



National Pesticide Program Integrative Toxicology Testing Strategy



PPDC Meeting, October 2005

The Testing and Risk Assessment Challenges

Given finite resources and time to generate and evaluate data,

When confronted with large numbers of chemicals to assess, which chemicals to evaluate first for a given adverse outcome?

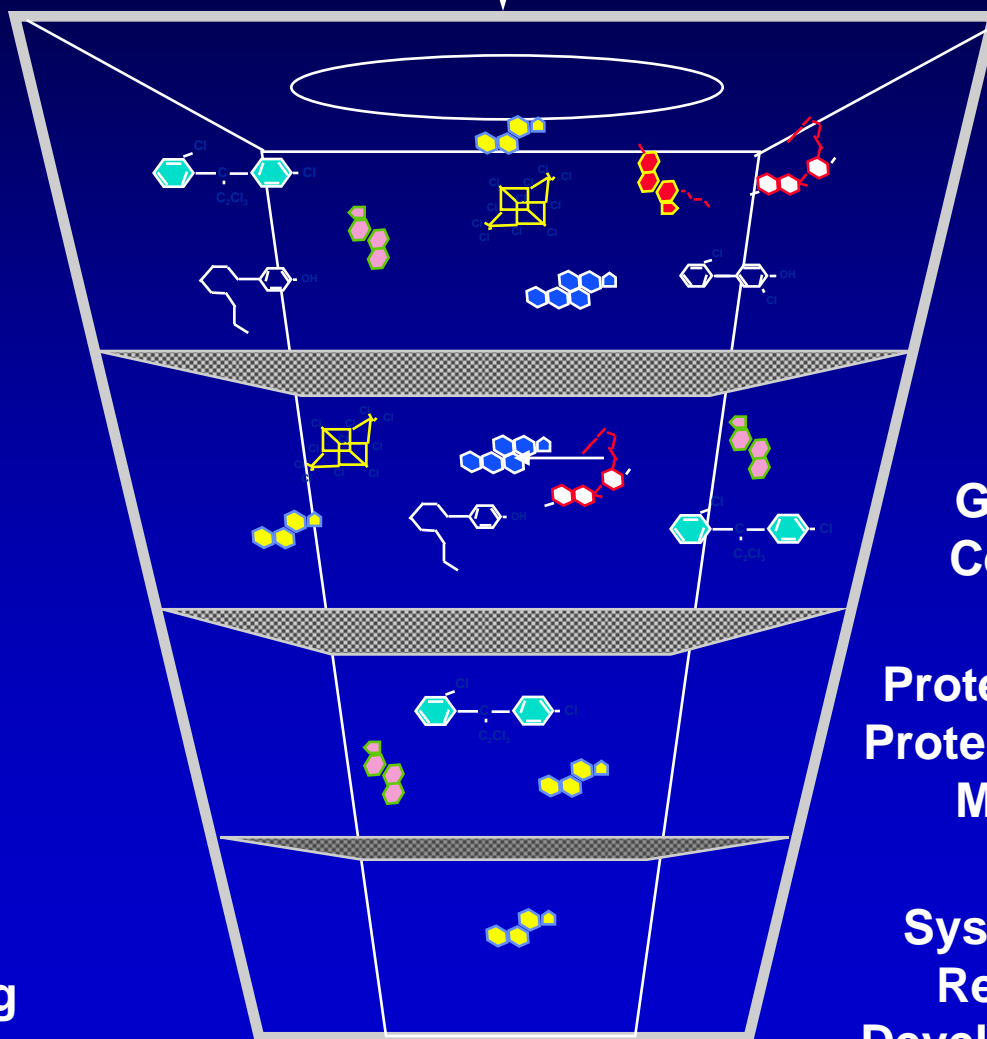
When confronted with many potential adverse outcomes for a given chemical, which outcomes are more likely?

Challenges faced by other EPA programs, FDA, NAS, and OECD/EU member countries and the regulated community.

Identifying Toxicological Potential

Non-Animal
Ranking &
Prioritization;
Screening

Chemical
Inventories



Partitioning;
Electrophilicity;
Redox Cycling;
Receptor Binding

Gene Activation;
Cellular Function

Protein Inhibition;
Protein Production;
Metabolism

Systemic effects,
Reproduction,
Development, Cancer

Existing Data and Models

Efficient
Animal Testing

The Testing and Assessment Challenges

NAS/NRC: Tiered Testing/Assessment

EPA: Computational Toxicology Program

FDA/CDER: Toxicogenomics in Drug Development

ILSI/HESI: Genomics in Risk Assessment

HESI/ASCA: Agricultural Chemicals

OECD: Integrative Testing/Assessment

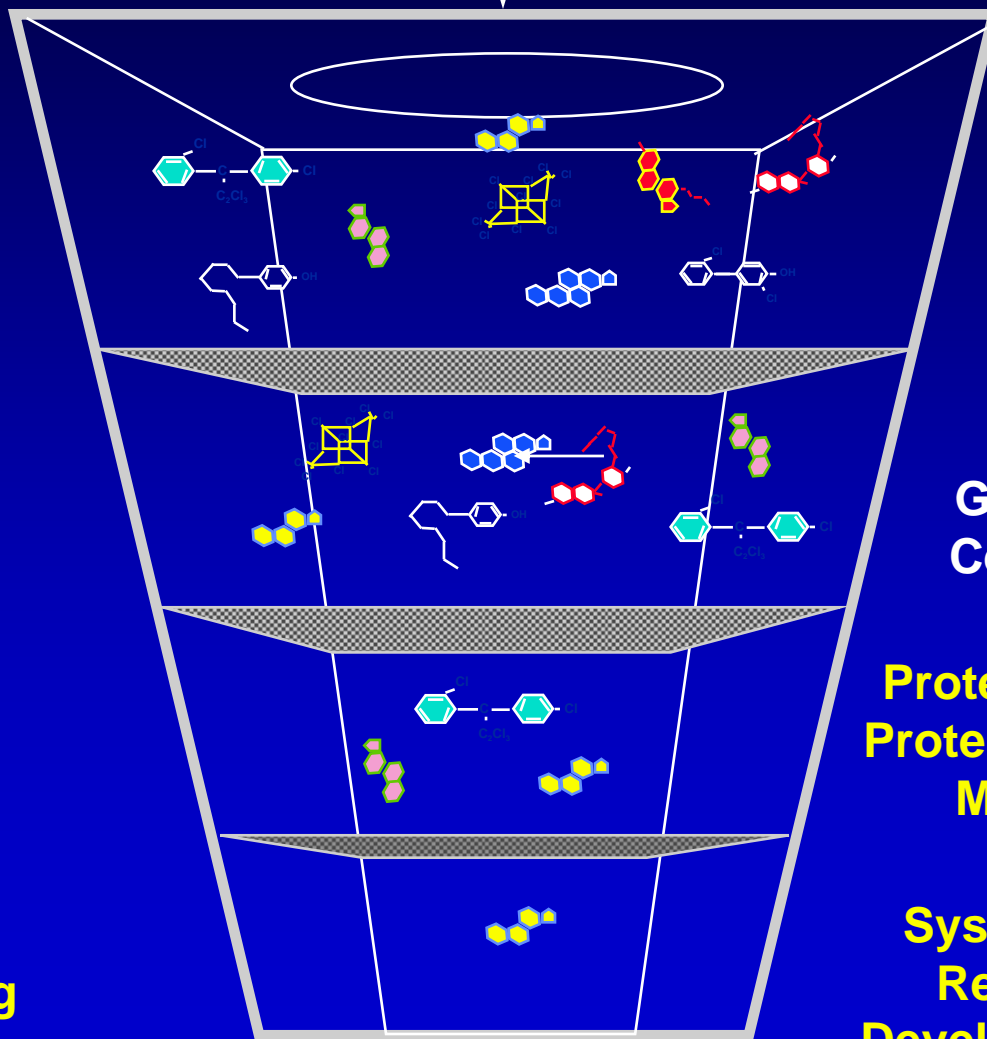
PRINCIPLES/GOALS OF NEXT GENERATION TOXICITY TESTING PARADIGM

- Sufficient, credible amount of data for assessment and management decisions; not an overwhelming amount of data.
- Reduced cost & time in data development.
- Reduced cost (FTE & \$) & time for EPA in reviewing and processing data.
- Reduced use of animal testing.
- Take full advantage in an expeditious manner of advances in science and technology.
- Credible peer-reviewed science for sound decisions.
- Clarity of data requirements for all interested stakeholders and consistent application.
- Transparency of transition process with full engagement of all interested parties.

Identifying Toxicological Potential

In silico and *In vitro* & Prioritization; Screening

Pesticide Inventories



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ILSI



International
Life Sciences
INSTITUTE

***ILSI- Health & Environmental
Sciences Institute's Tiered
Toxicology Testing Proposal
for Pesticide Chemicals***

**Technical Committee on
Agricultural Chemical Safety
Assessment (ACSA)**

June 2000-2005



Multi-Sector & International Participation

- **Academia**

- Imperial College London, Johns Hopkins University, Medical College of Wisconsin, Michigan State University, Mississippi State University, Università di Padua (Italy), University of California Riverside, University of Nottingham (UK), University of Southampton (UK)

- **Government**

- US--EPA (OPP, ORD)
- **International Government** -European Commission, European Food Safety Authority, German Federal Institute for Risk Assessment, Health Canada, OECD, Dutch RIVM

- **Agchem/chemical companies**

- BASF, Bayer CropScience, Dow AgroSciences, DuPont Crop Protection, Monsanto, Syngenta



HESI Technical Committee on Agricultural Chemical Safety Assessment (ACSA)

- Committee Objective
 - Reach consensus on a scientifically credible & viable approach for assessing the safety of pesticides more efficiently, with fewer animals, & with fewer artifacts &
- April 2001 Workshop
 - Recommendation- development of a “Tiered Testing Scheme” that provides assurance that a pesticide can be used without damaging human health & takes into account the toxicological properties & use pattern of the chemicals
- 3 Task Forces Established
 - Absorption, Distribution, Metabolism, Elimination; Systemic Toxicity; Life Stages

Charge to Task Forces: Tier-Testing Approach

- Introduce greater flexibility
- Science should drive the testing strategy
- Emphasize the importance of reducing & refining animal usage
- Ensure evaluation of all relevant toxicity parameters & identify a hierarchy of study types
- Integrate testing, in particular more useful metabolic/ kinetic
- Incorporate improved understanding of exposure

ASCA Project

- White papers posted on HESI web site
 - [http://hesi.ilsil.org/publications/pubsl
ist.cfm?publicationid=578](http://hesi.ilsil.org/publications/pubsl
ist.cfm?publicationid=578)
- To be published as a special issue of *Critical Reviews in Toxicology*



View on ACSA Proposal

Unresolved Issues

- Carcinogenicity Testing
- Triggers/criteria Used in Tiered Testing
- Consideration of Exposure
- Case Studies - Prospective Analysis

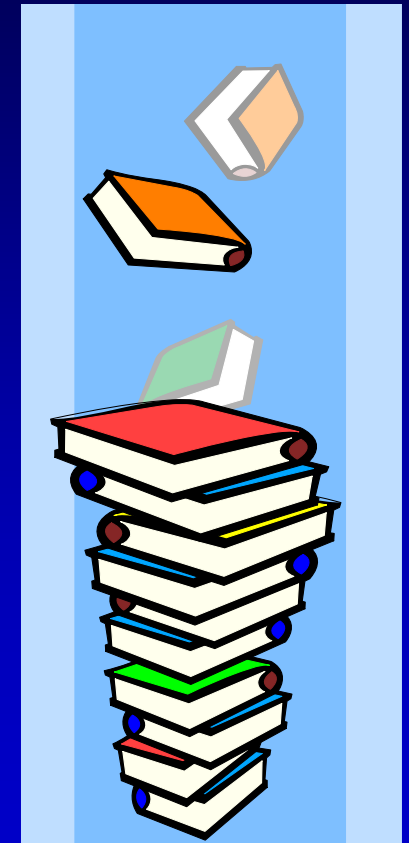


ASCA Proposal: Important Steps

- **Scientific Documentation**
 - **Feb. 05 FIFRA SAP Review: Comparison of results of dog studies on pesticides from 1-2 year studies with studies of shorter duration**
 - Generally supportive ---several major recommendations
 - Analysis of additional pesticides including those where dog studies were not used to set the RfD
 - Need to ensure all chemical classes represented
 - Harmonization at international work shop

ASCA Proposal: Important Steps

- Scientific Documentation
 - Ongoing work on other retrospective analyses
 - Rodent cancer bioassays
 - 1 generation versus 2 generation reproductive effects
 - Rat developmental neurotoxicity study



ACSA Proposal: Important Steps

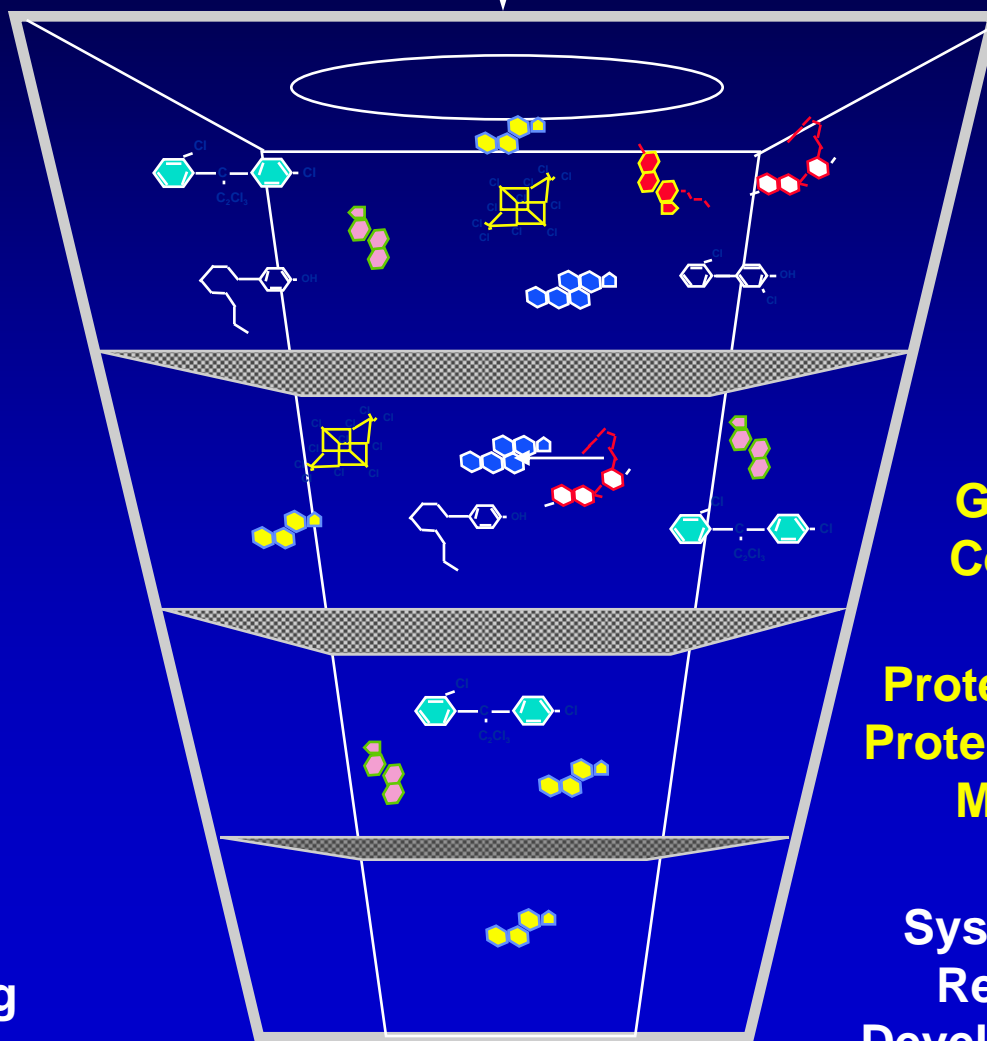
Harmonization and Consensus Building

- Work in several venues to gain international harmonization
 - Jan & Jun 05 OECD meetings
 - Nov 05 Intl HESI workshop/panel discussion)
- July training session on technical ILSI proposals (included CAL EPA & Health Canada)
- Started outreach with Stakeholders
 - May 158 workshop

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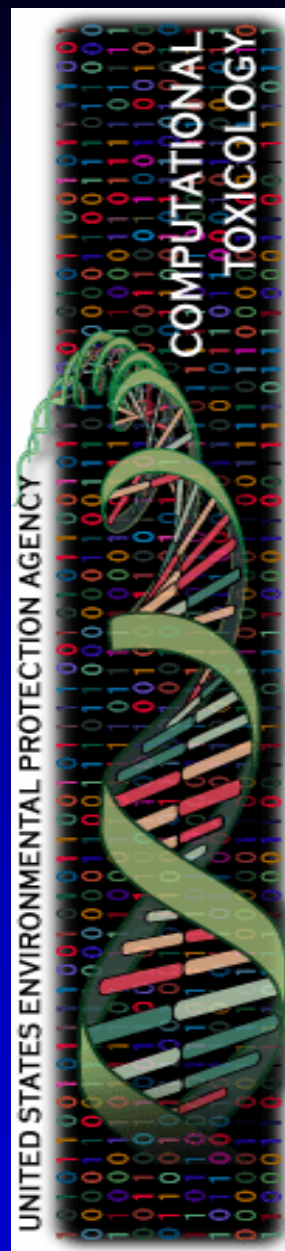
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EPA's Computational Toxicology Program

Technology-based, hypothesis-driven effort to increase the soundness of risk assessment decisions build capacity to prioritize, screen & evaluate chemicals by enhancing the predictive understanding of toxicity pathways

www.epa.gov/comptox



Integrative Testing and Assessments

- In summary, it will be critical to draw on several relevant activities
 - ILSI/HESI Proposal
 - EPA's Computational Toxicology Program
 - NAS/NCR: Tiered Testing/Assessment
 - OECD Integrative Testing and Assessment

Evolution of Integrative Pesticide Testing Scheme

Part 158
Goal: Establish Base Data Requirements
1984

Scientific Advances
Case-By-Case Application
1984 - 2005

Part 158 Update
Goal: Modify Regulations to Reflect Current Practice
Benefits: Clarity, Transparency, Consistency, and Good Foundation For Future Updates
1996 >>>>>

Scientific Advances
Enhanced Tiered Testing Approach
Goal: Refined & More Efficient Use of Current Data
Builds on current, mature animal & lab-based testing regime
• Case-by-case application
2002 >>>>>

Part 158 Update

Scientific Advances
Computational Toxicology/Genomics
Goal: Decreased cost/time/animal testing:
• Move from traditional animal & lab-based regime to In silico and in vitro-based paradigm
• Case-by-case application
2004 >>>>>

Part 158 Update

Evolution to Integrative Assessment

PARADIGM SHIFTS

Current Testing & Assess

Enhanced Tiered-Testing Approach

Computational Toxicology and Integrative Approach

SCOPE

Conventional Pesticides

Agricultural Pesticides
Human Health (ILSI)

Inert Ingredients
Anti-microbial & Conventional Pesticides

SCIENCE COMM. INVOLVEMENT

Range of External Peer review

Papers Awaiting Publication

Global Discussions; Workshops; Research

PROJECT STATUS

Test/Assess. Guidelines

Scientific Concepts Ready for Broader Discussion

NAS Report 2005/7

Scientific Tools & Concepts Under Develop't

STAKEHOLDER INVOLVEMENT

Case-by-Case Public Workshops
Intl Harmonization

[ILSI Workgroup Initial Outreach](#)

[PPDC Updates](#)