Overview of ORD Research Supporting the Application of Source-to-Dose-to-Effect Models for Cumulative Risk Assessment

Presenters: G Moser, K Crofton

Contributing Organizations: ORD: NHEERL, NERL, NCCT

B·O·S·C HUMAN HEALTH PROGRAM REVIEW RESEARCH TRIANGLE PARK, NORTH CAROLINA JANUARY 13-15 2009 RESEARCH & DEVELOPMENT

LTG 2 Poster 01

Science Questions

- Can a cumulative risk model be built that links environmental, exposure, dose, and effects data?
- What new scientific knowledge is needed to conduct cumulative risk assessments for chemicals with a common mode of action?
- How can the tools (models, computational methods, approaches) developed by ORD be used to inform and/or conduct cumulative risk assessments?

Research Goals

The US EPA is charged through a variety of regulatory mandates (*e.g.*, FQPA, CWA, CAA, Superfund) that require the Agency to determine risk from aggregate and cumulative exposures under different scenarios, including assessments of chemicals with a common mode of action, drinking water contaminants, and toxic waste contaminant mixtures. ORD has been integral in collaborating with the EPA Program Offices and developing and evaluating innovative approaches for such risk assessments. This ongoing research has evolved considerably over the past several years, building on our previous research and background. Our goal is to incorporate multiple facets of exposure, dose, and effects into cumulative risk assessments. While the concepts are applicable for a wide range of chemical exposures, recent focus has been on the CRAs for high-priority pesticides.

Research is needed to develop source-to-exposure models that simulate realistic distributions of human exposure to different chemicals through daily activities, and furthermore to determine how such exposures translate into internal doses at target sites for different classes of chemicals and different segments of the human population. Scientific information is needed on exposure characteristics such as magnitude, route, co-occurrence, and longitudinal exposures to chemicals.

Findings and Conclusions

The overall goal is to develop and enhance the scientific understanding, data, and modeling tools to support cumulative risk assessments that are based on state-of-the-art scientific approaches. ORD's research has supported this goal with development of methods and models for both describing and linking the data.

This source-to-exposure-to-effects model has been incorporated to a greater degree with each subsequent Cumulative Risk Assessment for pesticides, and is applicable for risk assessments of other chemicals as well.

Methods/Approach

Exposure Estimates

ORD's studies generating longitudinal and co-occurrence exposure data have been used to refine the Stochastic Human Exposure and Dose Simulation (SHEDS) model, providing:

- Improved estimates of multi-route and multi-chemical human exposure in terms of magnitude, frequency, and duration
- Investigation of the impact of longitudinal aspects of exposure (*e.g.*, single and multiple days)
- Relative contributions of route (*e.g.*, dermal and hand-to-mouth behaviors)
- Population variables (*e.g.*, age, gender)
- Relative contributions of individual components

http://www.epa.gov/scipoly/sap/tools/atozindex/sheds.htm

Link exposure outputs to internal dose metric

Dose Estimates

ORD's Exposure Related Dose Estimating Model (ERDEM) platform for PBPK/PD modeling:

- Simulates tissue levels at the site of action for multiple chemicals
- Predicts biological actions at simulated tissue levels
- Allows extrapolation across species
- Predicts levels of biomarkers of exposure and reverse dosimetry based on monitoring databases
- Allows analysis of kinetic interactions among components

http://www.epa.gov/heasd/products/erdem/erdem.htm

Link internal dose levels to biological effect

Effects Estimates

Dose-response research and data collection is critical for:

- Mode of action and basis for interactions
- *In vitro* and *in vivo* effects integrated with PBPK outputs
- Comparison of animal and human response at simulated tissue levels
- Variability within a population of response due to age, gender, *etc.*
- Use of new technologies for predictions of mixture responses

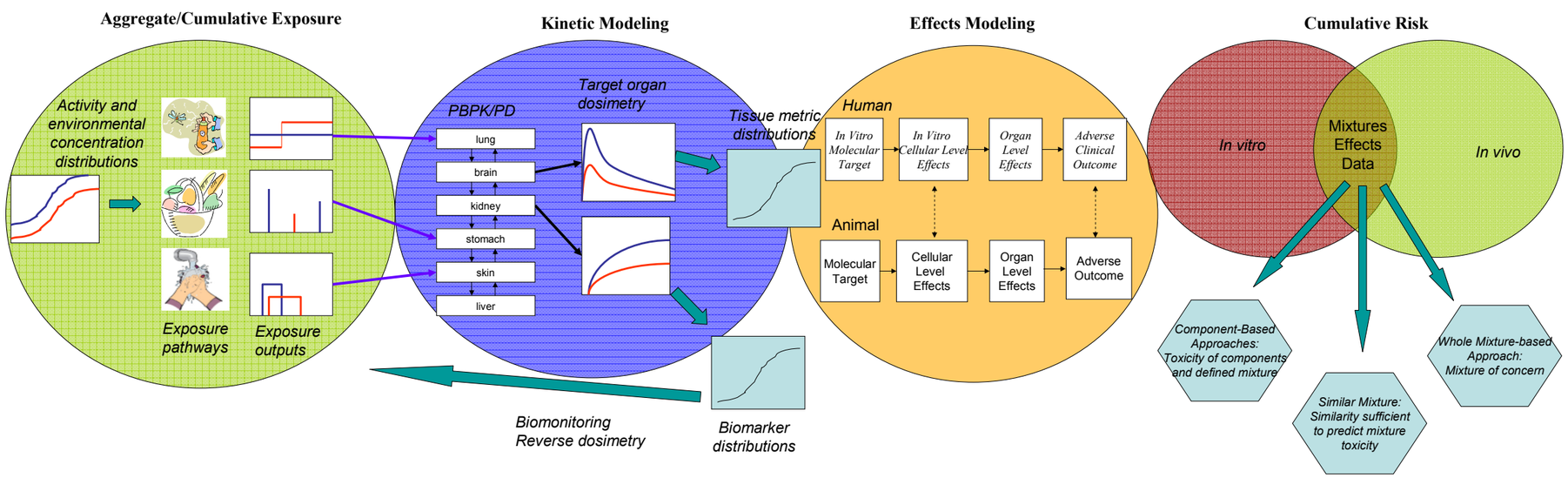
Test assumptions

Cumulative Effects Estimates

ORD's collaborations have resulted in models with which to test the assumption of additivity in defined chemical mixtures. Flexibility in the approaches allow studies of

- Any number of chemicals in a mixture
- Varying compositions, including those reflecting predicted environmental exposure levels
- Nonparallel dose-response slopes
- Interaction thresholds

Refined methods have also been developed to assess additivity when data for the mixture components are not available.



Impact and Outcomes

The enhanced science and products of this research will reduce uncertainty in risk assessment/management by:

- Providing OPP and other Agency risk assessors (*e.g.*, NCEA, Regions) with evaluated methods, models and guidance informing future exposure and cumulative risk assessments
- Providing OPP, OW, and OAR statistical models for deviations from additivity (see posters presented by Herr and Simmons, LTG2-2 and 3)
- Providing OPP with research and enhanced models supporting and improving CRA for *N*-methyl carbamates (see poster presented by Moser, LTG2-4)
- Providing OPP with ORD models for exposure-to-dose analyses for application to inform the upcoming CRA for pyrethroid pesticides (see poster presented by Tornero, LTG-5)
- Providing OPP with the results of research on pesticide mixtures and influences on joint responses that are being applied in the upcoming CRA for pyrethroid pesticides (see poster presented by Shafer, LTG2-6)
- Communicating enhanced science and research products through peer-reviewed publications.

Future Directions

Future directions for continuing to improve this source-to-exposure-to-effects paradigm are described in each of the specific posters.

Researchers Involved

NHEERL: Kevin Crofton
Mike DeVito
Ginger Moser
Dave Herr
Mike Hughes
Jane Ellen Simmons
Tim Shafer
NERL: Curt Dary
Rogelio Tornero-Velez
Valerie Zartarian
NCCT: Woody Setzer

Cumulative Risk

This poster does not necessarily reflect EPA policy. Mention of trade names or commercial products does not constitute endorsement or recommendation for use.