Overview of ORD Research – Developing and Applying Biomarkers of Human Exposure and Health Effects to Support Cumulative Risk Assessment

Presenters: Meta Bonner[1] and Maggie Breville[1]

Contributing Organizations: ORD: NCER[1], NCEA[2], NERL[3], NHEERL[4], NCER STAR Grants[5]

LTG 2 Poster 07

Science Questions

•What is the state of the science for using biomarkers in risk assessments?

•What new science and approaches are available to enhance the use of biomarkers in cumulative risk assessment?

•How can measures of exposure, effect, and susceptibility generated through research studies under environmentally-relevant conditions be linked to develop a conceptual model for identifying toxicological pathways from stressor source to adverse health effects?

•What tools are needed to inform the design of future exposure and epidemiological studies that will collect biomonitoring results?

Research Goals

ORD's intramural (ORD Laboratories and Centers) and extramural (Science to Achieve Results (STAR)) research is designed to produce state-of-the-science methods, measures, models, and guidance that can be used to:
1) inform and improve future Agency exposure and risk assessments;
2) improve our scientific knowledge regarding the exposure-dose-effects linkages;
3) design future exposure and epidemiological studies;
4) interpret the results from large-scale biomonitoring studies.

Findings and Conclusions

•Biomarkers have many potential uses for informing future cummlative risk assessments and for linking exposure and effects data.

•Understanding and interpreting biomarkers in terms of exposure is complex. Humans are continuously exposed to varying concentrations of multiple chemicals based on their proximity to sources and activities.

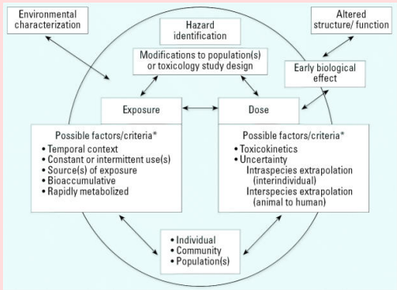
•PBPK models are increasingly being used to relate and interpret biomarker data in terms of exposure and susceptibility.

•Innovative system approaches have been developed to link exposure, biomarker, and effects data.

•New methods, approaches, and science have been developed that will inform the design of future exposure and epidemiological studies that will collect and interpret biomonitoring data.

Defining the State-of-the-Science

•September 2004 HESI,EPA, CDC, ATSDR, and ICCA co-sponsored international "Biomonitoring Workshop"
•September 2007 ORD "Public Health Applications of Human Biomonitoring Workshop"

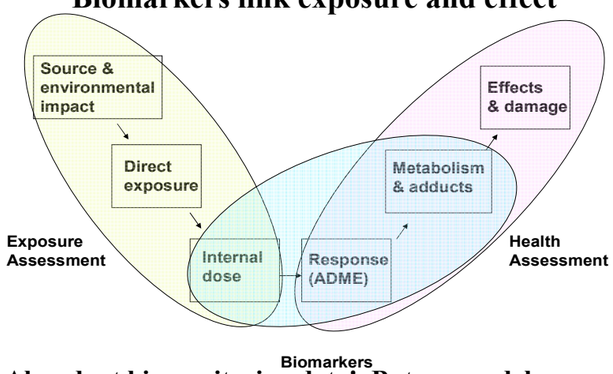


Key Findings, Needs, and Recommendations

•Develop consensus criteria for application/interpretation of biomonitoring data
•Generate human uptake and toxicokinetic data for species extrapolation
•Develop next generation PBPK and exposure models
•Develop dose metrics to identify biomarkers reflecting low-level exposure at/ near effect threshold
•Develop mechanistic/mode-of-action information by integrating proteomics and metabonomics
•Examine current risk assessment paradigm in the context of biomonitoring data
•Develop a risk communication strategy

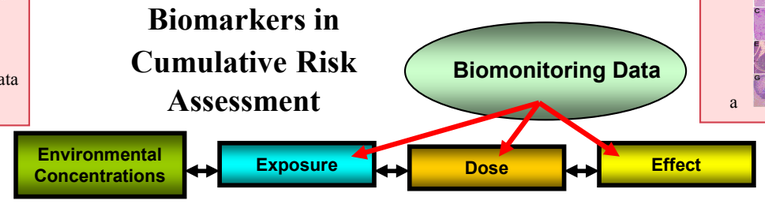
Approach

Biomarkers link exposure and effect



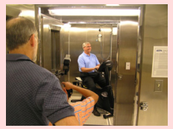
Abundant biomonitoring data! But, no models or approaches to interpret/link data for cumulative risk!!!

Biomarkers in Cumulative Risk Assessment

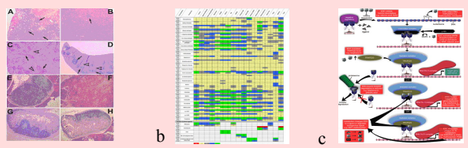


Systems Approaches for Using Biomarker Data

Intramural ORD Research (Poster LTG 2-9):
•Constructed conceptual model linking exposure-effect complexity
•Linked diesel exhaust exposure to uptake and early response
•Deduced mechanistic precursors; linked genotype, phenotype, and asthma outcome.



Extramural ORD Research:
•Identified key ligand-dependent transcription factor regulating xenobiotic, steroid, and bile acid metabolism
•Provided information on interspecies variation and activation via various ligands; supported EDC screening assays and animal models
•Observed differences in tissues and organs; developed a molecular-based biomarker model linking responses to chemical exposures
•Figures: a) Pregnane xenobiotic receptors and inflammatory lesions in liver, spleen, pancreas, and bowls, b)Steroid and xenobiotic receptor activation in human and animal models, c) Diagram of multiple modes of endocrine disruption.



Impact and Outcomes

•Providing risk assessors with real-world biomonitoring data and guidance for use in future exposure and cumulative risk assessments.
•Providing biomonitoring data that supports the development and evaluation of ORD exposure, PBPK/PD, and BBDR models.
•Providing ORD, CDC, EPA Program Offices and Regions, and other researchers with methods and models for relating exposure biomonitoring data with health effects.
•Providing ORD, CDC, EPA Program Offices and Regions, and other research organizations with methods and models for relating exposure biomonitoring data with human exposures, and ultimately sources of exposure.
•Providing ORD and other exposure scientists and epidemiologists with methods, models and approaches for designing and implementing future large scale exposure and epidemiological studies that will be collecting biomonitoring data.

Future Directions

•Additional research of biomarkers, exposure and dose that reveal the relationship between environmental stressors and health outcomes.
•Increasing the accuracy of health and environmental risk assessments by providing integrated modeling of biomarkers, exposure and PBPK/PD.
•Improving the understanding of the specific population vulnerabilities to environmental stressors and diseases.
•Provide further development of informed strategies for those making public health decisions.

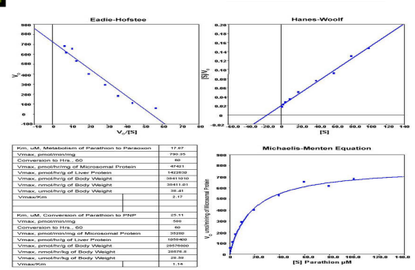
Researchers Involved

•ORD/EPA - M. Morgan, J. Pleil, M. Madden, J. Gallagher, L. Sheldon, H. Zenick
•CDC - L. Needham, D. Barr
•ILSI/HESI – N. Doerrer
•UC Berkeley - A. Bradman
•UC Irvine – M. Milnes, B. Blumberg, A. Garcia, E. Grossman
•Columbia University – R. Whyatt, V. Rauh, G. Perera, H. Andrews
•John Hopkins School of Public Health – T. Burke
•SUNY-Buffalo – J. Olsen, J. Knaak
•Japan NUS Co. Ltd – Y. Kawashima, Y.
•Okazaki Inst. Int. Bioscience, Japan – Y. Katsu.

Building the Science

Forward Assessment

ORD Research Accomplishments:
•Conducted measurement studies to understand the route, magnitude, frequency, co-occurrence, and duration of exposure (See LTG 3 posters)
•Conducted statistical analysis using multiple approaches to evaluate the relationship between environmental concentrations, exposures, and biomonitoring data (Poster 2-8)
•Evaluated intra- and inter-individual variability in exposure and corresponding biomarker measurements
•Used PBPK models with exposure scenarios to predict urinary excretion over time (Poster 2-5)
•Applied the updated scientific information to evaluate biomonitoring protocols
•Linked children's exposure and biomonitoring data (Poster 2-8, EPA/NIEHS Children's Centers, NCER RFAs



Building the Tools

Reverse Assessment

ORD Research Accomplishments:
•Developed exposure/PBPK models (see Poster 2-5, 2-6, 2-9; STAR grantees Olson and Knaak developed PBPK/PD model for pesticide metabolism; **RFA**: Interpretation of Biomarkers Using PBPK Modeling (2006)).
•Developed parathion PBPK model; applied to evaluate susceptibility. Diagrams show paraoxon formation from parathion in pooled sample of human liver microsomes. Individual sensitivity by age group estimated based on biomarkers of susceptibility (i.e., paraoxonase genotype and CYP2D6 phenotypes), exposure (i.e., urinary metabolites), and effects (i.e., blood acetylcholinesterase [AChE]; AChE / butyrylcholinesterase inhibition)
•Developed framework for applying models in exposure reconstruction (Poster 2-8)

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.