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Next Generation of Toxicology Testing Perspective on ACSA



Topics

- Challenges in Pesticide Health Risk Assessment
- Why Reconsider Current Data Requirements
- New ACSA Tiered Testing Approach
- Other Relevant Activities
- Next Steps

Programmatic Challenge

Areas of Increasing Emphasis

- Life stage sensitivities
- Mechanisms of toxicity
- Cumulative risk of common mechanism chemicals
- Risks associated with single or intermittent exposures
- Endocrine disruption



Programmatic Challenge

Conventional Food Use Pesticide Assessment

\$15 to 20M to generate full battery of tests

\$1M for the Agency to assess test results

5 to 7 years to license prior to PRIA

The Challenge of the Current Paradigm

Identifying lower risk active ingredients

Backlog in assessing inert ingredients

Difficulty in prioritizing scarce assessment resources

PRINCIPLES & GOALS OF NEXT GENERATION TOXICOLOGY TESTING PARADIGM

- **Sufficient, credible amount of data for assessment & management decisions; not an overwhelming amount of data**
- **Reduced cost & time in data development**
- **Reduced cost (FTE & \$) & time for EPA in reviewing & processing data**
- **Reduced use of animal testing**
- **Take full advantage of existing knowledge of pesticide database (~340 pesticide actives)**

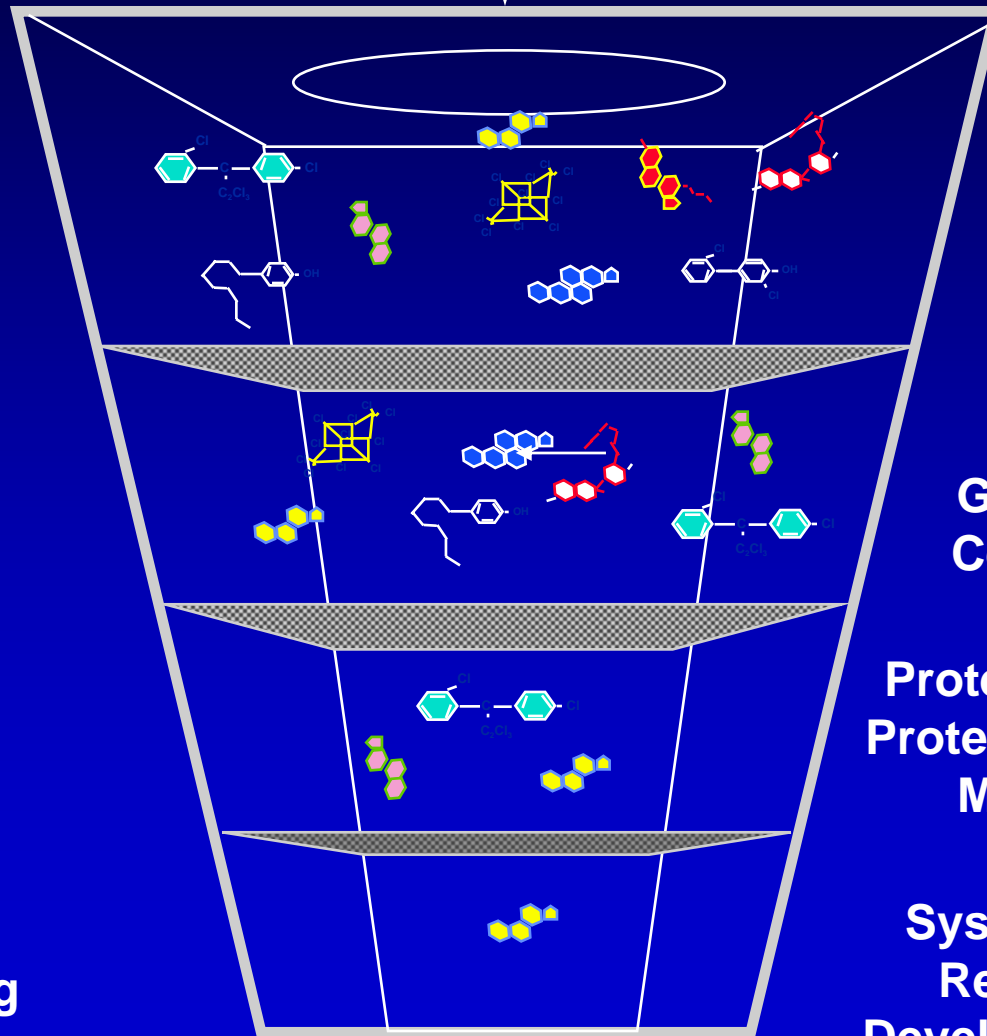
PRINCIPLES & GOALS OF NEXT GENERATION TOXICITY TESTING PARADIGM

- **Take full advantage of advances in science & technology in an expeditious manner**
- **Credible peer-reviewed science for sound decisions**
- **Clarity of data requirements for all interested stakeholders & consistent application**
- **Transparency of transition process with full engagement of all interested parties**

Goal: Identifying Toxicological Potential

Non-Animal
Ranking &
Prioritization;
Screening

Chemical Inventories (pesticide actives, inertes,
antimicrobials, high production volume
chemicals, etc)



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

Next Generation of Data Requirements

Relevant Activities

- Health & Environmental Sciences Institute (HESI) Tiered Toxicology Testing Proposal for Agricultural Chemicals
- USEPA's Computation Toxicology Program
- National Academy of Sciences project on Toxicity Testing & Assessment sponsored by the USEPA
- OECD Integrative Testing & Assessment

HESI Project on Agricultural Chemical Safety Assessment

- Important Milestone & Spring Board to Next Generation of Data Requirements
 - incorporates existing knowledge
 - reduces/refines/replaces animal usage
 - optimizes study design & allows flexibility
 - better integration of metabolic & kinetic data in the safety assessment process
 - takes exposure characteristics into account, including intermittent exposures & different routes of exposure



HESI Project on Agricultural Chemical Safety Assessment

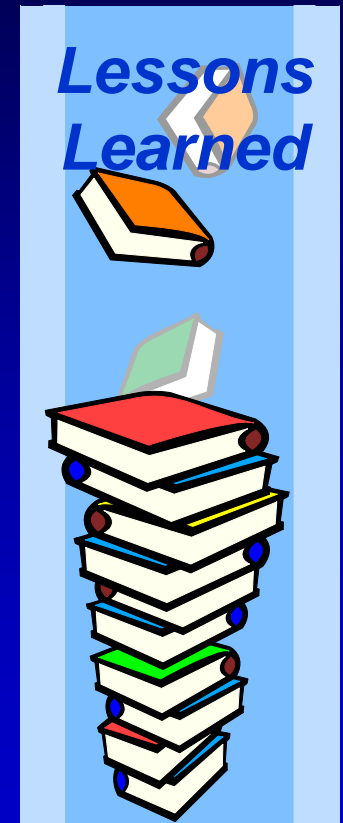
Unresolved Issues

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



Next Generation Toxicity Testing Paradigm: Important Steps

- **Scientific Documentation**
 - **SABRE DATABASE—65 pesticides**
 - **USEPA's Retrospective Analyses--ongoing**
 - Dog toxicity studies
 - Rodent cancer studies
 - Rat Multi-generation Reproductive Studies
 - Rat Neurodevelopmental Toxicity Studies



Next Generation Toxicity Testing Paradigm: Scientific Documentation

- Dog Toxicity Studies
 - No consistent international standard regarding the treatment duration
 - EPA currently requires both a 90 day & 1 year dog toxicity study for food use pesticides
 - EPA recently review results of dog studies on pesticides from 1-2 year studies with studies of shorter duration (<http://www.epa.gov/scipoly/sap/2005/may2/dogstudymay05.pdf>)
 - Concluded that limiting dog studies to a duration of 13 weeks would not result in the loss of any significant toxicity information

Dog Toxicity Studies

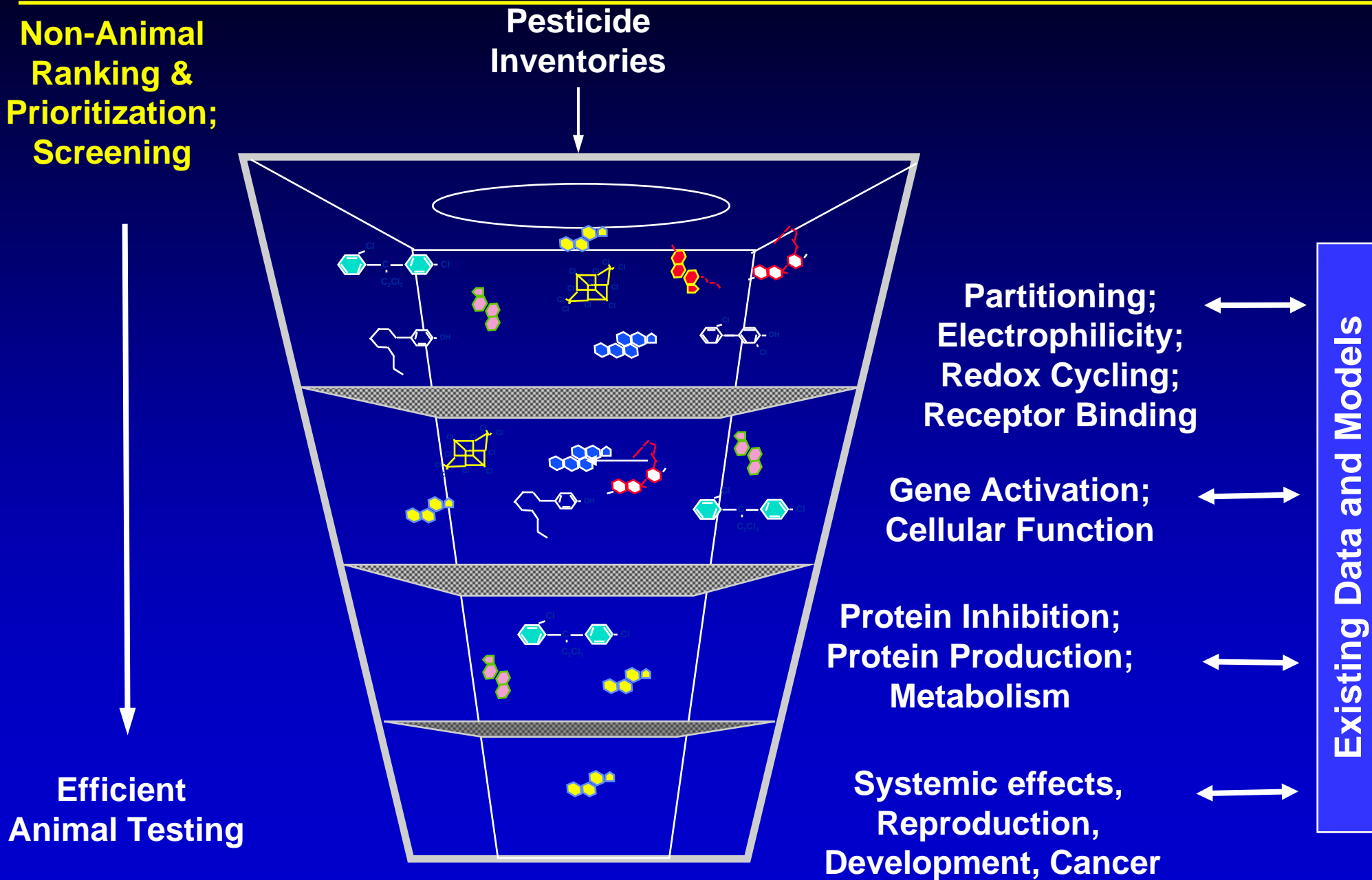
- **May 2005 FIFRA Scientific Advisory Panel Review**
(http://www.epa.gov/scipoly/sap/2005/may5/meetingminutesmay5_6_2005.pdf)
 - Generally supportive --several major recommendations
 - Analysis of additional pesticides including those where dog studies were not used to set the RfD
 - Need to ensure all chemical classes represented
 - Harmonization at international work shop

NEXT GENERATION TOXICITY TESTING PARADIGM: Important Steps

Harmonization & Consensus Building

- Work in several venues to gain international harmonization
 - EPA Outreach Efforts on ACSA
 - Jan & Jun 05 OECD meetings
 - Nov 05 Intl HESI workshop/panel discussion
 - July training of Staff on ACSA proposals (included California EPA & Health Canada)
- Started outreach with our Stakeholders
 - May workshop on our Part 158 revisions to data requirements
 - October PPDC meeting

Identifying Toxicological Potential



NEXT GENERATION OF TOXICITY TESTING PARADIGM

- In summary, it will be critical to draw on several relevant activities
 - Health & Environmental Sciences Institute (HESI) Tiered Toxicology Testing Proposal for Agricultural Chemicals
 - USEPA's Computation Toxicology Program
 - National Academy of Sciences project on Toxicity Testing & Assessment sponsored by the USEPA
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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



Phases/Sequence of Integration Scheme Development

Science Development

Research	Papers	Peer Review	Broad Disc.	Test Framework	Guideline Dev't
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Education & Outreach

Experts	Registrants	Interested Stakeholders	All
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Policy Development

Issue ID & Data	Stakeholder Engagement	Analysis	Option Selection
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Implementation

Pilot Test	Case-by-Case	Consistent Application
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Rulemaking

Development & Analysis	Proposal	Final
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How do we get there?

*Next Generation of Pesticide
Toxicology Data Requirements*



Global Perspective