EPA
United States
Environmental Protection
Agency

National Pesticide Program

Moving Toward a New Toxicology Testing Paradigm: Meeting Common Needs

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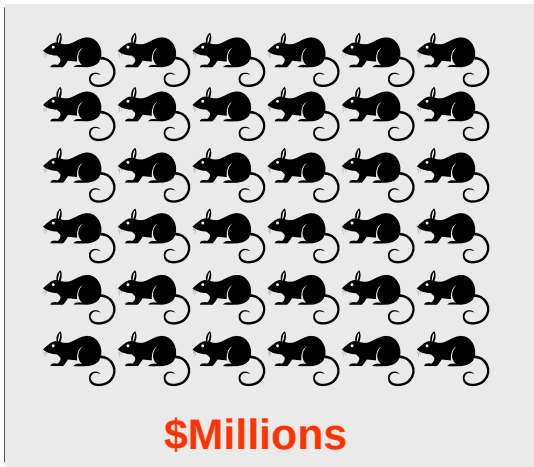
Office of Pesticide Programs
PPDC Meeting, May 21, 2008

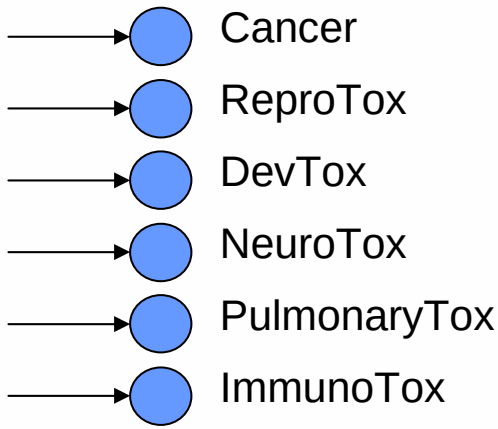
United States Environmental Protection Agency

- Topics
  - 2007 NAS Report on Future of Toxicity Testing
  - OPP's Vision/Activities for an Integrative Testing Paradigm
  - Transitioning New Science into Regulatory Practice
  - PPDC Workgroup Proposal

Current Toxicology Testing Paradigm

in vivo testing



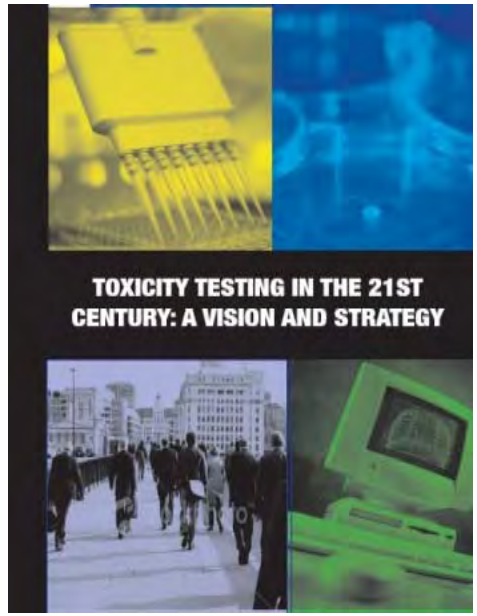


Generates in vivo animal data for all possible outcomes to determine which of all possible effects are relevant.

Why Change the Current Paradigm?

- Improve ability to carry out mission of protecting public health & the environment
- Increase efficiency& reliability in assessing & managing risks appropriately by focusing the regulated community, government, & interested parties on a pesticide's most likely hazards of concern for a given exposure situation
- Eliminate need for extensive animal testing (3Rs)
- Reduce cost & time in data development, review and processing

2007 NAS Report Toxicity Testing in the 21st Century



Sponsored by US EPA

Broader coverage of chemicals, end points, life stages

Use fewer animals; least suffering for those used

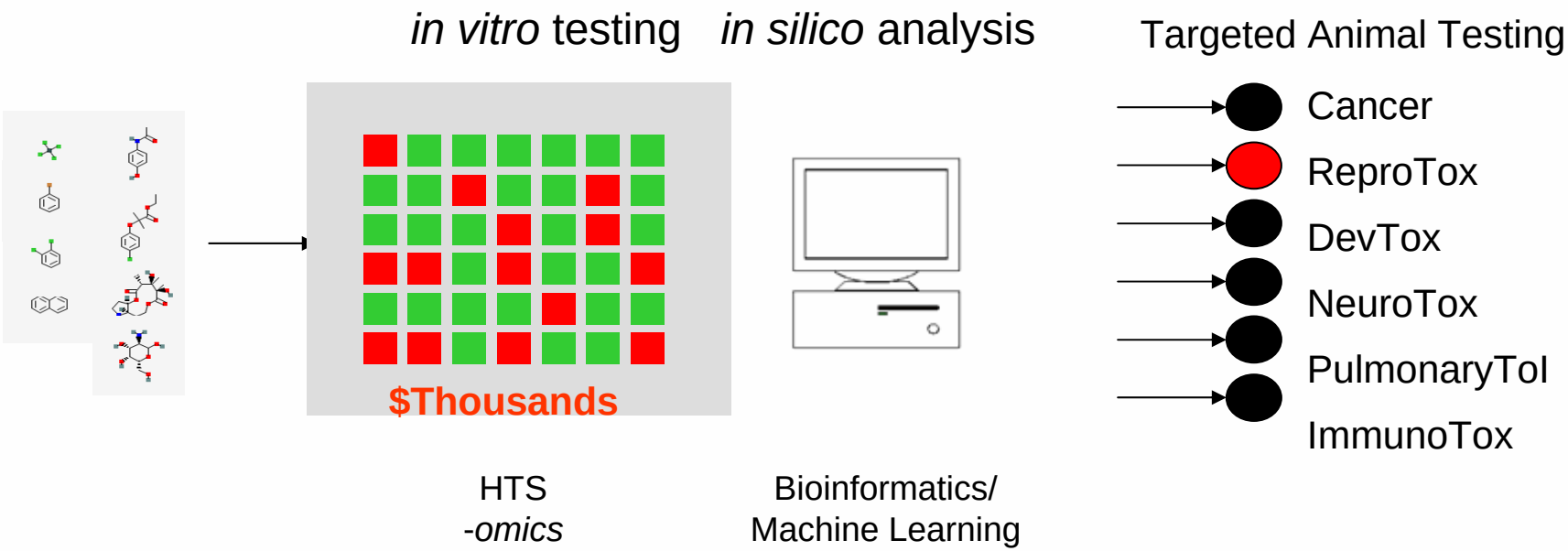
Consider New Technologies

Reduce cost & time of testing, increase efficiency & flexibility

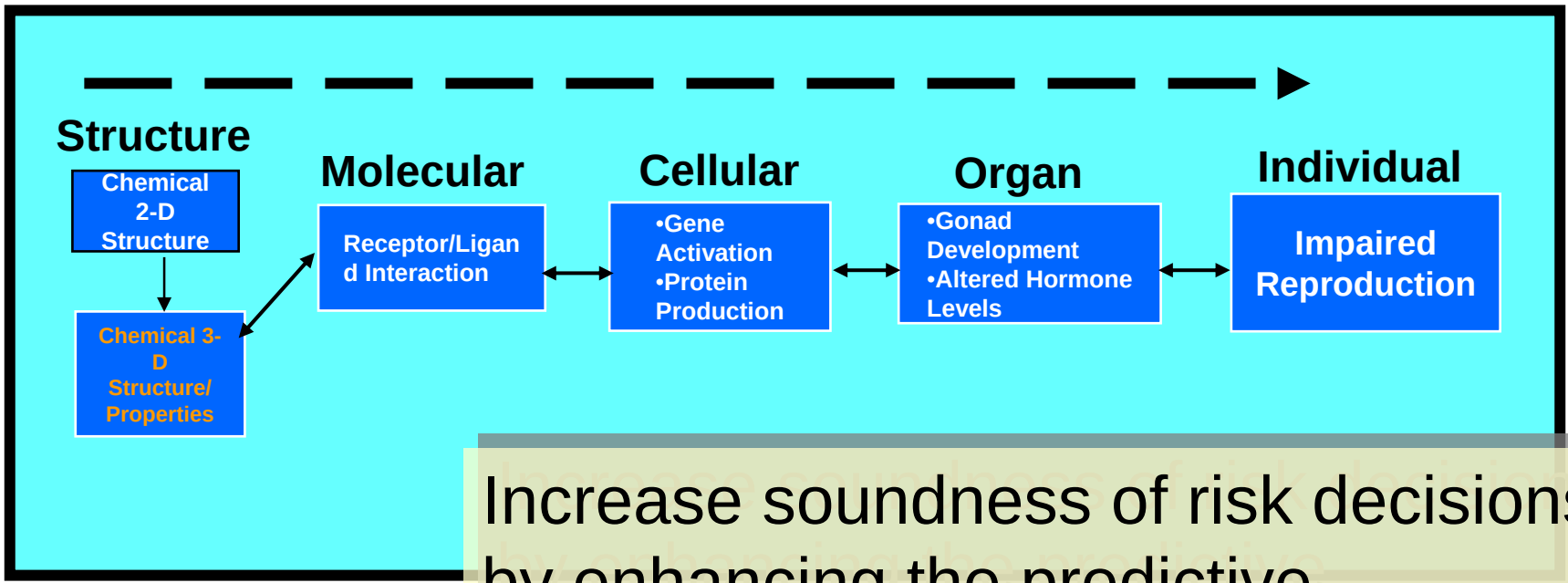
More robust scientific basis by providing mode of action & dosimetry information

2007 NAS Report
Transforming Toxicology

Combine in vitro testing & computational models to make predictions for In vivo outcomes & guide more targeted animal testing



Grounding the Predictions

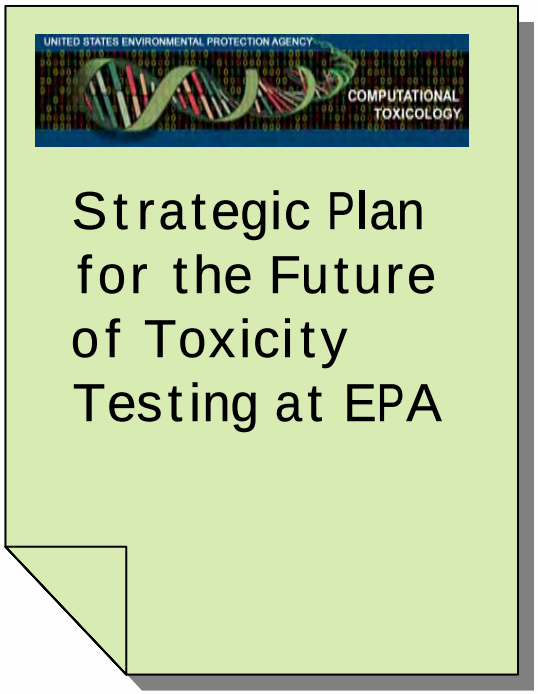


Increase soundness of risk decisions by enhancing the predictive understanding of toxicity pathways

NAS: Toxicity Testing Strategies

In Vivo	Tiered In Vivo	In Vitro & In Vivo	In Vitro
Animal Biology	Animal	Primarily Human	Primarily Human
High Doses	High	Broad Range	Broad Range
Low Throughput	Improved	High & Medium	High
Expensive	Less	Less	Less
Time Consuming	Less	Less	Less
Large Animal Usage	Fewer	Substantially fewer	Virtually no animal usage
Based on Apical Endpoints	Apical Endpoints	Critical Cellular Perturbations	Critical Cellular Perturbations
	Some Screening (in vitro, in silico)	Screening (in vitro, in silico) & studies focused on mechanism	In vitro & in silico

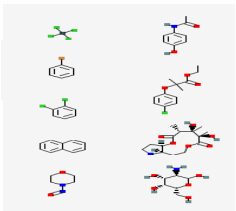
EPA's Future of Toxicity Testing Workgroup



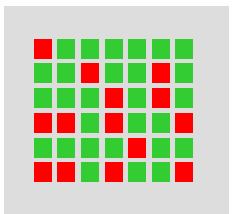
In response to the release of the NRC reports, EPA established & charged a cross-Agency work group, the Future of Toxicity Testing Workgroup (FTTW), under the auspices of the Science Policy Council. To develop an Agency Strategy that will serve as a blueprint for ensuring a leadership role for EPA in pursuing the directions and recommendations presented in the NRC report

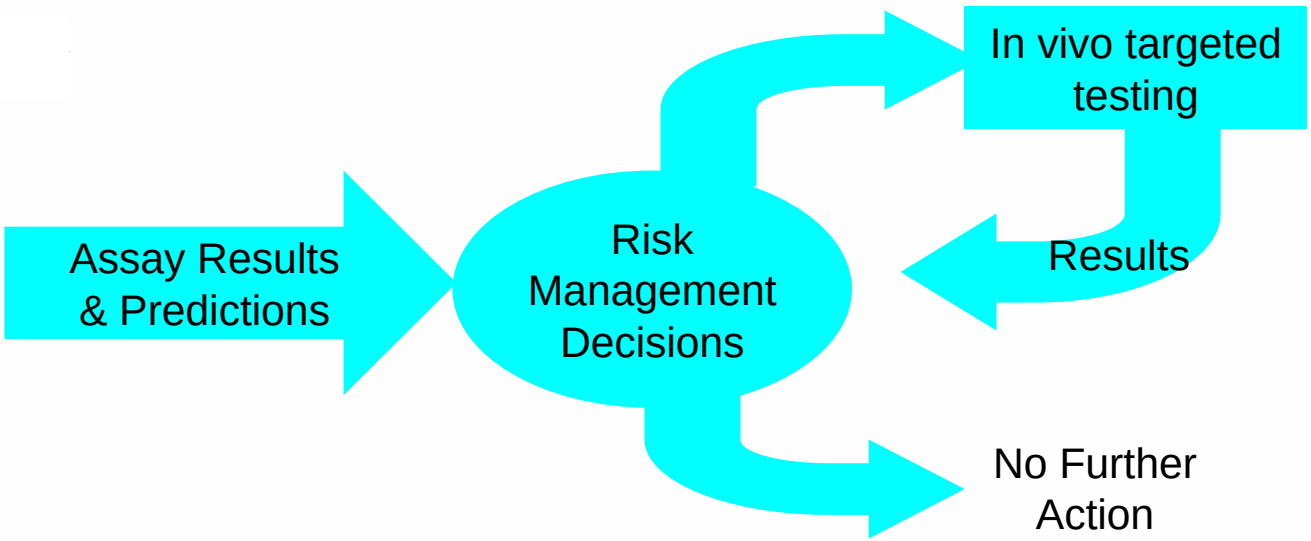
NAS Report Reflects OPP's vision

To move away from in vivo testing for "every possible adverse outcome" to a hypothesis-driven testing paradigm that uses existing data, computer models & in vitro data combined with estimates of exposure to better screen & evaluate chemicals by enhanced understanding of toxicity pathways



Exposure + Chemical Characterization + Screening Assay Suite





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Transforming Toxicology Testing

Will require a sustained effort over many years!

Timeline

Establish Data Storage & Management Systems, Elucidate Toxicity Pathways,

Develop & evaluate suite of High & Medium through put assays

Gain experience though testing in parallel with traditional assays

Progress toward a shift in paradigm

Current OPP Activities

- Promote use of Existing Agency's QSAR & Expert System Tools, e.g.,
  - Analogs & Categories
  - EPI Suite
  - ECO SAR
  - Oncologic®

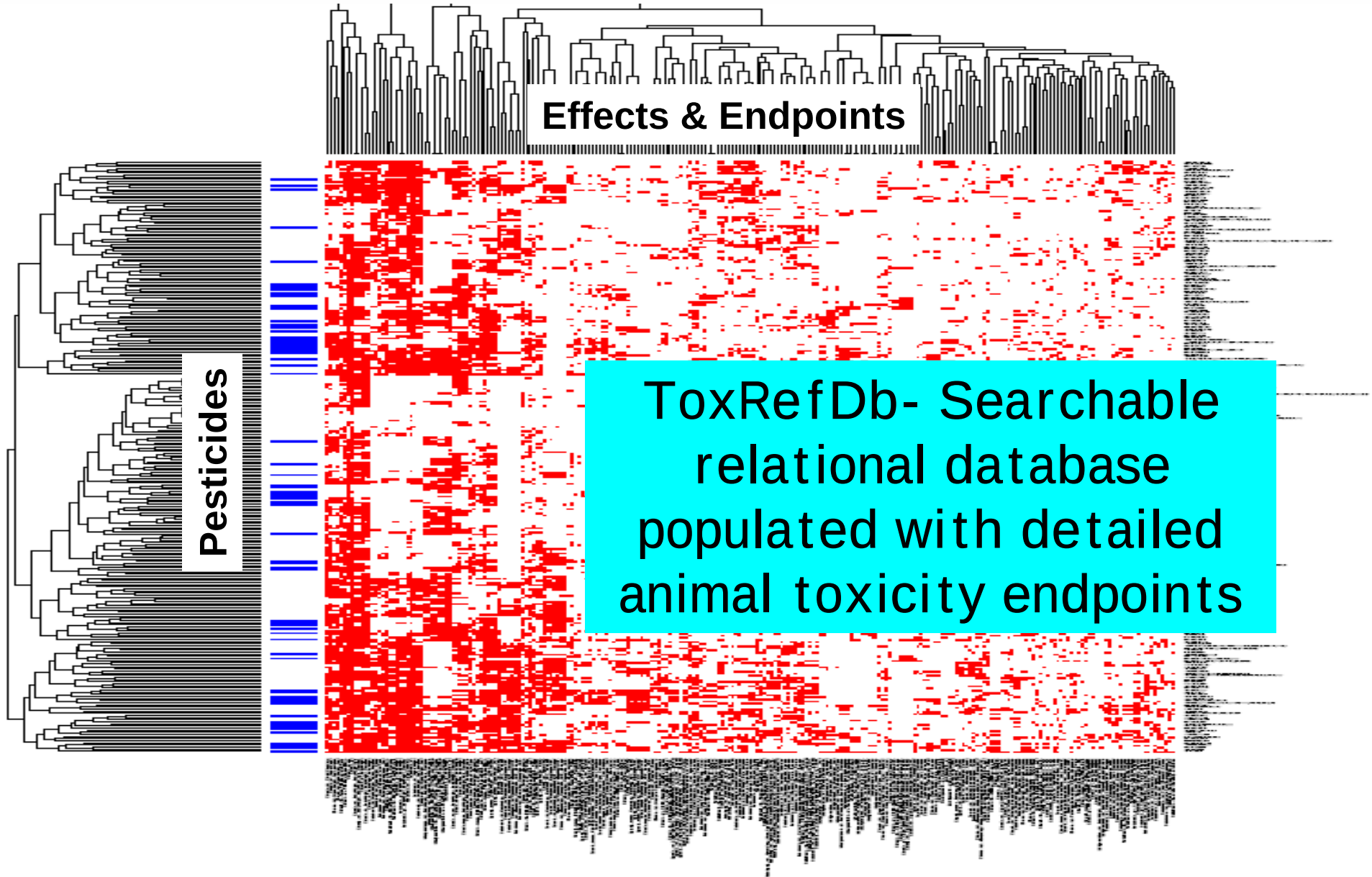
OECD QSAR Application Tool Box

Progress toward a shift in paradigm

Current OPP Activities

- Incorporating “Lessons Learned” by utilizing retrospective database analysis
  - Make existing animal testing more efficient, reliable & responsive to our risk assessment/management needs
  - Guide & support changes in data requirements
  - Identify & prioritize key issues associated with current toxicity tests
  - Enhance interpretation of data from current toxicity tests
  - Potential utility in toxicity predictions

New Knowledge-Base Tool
Capturing the Pesticide Animal Toxicity Data



Progress toward a shift in paradigm

OPP Retrospective Analyses

- Dog studies (completed)
  - USEPA, Length of Dog Toxicity Study(ies) that is Appropriate for Chronic RfD Determinations of Pesticide Chemicals 2006.
- Prenatal studies (ongoing)
  - rat versus rabbit - added value of additional test species
- Rodent Cancer Bioassay (ongoing)
  - Added value of the mouse cancer bioassay
- Reproductive studies (ongoing)
  - SOT abstract (Reeves et al., 2008); Added value of the F2 generation from rat reproductive toxicity studies

Progress toward a shift in paradigm

Near Term OPP Activities

- Next Generation 158 Data Requirements
  - Enhanced F1 Tiered Testing Approach
    - Accepting case-by-case studies under the Enhanced F1 Tiered Testing Approach
    - Proposed rule - 2010
    - Final rule - 2012
  - Plan to include SAR/QSAR in upcoming proposed data requirements for Antimicrobial Pesticides (158W).

Progress toward a shift in paradigm

ORD Research

- Knowledge-Bases
  - Mammalian toxicity (ToxRefDb)
  - Ecotoxicity (ECOTOX)
  - Metabolic maps (Metapath)
- Predictive Models
  - Adverse health effects based on biological activity profiling (ToxCast)
  - Degradates, Metabolites (Metabolic Simulator)
  - New Assays
    - In vitro, nonmammalian

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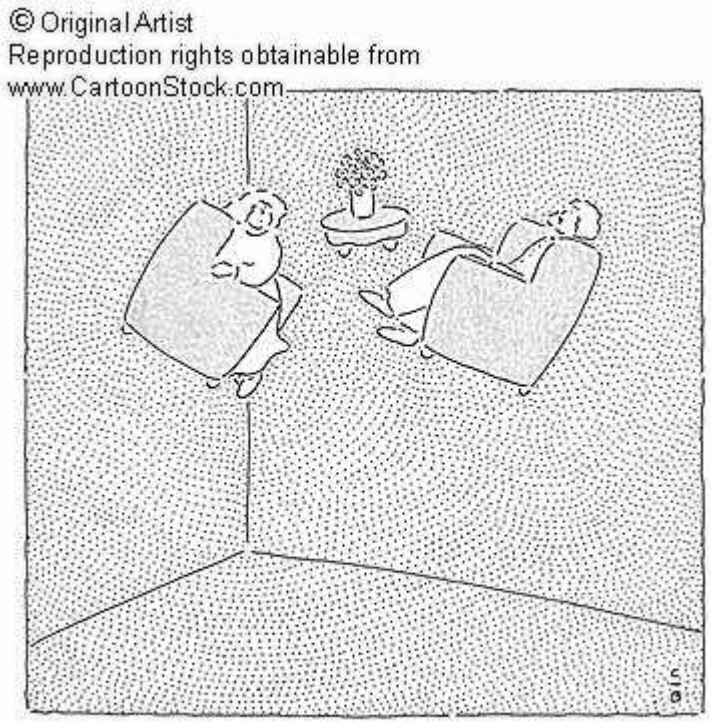
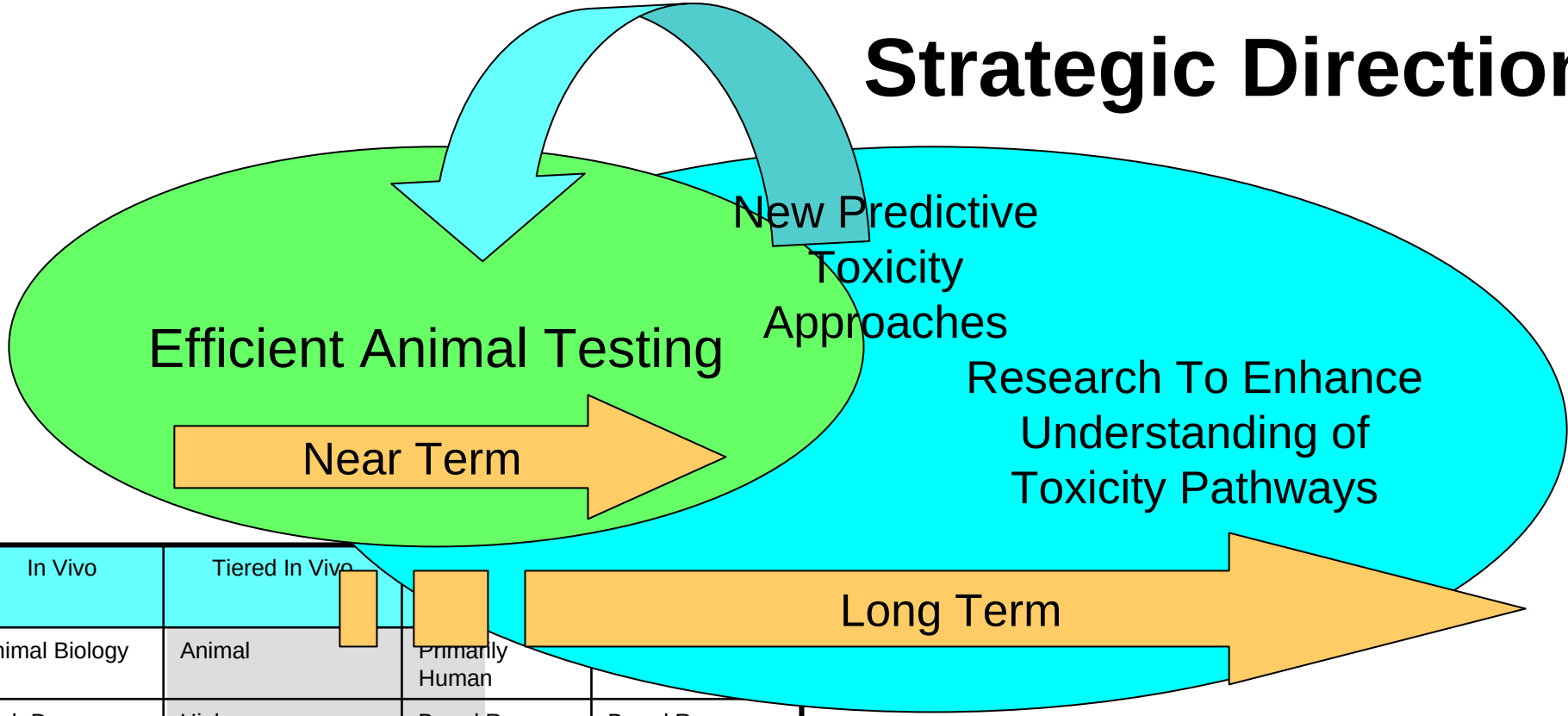
Transitioning New Science into Regulatory Application



"I'm in a period of transition right now."

Strategic Direction



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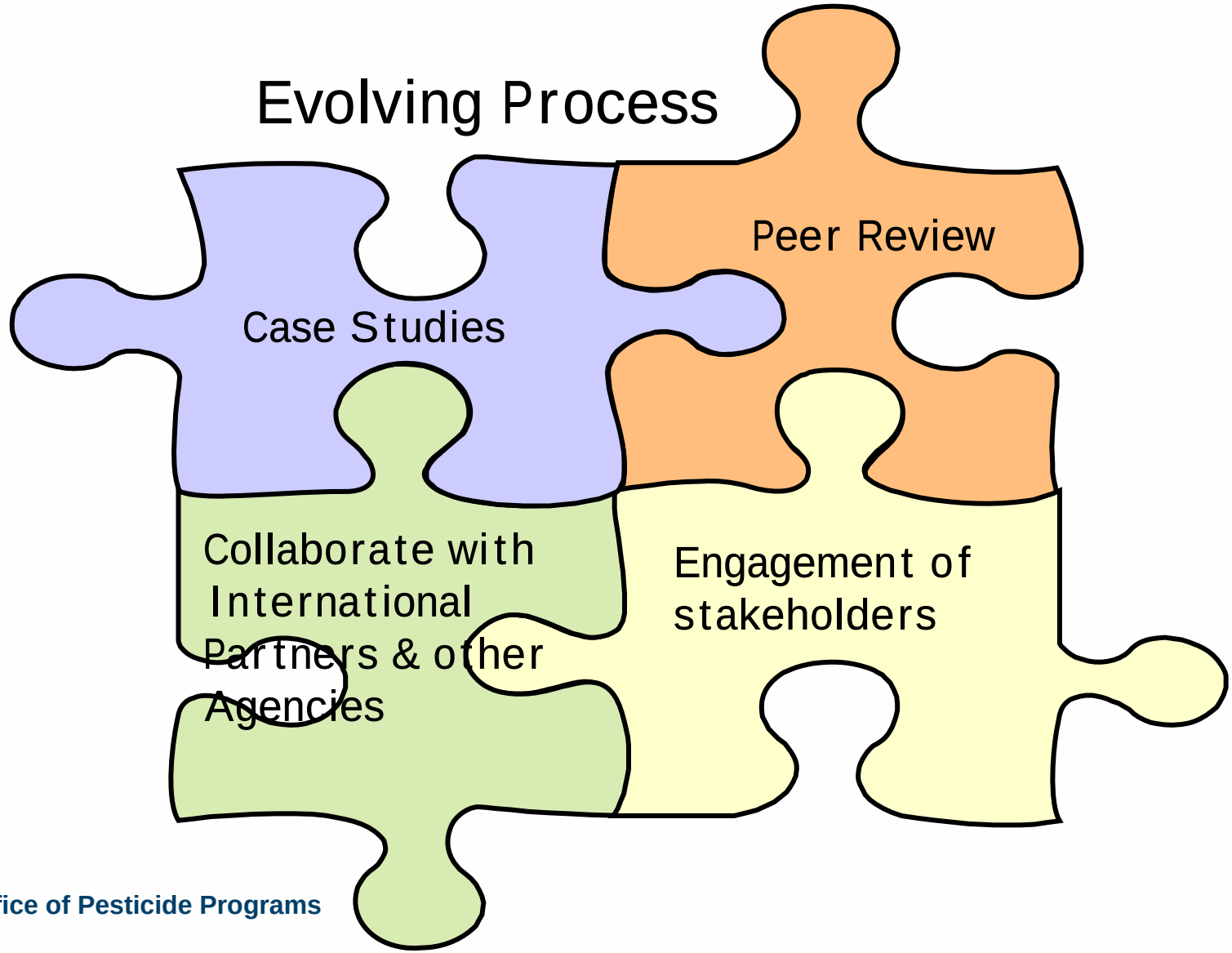
NCCT TOXCAST PROGRAM - 320 Chemicals

How do we get there?



Progress toward a shift in paradigm

Partnering with international agencies on technology-based, hypothesis-driven effort to build capacity to prioritize, screen & evaluate chemicals

- Washington D.C. OECD Workshop Dec 2007 hosted by OPPTS
  - Purpose: to discuss integrated approaches & to review case studies for regulatory hazard endpoints.
  - Overall endorsement of integrated testing
    - Advancing QSAR Modeling
    - Advancing the Category Approach

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Moving Forward

- Proposal to establish a PPDC Workgroup on New Toxicology Testing Paradigm
  - Purpose
    - Improve understanding of the perspectives of all stakeholders regarding new testing paradigm
    - Ensure input on key science products
    - Develop common understanding for appropriate use of new science/tools
    - Provide advice to EPA through PPDC (including how to best communicate this complex science to the general public)