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

Presentation to the PPDC

October 21, 2015

21st Century Testing & Assessment Paradigm

- OPP Vision
  - Integrative (Tiered)
  - Hypothesis-driven
  - Efficient & effective

Focus resources on risks of greatest concern

- Transition Strategy
  - Based on sound science and risk management needs
  - Research in concert with regulatory dialogue
  - Incremental application to decision making
  - Expert peer review and stakeholder involve

OPP Strategic Direction http://www.epa.gov/opp00001/science/testing-assessment.html

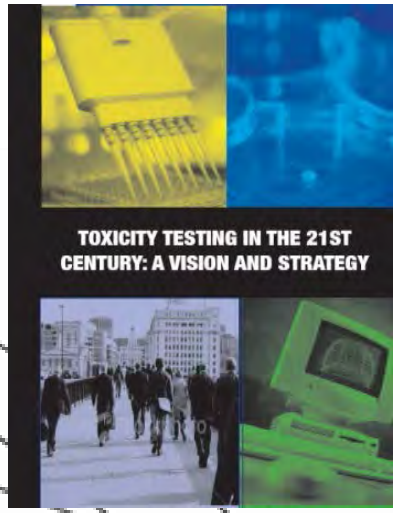
PPDC Workgroup: 21st Century Toxicology/ New Integrated Testing Strategies

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



PPDC 21st C Workgroup - Actions

- Presentations to Workgroup
  - QSAR, Metabolic Simulator, ToxCast
  - Smarter Animal Study Designs - Enhanced F1 Tiered Testing Approach
  - ICCVAM, OECD
  - OPP Policies and Guidance documents
- OPP Website
  - Pesticide Program's Strategic Direction for a Paradigm Shift in Testing and Assessment
  - Tool Matrix
  - Glossary of Terms
- Identify Stakeholder Issues

Tool Matrix (abbreviated)

Table 1. Priority Setting & Screening Computational Tools.

Goals/Uses/Benefits	Type	Examples of Current Tools	Examples of Tools in Development or Under Evaluation	Example Milestones
•Enhance ability to predict chemical toxicity by developing new models and populating existing models with pesticide based t… that co… metho… more b… evalua… pestici… •Fully "Integ… Appro… and As… build u… existin… use on…	•QSAR Models •Expert Systems •Knowledge Bases •Read Across from Analogs/Categories	**Existing** •ECOTOX •ASTER •ECOSAR •EPI Suite •PBT Profiler **New** …ACTor	•ToxRefDB •QSAR-Based Expert System for Predicting Estrogenic Activity •Metapath •Metabolic Simulator •Leadscope FDA QSAR …Models	•October 2007 – OPP's Residue of Concern Knowledgebase Subcommittee (ROCKS) is established to provide a systematic and consistent weight of evidence approach that fully utilizes available tools of computational toxicology to …

Table 2. Replacement or Alternative Tests to Traditional Animal Testing. These models are intended to replace a current *in vivo* animal test.

Goals/Uses/Benefits	Type	Examples of Current Tools	Examples of New Tools	Example Milestones
•To reduce, refine, and replace animal testing for those traditional animal studies performed for purposes of risk asse… labeling…	•*Non-testing computer-aided methods to determine*	Draize Rabbit Eye Test	Bovine Corneal Opacity and Permeability, …EpiOcular… &	May 2009 Interim Policy on Non-animal ocular irritation assays for antimicrobial cleaning anticipated to be used … the next 18 months

Table 3. New Risk Assessment Tools under consideration for a term longer than the tools in Table 1& 2. These tools are part of the risk assessment paradigm changes under consideration

Goal / Uses/Benefit	Examples of Types of Tools
•Develop the means to move, in a scientifically credible and transparent manner, from a paradigm that requires extensive animal hazard testing and generation of exposure data,, to a paradigm that provides the means to use a risk-based, hypothesis-driven approach that is based on full use of	•HTS and "omics" methods (genomics transcriptomics, proteomics,) to infor… mode of action and characterization toxicity pathways •System biology approaches for

PPDC 21st C Workgroup - Actions

- FACA Stakeholder Workshops
  - December 2010 – OPP's Strategic Vision: Integrated Testing and Assessment Strategies: Transitioning Research to Regulatory Practice
  - October 2011 - Diagnostic Tools & Biomarkers in Pesticide Medical Management, Exposure Surveillance, and Epidemiologic Research: State-of-the-Science, Challenges, and Opportunities
  - July 2013 – Where Vision Meets Action: Practical Application of 21st Century Methods

PPDC 21st C Workgroup - Actions

2012 Charge to the Workgroup following Biomonitoring Workshop

- Develop biomarker definitions
- Develop priority list of candidate pesticides for developing human health pesticide biomarkers for research and clinical applications.
  - Convene expert group to establish prioritization criteria & make recommendations on pesticides that should be the focus of further biomarker research and development
- 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

➢ Current Activity: Developing a publication on the need for pesticide biomarker tools

PPDC 21st C Workgroup - Actions

- 2013 Recommendation for OPP Goals and Metrics for Progress on Alternative Approaches for Acute Studies Used for Hazard Labeling
  - General Goal: Phase out animal testing for acute "6-pack" endpoints (acute oral, dermal, inhalation; dermal and eye irritation; dermal sensitization)
  - Specific near-term goals for acceptance of OECD *in vitro* studies and establishing waiver policies in 2015 and 2016

- Current Activity: OPP Metrics Workgroup
  - Goal: Develop an OPP process for measuring and reporting progress towards 21st C goals