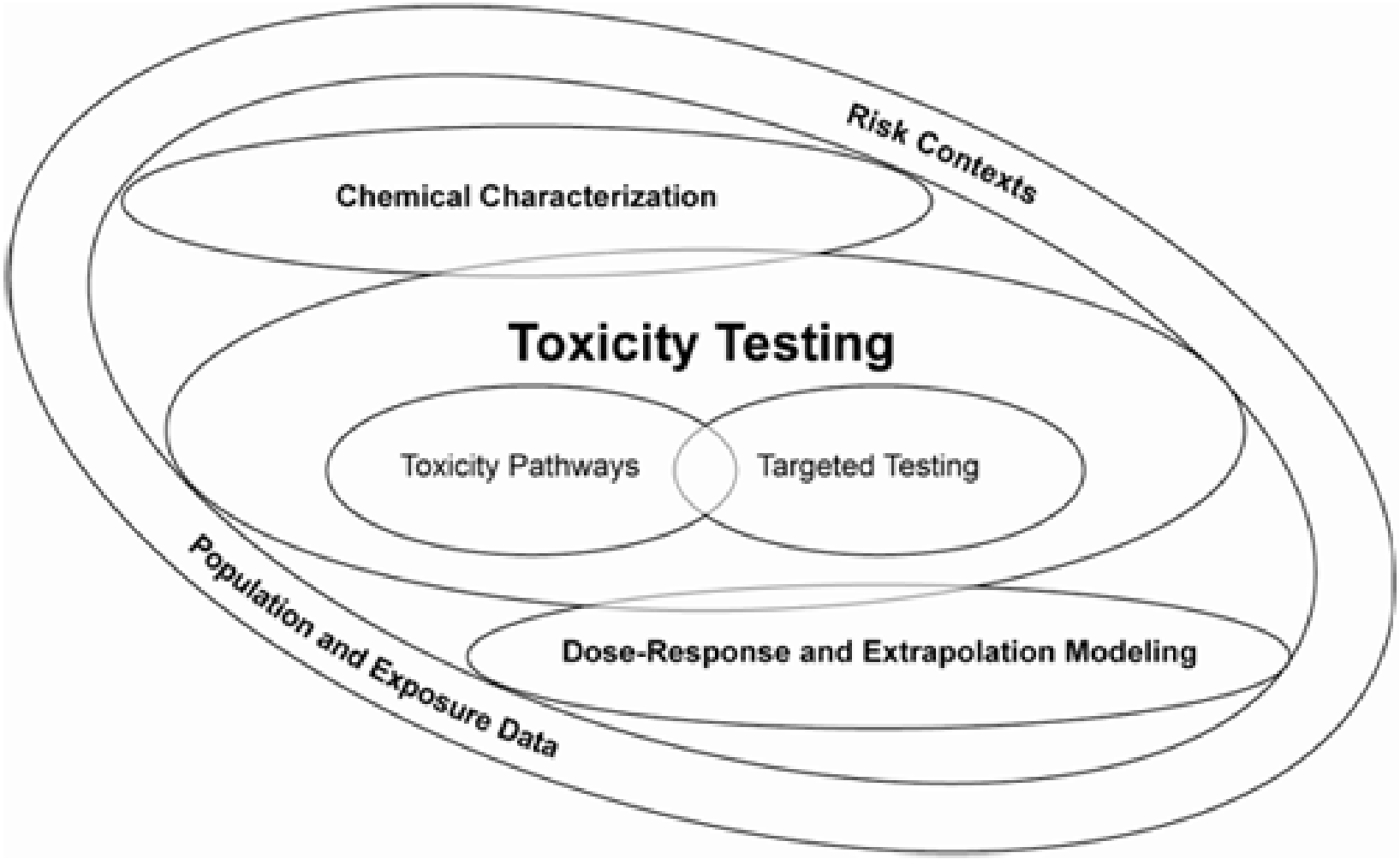
July 11, 2013

PPDC Workgroup: 21st Century Toxicology/New Integrated Testing Strategies (established 2008)

- Objective: Focus on communication & transition issues as EPA phases in new molecular and computational tools

Key transition activities include: identifying other internal and external applications of this 'new' science (e.g., improving agency decision-making capability by harnessing new data streams and **developing new diagnostic tools and biomarkers**) and providing process recommendations to transition to the new testing paradigm.

2007 NRC Toxicity Testing in 21st Century: A Vision & Strategy



Presentation Outline

- Workgroup Background and Workshop Highlights – Erik Janus (Monsanto Company)
- Metrics Proposal – Kristie Sullivan (PCRM)
- Update on Biomonitoring Subgroup Project – James Roberts (Medical University of South Carolina)

PPDC 21st C Workgroup - Actions

- FACA Stakeholder Workshops on Key Areas
  - December 13, 2010 – OPP's Strategic Vision: Integrated Testing and Assessment Strategies: Transitioning Research to Regulatory Practice
  - October 11, 2011 - Diagnostic Tools & Biomarkers in Pesticide Medical Management, Exposure Surveillance, and Epidemiologic Research: State-of-the-Science, Challenges, and Opportunities

Environmental Protection Agency - Pesticide Program Dialogue Committee
21st Century Toxicology/New Integrated Testing Strategies

Where Vision Meets Action: Practical Application of 21st Century Methods

July 2013 Stakeholder Workshop

The Workshop will be accessible by webinar at:

https://epa.connectsolutions.com/tox21century/

Call in number: 866-299-3188, code 703-308-0293

Workshop Purpose

- This one-day, non-technical workshop was intended to provide an opportunity to dialogue with stakeholders on how OPP envisions applying new science to change the way we evaluate the risks of pesticides, and to examine the challenges and benefits of making this transition.
- Goals of the meeting:
- (1) explore the regulatory application of alternative 21st Century methods to transition away from traditional chemical testing approaches,
- (2) examine the challenges of making this transition, and
- (3) discuss building confidence in these alternative methods in the support of pesticide registrations.

Workshop Background

- This workshop builds on the 2010 workshop on the Office of Pesticide Program's strategic vision and application of 21st Century science to improve and transform pesticide risk management by enhancing our ability to use integrated approaches to testing and assessment (IATA).

AGENDA

Welcome and Introduction

- Steven Bradbury, PhD, Director, Office of Pesticide Programs, Office of Chemical Safety and Pollution Prevention (OCSPP), EPA

Plenary Speaker

- Tina Bahadori, National Program Director, Chemical Safety for Sustainability Program, Office of Research and Development (ORD)

Session One: Understanding the Adverse Outcome Pathway Framework

Session Two: Case Studies of New Science Advances in Adverse Outcome Pathway Development and their Regulatory Application

- Endocrine Adverse Outcome Pathways
- Ecological Adverse Outcome Pathways
- Dermal Sensitization Adverse Outcome Pathway

Session Three: Benefits of and Challenges to Implement Alternative 21st Century Methods

- Multiple perspectives from industry, government, animal advocacy and environmental NGO organizations

Panel Discussion : Building Confidence in the Regulatory Application of Alternative 21st Century Methods for Evaluating Pesticides

AOP Framework

- Workshop developed around the concept of the AOP framework for organizing and analyzing information related to toxicological mode-of-action data that underlies 21st Century models and tools
- Challenges of managing chemical risks
  - Many chemicals
  - Many possible adverse effects
  - Many species/biological systems
  - Finite resources/time
  - Need for transparent, scientifically sound decisions

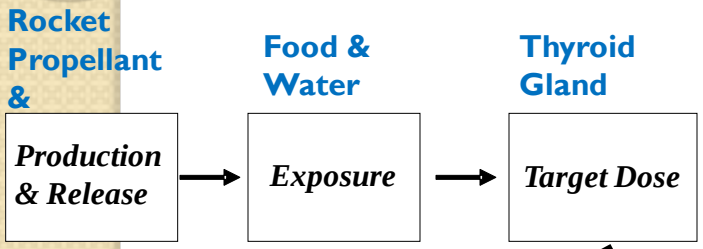
AOP Uses

1. **Improved predictions of toxicity via decreased uncertainty**
   - Increases level of confidence in the relationship between measured data and adverse outcomes that is critical for risk assessments
2. **Can be life-stage specific**
3. **Enhance species-to-species extrapolation**
4. **Identification of data gaps *(vs. data needs)***
   - Construction of an AOP should identify the data critical to build a useful model ("needs") as well as data of no use to model ("gaps")
5. **Provide molecular targets for development of *in vitro* screening assays and, ultimately, compound- or class-specific integrated testing systems**
6. **"Holy Grail" is development of predictive computational models**
   - If the initial molecular event ("tipping point") predicts the adverse outcome – then you don't need to measure the outcome itself

SOP, AOP, MOA, ToxPathway

- **Definition:** The continuum or cascade of measurable events starting from release into the environment and ending at an adverse outcome (USEPA 2003).
- **Example**: Perchlorate

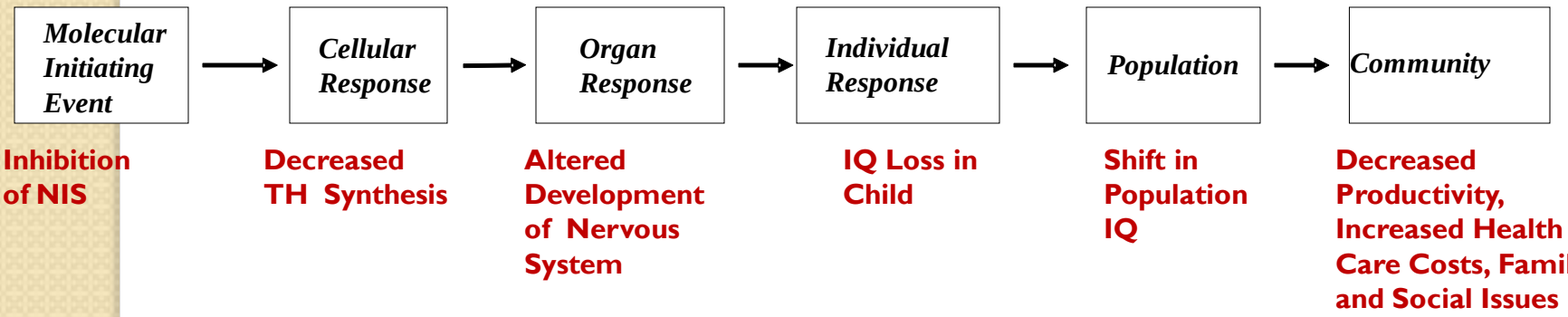
Exposure



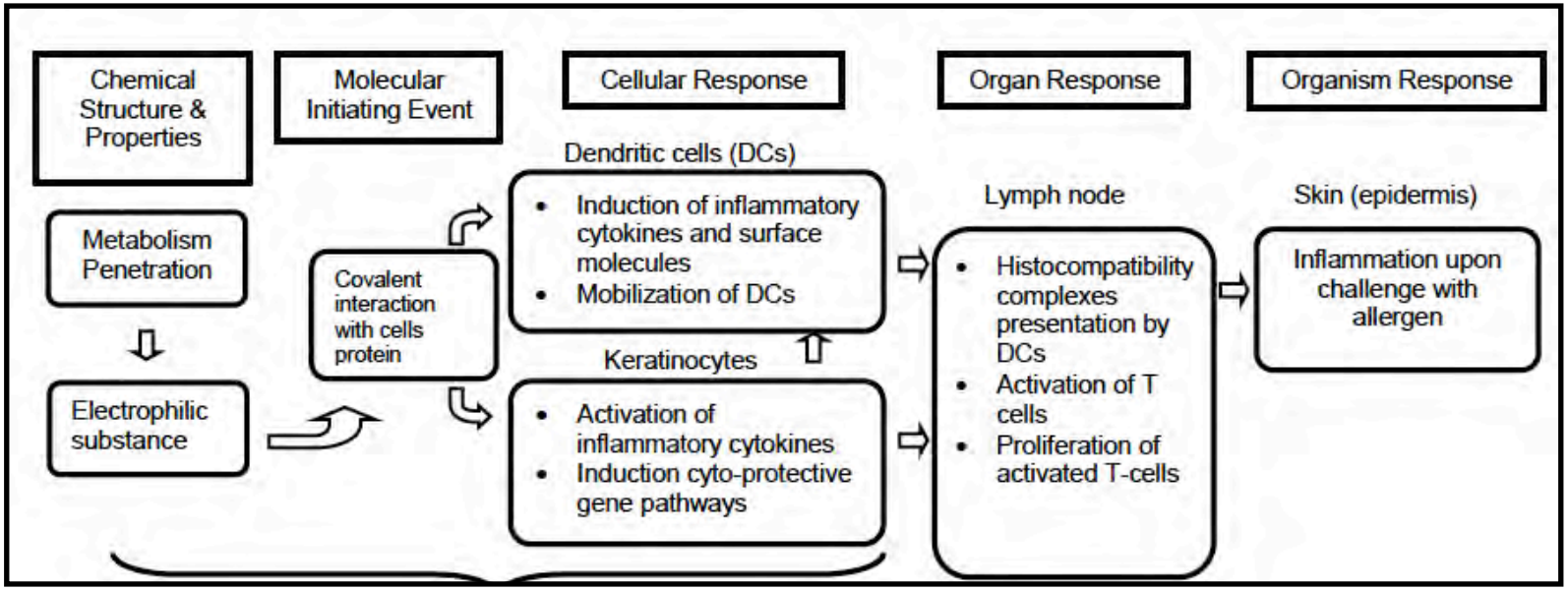
Uses:

- Qualitatively links actual use of chemicals to adverse outcomes
- Can be used to link exposure, toxicokinetic and toxicodynamic models to qualitatively predict outcomes
- Basis for causative & quantitative models

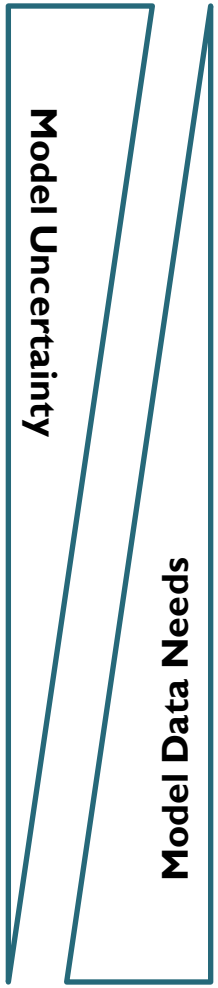
Adverse Outcome Pathway



AOP Framework – Skin Sensitization

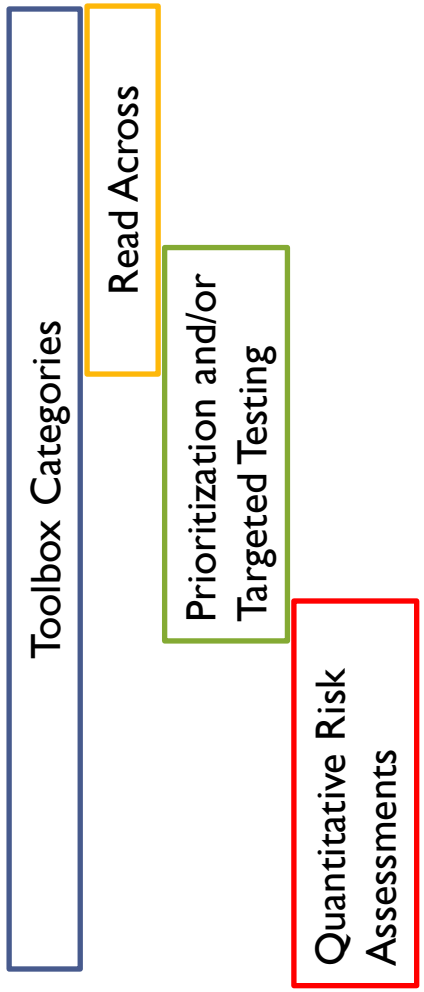


AOP Continuum

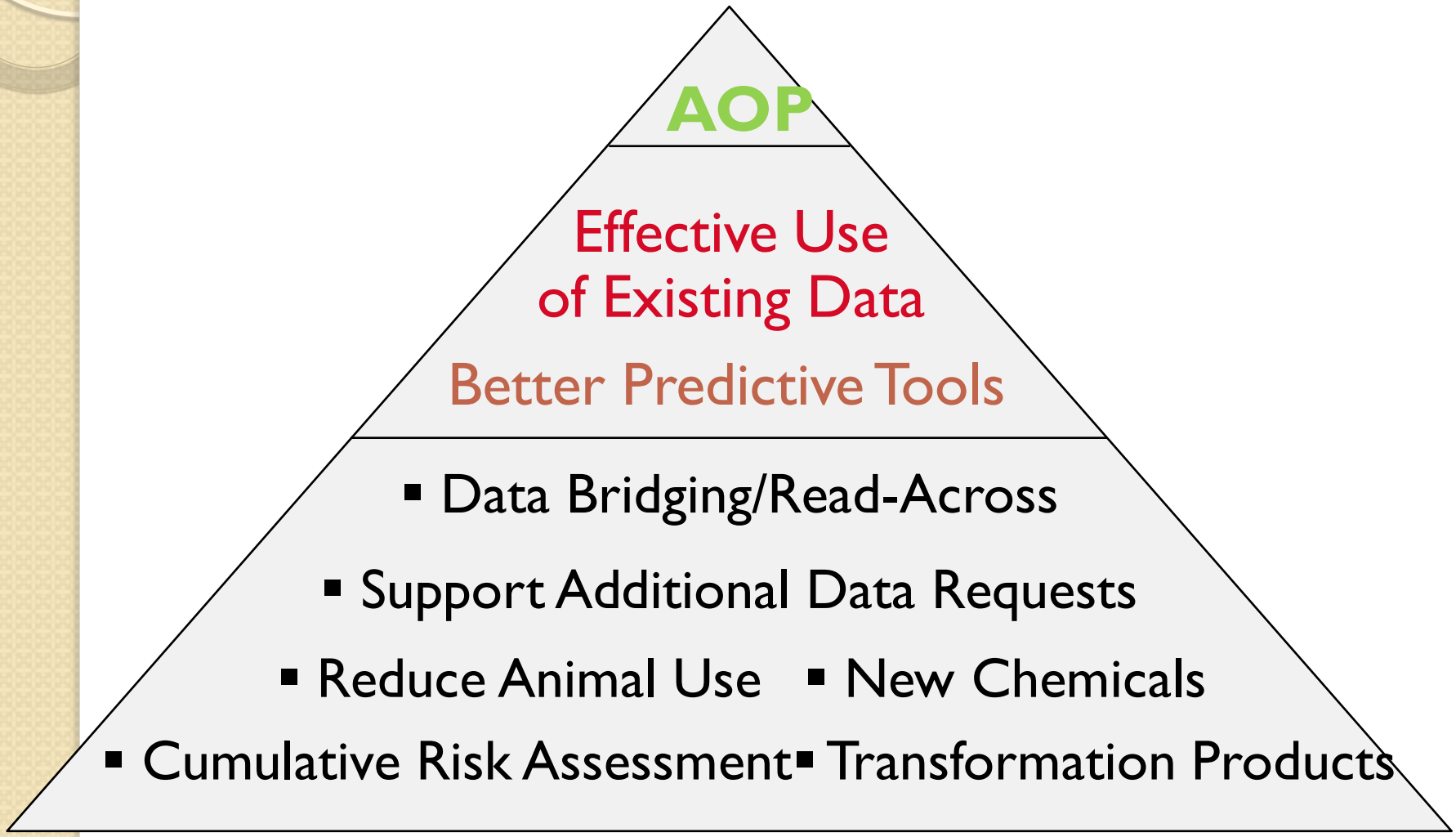


- **Simple correlative**
  - Links between inherent chemical properties and outcomes
- **Qualitative**
  - Known links between key events and outcomes
  - No complete set of key events – contains correlative "leaps"
  - Causative
- **Quantitative**
  - *Predictive quantitative models*

Domains of Application



Utility of AOPs



Highlights and Perspectives on the Benefits of and Challenges to using 21st Century Methods

- New tools will provide a more informed risk assessment (tox endpoints, uncertainty)
- Statutes give EPA flexibility to use the best science possible. EPA wants to implement practical applications of the science - today
- Advancements can be achieved through individual companies working with EPA on novel studies.
  - Develop new testing strategies grounded in biology to define data needs
  - Use information we have to be smarter about the studies we conduct. E.g. combining studies on multiple endpoints

Highlights and Perspectives on the Benefits of and Challenges to using 21st Century Methods

- EPA's research program is moving from a focus on 'perfect science' to impactful, timely, relevant science that is "fit for purpose"
- Benefits of 21st Century methods:
  - Across-the-board interest in reducing animal testing
  - More efficient assessment of greater number of chemicals, endpoints, species, etc.

Highlights and Perspectives on the Benefits of and Challenges to using 21st Century Methods

- Challenges that remain in implementation:
  - Models aren't perfect. Important to use other information and data as well as mechanistic data
  - More collaboration (interagency, public-private, international) is critical to moving science forward
  - Data management is a critical challenge that would be best addressed with common parameters and formats
  - Methods validation, regulatory acceptance and global harmonization of new test guidelines

Key Discussion Topics

- Performance-based approaches to methods validation are needed
  - New approaches are needed as "classical validation" won't work (see new Part 158W data requirements for antimicrobials)
- How much is enough? When is AOP ready to be used in regulatory decision-making?
  - Depends on how it will be used; depends on mandate
  - Demonstrating clear, quantitative linkages will be essential
  - Qualitative applications can be used before quantitative applications are realized
  - For example, DoD ecological case study is a model designed for certain mission-specific applications, but is it ready for OPP use in risk assessment? Fit for purpose?

Key Discussion Topics

- Open and transparent, independent peer review, all stakeholders need to be a part
  - OECD AOPs website – lists all AOPs currently being worked on – can/need to contribute to this work
- How can EPA and its partners continue to drive this work?
  - Communication and outreach by EPA – what's next for workgroup to help EPA engage/move forward/support?
  - Establishing "metrics for success"
  - Ensuring process-related issues, such as resources for data management

PPDC Tox 21/Integrated Testing Strategy Work Group

Proposal For Goals and Metrics for Acute Toxicity Studies

PURPOSE

In the context of acute hazard labeling studies, revisit, augment and implement metrics for improved efficiency by setting specific goals and measuring progress to achieve these goals.

GENERAL GOALS

- Phase out animal testing for acute "6-pack" endpoints (acute oral, dermal, inhalation; dermal and eye irritation; dermal sensitization)
- Consistent and regular reductions in the numbers of animals used for acute tests
- Consistent and regular increases in the use of non-animal methods and existing information used to make regulatory decisions

SPECIFIC GOALS

- Allow OECD-approved in vitro skin irritation method for registration for all chemistries during 2015 Calendar Year
- Accept suite of in vitro tests for skin sensitization within 6 months of acceptance at the OECD level
- Phase out multiple routes of exposure (by developing reliable route-to-route extrapolation principles or other comprehensive waiving policies)
  - Phase out acute dermal test for majority of registrations within 3 years

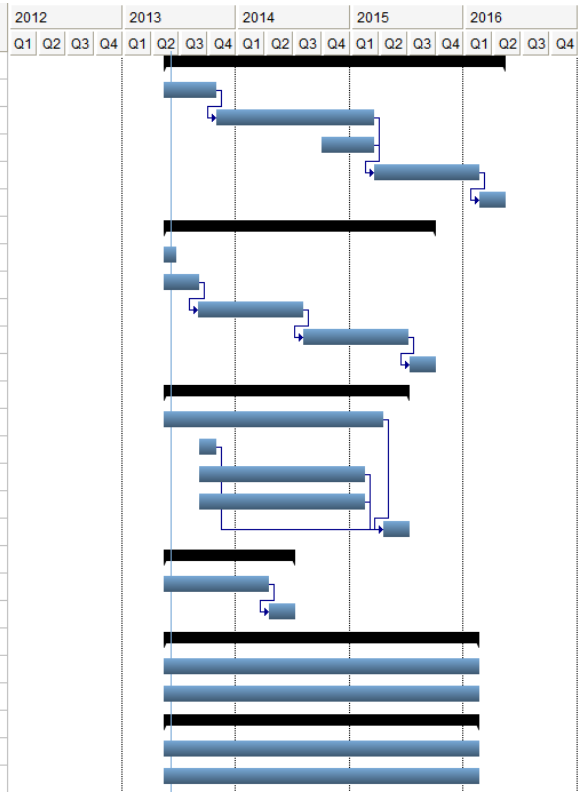
METHODS ACCEPTANCE STATUS

			REGULATORY STATUS			
ANIMAL TEST	NUMBER OF ANIMALS	ALTERNATIVE TEST	OECD	US	OPP	OTHER
Skin Irritation (severe)	3 rabbits	Reconstructed Human Epidermis models (various)	OECD TG 431 (2004)	ICCVAM 2002	Accepted	
Skin Irritation (mild)		Reconstructed Human Epidermis models (various)	OECD TG 439 (2010)			
Eye Irritation (severe)	3 rabbits	Bovine corneal opacity permeability (BCOP) test	OECD TG 437 (2009)	ICCVAM (2007)	Replaces rabbit for antimicrobial cleaning products	Now validated for "non-irritants" for EPA and GHS classification systems
		Cytosensor Microphysiometer modified (cytotoxicity/cell-based assay)		ICCVAM (2010)*	Replaces rabbit for antimicrobial cleaning products	
		Fluorescein Leakage (cytotoxicity/cell-based assay)	OECD TG 460 (2011)			
		Isolated chicken eye (ICE) test	OECD TG 438 (2009)	ICCVAM (2007)		Now validated for "non-irritants" for GHS classification system
Eye Irritation (mild)		Cytosensor Microphysiometer modified		ICCVAM (2010)*	Replaces rabbit for antimicrobial cleaning products	
		EpiOcular (MatTek)			Replaces rabbit for antimicrobial cleaning products	
Sensitisation	32 guinea pigs or 16-33 mice	Direct Peptide Reactivity Assay (DPRA)	OECD TG drafting			ECVAM validation pending
		Keratinosens assay	OECD TG drafting			ECVAM validation pending
		Myeloid U937 Skin Sensitization Test (MUSST)				ECVAM validation pending
		Human Cell Line Activation Test (h-CLAT)				ECVAM validation pending
	16 or 33 mice	Local Lymph Node Assay (LLNA) or reduced LLNA (rLLNA)	OECD 429 (2002/2010)	ICCVAM (2008)	Accepted	
Acute Dermal Toxicity	20 rabbits					Opportunities for bridging or waiving exist.
Acute Oral Toxicity	7 rats (average)					Opportunities for bridging or waiving exist.
Acute Inhalation Toxicity	20 rats					Opportunities for bridging or waiving exist.

*Only for certain chemicals and in a WOE approach

METHODS ACCEPTANCE GANTT CHART

	Name	Duration	Start	Finish	Predecessors
1	**Skin Irritation**	**780d**	**05/10/2013**	**05/05/2016**	
2	Determine needs for EPA acceptance	6m	05/10/2013	10/24/2013	
3	Collect necessary data	18m	10/25/2013	03/12/2015	2
4	Assess according to EPA class. system	6m	09/26/2014	03/12/2015	
5	EPA begins pilot program to accept in vitro data	12m	03/13/2015	02/11/2016	3,4
6	If appropriate, EPA publishes acceptance policy	3m	02/12/2016	05/05/2016	5
7	**Eye Irritation**	**620d?**	**05/10/2013**	**09/24/2015**	
8	Finalize AMB CP non-animal strategy	27d?	05/10/2013	06/17/2013	
9	Determine appl. of AMB CP strategy to all pesticides	4m	05/10/2013	08/29/2013	
10	Collect necessary data	12m	08/30/2013	07/31/2014	9
11	EPA begins pilot program to accept in vitro data	12m	08/01/2014	07/02/2015	10
12	If appropriate, EPA publishes acceptance policy	3m	07/03/2015	09/24/2015	11
13	**Dermal Sensitisation**	**560d?**	**05/10/2013**	**07/02/2015**	
14	OECD TG drafting and acceptance	25m	05/10/2013	04/09/2015	
15	Examine validation data for applicability domain	2m	09/02/2013	10/25/2013	
16	EPA experts participate in TG discussions	379d?	09/02/2013	02/12/2015	
17	Stakeholders participate in testing strategy discussions	380d?	09/02/2013	02/13/2015	
18	If appropriate, EPA publishes acceptance policy	3m	04/10/2015	07/02/2015	14,15,16,17
19	**Acute Dermal Toxicity**	**300d**	**05/10/2013**	**07/03/2014**	
20	EPA assess value of endpoint	12m	05/10/2013	04/10/2014	
21	If appropriate, EPA publishes policy accepting oral values & WOE	3m	04/11/2014	07/03/2014	20
22	**Acute Oral toxicity**	**720d**	**05/10/2013**	**02/11/2016**	
23	EPA participates in AOP development	36m	05/10/2013	02/11/2016	
24	EPA participates in test method assessment	36m	05/10/2013	02/11/2016	
25	**Acute Inhalation Toxicity**	**720d**	**05/10/2013**	**02/11/2016**	
26	EPA participates in AOP development	36m	05/10/2013	02/11/2016	
27	EPA participates in test method assessment	36m	05/10/2013	02/11/2016	



PROPOSED NEAR-TERM METRICS

- Number of in vitro tests submitted per endpoint per year
- Number of acute animal tests submitted per endpoint per year
- Estimate of animals used in acute tests per year
- Number of dossiers with "alternative approaches" submitted per year
  - Considering approaches to track

Priority Pesticide List

Goal: Develop a priority list of candidate pesticides for exploring the process of developing human health pesticide biomarkers for research and clinical applications

Method: Expert Panel to develop and apply criteria

Proposal to the PPDC

- Charge to the Workgroup
  - Develop priority list of candidate pesticides for developing human health pesticide biomarkers for research and clinical applications. Convene expert group and agree upon criteria for developing list
  - Create pesticide use case(s) to encourage funding for research on rapid diagnostic methods for pesticides to enable clinical trials and point-of-need diagnostics
  - Develop biomarker definitions
- Progress of Expert Group for the Development of a Priority Pesticide List
  - Expert group of scientists and public health professionals from industry, NGOs, academia, the medical community & EPA
  - Charge: Establish prioritization criteria & make recommendations on pesticides that should be the focus of further biomarker research and development

Expert members

PPDC 21st Century Toxicology/New Integrated Testing Strategies Workgroup

Priority Pesticide List: Subject Matter Expert Group

Name	Affiliation	Expertise
Subject Matter Experts		
Geoff Calvert	CDC/NIOSH	Occupational Epidemiology, Pesticide Incident Surveillance
Matthew Keifer	Marshfield Clinic	Environmental & Occupational Medicine, Epidemiology
Daniel Sudakin	Oregon State University, NPIC	Medical Toxicology, Pesticide Incident Surveillance
Jimmy Roberts	Medical University of South Carolina	Environmental Medicine, Pediatrics
Asa Bradman	University of California - Berkeley	Pesticide Biomonitoring, Epidemiology
Amy Liebman	Migrant Clinicians Network	Environmental and Occupational Health, Migrant Farmworker Healthcare
Jeff Burgess	University of Arizona	Environmental & Occupational Health
Mike Bartels	Dow Chemical	Medical Toxicologist
Tammi Schaeffer	Rocky Mountain Poison Center	Medical Toxicologist
Cheryl Cleveland	Dow Chemical	
EPA Representatives		
Steve Jarboe	EPA/OPP/BEAD	Pesticide Usage Data
Ed Scollon	EPA/OPP/HED	Toxicologist
Aaron Niman	EPA/OPP/HED	Exposure Assessment, Public Health & Incidence Surveillance
Vicki Dellarco	EPA/OPP/IO	
Jennifer McLain	EPA/OPP/AD	
Stephen Edwards	EPA/ORD	Biomarker Research

Primary Criteria

- High prevalence of reported poisonings with moderate to severe toxic effects
- High prevalence of exposures (regardless of toxicity)
- High acute toxicity/lethality (regardless of exposure)

Secondary criteria

- Inappropriate treatment/delayed or misdiagnosis
- Treatment available
- Sites of pesticide use (homes, schools, pets)

- Additionally, in agreement that will focus on chemical class, not individual a.i.

Next Steps

- Identify data additional sources
  - Poison Control Center
  - CA Pesticide Incident Surveillance Program
  - SENSOR
  - NHANES
  - CA Use reporting database
  - EPA usage data
  - Animal toxicity data
- Apply criteria to develop Priority Pesticide List
  - Preliminary list: pyrethroids, OP's, carbamates, fipronil, neonicotinoids, phosphene, paraquat, diquat