2-12-07 Draft Agenda

2007 Toxicology and Risk Assessment Conference

Emerging Issues and Challenges in Risk Assessment

April 23 – 26, 2007

Monday, April 23, 2007 **1:00 p.m. - 5:00 p.m.**

Workshops

11:30 a.m. - 5:00 p.m.	**Registration**
1:00 p.m. - 5:00 p.m.	**Workshops W-1, W-2, W-3 and W-4, Discussion Session**
2:30 p.m. - 3:00 p.m.	**Break**

Workshop Coordinator:
Zwayer, Bette, *U.S. EPA, Office of Research and Development, National Center for Environmental Assessment*

W-1. NIOSH Direct Reading Instrument/Direct Reading Methods Initiative

Chair:
Snawder, John, Ph.D., *National Institute for Occupational Safety and Health*

The NIOSH Program Portfolio focuses on programmatic relevance, quality, and impact, and includes eight industry sectors, 15 cross-sectors, and 7 coordinated emphasis areas. Within the Program Portfolio, Exposure Assessment is identified as one of the coordinated emphasis areas. To address fundamental issues in Exposure Assessment, and to assess the potential associated with direct-reading technologies, this session will address the development, evaluation, applications, and needs for direct-reading methods. These direct-reading methods may be applicable to any workplace hazard including gases, vapors, biological agents, aerosols (dusts, mists, fumes, nanoparticles), noise, radiation, and stressors, and may be applicable to any workplace or in any work situation such as manufacturing, mining and emergency response.

W-2. The Power of Aggregated Toxicity Data

Chair:
Woodall, George M., Jr., Ph.D., *U.S. EPA, Office of Research and Development, National Center for Environmental Assessment*

Quantitative risk assessment relies upon having detailed exposure-response data (minimum details by exposure group in dichotomous measures include number of

animals and incidence, and values by individual animal for continuous measures). This level of detail is often not reported in published studies due to journal space limitations, especially for continuous measures, and means with or without a measure of variability are usually all that is published. Biologically-based models (e.g., PBPK) are more commonly being applied to risk assessment for a number of reasons. Collections of biological parameters as inputs into PBPK models (both chemical-specific and more general physiological parameters) are also an open need to help expedite their use. Structure activity relationship information is also being called upon to help fill-in knowledge gaps about specific chemicals where data from related chemicals may be available. The utility of distributed database systems (e.g., DSSTox - http://www.epa.gov/ncct/dsstox/index.html) is one avenue for allowing greater connectivity between existing data sources with a minimum of additional resource allocations. Health effect reference values (e.g., reference dose [RfD] and reference concentration [RfC] values) are derived as a part of this hazard assessment process and originate from various sources, each with its own uses and purposes. Comparisons of the available reference values presented both graphically and in detailed tables have proven useful in the risk management decision process (e.g., the OAQPS Toxicity Tables - http://www.epa.gov/ttn/atw/toxsource/summary.html). In this workshop, many of the ongoing efforts within the U.S. EPA, ATSDR, and other agencies (State, Federal and International) to use the existing toxicity data will be discussed, along with the potential for more innovative collaboration in the use of existing and new sources of information in risk assessment. The use of aggregations of toxicity study results (exposure-response, (Q)SAR, PBPK parameters) will be examined as a means to expedite the hazard identification and exposure-response relationship steps of the risk assessment paradigm, and to improve the resulting estimates of risk. As a part of this discussion, the use of innovative presentations of the aggregated information will be presented, as will techniques to present relevant comparisons between the resultant health effect reference values.

W-3. Intermediate Topics in Health Risk Assessment of Chemical Mixtures

Co-chairs:
Teuschler, Linda K., M.S., *U.S. EPA, Office of Research and Development, National Center for Environmental Assessment*
Mumtaz, Moiz, Ph.D., D.A.B.T., *Agency for Toxic Substances and Disease Registry*
Rice, Glenn E., M.S., *U.S. EPA, Office of Research and Development, National Center for Environmental Assessment*
Hertzberg, Richard C., Ph.D., *Emory University*

This half-day workshop presents intermediate topics and hands-on exercises on risk based methodologies for assessing cumulative health risk from exposure to chemical mixtures, emphasizing issues such as multiple route exposures, internal dose metrics, pharmacokinetic modeling and toxicological interactions. A brief overview will be given on basic concepts and terminology; the bulk of the course will introduce cutting edge chemical mixture health risk assessment risk issues, explanation of state-of-the-art methods, and hands on exercises for several important classes of chemical mixtures (e.g., pesticides, metals, drinking water disinfection by-products). Workshop topics include: methods for incorporating and interpreting toxicologic interactions data in a risk assessment; discussions of exposure issues unique to chemical mixtures (e.g., environmental transformations); use of physiologically-based pharmacokinetic modeling

of interactions and multiple route exposure assessment; and assessing mixtures of chemicals representing similar and dissimilar toxic modes of action. The content of this workshop includes a general overview of chemical mixture health risk assessment data evaluation and procedures, a detailed description of several new methods, and in-depth hands-on exercises with test data sets. Discussions include real world examples, exercise results, issues for application of the procedures, and general questions and comments. **Participants are asked to bring a calculator.**

This course provides information on the latest methods for chemical mixtures health risk assessment. It targets people familiar with chemical mixtures risk assessment who are interested in stretching beyond simple concepts. For example, interested individuals might include those who have: conducted Superfund/RCRA site assessments, worked on Food Quality Protection Act (1996) issues regarding cumulative risk, studied community based risk assessments of multiple chemicals, conducted pharmacokinetics modeling, applied methods based on additivity concepts (e.g., hazard index, response addition) to simple chemical mixtures, been involved with human or toxicological studies on chemical mixtures, or taken an introductory course in Chemical Mixtures Health Risk Assessment. Emphasis will be on the presentation of new approaches and hands-on exercises representing the latest thinking in this area.

W-4. Replacing Default Values for Uncertainty Factors with Chemical Specific Adjustment Factors: Reducing Uncertainty in Noncancer Risk Assessment

Co-chairs:

Haber, Lynne, Ph.D., D.A.B.T., *Toxicology Excellence for Risk Assessment*

Zhao, Jay, M.P.H., Ph.D., D.A.B.T., *Toxicology Excellence for Risk Assessment*

The World Health Organization, through the International Programme on Chemical Safety (IPCS), has established guidance on the use of mechanistic data to replace default uncertainty factors for interspecies extrapolation and intraspecies variability in deriving risk values such as Reference Doses (RfDs) and Tolerable Concentrations (TCs). This guidance informs the choice and application of data that can be used to replace defaults with chemical specific adjustment factors (CSAFs), resulting in values that better reflect the data for the chemical of interest. CSAFs fall on the continuum of the use of data in deriving risk values. At one end of the continuum is the use of the traditional defaults, while at the other end is the use of extensive chemical-specific data in physiologically-based pharmacokinetic (PBPK) modeling, or even biologically-based dose-response (BBDR) modeling. In between these two extremes are the use of categorical defaults (e.g., the dosimetric approach used in the U.S. EPA's RfC and cancer risk assessment methods), and CSAFs. The CSAF framework is based on early work by Renwick and applied by IPCS. This approach first subdivides the uncertainty factors for interspecies differences (UFA) and human variability (UFH) into toxicokinetic (TK) and toxicodynamic (TD) components. The data relevant for each subcomponent is then evaluated to determine whether chemical-specific data can be used in place of the default. Any one or all of these four subfactors can be replaced by chemical-specific data. Use of the CSAF framework allows the improved use of available data in deriving risk values, and can assist in targeting new studies to address uncertainties and lead to more accurate risk values. CSAFs have been used by the U.S. EPA in deriving an RfD for boron and by Health Canada in deriving a TC for 2-butoxyethanol. This half-day workshop will provide a brief review of the use of uncertainty factors and historical perspective on the reliance on quantitative data to develop values for inter- and intraspecies extrapolation. The course will focus on the IPCS methodology for CSAF

development, including the thinking process and steps used for evaluating data. Examples and classroom activities will be used as instructional aids.

Discussion Session: The United States Environmental Protection Agency's Integrated Risk Information System (IRIS): An Overview and Update
Attendees open

Co-chairs:
Rieth, Susan, M.P.H., *U.S. EPA, Office of Research and Development, National Center for Environmental Assessment, IRIS Program Director*
Strong, Jamie B., Ph.D., *U.S. EPA, Office of Research and Development, National Center for Environmental Assessment, IRIS Program*
Hawkins, Belinda S., Ph.D., D.A.B.T., *U.S. EPA, Office of Research and Development, National Center for Environmental Assessment*

U.S. EPA's IRIS Program develops Agency-wide positions on the potential human health effects from exposure to various chemical substances found in the environment. These positions and their scientific justifications are presented on the EPA internet database [www.epa.gov/iris]. IRIS health assessments provide toxicity information often used by EPA regulatory programs, states and international governments to make decisions on national environmental standards and waste site cleanups. The development of each IRIS assessment involves a survey and summary of health effects information, and an evaluation of its qualitative and quantitative significance. The science upon which the IRIS program relies is evolving, indicating the need for continued updates to assessments on the database. Each new assessment and reassessment requires EPA to fully evaluate new science as well as apply new risk assessment methodologies. Examples of issues related to EPA's IRIS assessments from the past several years and several on-going assessments will be presented in this session for discussion. These examples illustrate a range of advances in risk assessment and innovations in IRIS assessments, including the application of mode of action information to both noncancer and cancer assessments, assessment of hazard from less-than-lifetime exposures, use of human data in assessments, use of benchmark dose methods and PBPK modeling, and characterization of uncertainty.

6:00 p.m. – 10:00 p.m. **Social Event – TBD**

Tuesday, April 24, 2007 **8:00 a.m. – 11:45 a.m.**

Morning Session

8:00 a.m. – 8:15 a.m. **Opening Remarks**

1. Plenary Title
Co-Chairs:
Keshava, Nagu, Ph.D., *U.S. EPA, Office of Research and Development, National Center for Environmental Assessment*
Roszell, Laurie E., Ph.D., D.A.B.T., *U.S. Army Center for Health Promotion and Preventive Medicine*

8:15 a.m. **Answering DoD's Emerging Contaminant Challenge: How Risk Assessment Supports the Enterprise**
Cunniff, Shannon E., M.S., *Office of the Deputy Under Secretary of Defense (Installations and Environment), Director, Emerging Contaminants*

9:00 a.m. **Recent Issues and Challenges in Health Assessments**
Vandenberg, John J., Ph.D., *U.S. EPA, Office of Research and Development, National Center for Environmental Assessment, Associate Director for Health*

9:45 a.m. **Break**

10:15 a.m. **Title**
Slikker, William, Jr., Ph.D., *Food and Drug Administration, Director, National Center for Toxicological Research*

10:45 a.m. **Title**
Cogliano, Vincent James, Ph.D., *International Agency for Research on Cancer, Head, IARC Monograph Programme*

11:15 a.m. **Panel Discussion**

11:45 a.m. – 1:00 p.m. **Lunch**

Tuesday, April 24, 2007 **1:00 p.m. – 5:00 p.m.**

Afternoon Sessions

1:00 p.m. – 5:00 p.m. **Sessions 2A, 2B and 2C**

3:00 p.m. – 3:30 p.m. **Break**

5:00 p.m. – 6:30 p.m. **Panel Discussion**

2A. Uncertainty and Variability in Dose-Response Assessment

Co-chairs:
Mattie, David R., Ph.D., D.A.B.T., *Air Force Research Laboratory, Applied Biotechnology Branch*
Swartout, Jeffrey, M.S., *U.S. EPA, Office of Research and Development, National Center for Environmental Assessment*

Predictions of risk (response) are often made from the extrapolation of findings from one species to another, from general populations to susceptible individuals, and to exposures far below the observed range. Uncertainty and variability inherent to any data set and to any physical or biological model make interpretation of the predictions difficult, particularly as variability is always confounded by uncertainty., While confidence in a single-population dose-response analysis can often be presented in a straightforward manner (e.g., confidence bounds), complications arise when multiple extrapolations are incorporated into one model, entailing the combination of multiple data sets. The establishment of Reference levels for human health risk assessment presents an instance where multiple data sets are combined and results extrapolated to produce a final value. While the Reference Dose concept was originally communicated as less than a "bright line" concept ("with uncertainty spanning perhaps an order of magnitude"), present needs for more quantification, and for economic comparisons require the prediction of actual response levels, rather than ambiguous pseudo-threshold reference values, such as the RfD. Additional treatment of variability can inform the distribution of extrapolated values, but an uncertainty analysis is required to determine the level of confidence that can be placed in measures of variability. This session will present basic methods for determining the impact of parameter uncertainty and variability, demonstrate uncertainty analysis for a dose-response data set, communicate probabilistic methods used for inter and intraspecies extrapolation, present a PBPK modeling-based approach to assessing human variability and demonstrate an uncertainty analysis applied to the output of a PBPK model.

Toxicokinetic and Toxicodynamic Considerations in the Derivation of Traditional Animal- to-Human and Human-to-Sensitive Human Uncertainty Factors (UF_A and UF_H) - A Historical Perspective

Gift, Jeffrey S., Ph.D., *U.S. EPA, Office of Research and Development, National Center for Environmental Assessment*

Uncertainties in PBPK Model Development and an Example Application for Dose-response Assessment

Gearhart, Jeffery M., Ph.D., D.A.B.T., *The Henry M. Jackson Foundation for the Advancement of Military Medicine, Inc., Air Force Research Laboratory, Applied Biotechnology Branch*

Analysis of Uncertainty and Variability in PBPK Dose Metric Predictions

Hack, C. Eric, M.S., *The Henry M. Jackson Foundation for the Advancement of Military Medicine, Inc., Air Force Research Laboratory, Applied Biotechnology Branch*

Human Interindividual Variability in Pharmacokinetic and Pharmacodynamic Parameters

Hattis, Dale, Ph.D., *Clark University*
Modeling Animal-to-human Extrapolation of Threshold-Acting Responses to Chemical Exposures
Swartout, Jeffrey, M.S., *U.S. EPA, Office of Research and Development, National Center for Environmental Assessment*

Characterizing Interspecies Uncertainty for Animal-to-human Extrapolation of Noncancer Effects
Keenan, Russell, E., Ph.D., *AMEC Earth & Environmental, Inc.*

2B. Recent Advances in Toxicity and Risk Assessment of RDX

Co-Chairs:
Reddy, Gunda, Ph.D., D.A.B.T., *U.S. Army Center for Health Promotion and Preventive Medicine*
Hawkins, Belinda S., Ph.D., D.A.B.T., *U.S. EPA, Office of Research and Development, National Center for Environmental Assessment*

The nitramine compounds, such as cyclotrimethyltrinitramine (RDX), have been used extensively in military munitions since World War II. The widespread manufacturing and military use of RDX has resulted in contamination of soil, water and sediment at Army installations and wastewater disposal sites. Contamination has also been reported at military ranges. Environmental RDX contamination may be hazardous to both human health and ecosystems. The Department of Defense (DOD) initially conducted toxicity evaluations of RDX in the early 1980s and an oral RfD, drinking water health advisories and remediation standards were subsequently developed. In this session, recent toxicity data on RDX will be presented and its implication for future RDX risk assessment will be discussed.

1:00 p.m. **Introduction**
Hawkins, Belinda S., Ph.D., D.A.B.T., *U.S. EPA, Office of Research and Development, National Center for Environmental Assessment*

1:05 p.m. **Subchronic Oral Toxicity of RDX in Fischer-344 Rats**
Crouse, Lee C.B., M.S., *U.S. Army Center for Health Promotion and Preventive Medicine*

1: 45 p.m. **Toxicokinetics and Metabolism of ^{14}C-RDX in Yucatan Minipigs**

Reddy, Gunda, Ph.D., D.A.B.T., *U.S. Army Center for Health Promotion and Preventive Medicine*
Major, Michael A., Ph.D., D.A.B.T., *U.S. Army Center for Health Promotion and Preventive Medicine*

2:20 p.m. **Physiologically-based Pharmacokinetic Modeling of RDX in Rats**
Krishnan, Kannan, Ph.D., *University of Montreal, Canada*

3:00 p.m. **Break**

3:30 p.m. **Reevaluation of Carcinogenicity of RDX**
Major, Michael A., Ph.D., D.A.B.T., *U.S. Army Center for Health Promotion and Preventive Medicine*

4:00 p.m. **Acute and Subchronic Effects of RDX and its Transformation Products**
Cobb, George P., Ph.D., *Texas Tech University, The Institute of Environmental and Human Health*

4:30 p.m. **Fate and Metabolism of RDX in the Environment**
Hawari, Jalal, Ph.D., *National Research Council of Canada, Montreal, Canada*

2C. The Use of Epidemiologic Data for Risk Assessment Applications

Co-chairs:
Wright, J. Michael, Sc.D., *U.S. EPA, Office of Research and Development, National Center for Environmental Assessment*
Park, Robert M., M.S., *National Institute for Occupational Safety and Health*

Epidemiological data can be used to inform each step of the risk assessment paradigm. This session focuses on the challenges of using epidemiological data for risk assessment applications. The following presentations will highlight the strengths and weaknesses of using existing epidemiological data in risk assessments, including discussion of the concordance between toxicological and epidemiological data. Results will be presented from recent and ongoing epidemiological studies that have helped advance exposure and risk assessment approaches.

1:00 p.m. **Arsenic In Drinking Water And Human Health Effects**
Hopenhayn, Claudia, Ph.D., *University of Kentucky, College of Publlic Health, Department of Epidemiology*

1:40 p.m. **Risk of Leukemia at Low-Doses: The NIOSH Multi-site Leukemia Case-control Study**
Schubauer-Berigan, Mary K., Ph.D., *National Institute for Occupational Safety and Health*

2:20 p.m. **Use of Epidemiology Data in IRIS Assessments**
Persad, Amanda, Ph.D., D.A.B.T., *U.S. EPA, Office of Research and Development, National Center for Environmental Assessment*

3:00 p.m. **Break**

3:30 p.m. **Using Human Data to Protect Public Health**
Dourson, Michael, Ph.D., D.A.B.T., *Toxicology Excellence for Risk Assessment.*

4:00 p.m. **Are We Ready to Consider Genetic Susceptibility in Risk Assessment?**
Carreón-Valencia, Tania, Ph.D., *National Institute for Occupational Safety and Health; University of Cincinnati, Department of Environmental Health*

4:30 p.m. **Pitfalls of Neonatal Biomonitoring: Clinical Versus Scientific Interpretation**
Williams, Bryan L., Ph.D., *University of Tennessee Health Science Center, Department of Pediatrics*

Panel Discussion Session: Federal Agency Toxicology Training Needs: New Faces and New Tools for the 21st Century

5:00 – 6:30 p.m.

Rappoteur:
Fowler, Bruce A., Ph.D., Fellow A.T.S., *Agency for Toxic Substances and Disease Registry, Senior Biomedical Research Service*

There is growing concern in a number of Federal agencies with regard to the retirement of experienced toxicologists and the apparent dearth of well-trained replacements to replace them. This problem is only becoming more acute due to budget cutbacks and the advent of new chemical challenges resulting from high technology. Toxicologists from several Federal agencies are being asked to address chemical safety issues for nanotechnology products, biotechnology innovations, and concerns related to potential chemical/biological terror agents in a timely manner. To address these issues, the next generation of toxicologists will need new tools and cutting edge training, and they must be produced in sufficient numbers to effectively replace the current cadre of toxicologists as they retire or move to other sectors. A necessary first step in assuring that a gap in qualified toxicologist does not occur in the Federal sector is to begin a dialogue among the various Federal agencies on projected future needs in toxicology and what sorts of training would be advantageous. We quite simply need to get a clear picture of what sorts of toxicologists and in what numbers will be needed over the next 10 years in the Federal sector. Similar evaluations should also be conducted for the academic and industrial sectors but this session could be a first step towards addressing this problem at a meeting where most of the concerned Federal agencies are present. This information could then be transmitted to those agencies that support toxicology training programs (i.e., NIEHS) and professional organizations such as the SOT and ACT which are concerned with toxicology training issues. It is likely that this session will be an "ice-breaker" on this cross-cutting topic and follow-up discussions will be needed to develop an effective approach to these training needs. Speakers from the various Federal agencies will present overview estimates of toxicological needs for their respective agencies followed by an open discussion.

An Overview of the Problem
Schwetz, Bernard A., D.V.M., Ph.D., *Department of Health and Human Services, Director, Office for Human Research Protections*

Major, Michael A., Ph.D., D.A.B.T., *U.S. Army Center for Health Promotion and Preventive Medicine*

Zenick, Harold, Ph.D., *U.S. EPA, Office of Research and Development, Director, National Health and Environmental Effects Research Laboratory*

Slikker, William, Jr., Ph.D., *Food and Drug Administration, Director, National Center for Toxicological Research*

Castranova, Vincent, Ph.D., *National Institute for Occupational Safety and Health, Health Effects Laboratory Division*

Shreffler, Carol, Ph.D., *National Institutes of Health, National Institute of Environmental Health Sciences*

De Rosa, Christopher T. , Ph.D., *Agency for Toxic Substances and Disease Registry, Director, Division of Toxicology* or Fowler, Bruce A., Fellow A.T.S., *Agency for Toxic Substances and Disease Registry, Senior Biomedical Research Service*

Tuesday, April 24, 2007 **6:00 p.m. – 8:00 p.m.**

Evening Session

Poster Session/Reception

Co-chairs:
Stevens, Sean, Lt., *Air Force Research Laboratory, Applied Biotechnology Branch*
Daunt, Patricia A., *U.S. EPA, Office of Research and Development, National Center for Environmental Assessment*

Wednesday, April 25, 2007 **8:00 a.m. – 11:45 a.m.**

Morning Sessions

3A. Cumulative Health Risk Assessment: Advances in Approaches

Co-chairs:
Teuschler, Linda K., M.S., *U.S. EPA, Office of Research and Development, National Center for Environmental Assessment*
Roszell, Laurie E., Ph.D., D.A.B.T., *U.S. Army Center for Health Promotion and Preventive Medicine*

Cumulative risk assessment (CRA) has been defined as, “the combined risks from aggregate exposures to multiple agents or stressors”, where agents or stressors may include chemicals, as well as biological or physical agents (e.g., microbial exposures, stress, nutritional status), or the absence of a necessity such as habitat (US EPA’s 2003 *Framework for CRA*). CRA, then, is an analysis, characterization, and possible quantification of the combined risks to health or the environment from multiple agents or stressors. As such, it is an important concept to scientists investigating environmental justice concerns, community based health risks, and combinations of stressors under adverse conditions such as industrial settings and military combat. Government organizations have published documents dealing with specific aspects of cumulative risk, such as chemical mixture risk assessment, planning and scoping, stakeholder involvement, and health risks from exposure to mixtures of pesticides that share a common toxic mode of action. New information and approaches are being developed to evaluate other aspects of cumulative risk, e.g., consideration of the composite impact of multiple health effects, grouping chemicals based on exposure characteristics and toxic endpoints, exploring the concept of vulnerability for susceptible subpopulations and

differentially exposed people, and the emphasis on the iteration and collaboration between exposure assessment and dose-response assessment to ensure compatible and relevant information. Potential users of cumulative risk information include governmental and industrial risk assessors involved in multi-chemical, population-focused assessments such as, Superfund site assessment and remediation, drinking water treatment system evaluation, pesticide mixture exposures, adverse combat conditions that include chemical exposures and other stressors, and communities with environmental justice concerns.

An Overview of EPA's Activities in Cumulative Risk Assessment
Callahan, Michael A., Ph.M., *U.S. EPA, Region 6*

Exposure Assessment Methods for Cumulative Chemical Risks
Rice, Glenn E., M.S., *U.S. EPA, Office of Research and Development, National Center for Environmental Assessment*

Interactive Effects of Co-exposure to Lead, Cadmium, or Arsenic at Lowest Observed Effect Levels: Nephrotoxicities, Oxidatve Damage, and Stress Response
Wang, Gensheng, Ph.D., *University of Texas, M.D. Anderson Cancer Center, Experimental Radiation Oncology*

Studies of the Effects of Stress on Neurotoxicity
Jortner, Bernard S., D.V.M., D.A.C.V.P., *Virginia Tech, Virginia-Maryland Regional College of Veterinary Medicine*

Thermoregulatory Responses to Environmental Stressors: The Interaction of Thermal Stress and Toxicant Exposure
Leon, Lisa R., Ph.D. *U.S. Army Research Institute of Environmental Medicine, Thermal Mountain Medicine Division*

Risk Assessment in International Military Operations
Stricklin, Daniela, Ph.D., M.P.H., *FOI, Swedish Defense Research Agency, Umeå, Sweden*

3B. Predictive vs Protective Risk Analysis

Co-chairs:
Hinz, John, Ph.D., *Air Force Institute for Operational Health*
Johnson, Joleen, M.H.S., *U.S. Army Center for Health Promotion and Preventive Medicine*

An important application of the science of toxicology to societal issues is the derivation of exposure limits that are protective of human health and the environment. Extrapolation from controlled laboratory experiments to occupational or environmental human exposures is generally accompanied by the use of corrective factors to account for differences between human responses and laboratory animal responses. While these corrections are termed “uncertainty factors”, and uncertainty can theoretically exist in either direction, they are generally used to decrease exposure values in the interest of being protective. In those cases where accurate realistic predictions of consequences

are required to compare competing risks, prioritize the application of limited resources, or to minimize lives lost, protective risk assessment methodologies do not provide the required realistic predictive power. This session will examine the need for new methodologies for realistic predictive risk assessment to support prioritizing and decision-making in situations where critical trade-offs exist or to provide information on potential health outcomes as consequence of unavoidable exposures.

Framework for Human Relevance Analysis in Risk Assessment
Meek, M.E. (Bette), Ph.D., *Health Canada, Safe Environments Programme, Ottawa, Ontario*

Predicting Risk above EPA Reference Doses (RfD)
Dourson, Michael , Ph.D., D.A.B.T., *Toxicology Excellence in Risk Assessment*

TBD

Break

Evidence-based Toxicology in Derivation of a *bis*-Phenol A Oral Reference Dose
Willhite, Calvin, Ph.D., *Department of Toxic Substances Control, State of Calfornia*

Estimating Exposure Concentrations of Acrolein that Result in Toxic Effects – Eye Irritation to Death
Kutzman, Raymond, Ph.D., D.A.B.T., *Mitretek Systems*

Predictive vs Protective Aspects of AEGLs
Tobin, Paul S., Ph.D., *U.S. EPA, Office of Pollution Prevention and Toxics*

3C. Biomarkers of Exposure and Effects

Co-chairs:
Keshava, Nagu, Ph.D., *U.S. EPA, Office of Research and Development, National enter for Environmental Assessment*
Fowler, Bruce A., Ph.D., Fellow A.T.S., *Agency for Toxic Substances and Disease Registry, Senior Biomedical Research Service*

Identification of new biomarkers is rapidly increasing with the availability of advanced and sensitive techniques. With the continuing advances in genomics, proteomics and other computational technologies, an improvement in designing future biomarker studies is expected which will facilitate the identification of risk to human population. For example, ProteinChip technology coupled with surface-enhanced laser desorption/ionization time-of-f light mass spectrometry facilitates protein profiling of complex biological mixtures These biomarkers of exposure, effect and susceptibility are effectively being used in providing new insights into the progression of a disease. In this session, a series of presentation will include identification of biomarkers using new tools/technology will be presented.

8:00 a.m. **Introduction: Use of Biomarkers in Risk Assessment – a Brief Overview**
Keshava, Nagu, Ph.D., *U.S. EPA, Office of Research and Development, National Center for Environmental Assessment*

8:15 a.m. **Chromosomal Alterations as Biomarkers of Cancer and Hereditable Risks in Human Populations**
Eastmond, David A., Ph.D., *University of California, Environmental Toxicology and Department of Cell Biology*

8:45 a.m. **Urinary Mutagenicity: A Biomarker of Genotoxic Exposures via Air, Water, and Diet**
DeMarini, David, Ph.D., *U.S. EPA, Office of Research and Development, National Health Environmental and Effects Research Laboratory*

9:15 a.m. **Genetic Changes as Biomarkers of Mouse Lung Adenocarcinoma: Comparison to Human**
Sargeant, Linda, Ph.D., *National Institute for Occupational Safety and Health*

9:45 a.m. **Break**

10:15 a.m. **Proteomic and Metabolomic Biomarker**
Fowler, Bruce A., Ph.D., Fellow A.T.S., *Agency for Toxic Substances and Disease Registry, Senior Biomedical Research Service*

10:45 a.m. **Biomarker-based OELs and Risk Assessments**
Savage, Russell E., Jr., Ph.D., *National Institute for Occupational Safety and Health*

11:15 a.m. **Integrated Bioinformatics – An FDA Experience**
Weida Tong, Ph.D., *Food and Drug Administration, National Center for Toxicological Research*

Afternoon Sessions

1:00 p.m. – 5:00 p.m. **Sessions 4A, 4B and 4C**

3:00 p.m. – 3:30 p.m. **Break**

4A. Health Hazards of Particulate Matter/Nanomaterials

Co-Chairs:
Chapman, Gail D., Commander, MBA, Ph.D., *U.S. Navy, Naval Health Research Center Detachment, Environmental Health Effects Laboratory*
Harvey, Lana D., M.S., *Air Force Institute for Operational Health, Health Risk Assessment Branch*

Adverse health effects resulting from exposure to dusts, soils and other geologic materials as well as engineered nanomaterials.

Do the health effects of particulate matter, e.g., dusts, soils, other geological materials, correlate to that of engineered nanomaterial in the mammalian system? How can we use what we know about the circumstances in which these materials and processes can be harmful so that serious environmental health problems can be reduced or avoided? Through a combination of in vivo and in vitro studies as well as traditional toxicology using epidemiological studies and reviews, researchers have assessed what is known regarding PM exposure and its concomitant health effects. With the advent of nanotechnology and the exploitation of molecule structure and processes to form novel materials with new applications such as biosensors, protective coatings, medical therapeutics, etc., the potential for health risk is magnified by the rate of development of these technologies, their "new frontier" applications and the lack of standardized technologies to determine their risks. Given that all chemicals can be toxic depending on dose, exposure and duration, the implications are mindboggling with regard to the potential cradle to grave interactions with biomaterial of these manufactured nanomaterials. Additionally, occupational health risks associated with manufacturing are not yet clearly understood. This session aims to discuss the health effects of particulate matter/nanomaterials through the fields of toxicological geochemistry and medical geology, then move on to some comparative toxicology of air pollution particles, the epidemiology of PM exposures, and the toxicity of ultra/nanoparticles both man-made and natural in origin.

1:00 p.m. **Introduction**
????????

1:10 p.m. **The Impacts of Natural Mineral Dust on Human Health**
Finkelman, Robert B., Ph.D., *University of Texas at Dallas*

1:45 p.m. **The Toxicological Geochemistry of Dusts, Soils, and Other Earth Materials**
Plumlee, Geoffrey S., Ph.D., *U.S. Geological Survey*

2:20 p.m. **Chemical and Microspectroscopic Characterization of PM_{20-40} and $PM_{>10}$**
Lyles, Mark B., CDR, DC, *United States Naval Reserve, M53 Future Plans and Strategies – Exercises, Bureau of Medicine and Surgery*

3:00 p.m. **Break**

3:30 p.m. **Epidemiological Insights into the Clinical Implications of Elevated Particulate Matter Levels in Deployed Settings**
Weese, Coleen B., M.D. M.P.H., FACOEM, *U.S. Army Center for Health Promotion and Preventive Medicine, Occupational and Environmental Medicine Program*

4:00 p.m. **Approaches for Assessing Toxicological Properties of Engineered and Environmental Nanomaterials**
Finkelstein, Jacob N., Ph.D., *University of Rochester School of Medicine*

4:30 p.m. **The Cardiovascular Effects of Pulmonary Exposure to Nanoparticles**
Castranova, Vincent, Ph.D., *National Institute for Occupational Safety and Health, Health Effects Laboratory Division*

4B. Contemporary Issues and Approaches in Children's Risk Assessment

Co-chairs:
Barone, Stanley, Jr., Ph.D., *U.S. EPA, Office of Research and Development, National Center for Environmental Assessment*
Moffett, Daphne B., CDR, Ph.D., *U.S. Public Health Service, Agency for Toxic Substances and Disease Registry*

Examination of population variability in response remains a vexing problem for risk assessors and public health policy makers. This population variability is predicated on differences in vulnerability due to exposure and intrinsic factors like critical windows of susceptibility. In the last year, additional guidance and approaches have been proposed which have significant bearing on assessment of the health effects following exposures during early lifestage. These current approaches employ contemporary toxicological principles including methods and models using pharmacokinetic and pharmacodynamic information to inform mode of action that may explain adverse health outcomes. It has become increasingly apparent that exposures occurring during these critical developmental windows may not manifest into adverse health outcomes until much later in life. This complicates the assessment of risk for developmental exposures to environmental agents.

1:00 p.m. **Overview of Children's Risk Assessment Framework: Employing a Lifestage Approach**
Barone, Stanley, Jr., Ph.D., *U.S. EPA, Office of Research and Development, National Center for Environmental Assessment*

1:30 p.m. **Overview of the Revisions to the Child-specific Exposure Factors Handbook**
Moya, Jacqueline, Ph.D., *U.S. EPA, Office of Research and Development, National Center for Environmental Assessment*

2:00 p.m. **Application of Probabilistic Approaches to Children's Exposure Estimation**
Cohen-Hubal, Elaine, ?????U.S. EPA, Office of Research and Development, *National Center for Computational Toxicology*

2:30 p.m. **Association of Biomarkers of Exposure with Neurological Effects in Children**
Stewart, Paul., Ph.D., *University of New York at Oswego, Department of Psychology*

3:00 p.m. **Break**

3:30 p.m. **Evaluation of Risk in a Multi-Stressor Environment?**
Pohl, Hana, M.D., Ph.D., *Agency for Toxic Substances and Disease Registry, Division of Toxicology and Environmental Medicine*

4:00 p.m. **A Clinician's Perspective on How Do We Communicate Community Risk and Individual Risk**
Foreman, Joel, M.D., *George Washington University, Mid-Atlantic Center for Children's Health and the Environment*

4:30 p.m. **Panel Discussion**

4C. Assessment of Microbial Risks from Drinking Water: The Role of Quantitative Microbial Risk Assessment in Regulatory Support

Co-chairs:
Rothermich, Mary, Ph.D., M.P.H., *U.S. EPA, Office of Research and Development, National Center for Environmental Assessment*
Swartout, Jeffrey, B.S., *U.S. EPA, Office of Research and Development, National Center for Environmental Assessment*

The U.S. EPA utilizes scientific and public health information to formulate policies and regulations for drinking water protection, treatment, and distribution. The Agency emphasizes risk-based decision making, and there has been considerable progress in the development and application of risk assessment methods for evaluating the human health risks associated with environmental exposures to toxic chemicals. More recently, statistical methods for estimating the risk of infection from exposure to low doses of pathogenic microorganisms have been developed and risk assessors have used quantitative risk assessment methodology to estimate the human health risk associated with environmental exposures to microbes. The Agency has already employed a formal risk assessment methodology, structured according to the basic National Academy of Sciences paradigm for chemical risk assessment, to conduct the microbial risk assessments used for the economic analyses for the Long Term 2 Enhanced Surface Water Treatment Rule and the Groundwater Rule. However, unique characteristics of pathogens and infectious diseases, as well as extremely limited data, have raised various scientific issues associated with quantitative microbial risk assessments (QMRAs). This session includes presentations that illustrate some of the complex issues associated with the rigorous conduct of QMRA. These include a discussion of the potential applications of QMRA analyses for drinking water standards; an analysis of the dose-response functions used for QMRA and the uncertainties associated with the human data that is used; the exposure assessment challenges that confront us; the dynamic nature of infectious disease transmission systems; and the implications of population immunity.

1:00 p.m. **The Role of Risk Assessment in Drinking Water Regulation Development and Current Perspectives on Such Application to Support a Potential Revised TCR/DSR**
Regli, Stig, M.S., *U.S. EPA, Office of Water, Office of Ground Water and Drinking Water*

1:40 p.m. **Estimating Pathogen Exposures – The Critical Challenge for QMRA to Support Regulation and Management of Waters**
Ashbolt, Nicholas J., Ph.D., *U.S. EPA, National Exposure Research Laboratory*

2:20 p.m. **The Effect of Record Length on the Assessed Microbial Dose in Drinking Water**
Englehardt, James, Ph.D., *University of Miami*

3:00 p.m. **Break**

3:30 p.m. **The Utility of Pathogen Dose-response Data for Human Health Risk Assessment**
Swartout, Jeffrey, B.S., *U.S. EPA, Office of Research and Development, National Center for Environmental Assessment*

4:00 p.m. **Disease Transmission Models for Public Health Decision Making**
Eisenberg, Joseph, N.S., Ph.D., M.P.H., *University of Michigan*

4:30 p.m. **Panel Discussion**

Thursday, April 27, 2007 **8:00 a.m. - 4:00 p.m.**

Workshops

Workshop Chair:
Zwayer, Bette, *U.S. EPA, Office of Research and Development, National Center for Environmental Assessment*

8:00 a.m. - 12:00 p.m. **Workshop W-5, Discussion Session**

8:00 a.m. - 4:00 p.m. **Workshop W-6, W-7**

10:00 a.m. - 10:20 a.m. **Break**

2:10 p.m. - 2:30 p.m. **Break**

1 hour 15 minute **Lunch Break**

W-5. A Risk Communication Primer

Presenters:
Forrest, Melissa, B.S., *Environmental Programs Directorate, Navy Environmental Health Center*
Markwith, Glenn Paige, B.S., *Environmental Programs Directorate, Navy Environmental Health Center*

This short course provided by the Navy Environmental Health Center in Portsmouth, VA is an introduction to the basic concepts and principles of effective risk communication.

The program highlights key elements of a successful risk communication strategy, identifies potential barriers to effective communication, explains good key message content and development and discusses the mechanics of managing a successful open house public meeting. The course uses interactive examples, media clips and DoD site and topic-specific examples to illustrate key points. It is highly recommended for those that are new to the risk communication field as well as seasoned program managers seeking to brush up on their risk communication skills.

Discussion Session: Chemicals and Substances of Common and Emerging Concern
Attendees open

Co-chairs:
Mattie, David R., Ph.D., D.A.B.T., *Air Force Research Laboratory, Applied Biotechnology Branch*
Johnson, Mark S., Ph.D., *U.S. Army Center for Health Promotion and Preventive Medicine, Health Effects Research Program*

National defense requires the use of a vast number of chemical substances, many common to industrial use and many specific to the military (e.g., energetics, propellants, explosives, etc.). Training and testing of equipment that uses these substances can result in the contamination of the environment at varying levels in various media. For the military unique substances, data is still necessary for a complete evaluation of health risks, both ecological and human. Participants of this discussion group will discuss chemical compounds of common concern that require additional data to help reduce uncertainty and accurately assess the risks from exposure, both human and ecological. Participants will also be asked to identify their chemicals of highest concern. Known exposure consequences, identification of remaining research needs for establishing reasonable exposure standards and regulatory issues are potential discussion topics as time permits. Updates on issues, relevant organizations and status of highest priority chemicals will be presented or made available as well.

W-6. EPA's CatReg Software for Concentration (Dose)-Time-Response Relationships

Presenters:
Brown, Kenneth G., Ph.D., *KB, Inc.*
Howard, Angela, Ph.D., *U.S. EPA, Office of Research and Development, National Center for Environmental Assessment*
Gift, Jeffrey S., Ph.D., *U.S. EPA, Office of Research and Development, National Center for Environmental Assessment*

Attendees of this course will receive an introduction to the use of the CatReg Software program in the analysis of toxicological data for chemical risk assessment. CatReg uses a categorical regression approach to data analysis. There are often categories of severity of an adverse response (e.g., no effect, mild effect, irreversible effect, life-threatening effect) that can provide additional information to supplement traditional dose-response assessment methods. It is particularly well suited to the assessment of risk where exposure duration may be an important factor in the occurrence of adverse effects. CatReg allows users to estimate, for example, the doses across exposure

durations (time) that would have a 10% probability (ERC_{10}) of causing a particular effect severity or higher, taking into account the exposure concentrations and durations that cause effects in all user defined severity categories.

This course will discuss options available within CatReg, including modeling options (e.g., probit/log-probit or logit/log-logit), and other options for addressing the relationship between response curves of different severity levels. Other features that will be highlighted through case examples include: (1) the calculation of the value of the parameter "n" in C^nT (as proposed by ten Berge et al., 1986) which can be estimated for concentration-time relationships; (2) how to use stratification (i.e., segregation of data to compare results) and (3) testing to determine how covariates that differ between studies, such as species, affect the concentration-response relationship.

W-7. Epidemiologic Fundamentals for Risk Assessment Applications

Presenters:
Wright, J. Michael, Sc.D., *U.S. EPA, Office of Research and Development, National Center for Environmental Assessment*
Murphy, Patricia A., Ph.D., M.P.H., *U.S. EPA, Office of Research and Development, National Center for Environmental Assessment*
Egorov, Andrey, Sc.D., *U.S. EPA, Office of Research and Development, National Center for Environmental Assessment*
Bateson, Thomas, Sc.D., *U.S. EPA, Office of Research and Development, National Center for Environmental Assessment*

Data and information from epidemiologic studies can be used qualitatively and quantitatively in the different phases of risk analysis. This is a full day workshop devoted to the introduction of epidemiologic principles and general applications of epidemiologic information in risk analysis. The workshop is targeted to the non-epidemiologist working in the general area of environmental health risk assessment. The goal for workshop participants is to become intelligent consumers of epidemiologic information and recognize opportunities for its appropriate application in different risk assessment activities. Participants can take either half or the full session, but material in the first half will be similar to that taught in previous years.

In the first half of the workshop, participants will be introduced to elements of epidemiologic study design and the interpretation of common measures of association. The impact of bias and confounding on relative risk estimates will also be examined. Discussions will focus on identifying strengths and limitations of different types of human data. The first half of the workshop will conclude with a practical exercise in assessing study validity and drawing causal inferences from observational epidemiologic data. The second half of the workshop will be devoted to more advanced epidemiologic principles and include some calculation of common measures of association (calculators required). Introductory statistical principles will also be discussed with application to epidemiologic analyses. This will include defining various types of analytical techniques (e.g., linear, logistic and Poisson regression), with illustrations provided relative to different types of epidemiologic study designs. Case studies where human data was used in risk assessment will also be examined.