Cumulative Risk Characterization Research in US EPA's National Center for Computational Toxicology

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Science Question

Characterizing cumulative risk and understanding exposure-outcome relationships requires collection and analysis of a wide range of data. Information on the characteristics of multiple stressors (chemical, physical, biological and psychosocial), the characteristics of the human receptor (genetics, health status, life stage, behaviors, social factors, etc.) at multiple levels of organization (individual, community, population), and the temporal and spatial patterns of exposures and outcomes must be combined to assess cumulative risk. To meet the increasingly complex needs for cumulative risk assessment, the Agency requires a sound scientific understanding of the systems that are being assessed and appropriate tools and approaches for characterizing these systems.

Research Goals

The goal of this research is to identify and apply emerging technologies and computational approaches to efficiently manage, analyze, and represent multifactorial data to improve interpretation of human exposure data and increase understanding of the complex relationship between environmental factors and human health outcomes.

Methods/Approach

To address the significant challenges associate with characterizing cumulative risks, the following will be applied:

- •A **systems approach** (use of engineering principles to develop conceptual and mathematical models of the human-receptor, source-to-outcome system),
- •A **human-receptor-based framework** (defines the receptor as the system of interest), and
- •Emerging technologies and computational tools (**nanotechnology-enabled sensors, visual analytics**).

Systems Approach: By combining emerging computational tools to improve consideration of all available data with increased understanding of mechanistic underpinnings of the system, more efficient approaches for characterizing cumulative risk can be developed. A systems biology or engineering approach includes:

Clear definition of systems

Evaluate processes from forward and reverse directions

Identify, quantify rate-limiting/driving factors

Focus measurement/experimental studies on important metrics

Mathematical models, become hypotheses that are testable.

Frameworks

Here a framework refers to a conceptual model. Three important purposes for conceptual models are discussed by Suter (1999).

- •Creation of a conceptual model compels the assessor to clarify assumptions.
- •A conceptual model serves as a communication tool to aid in describing complex processes.
- •Good conceptual models provide the basis for organizing and conducting exposure studies, multi-factorial analyses, and risk assessments.

Human-Receptor-Based Framework: Traditionally, the conceptual models for a human-health risk assessment has been developed in the context of the source-to-effects paradigm. However, as the risk assessment becomes more complex, some limitations in the source-to-effect model become apparent. A receptor-oriented risk assessment is based on the characteristics of the person or population of interest. This receptor-oriented approach is particularly important when considering aggregate exposures to multiple stressors. Using this approach, the large number of factors and the associated variability and uncertainties can be collected and tracked.

1) <u>Using Biomarkers to Inform Cumulative Risk Assessment</u>

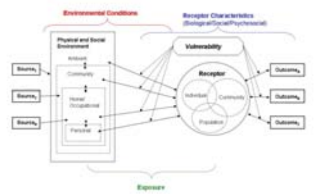
A framework was developed (Cohen Hubal, in press; Ryan et al, submitted) to provide the conceptual basis for considering biomonitoring data and other health metrics in assessment of cumulative exposure and risk. In this framework, biomonitoring and other health data are used to characterize the receptor (individual, community or population), potential exposures, and health outcomes. By considering an array of metrics across the exposure-outcome continuum, this framework begins to address the multi-factorial nature of environmental disease and cumulative risk.

Partners: US EPA Risk Assessment Forum Cumulative Risk Technical Working Group; P. Barry Ryan, Emory; Thomas A. Burke, Johns Hopkins ; Jerry J. Cura, Menzie-Cura &Associates; Thomas E. McKone, Berkeley

2) <u>Vulnerability as a Function of Individual and Group Resources in Cumulative Risk Assessment</u>

Vulnerability is related to the capacity of individuals or groups to respond to and recover from stressors. A conceptual model for including vulnerability factors as an integral component of cumulative risk assessment was developed. This conceptual model was used to classify vulnerability factors for cumulative risk assessment and is being evaluated within the context of recent disasters such as Hurricane Katrina. This approach lends important insight into the complex relationships and interactions among the characteristics of ecological environments, the community context (infrastructure, support systems, preparedness, complexity, etc.) and response and recovery (deFur, et al., submitted).

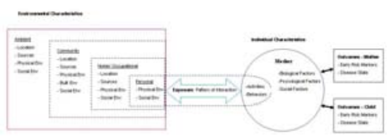
Partners: US EPA Risk Assessment Forum Cumulative Risk Technical Working Group; Peter deFur, Environmental Stewardship Concepts; Gary Evans, Cornell University;Amy Kyle, University of California Berkeley; Rachel Morello-Frosch, Brown University; David Williams, University of Michigan.



3) <u>Conceptual Model for Characterizing Environmental Exposures Related to Maternal and Child Development and Health</u>

For children, we are interested in understanding the relationships between exposures and outcomes, over the course of development. As a first step toward applying a systems approach to improve understanding of the impact of environmental exposures on child health, a conceptual model of how environmental factors impact maternal and child development is being developed. This model is being developed for use in the North Carolina Children's Cohort Pilot Study being conducted by NHEERL. The NHEERL study will enroll women before and during pregnancy, and follow them, their partners, and their child from the preconception period, pregnancy, birth, and through the first 18 months of childhood. Study questionnaire and sampling domains are currently being superimposed on the conceptual framework to aid in development of study hypotheses.

Partners: Pauline Mendola and Lynne Messer, US EPA National Human and Environmental Effects Laboratory (NHEERL), Human Studies Division



Computational Tools: Visual Analytics

Application of emerging computational tools will allow the Agency to optimize utility of collected data, improve understanding of complex exposure-outcome systems, and improve cumulative risk assessment. ***Visual analytics*** facilitates analytical reasoning by using interactive visual interfaces. Visual analytics is an outgrowth of the fields of data mining and scientific and information visualization but includes aspects from other fields, including knowledge management, statistical analysis, cognitive science, and decision science. In addition to using data to test hypotheses as with more conventional statistical analysis tools, visual analytic tools can potentially be applied to complex data sets to develop hypotheses.

1) <u>Review of Visual Analytic Tools, Demonstration of a Selected Tool for Analysis of Human Exposure Data</u>

The objective of this research activity is to begin to identify and evaluate visual analytic tools required for characterizing multi-factorial relationships between environmental factors and human health outcomes. Tasks planned under this activity are as follows:

Investigate available and popular commercial off-the-shelf (COTS) visual analytic tools.

Investigate common and specialized visual analytic techniques.

Practice visual analytic techniques using a selected COTS tool and a publicly available dataset. Currently use CTEPP or NHEXAS data is proposed to explore the potential of visual analytics to facilitate evaluation of relationships between environmental and biological measures of exposure.

To date over 50 software packages have been identified that have been designed and marketed as visual analytics tools. The software are being categorized based on the type of date these are designed to handle and are being screened for utility in addressing the analysis needs for human exposure and environmental health studies. In addition, a taxonomy for classifying and applying visual analytic tools has been proposed as follows.

- •**Goal**: data interrogation (hypothesis testing), gap analysis (hypothesis development), interpretation
- •**Process Points**: data management/manipulation, data mining/analysis, info representation
- •**Data Types**: hierarchical, network, temporal, spatial (1D, 2D, 3D)
- •**Features (what analyzing for):** correlations, clusters, outliers, gaps

Partners: Robert Hubal, RTI International, US EPA NERL

2) <u>Cross-Center Project to Analyze OP Biomonitoring Data</u>

A working group is being formed with the assistance of the ILSI HESI Biomonitoring Technical Committee to conduct analyses across the different studies by pooling relevant data. Because each study was designed to address different research questions, analysis of the pooled data is likely to be difficult. As such, this activity may provide a useful demonstration of potential strengths and limitations of existing visual analytic tools for evaluating relationships between environmental factors and children's exposure.

Partners: US EPA NERL, USEAP NCER, ILSI HESI, STAR Children's Centers Investigators (Asa Bradman, Berkeley; Robin Whyatt, Columbia; Richard Fenske, University of Washington).

3) <u>Modeling Distribution of SVOC's in the Indoor Environment: Consideration of Data Collected in Laboratory Chambers, the EPA Test House, and Exposure Field Studies</u>.

In this research activity, mechanistic understanding developed by modeling SVOC emissions measured in controlled laboratory studies (Xu et al, 2006) will be used to provide insight into results of real-world measurements collected in a children's exposure study (CTEPP). The Xu et al model was based on measured emissions of di-2-ethylhexyl phthalate (DEHP) from vinyl flooring. Compared to the simple chamber system studied, a regular indoor environment has many other types of surface that will adsorb SVOCs to different extents. The emission rate measured in the test chambers may therefore be vastly different to the actual emission rate from the exact same material into a typical indoor environment. The Xu et al model will be applied using adsorption isotherms for di-n-butylpthalate (DBP) developed using measured concentrations of DBP from the CTEPP study. In this way, the fundamental mechanisms and the properties of specific SVOCs can be combined with real-world human exposure measurement data to provide insight into important exposure sources and pathways.

Partners: Peter Egeghy, US EPA (NERL), John Little, Virginia Tech; Wale Adeniji, US EPA Region 7

Monitoring Tools

A major challenge in reducing uncertainty in environmental risk assessment is the limited availability of efficient and affordable methods for comprehensively monitoring exposures. Recent advances in nanotechnology and related development of small-scale sensors provide the potential to address this gap. Nanoscale technologies offer potential to improve exposure assessment by facilitating collection of large numbers of measurements on very small numbers of molecules at a low cost

Currently, possible to develop micro- and nano-scale sensor arrays that can detect specific sets of harmful agents in the environment

Provided adequate informatics support, these sensors can be used to monitor agents in real time and resulting data can be accessed remotely

Potential also exists to extend these small-scale monitoring systems to the individual level to detect personal exposures and *in vivo* distributions of toxicants.

1) <u>Nanotechnology Applications in Environmental Health: Big Plans for Little Particles Workshop held April 20, 2006 in Research Triangle Park, NC</u>

This workshop convened top nanotechnologists and environmental and ecosystems health researchers for a discussion about the use of nanotechnology, particularly nanosensors, in environmental monitoring, human exposure research, and ecosystems research.

Proposed next step is to solicit a few proof-of-concept projects for monitoring exposure, dose, and early effects from EPA scientists. A small scientist-to-scientist meeting would then be convened at Oak Ridge National Labs so that nanotechnology researchers could learn about these high-priority projects, and EPA researchers could learn more about potential of the nanotechnologies to address these sensor needs. By holding the meeting at Oak Ridge, EPA researchers could tour the nano fabrication facilities and view a broad variety of technologies.

Partners: Oak Ridge Center for Advanced Studies (ORCAS) and the US EPA NERL

2) <u>Multi-Channel Immuno-Sensors for Detection of Pyrethroids</u>

In this project, a novel biochip-based technology will be developed for analysis of pyrethroids in liquid samples such as water or food. The analyses will be performed by competitive immunoassay using pyrethroid-specific antibodies. Competition will be measured between the antigen in a sample and the antigen immobilized on the biochip surface for binding with the pyrethroid-specific antibodies. The biochip will be integrated into a micro-fluidic device that allows simple and rapid sample treatment. For this format, the analytes representing pyrethroid fragments will be immobilized on the biochip. The analyzed sample will be pre-incubated with a cocktail of pyrethroid-specific antibodies during 3-5 min and pumped through a cuvette with the biochip. The free antibodies will be captured on the surface of the biochip while the sample flows through the cuvette. Such binding of antibodies will be directly read out by a new original biosensor system designated for simultaneous detection and identification of multiple bio- and chemical agents. A "one-dimensional Picoscope" (1D Picoscope) will be developed that will be able to measure thickness changes arising after absorption of antigen/antibody with picometer resolution in depth and standard optical lateral resolution. The instrument will allow employment of a simple microscope glass slip as a sensor chip without deposition of any metal or dielectric film.

Partners: Petr I. Nikitin, V.A. Nesmeyanov, Russian Academy of Science; US EPA OIA

3) <u>HESI Biomonitoring Working Group: Subcommittee on Nanotechnology-Enabled Sensors for Improving Interpretation of Biomonitoring Data.</u>

A subcommittee focused on application of nanotechnology-enabled sensors for improved interpretation of human exposure biomonitoring data has be approved by the ILSI HESI Biomonitoring Working Group. Currently, the proposed objectives for this group are as to:

Delineate small-scale sensor technologies with potential applicability for monitoring exposure media concentrations, personal exposures, and in vivo distributions of toxicants.

Develop technical requirements for small-scale sensor technologies applied to monitor human exposure.

Partners: ILSI HESI, US EPA NERL

Results/Conclusions

Significant research activities have been initiated to provide new approaches and tools for characterizing cumulative risk.

Impact and Outcomes

Across EPA, program and regional offices are being called on to assess cumulative risk resulting from real-world exposures. Multi-factorial analyses of one form or another are required: to conduct national-scale regulatory-based risk assessments; to conduct community-based risk screening and remediation; to support epidemiology studies investigating gene-environment interactions; and to characterize exposure and risk for public health tracking. The approaches and tools developed through this research will help the Agency meet the increasingly complex needs for cumulative risk assessment.

Future Directions

Results of the projects described here will provide guidance on future directions. It is anticipated that application of a systems biology approach and receptor-based frameworks will provide useful conceptual models to begin to characterize cumulative risk. It is hoped that visual analytic tools and analysis techniques will be identified that can be used by the Agency to improve understanding of exposure-outcome relationships and to characterize cumulative risk. Should preliminary work demonstrate the potential of these tools we plan to identify a proof-of-concept project to demonstrate application of visual analytics for cumulative risk assessment.

References

Cohen Hubal, EA. Uso de los Datos de Biomonitoreo para Informar sobre la Evaluación de la Exposición Infantil [Using Biomonitoring Data to Inform Exposure Assessment in Children] Journal of the Argentinan Society of Toxicology. (In Press)

deFur, PL, GW Evans, EA Cohen Hubal, AD Kyle, RA Morello-Frosch, and D Williams. (2006) Vulnerability as a Function of Individual and Group Resources in Cumulative Risk Assessment. (Submitted)

Xu, Y and JC Little. (2006) Predicting Emissions of SVOCs from Polymeric Materials and Their Interaction with Airborne Particles. Environ. Sci. Technol. 2006, 40, 456-461

Ryan, PB, TA Burke, EA Cohen Hubal, JJ Cura, and TE McKone. (2006) Using Biomarkers to Inform Cumulative Risk Assessment. (Submitted)

Suter, GW II. 1999. Developing Conceptual Models for Complex Ecological Risk Assessments. Human and Ecological Risk Assessment. 5(2) 375-396.

Long Term Goal III

COMPUTATIONAL TOXICOLOGY