



**US Environmental Protection Agency  
Office of Pesticide Programs**

**Tools for Integrated Approaches to  
Testing and Assessment**

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## **TOOLS FOR INTEGRATED APPROACHES TO TESTING AND ASSESSMENT FOR ECOLOGICAL AND HUMAN HEALTH**

The following tables reflect the Office of Pesticide Program's near (1-5 years) and long term (5-10 years) plans to incorporate new scientific tools for Integrated Approaches to Testing and Assessment. The priority setting and screening tools listed in Tables 1 and 2 would be applied in the near term within our current assessment practice for making decisions regarding the safety of pesticides for both humans and wildlife.

The tools listed in Table 1 are designed to make existing animal tests more focused on risk assessment and management needs by guiding or prioritizing work on an individual chemical or on groups of chemicals.

The key objective of tools listed in Table 2 is to replace an animal test with reliable non-animal methods and to ensure the efficiency of animal testing by using tiered testing or improving study designs.

Table 3 represents the longer term effort that will transition our current practice into a new risk assessment paradigm using fewer whole animal tests. This new paradigm relies on an understanding how chemicals perturb toxicity or disease pathways in humans and the environment.

**Table 1: Priority Setting and Screening Computational Predictive Tools**

**Table 2: Replacement Tests or Modified Protocols to Traditional Animal Studies**

**Table 3: Longer Term Tool Development to Support a Paradigm Shift in Testing and Assessment**

The tools listed in Tables 1 and 2 will enable a transition into a new paradigm of toxicity testing. Essential to shifting toward a new paradigm is the building of improved predictive models (i.e, Tables 1 & 2) along with fundamental research that identifies critical pathways of toxicity and establishes linkages across the different levels of biological organization (chemical interaction with a molecular target, cellular response, tissue, or organ effect and consequent adverse effect on the organism).

**Table 1. Priority Setting and Screening Computational Predictive Tools.** In the near term (1-5 years), OPP plans to build capacity and expand its suite of computational tools to allow more efficient toxicity testing by quickly identifying the likelihood of potential toxicity effects without conducting the full set of *in vivo* toxicological studies, and to allow more spatially explicit risk assessments that would identify specific habitat and areas of potentially high exposure. These tools largely draw on profiles of substances with similar physio/chemical properties and biological modes of action.

Goals/Uses/Benefits	Type	Examples of Tools	Examples of Tools in Development or Under Evaluation	Example OPP Milestones
<ul style="list-style-type: none"> <li>• Enhance ability to predict chemical toxicity by developing new models and populating existing models with pesticide based training sets so that computational methods are more useful for pesticides</li> <li>• Build upon already existing knowledge for use on data-limited chemicals, such as the pesticide inert ingredients, certain antimicrobial pesticides, metabolites and environmental degradates of pesticides as well as manufacturing process impurities</li> <li>• Reduce animal testing by appropriately directing data generation toward the most likely hazards/risk of concern</li> </ul>	<p><b><u>Models that use existing knowledge</u></b></p> <ul style="list-style-type: none"> <li>• QSAR Models</li> <li>• Expert Systems</li> <li>• Knowledge Bases</li> <li>• Read Across from Analogs/Categories</li> </ul>	<p><b><u>Existing</u></b></p> <ul style="list-style-type: none"> <li>• ECOTOX</li> <li>• ASTER</li> <li>• ECOSAR</li> <li>• EPI Suite</li> <li>• PBT Profiler</li> <li>• Oncologic</li> </ul> <p><b><u>New</u></b></p> <ul style="list-style-type: none"> <li>• ACTor</li> <li>• DSSTox</li> <li>• Metapath</li> <li>• ToxRefDB</li> </ul>	<ul style="list-style-type: none"> <li>• QSAR-Based Expert System for Predicting Estrogenic Activity</li> <li>• Metabolic Simulator</li> <li>• FDA QSAR Models –<b>expansion to pesticide chemicals</b></li> </ul>	<ul style="list-style-type: none"> <li>• 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</li> <li>• December 2007– EPA hosted Integrated Approaches to Testing and Assessment Organization for Economic Cooperation and Development (OECD) Workshop</li> <li>• December 2009 – Letter agreement is signed between FDA and OPP to build toxicity databases on pharmaceuticals and pesticides to support better hazard predictions across different chemical classes and modes of action</li> <li>• February/August 2009 – OECD</li> </ul>

Goals/Uses/Benefits	Type	Examples of Tools	Examples of Tools in Development or Under Evaluation	Example OPP Milestones
				<p>Expert Consultation and August FIFRA SAP Review on QSAR-Based Expert System for Predicting Estrogenic Activity for food use inert ingredients and anti-microbial pesticides</p> <ul style="list-style-type: none"> <li>• March 2011 – OPP and Canada’s Pest Management Regulatory Agency (PMRA) conducted a validation exercise for approximately 50 pesticides with three different QSAR models to determine whether these models could predict known pesticide toxicities</li> <li>• May 2010 – Metapath is a computational tool, providing a relational and searchable metabolism pathway database with embedded data evaluation tools. It was proposed as a project for international developed across the global pesticide regulatory agencies and in May 2010 was accepted by the OECD Working Group on Pesticides. Along with this project is an established Metapath users’ group currently composed of representatives from member countries. A dialogue underway to explore further international partnerships</li> </ul>

Goals/Uses/Benefits	Type	Examples of Tools	Examples of Tools in Development or Under Evaluation	Example OPP Milestones
	<p><b><u>Models based on generation of new data:</u></b></p> <ul style="list-style-type: none"> <li>• Bioactivity Profiling with <i>in vitro</i> High Throughput (HTP) Systems</li> </ul>		<p>ToxCast™ Research Program (<a href="http://www.epa.gov/ncct/toxcast">http://www.epa.gov/ncct/toxcast</a>)</p>	<ul style="list-style-type: none"> <li>• May 2009 – Analysis of HTS data on ~300 pesticides (ToxCast Data Summit Meeting: <a href="http://www.epa.gov/ncct/toxcast/summit.html">http://www.epa.gov/ncct/toxcast/summit.html</a>)</li> <li>• Spring-Summer 2009/10 – Selection of additional chemicals (including inert ingredients and pesticide active ingredients) for 2nd Phase of the ToxCast research program</li> <li>• 2011/12 – SAP meeting on ToxCast predictive application</li> <li>• 2012/13 – ToxCast implementation</li> </ul>

**Table 2. Replacement Tests or Modified Protocols to Traditional Animal Studies.** These models are intended to replace animal testing or reduce animal usage in *in vivo* tests in the near term (1-5 years).

Goals/Uses/Benefits	Type	Examples of Current Tools	Examples of New Tools	Example Milestones
<ul style="list-style-type: none"> <li>To reduce, refine, and replace animal testing for those traditional animal studies performed for purposes of risk assessment or labeling</li> </ul>	<ul style="list-style-type: none"> <li>Non-testing computer-aided methods to determine need for a specific study</li> <li><i>In vitro</i> model to replace an animal test</li> <li>Redesigned animal study that maximizes the information gained and results in a reduction in the number of animal studies performed</li> </ul>	Standard animal toxicity guideline tests	QSAR/SAR in lieu of animal testing Alt-LLNA TTC-RSI	<ul style="list-style-type: none"> <li>EPA White Paper on “Use of Structure-Activity Relationship (SAR) Information and Quantitative SAR (QSAR) Modeling for Fulfilling Data Requirements for Antimicrobial Pesticide Chemicals and Informing EPA’s Risk Management Process” in support of proposed rule on data requirements for antimicrobial pesticides. (Docket: 2008-0110 Document 0045)</li> </ul> <p><a href="http://www.regulations.gov/fdmspublic/ContentViewer?objectId=0900006480665444&amp;disposition=attachment&amp;contentType=pdf">http://www.regulations.gov/fdmspublic/ContentViewer?objectId=0900006480665444&amp;disposition=attachment&amp;contentType=pdf</a></p>
		Up and Down Method for Acute Toxicity (LD50) Testing (replaces traditional Acute LD50 Toxicity Test)		<ul style="list-style-type: none"> <li>Adopted</li> </ul>
		Draize rabbit eye test	Non-animal approaches to labeling for eye irritation hazards, e.g., Bovine Corneal Opacity and Permeability,	<ul style="list-style-type: none"> <li>May 2009 Interim Pilot using non-animal assays for labeling antimicrobial cleaning products for ocular irritation/hazard (at <a href="http://www.epa.gov/oppad001">http://www.epa.gov/oppad001</a>)</li> </ul>

			EpiOcular, and Cytosensor Microphysiometer assays	<ul style="list-style-type: none"> <li>• 2010: Pilot data submissions begin. Pilot to be extended for another year</li> </ul>
		Guinea Pig Maximization or Buehler Test	Several <i>in vitro</i> assays for skin sensitization are under evaluation or development that would replace <i>in vivo</i> testing	<ul style="list-style-type: none"> <li>• Currently under evaluation by ICCVAM and test guidelines under development by OECD; the assays are anticipated to be used over the next 1-3 years</li> </ul>
		2-generation reproductive toxicity study Data Requirement: Reproduction and fertility effects (Guideline 870.3800)	Redesigned Extended One-Generation Reproductive Study	<ul style="list-style-type: none"> <li>• Enhanced F1 Tiered Testing Approach undergoing OECD test guidelines development</li> </ul>
		Physiologically Based Pharmacokinetic (PBPK) Models to refine dose selection and animal usage in toxicity studies	Work underway to design PK studies as part of standard toxicity studies to improve dose selection, dose response, and species extrapolations	<ul style="list-style-type: none"> <li>• August 16 - 17, 2007 – Assessing Approaches for the Development of PBPK Models of Pyrethroid Pesticides <a href="http://www.epa.gov/scipoly/sap/meetings/2007/081607_mtg.htm">http://www.epa.gov/scipoly/sap/meetings/2007/081607_mtg.htm</a></li> </ul>
		Toxicogenomics data extracted from traditional animal studies	Application of HTS, toxicogenomics to inform toxicity or disease pathways	<ul style="list-style-type: none"> <li>• 2011 SAP consultation on integrated approaches to the development and interpretation of toxicity pathways using several case studies including conazoles</li> </ul>

**Table 3. Longer Term (5-10 years) Tool Development to Support a Paradigm Shift in Testing and Assessment.**

Goal / Uses/Benefit	Examples of Types of Tools
<ul style="list-style-type: none"> <li>• 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. These tools must be grounded by knowledge of toxicity pathways that are perturbed under realistic exposure conditions.</li> <li>• More accurate and focused risk assessments and risk management</li> <li>• Risk assessments based on understanding of mode of action</li> <li>• Substantial reduced reliance on animal testing</li> <li>• Enhance scale dependent quantification and characterization of exposure for different ecological habitats</li> </ul>	<ul style="list-style-type: none"> <li>• HTS and “omics” methods (genomics, transcriptomics, proteomics,) to inform mode of action and identification of toxicity pathways</li> <li>• Virtual Organ Models (e.g., virtual liver and embryo)</li> <li>• System biology approaches</li> <li>• New generation of environmental modeling tools for fate, transport and exposure</li> <li>• Well-characterized biomarkers of effect and exposure</li> <li>• GUS software and related models (example: Spatially explicit PRZM model)</li> </ul>