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15-17 February 2006

Focus Session: Experiences using integrated approaches to fulfil information requirements for Testing and Assessment

Contribution by US EPA
(National Pesticide Program – Moving toward a hypothesis-driven toxicology testing paradigm: meeting common needs)

National Pesticide Program
Moving Toward a Hypothesis-Driven Toxicology Testing Paradigm: Meeting Common Needs

Anne E. Lindsay, Deputy Director, Office of Pesticide Programs
January 31, 2006

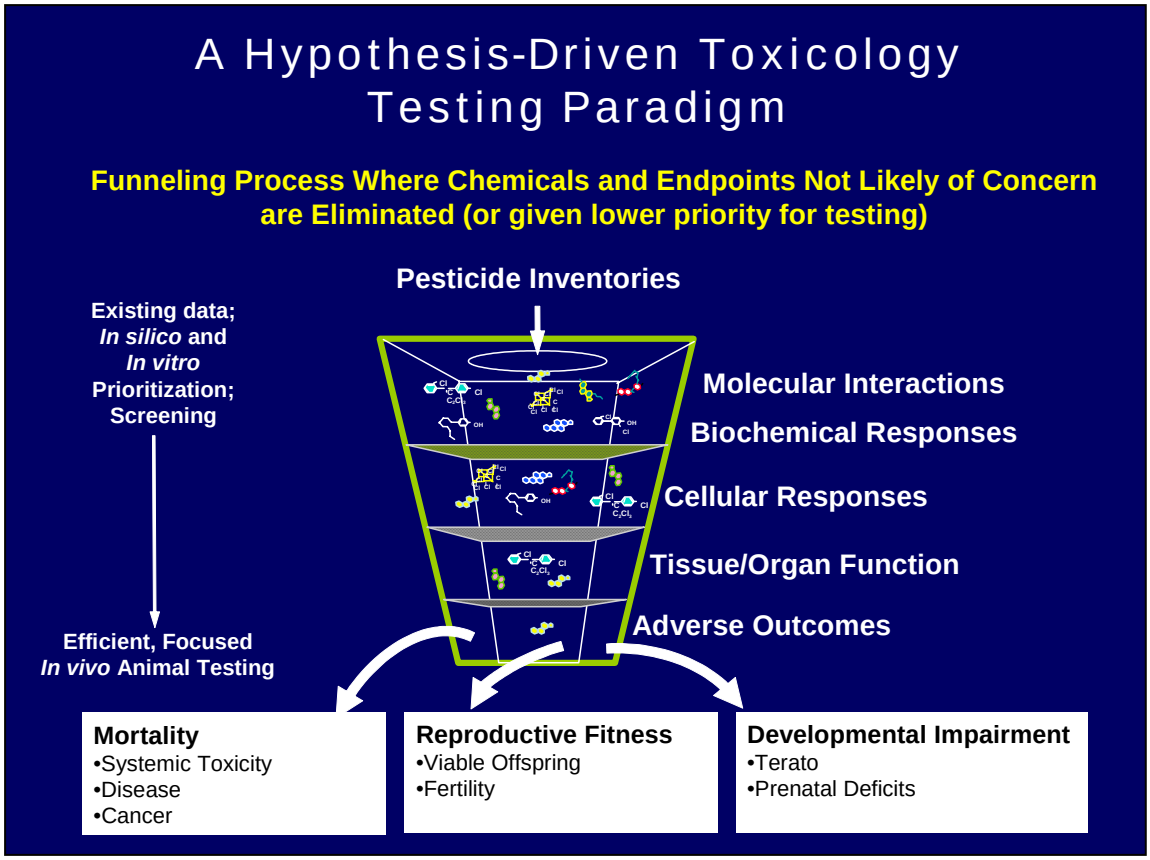
The Office of Pesticide Programs of the U.S. Environmental Protection Agency (EPA) has developed a long-term vision for change in the current toxicology testing paradigm for pesticides that would result in improved, more accurate and efficient risk assessment and risk management. EPA's Office of Pesticide Programs is responsible for registering new pesticides before they may be used in the United States. The Agency also periodically reevaluates the safety of existing registered pesticides. There are approximately 1,100 active ingredients and 2,500 inert ingredients, comprising approximately 19,000 existing registered products (including agricultural chemicals, antimicrobials, and consumer products). Each year, EPA makes over 5,000 regulatory decisions, registering between 10 and 12 new conventional chemicals, 12 new biopesticides, and 2 new antimicrobials. Additionally, EPA may register as many as 240 new uses of currently registered active ingredients. Approximately 55 new inerts ingredients are registered each year. Finally, the Agency currently reevaluates approximately 18 registered conventional chemicals and 3 antimicrobial pesticides each year through its reregistration program. Reregistration will be completed in 2008. EPA is launching a successor program (Registration Review) that will continuously reevaluate pesticides on a 15-year cycle.

The current toxicology testing paradigm requires extensive hazard testing followed by the elimination of information not relevant to the risk assessment. For food use pesticides, *in vivo* animal data are generated for all possible outcomes to determine which of all possible adverse effects are relevant. EPA requires registrants to generate testing for a wide range of endpoints (e.g., two-generation reproductive studies; subchronic and chronic studies in rodents and dogs; cancer bioassays in mice and rats; developmental neurotoxicity tests in animals; etc.). For a conventional agricultural pesticide this battery of tests costs an applicant $6 million and takes the government approximately 17-38 months to review the data, at a cost of approximately $1.25 million per pesticide. For antimicrobial pesticides and inert ingredients, testing for all possible adverse effects is not automatically required. Instead, the Agency must formulate a reasonable hypothesis in order to require long-term *in vivo* tests. In short, the Agency must manage and review large amounts of data, primarily from pesticide producers but also from other sources. EPA must maintain reliable schedules and meet statutory deadlines for both new and existing pesticides. The time it takes to make decisions affects both delivery of public health protection and access to benefits.

The vision is to move from a paradigm that involves requiring *in vivo* testing for "every possible adverse outcome" to a hypothesis-driven paradigm where existing data, *in silico (*computer simulated*)* models (e.g., structure activity relationships or SARs), and *in vitro* data, combined with estimates of exposure, are used to determine what specific *in vivo* tests are required. Such a paradigm shift would significantly improve EPA's ability to carry out its mission of protecting public health and the environment. It would focus on the most likely hazards of concern and determine what specific effects data for each chemical and exposure situation are essential to assess and manage risks appropriately. The approach would use screening and priority setting to eliminate the need for requiring a battery of tests focused on all possible adverse outcomes. Additionally, it would lower the costs for the government and tax payers because the Agency could avoid reviewing unnecessary tests. For the pesticide-producing industry, this approach would eliminate complex and expensive *in vivo* testing. It would also reduce the use of animals in testing. Finally, it would improve health and environmental protection and increase efficiency by focusing the regulated community, government, and

interested parties on chemicals and endpoints of greatest concern. In short, this paradigm shift would better meet the needs of EPA risk managers and those in the broader community of stakeholders engaged in risk assessment and risk management. Development and implementation of this new, integrated approach to the testing and assessment of pesticides will be a challenge and long-term goal (i.e., over the next 10 years). This new approach cannot be adopted and implemented over night. Scientific tools and knowledge must be advanced and public understanding and confidence must be developed. But if we begin this process of change together, we will be able to meet common needs for the best science and the best health and environmental protection in cost-effective ways.

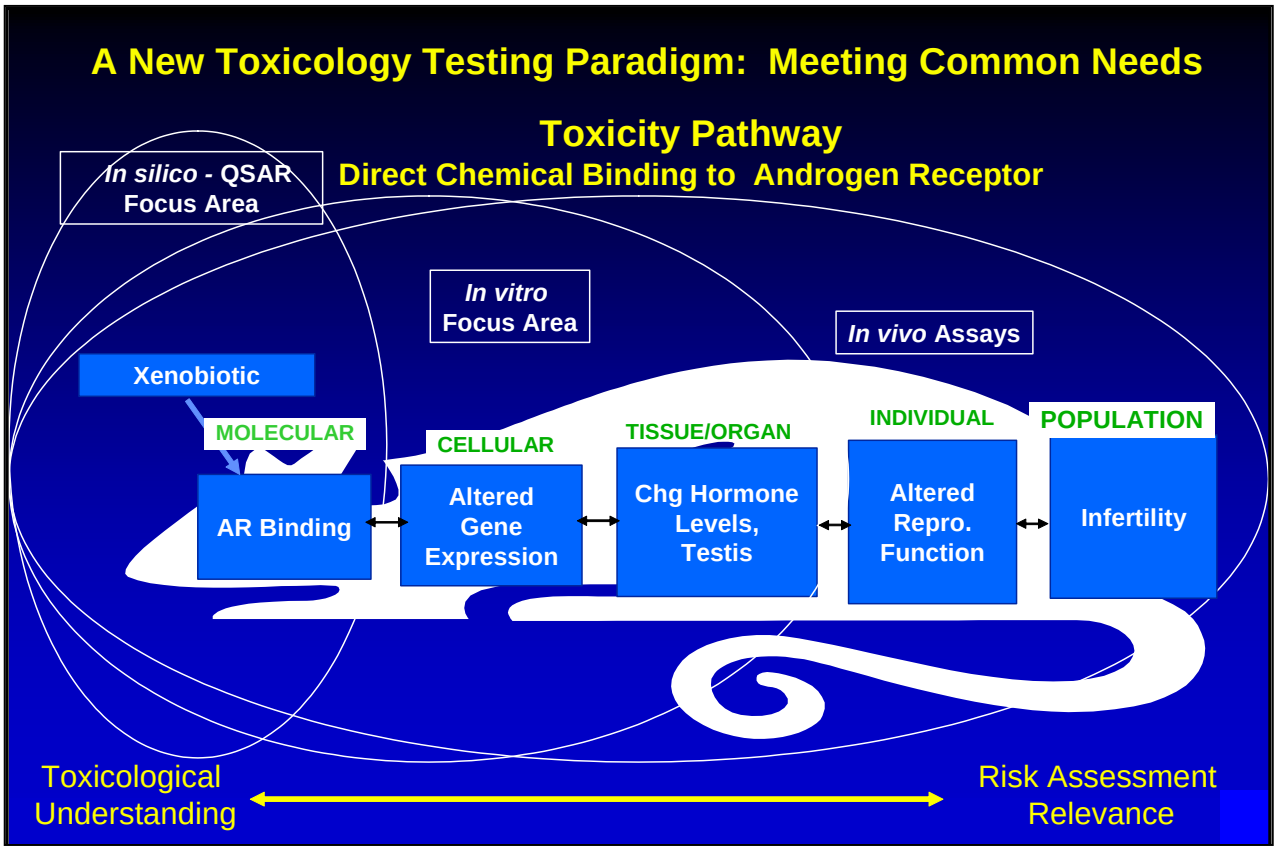
A Hypothesis-Driven Toxicology Testing Paradigm



Conceptually, this new approach is a funneling process where chemicals and endpoints are eliminated (or given a lower priority) for *in vivo* testing. Envision the entire pesticide inventory at the top of the funnel. The goal is to advance *in silico*, *in vitro*, and efficient, focused *in vivo* testing so that pesticides in the inventory are tested in animals only for those endpoints most relevant to each pesticide's intended use. By considering existing knowledge including structure activity relationships for members of a chemical series, the mode of action for members of a mechanistic series, and data from a battery of *in silico* models and *in vitro* assays, EPA can evaluate the potential of chemicals to initiate molecular interactions that are the basis for causing adverse effects. At each level of biological organization (starting with the molecular characteristics of the compound), as the potential for a chemical (or a group of chemicals) to elicit toxicological effects is refined in the context of likely human exposure, there is a reduction in the amount of testing at each higher level of biological organization. Therefore, instead of every chemical being tested for every possible endpoint in an *in vivo* testing

battery, only those *in vivo* tests that are rational for a chemical's toxicological potential at a relevant expected environmental exposure are required.

Example Using Hypothesis-Driven Paradigm Tools



By understanding the likelihood of effects at lower levels of biological organization, EPA can determine if more expensive and time-consuming testing at higher levels of biological organization are needed, thereby eliminating from *in vivo* testing those pesticides that do not show potential to initiate the chain of events necessary to cause adverse outcomes for the specific toxicity pathway. This type of approach leads to a more efficient testing strategy in that not every single chemical or endpoint needs to be evaluated in an expensive animal model.

For example, an EPA assessment predicts, based on Quantitative Structure Activity Relationship (QSAR), that a pesticide can bind to the androgen receptor (AR). This hypothesis is then confirmed using *in vitro* or short-term studies. Binding to the AR can potentially result in changes in gene expression as shown by genomics, which in turn can lead to hormonal changes (e.g., testosterone) as shown in a short-term animal model.

The change in testosterone can potentially lead to altered reproductive function and affect fertility in an exposed population. So an understanding of the molecular characteristics of the pesticide and the chemical gene interactions may allow the Agency to better predict and characterize the ultimate adverse health outcomes most relevant to humans.

Shifting to a Hypothesis-Driven Paradigm

EPA is aware that there will be challenges to a shift in paradigm, and substantial research will be needed to support this hypothesis-based paradigm. EPA has commissioned a National Academy of Sciences (NAS) committee to provide the Agency with specific feedback and advice on critical research activity and the science and public policy issues necessary to achieve the vision. NAS will prepare a report with its recommendations by early 2008. As understanding, confidence, and consensus around the changes inherent in this proposal develop, the Agency plans to implement appropriate changes in regulatory practice as well—initially on a case-by-case basis. Ultimately, EPA will explore and make appropriate changes to regulations and test guidelines as well.

The Agency's short-term goal is to make the existing animal testing paradigm more efficient, reliable, and responsive to its risk assessment and management needs. The International Life Sciences Institute, Health and Environmental Sciences Institute's (ILSI- HESI) tiered-testing proposal on Agricultural Chemical Safety Assessment (ACSA) is consistent with EPA's vision of a more efficient and reliable science-based paradigm**.** Some additional plans under way in order to build a foundation and consensus for the new hypothesis-driven toxicology testing paradigm include:

- ☑ Coordinating Agency regulatory and research programs. For example, the Office of Pesticide Programs will coordinate with EPA's Offices of Pollution, Prevention and Toxics; Science Coordination and Policy; and Research and Development on the computational toxicology program so that the Agency can have a greater reliance on emerging computational and genomic tools
- ☑ Analyzing the need for some of the current data requirements by conducting retrospective analyses of pesticide data for key endpoints such as:
  - < Dog Toxicity Studies
  - < Rodent Cancer Studies
  - < Rat Multi-generation Reproductive Studies
- ☑ Conducting an Inert Ingredient SAR Analysis
- ☑ Partnering with other federal agencies and regulatory and research agencies in other countries through existing international fora (e.g., NAFTA, OECD, WHO)
- ☑ Working with the regulated community and other stakeholders
- ☑ Supporting the development and use of enhanced and new testing approaches and other analytic techniques
- ☑ Incorporating lessons learned into regulatory practice

EPA welcomes comments from the OECD international community. This OECD Joint Meeting provides an excellent forum for discussion on this topic. EPA looks forward to providing periodic updates on the Agency's progress to the Joint Meeting.

Slide 1

National Pesticide Program

Moving Toward a Hypothesis-Driven Toxicology Testing Paradigm:
Meeting Common Needs

Anne E. Lindsay, Deputy Director
Office of Pesticide Programs
6 February 2006

Slide 2

Vision for Change in the Current Toxicology Testing Paradigm

- The current toxicology testing paradigm involves requiring *in vivo* testing for "every possible adverse outcome"
  - EPA typically requires a full battery of tests, including one- and two-generation reproductive studies in mammals, birds and fish; subchronic and chronic studies in rodents and dogs; cancer bioassays in mice and rats; developmental neurotoxicity studies using animals

Slide 3

Vision for Change in the Current Toxicology Testing Paradigm

- EPA has developed a long-term vision to move to a hypothesis-driven toxicology testing paradigm within the next 10 years
  - Use existing data, *in silico* models, and *in vitro* data, combined with estimates of exposure, to determine what specific *in vivo* tests are required
  - ILSI- HESI tiered-testing proposal on Agricultural Chemical Safety Assessment is consistent with EPA's vision

Slide 4

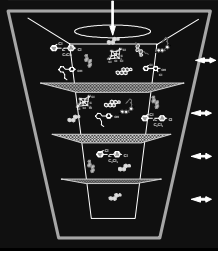
Hypothesis-Driven Toxicology Testing Paradigm

- Instead of requiring a full battery of tests, in a hypothesis-driven toxicology testing paradigm, by first gaining an understanding of the molecular characteristics of the pesticide and the chemical gene interactions, the Agency may be able to better predict and characterize the ultimate adverse outcomes most relevant to humans, aquatic life and wildlife.
- This type of approach leads to a more efficient testing strategy in that not every single chemical or endpoint needs to be evaluated in an expensive animal model.

Slide 5

Hypothesis-Driven Toxicology Testing Paradigm

Screening and Prioritization. **Use existing data, *in silico,* and *in vitro* data *to* evaluate the potential of chemicals in inventory to initiate molecular interactions that are the basis for causing adverse effects. At each level of biological organization (starting with the molecular characteristics of the compound), as the potential for a chemical (or a group of chemicals) to elicit adverse toxicological effects is refined in the context of likely human exposure, there is a reduction in the amount of testing needed. EPA is then able to determine if there is a need for efficient, focused *In vivo* animal testing.**



Molecular Interactions

Biochemical Responses

Cellular Responses

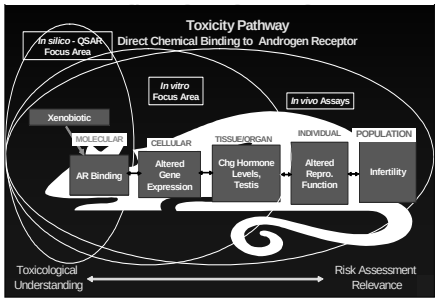
Tissue/Organ Function

Adverse Outcomes:

Mortality? Reproductive Fitness? Developmental Impairment?

Slide 6

Example of Hypothesis-Driven Paradigm



- EPA assessment predicts, based on Quantitative Structure Activity Relationship (QSAR), that a pesticide can bind to the androgen receptor (AR).
- Hypothesis is then confirmed using *in vitro* or short-term studies.
  - Binding to the AR can potentially result in changes in gene expression as shown by genomics, which in turn can lead to hormonal changes (e.g., testosterone) as shown in a short-term animal model. Change in testosterone can potentially lead to altered reproductive function and affect fertility in an exposed population.

Slide 7

Why a Shift in Paradigm?

- Improve ability to carry out EPA mission of protecting public health and the environment
- Increase efficiency by focusing the regulated community, government, and interested parties on a pesticide's most likely hazards of concern
  - Determine what specific effects data for each chemical and exposure situation are essential to assess and manage risks appropriately
  - Use screening and priority setting to eliminate the need for requiring a battery of tests focused on all possible adverse outcomes

Slide 8

Why a Shift in Paradigm?

- Lower the costs for the government and taxpayers because the Agency could avoid reviewing unnecessary tests
- Eliminate complex and expensive *in vivo* testing for the pesticide-producing industry
- Reduce the use of animals in testing

Slide 9

Implementing Change

- Development and implementation of this new, integrated approach to the testing and assessment of pesticides will be a challenge and will take place over the next 10 years
- Scientific tools and knowledge must be advanced and public understanding and confidence must be developed

Slide 10

Implementing Change

- Commissioned a National Academy of Sciences (NAS) committee to provide feedback on critical research activity and the science and public policy issues necessary to achieve the vision
  - NAS will prepare a report with its recommendations by early 2008
- If we begin this process of change together, we will be able to meet common needs for the best science and the best health and environmental protection in cost-effective ways

Slide 11

EPA's Next Steps

- Coordinate with EPA's Offices of Pollution, Prevention and Toxics; Science Coordination and Policy; and Research and Development on the computational toxicology program
  - Will allow the Agency to have a greater reliance on emerging computational and genomic tools

Slide 12

EPA's Next Steps

- Analyze need for some current data requirements by conducting retrospective analyses of pesticide data for key endpoints such as:
  - Dog toxicity studies, rodent cancer studies, and rat multi-generation reproductive studies
- Conduct an inert ingredient SAR Analysis
- Partner with other federal agencies and regulatory and research agencies in other countries through existing international fora (e.g., NAFTA, OECD, WHO)

Slide 13

EPA's Next Steps

- Work with the regulated community and other stakeholders
- Support the development and use of enhanced and new testing approaches and other analytic techniques
- Incorporate lessons learned into regulatory practice on a case-by-case basis.
- Ultimately, explore and make appropriate changes to regulations and test guidelines

Slide 14

Conclusion

- EPA welcomes comments from the OECD international community
- This OECD Joint Meeting provides an excellent forum for discussion on this topic
- EPA looks forward to providing periodic updates on the Agency's progress to the Joint Meeting