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

- 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 involvement

OPP Strategic Direction  http://www.epa.gov/opp00001/science/testing-assessment.html
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.
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
### Table 1. Priority Setting & Screening Computational Tools.

<table>
<thead>
<tr>
<th>Goals/Uses/Benefits</th>
<th>Type</th>
<th>Examples of Current Tools</th>
<th>Examples of Tools in Development or Under Evaluation</th>
<th>Example Milestones</th>
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<tbody>
<tr>
<td>• Enhance ability to predict chemical toxicity by developing new models and populating existing models with pesticide based training sets so that computational methods can be used more broadly in hazard evaluations of pesticides</td>
<td>QSAR Models</td>
<td>Existing</td>
<td>ToxRefDB</td>
<td>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 develop hazard determinations for pesticide metabolites, residues and environmental degradates of concern.</td>
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<td>Knowledge Bases</td>
<td>ECOSAR</td>
<td>Metapath</td>
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<td>Read Across from Analogos/Categories</td>
<td>EPI Suite</td>
<td>Metabolic Simulator</td>
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<td>PBT Profiler</td>
<td>QSAR-Based Expert System for Predicting Estrogenic Activity</td>
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<td></td>
<td>New</td>
<td>ACTor</td>
<td>Metabolic Simulator</td>
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<td>ToxCastTM Research Program (<a href="http://www.epa.gov/ncct/tocast">http://www.epa.gov/ncct/tocast</a>)</td>
<td>Leadscope FDA QSAR Models</td>
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### Table 2. Replacement or Alternative Tests to Traditional Animal Testing. These models are intended to replace a current in vivo animal test.

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<tr>
<th>Goals/Uses/Benefits</th>
<th>Type</th>
<th>Examples of Current Tools</th>
<th>Examples of New Tools</th>
<th>Example Milestones</th>
</tr>
</thead>
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<tr>
<td>• To reduce, refine, and replace animal testing for those traditional animal studies performed for purposes of risk assessment and labeling</td>
<td>Non-testing computer-aided methods to determine</td>
<td>Draize Rabbit Eye Test</td>
<td>Bovine Corneal Opacity and Permeability, EpiOcular, &amp;</td>
<td>May 2009 Interim Policy on Non-animal ocular irritation assays for antimicrobial cleaning anticipated to be used over the next 18 months</td>
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### Table 3. New Risk Assessment Tools under consideration for a term longer than the tools in Tables 1 & 2. These tools are part of the risk assessment paradigm changes under consideration

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<tr>
<th>Goal / Uses/Benefit</th>
<th>Examples of Types of Tools</th>
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<td>• 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 new data and tools</td>
<td>• HTS and “omics” methods (genomics, transcriptomics, proteomics,) to inform mode of action and characterization of toxicity pathways</td>
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<td>• System biology approaches for</td>
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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
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
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