Pesticide Program Dialogue Committee

21st Century Toxicology/New Integrated Testing Strategies Workgroup

Co-Chairs: Drs Steven Bradbury and Vicki Dellarco

April 22-23, 2009

Pesticide Program Dialogue Committee 21st Century Toxicology/New Integrated Testing Strategies Workgroup

Objective

This work group will focus on communication & transition issues as EPA phases in new predictive and testing methods over the next three to five years. This work group will help to focus EPA's efforts on the key activities needed for successful communication and transition.

Key communication activities include identifying ways to improve understanding and communicate complex science to all stakeholders.

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.

Workgroup Members

Berger, Lori - California Specialty Crops Council
Botts, Dan - Florida Fruit and Vegetable
Brown, Elizabeth - Steptoe & Johnson
Chan, Peter - Pest Management Regulatory Agency (Canada)
Cox, Caroline - Center for Environmental Health
Dahl, Erica - Institute for In Vitro Sciences
Daiker, Davis - Florida Department of Ag & Consumer Services
Ferenc, Susan - Chemical Producers Distributors Association
Fry, Michael - American Bird Conservancy
Howard, Dennis - Florida Department of Agriculture & Consumer Services
Janus, Erik - CropLife America
Keifer, Matthew, University of Washington
Liebman, Amy - Migrant Clinicians Network
Matthews, Edwin - Food and Drug Administration
McKernan, Moira - American Bird Conservancy
Paterson, Joel - Pest Management Regulatory Agency (Canada)
Patterson, Gary - California DPR
Roberts, James - Medical University of South Carolina
Sass, Jennifer - Natural Resources Defense Council
Schell, John - ENTRIX, Inc.
Seidle, Troy - Humane Society of the US/International
Sullivan, Kristie - Physicians Committee for Responsible Medicine
Wegmeyer, Tyler - American Farm Bureau Federation
Whalon, Mark - Michigan State University
Willett, Catherine - People for the Ethical Treatment of Animals

Presentations to Workgroup

- **Computational Approaches**
  - **Current**
    - QSAR Overview - P. Schmieder (EPA/ORD)
    - OPPTS QSAR Systems & OECD QSAR Tool Box - T. Henry (OPPTS)
    - FDA QSAR systems – E. Matthews (FDA)
    - Proposed Regulations QSAR/SAR & 158W by J. McLain etal (OPP)
  - **Under Evaluation or Development**
    - Update on Research Using in vitro & Computer-based Tools for Screening Potential Estrogenic Activity by P. Schmieder (ORD)
    - ToxCast™ - D. Dix (ORD)
- **Smarter Animal Study Designs**
  - Enhanced F1 Tiered Testing Approach - E. Mendez, (OPP)
  - Cancer Bioassay Retrospective Analysis - M. Manibusan (OPP)

New Website to be Launched in May 2009

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Integrated Approach to Testing and Assessment

Quick Resources

- In the Spotlight
- PPDC Workgroup: Testing in the 21st Century
- Science Activities (ToxCast Pesticides)
- NRC Report on Toxicity Testing in the 21st Century
- Publications of Interest
- Other Web Resources
- Key Terms

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A Vision to Incorporate an Integrated Approach to Pesticide Testing and Assessment

Pesticide Program Strategic Direction for a Paradigm Shift in Toxicity Testing and Assessment

EPA's Office of Pesticide Programs is committed to protecting public health and the environment through application of the latest scientific tools to increase the reliability and effectiveness in assessing and managing potential pesticide risks.

The Critical Path to Realize an Integrated Approach

Our critical path focuses on fully utilizing an integrated approach to testing and assessment. The goal is to move toward a new paradigm where *in vivo* (animal) testing is targeted to the most likely hazards of concern. By developing a progressive, tiered testing approach we will have the specific data needed for human health and ecological risk assessments sooner and at a lower cost. This tiered approach starts with hazard-based hypotheses about the plausible toxicological potential of a pesticide or group of pesticides based on physical-chemical properties and existing exposure and toxicity information that is combined with computer modeling and 'new' diagnostic *in vitro* (non-animal) assays. The path forward will require an improved ability to predict chemical toxicity and exposure through application of efficient and effective screening tools. New technological advances to support more effective means of screening chemicals for potential effects will include computer modeling to predict chemical toxicity and exposure as well as rapid *in vitro* assays that provide biological profiles of the toxicological potential of chemicals. Our strategic plan also includes the development of increasingly effective laboratory animal tests that are designed to maximize the information generated about the nature of the effects being studied.

These advances will be incorporated

Over the next several years, EPA's Office of Pesticide Programs (OPP) will transform and improve our approach to pesticide risk management by enhancing our ability to use integrated approaches to testing and assessment.

Why a paradigm shift now?

- This is a critical time. Science is rapidly advancing and new technologies are emerging.
- Preparing now will enable OPP to take advantage of advances as soon as they are available in an open and transparent manner

What are the benefits of this paradigm shift?

- Potential to significantly speed risk assessments.
- Potential to evaluate many more chemicals across a broader range of potential effects
- Potential to increase our ability to assess the risks posed by mixtures.
- Enhanced predictive ability to determine whether animal testing is needed to refine a risk assessment and to inform management decisions.
- Refining and reducing animal testing by maximizing information obtained from animal studies, and focusing on endpoints of concern
- Enhancing the quality of risk assessment and risk management decisions.

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Key Terms

- ***In vitro* -** experiments or tests done under controlled experimental conditions outside of outside of the body, such as in a test tube or laboratory dish. These assays tend to focus on organs, tissues, cells, cellular components, protiens, and/or biomolecules.

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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 training sets so 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 develop hazard determinations for

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 ass… 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 over the next 18 months

Table 3. New Risk Assessment Tools under consideration for a term longer than the tools in Tabl… 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 computational toxicology tools and identification of critical	•HTS and "omics" methods (genomics transcriptomics, proteomics,) to infor… mode of action and characterization toxicity pathways •System biology approaches for predictive environmental and human

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Integrated Approach to Testing and Assessment

It will take time and substantial research to fully realize our vision &

for a Paradigm
Assessment

Understanding
Assessment

Tool Matrix

Partnerships

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Many thanks to our workgroup members!

& OPP staff:
Claire Gesalman
Kaythi Han
Niva Kramek
Mary Manibusan
Jennifer McLain
Vera Au

Panel Discussion

What does the 21st Century Toxicology/New Integrated Testing Strategies Initiative Mean?

- What types of information or communication strategies might be needed from EPA to allow one to "feel more comfortable" with the shift to less animal testing and less data generation?
- What will EPA need to address in terms of communicating how this new approach might change risk assessments or risk-based decisions?
- How could EPA communicate where it is along the transition continuum, which may be faster in some areas than others?

Discussants

- Erik Janus (CropLife America)
- Caroline Cox (Center for Environmental Health)
- Kristie Sullivan (Physicians Committee for Responsible Medicine)
- Michael Fry (American Bird Conservancy)
- Elizabeth Brown (Steptoe & Johnson/ACC Biocides Panel)