

US EPA ARCHIVE DOCUMENT



# 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?**

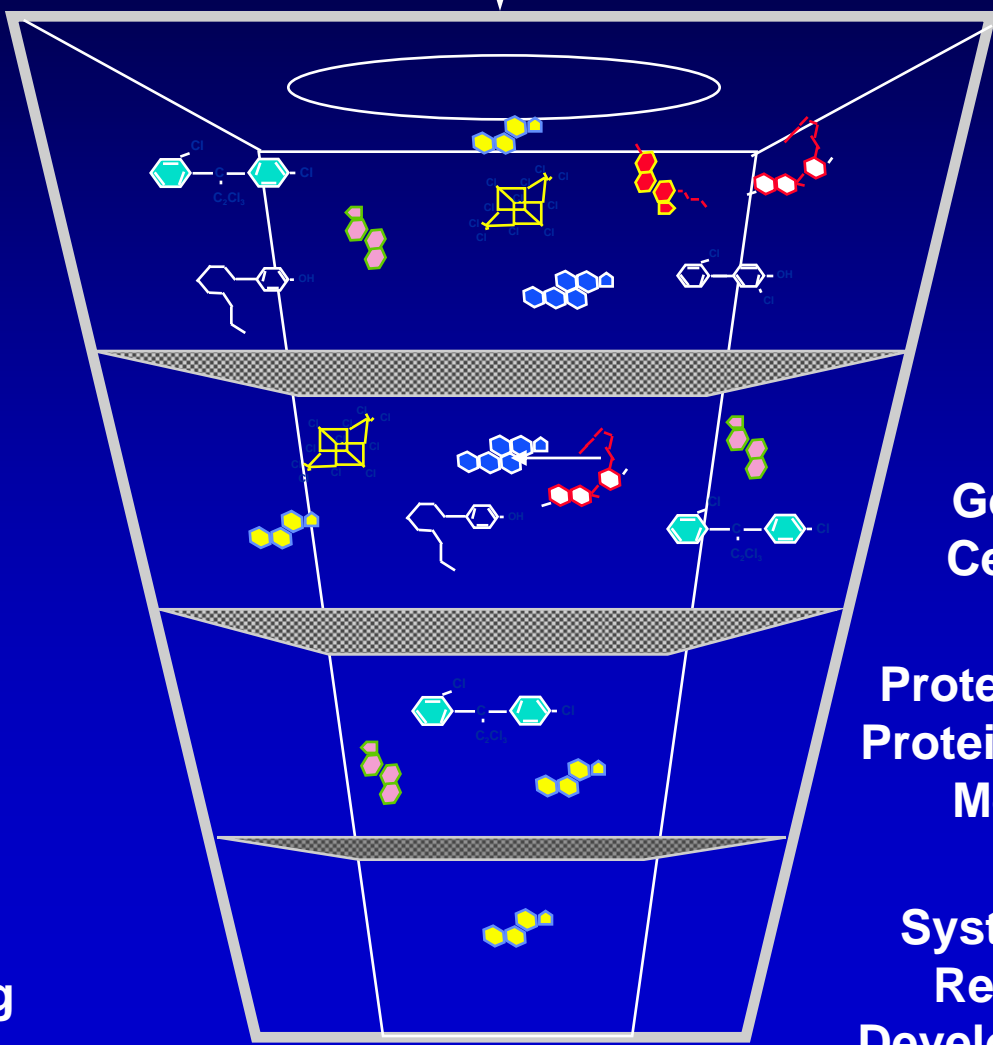
*Challenges faced by other EPA programs, FDA, NAS, and OECD/EU member countries and the regulated community.*

# Identifying Toxicological Potential

US EPA ARCHIVE DOCUMENT

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

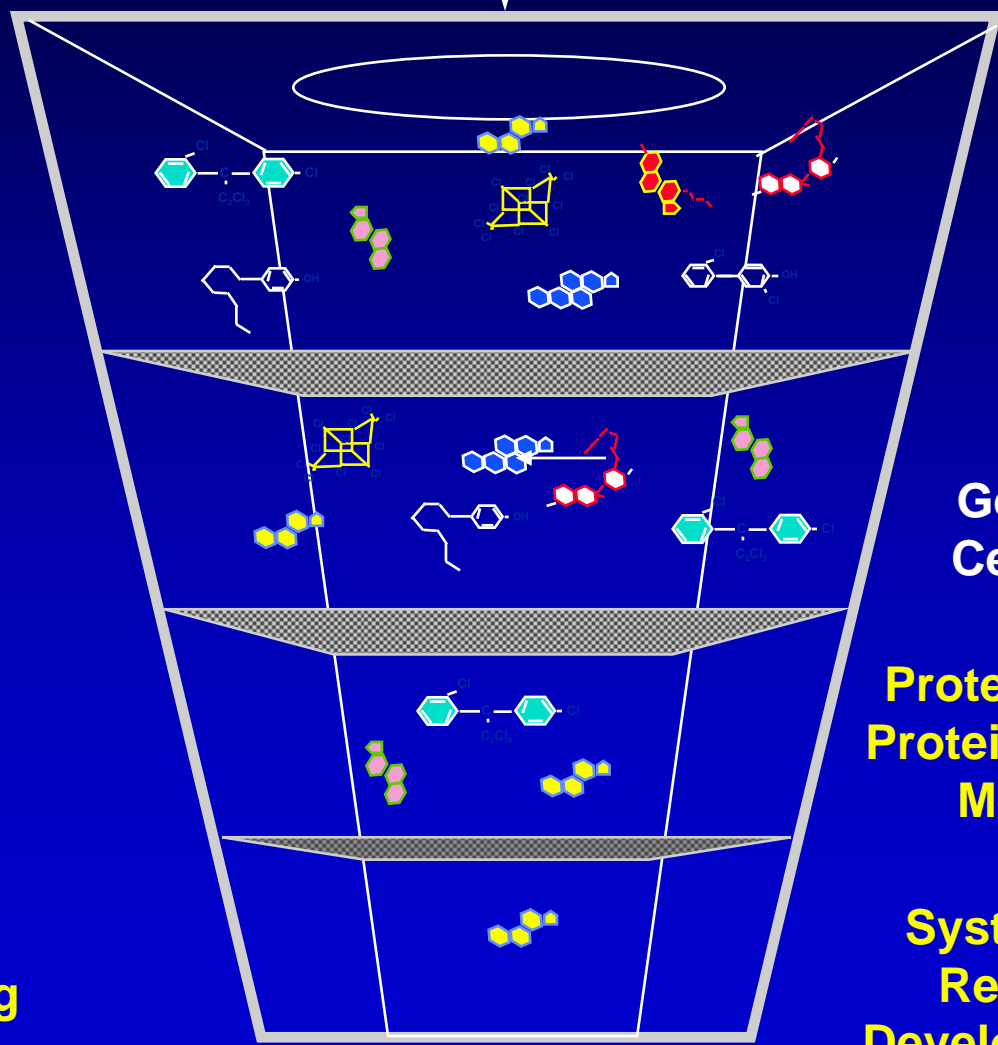
- Sufficient, credible amount of data for assessment and management decisions; not an overwhelming amount of data.
- Reduced cost & time in data development.
- Reduced cost (FTE & \$) & time for EPA in reviewing and processing data.
- Reduced use of animal testing.
- Take full advantage in an expeditious 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

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*In silico* and *In vitro* & Prioritization; Screening

Pesticide Inventories



Partitioning;  
Electrophilicity;  
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Existing Data and Models

Efficient Animal Testing

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

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- 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/pubslst.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

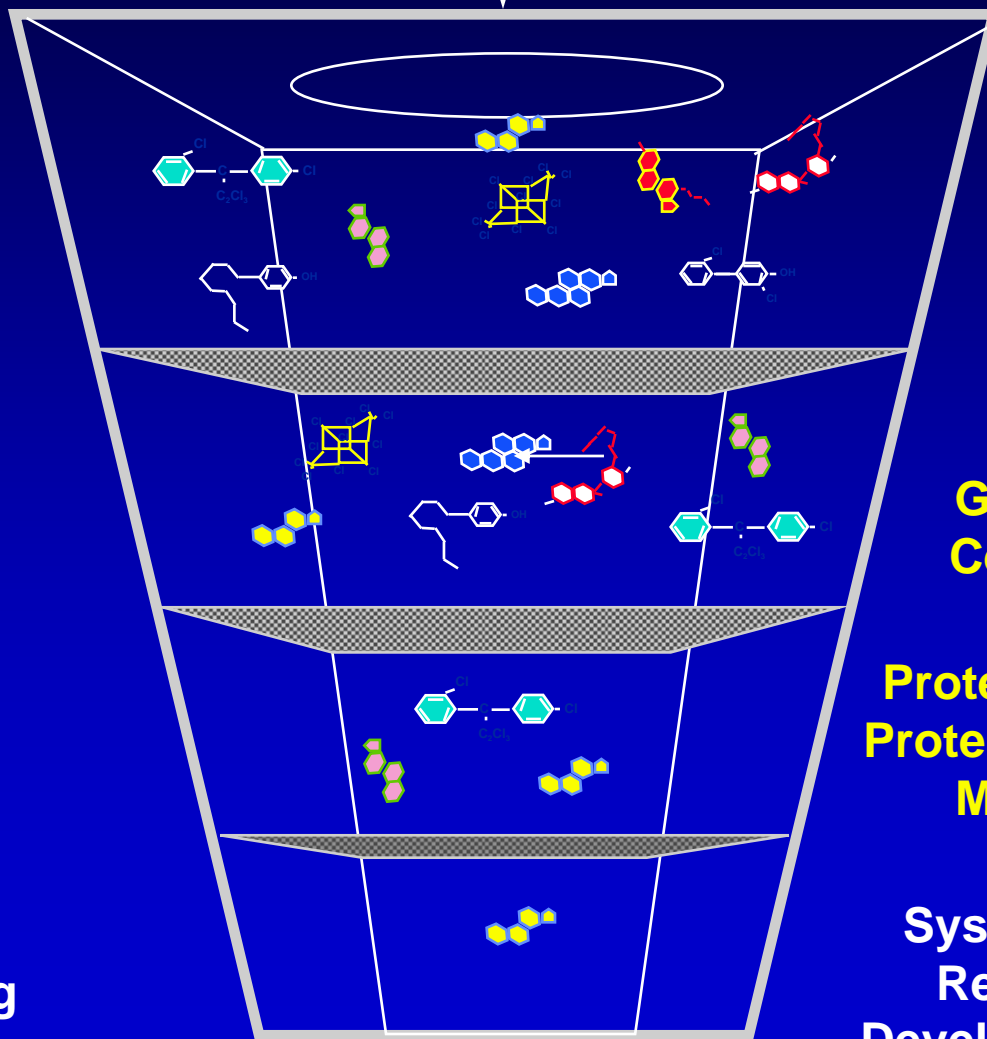


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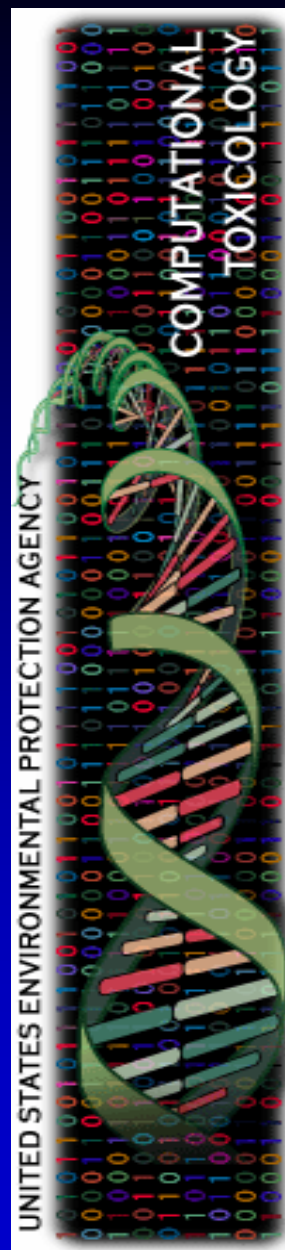
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## EPA's Computational Toxicology Program

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](http://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](#)