

Draft Agenda: 1-31-08

2008 Toxicology and Risk Assessment Conference

The Complexity of Uncertainty: Dealing with Known Unknowns

April 14 – 17, 2008

Conference Co-Chairs: Lambert, Jason C., Ph.D., D.A.B.T., *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*

Monday, April 14, 2008

1:00 p.m. – 5:00 p.m.

Workshops

Workshop Chair:

Zwayer, Bette, C.P.M., *U.S. EPA, Office of Research and Development, National Center for Environmental Assessment*

11:30 a.m. – 5:00 p.m.

Registration

1:00 p.m. – 5:00 p.m.

Workshops W-1, W-2 and W-3

2:30 p.m. – 3:00 p.m.

Break

W-1. Replacing Default Values for Uncertainty Factors

Presenters:

Lipscomb, John C., Ph.D., D.A.B.T., *U.S. EPA, Office of Research and Development, National Center for Environmental Assessment*

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

Zhao, Q. Jay, M.P.H., Ph.D., D.A.B.T., *U.S. EPA, Office of Research and Development, National Center for Environmental 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 is 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. **Participants are asked to bring a calculator.**

W-2. Intermediate Topics in Health Risk Assessment of Chemical Mixtures

Presenters:

Teuschler, Linda K., M.S., *U.S. EPA, Office of Research and Development, National Center for Environmental Assessment*

Mumtaz, Moiz M., 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 methodologies for assessing cumulative health risk from exposure to chemical mixtures, emphasizing issues such as additivity methods, internal dose metrics, physiologically-based pharmacokinetic modeling, toxicological interactions and multiple route exposures. A brief overview will be given on basic concepts and terminology, with the bulk of the course focused on advanced chemical mixture health risk assessment methods with exercises for several important classes of chemical mixtures (e.g., pesticides, metals, drinking water disinfection by-products). Workshop topics include: the development of Relative Potency Factors based on internal dose metrics; mechanistic information and interpretation of toxicological interactions; PBPK modeling of changes in kinetics for a binary mixture; and chemical mixtures risk assessment using multiple route exposures. Discussions include real world examples, exercise results, and general questions and comments.

This course 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, conducted pharmacokinetic modeling, been involved with epidemiological 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-3. Toxicogenomics in Risk Assessment

Presenters:

Hess-Wilson, Janet K., Ph.D., *U.S. EPA, Office of Research and Development, National Center for Environmental Assessment*

Cohen-Hubal, Elaine, Ph.D., *U.S. EPA, Office of Research and Development, National Center for Computational Toxicology*

Ho, Shuk-mei, Ph.D., *University of Cincinnati, College of Medicine*

Nebert, Daniel W., M.D., *University of Cincinnati, College of Medicine*

Toxicogenomics is the discipline that aims to study the complex gene-environment interaction of the cell's genome with a chemical and the associated disease outcome, and is an emerging powerful tool for evaluating the exposure to and effects of environmental stressors. Toxicogenomics has the potential to (1) improve our understanding of an organisms' response to environmental stressors, (2) advance the

development of predictive biomarkers of effect or susceptibility, and (3) enhance the understanding of the molecular mechanisms of toxicity. Advances in genomics have considerable implications for the field of toxicology and risk assessment practices. The workshop will present an introduction to the science and methodologies of genomic research that has direct implications for risk assessment. Presentations will link computational and genomic information to adverse outcomes and demonstrate appropriate usage and interpretation of genomic information for risk and hazard assessment.

Social Event

6:00 p.m. – 10:00 p.m.

*Dinner with the Sharks at
the Newport Aquarium*

Tuesday, April 15, 2008

8:00 a.m. – 11:45 a.m.

Morning Session

8:00 a.m. – 8:15 a.m.

Opening Remarks

Conference Co-Chairs:

Lambert, Jason C., Ph.D., D.A.B.T., *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. – 11:45 a.m.

Plenary Session

9:45 a.m. – 10:15 a.m.

Break

1. Uncertainty in Toxicology and Risk Assessment: How do you Deal with Moving Targets?

Co-Chairs:

Lambert, Jason C., Ph.D., D.A.B.T., *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*

One of the more challenging aspects of both the qualitative interpretation of toxicity data and translation to quantitative estimates of risk is accounting for the uncertainties inherent in the application to human health assessment. Ecosystems and human populations are constantly changing; at the same time the chemical, physical and/or biological stressors to which these systems are exposed are in flux. Exposure and toxicity information pertaining to dose-response and temporal relationships among or between various stressors in exposed populations is limited, leading to uncertainty. Therefore, in risk assessment, uncertainties may arise from extrapolation within or between species, from high experimental dose to low dose, complex exposure scenarios and/or diverse populations.

The goal of this session is to present a broad range of issues and challenges addressing some of these uncertainties. The keynote address highlights the importance of characterizing uncertainty when assessing risk. The presentations following the keynote will address biological or statistical uncertainties in assessing risk across the paradigm, i.e., from identification of potential hazards, dose-response and

exposure assessment, to the application of those data to human populations. This will include addressing the difficulties that arise when populations are exposed to a myriad of stressors, some known and others unknown.

8:15 a.m. Hypothesis-Based Weight of Evidence to Separate Qualitative and Quantitative Aspects of Uncertainty in Risk Assessment

Rhomberg, Lorenz R., Ph.D., Principal, *Gradient Corporation*

9:00 a.m. Application of Computer Simulation to Toxicology and Risk Assessment: Multi-scale Modeling

Yang, Raymond S.H., Ph.D., Fellow A.T.S., *Colorado State University, College of Veterinary Medicine and Biomedical Sciences*

9:35 a.m. The Military Perspective of Uncertainty

Embry, Ellen, M.S., *Office of the Assistant Secretary of Defense, Deputy Assistant Secretary of Defense for Force Health Protection and Readiness*

10:10 a.m. Break

10:40 a.m. Risk Regulation in 3-D: How to See Costs and Benefits as they Truly Are

Finkel, Adam M., Sc.D., M.P.P., C.I.H., *University of Medicine and Dentistry of New Jersey, School of Public Health*

11:15 a.m. Panel Discussion

11:45 a.m. – 1:00 p.m. Lunch

Tuesday, April 15, 2008

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

2A. Pharmaceutical-Related Issues Across Toxicology Disciplines

Co-Chairs:

Roe, Amy L., Ph.D., D.A.B.T., *Procter & Gamble*

Hawkins, Belinda S., Ph.D., D.A.B.T., *U.S. EPA, Office of Research and Development, National Center for Environmental Assessment*

The management of pharmaceutical-related issues and exposures can involve very broad and diverse fields of toxicology. In addition to the obvious issues of safety and efficacy that must be met to serve patient needs, controlling exposures in manufacturing and health care personnel, developing risk assessments for un-planned exposures, and the less intuitive impact of pharmaceuticals in the environment must be considered. This session will attempt to cover pharmaceuticals as a toxicant class in a series of presentations from various perspectives across industry, academia and regulatory/government.

1:00 p.m. Introduction

Roe, Amy L., Ph.D., D.A.B.T., *Procter & Gamble*

- 1:15 p.m. Hazardous Drug Exposures to Health Care Workers**
Connor, Thomas, Ph.D., *National Institute for Occupational Safety and Health*
- 1:40 p.m. Risk Management of Genotoxic Compounds in the Manufacture of Pharmaceuticals**
Bercu, Joel P., M.P.H., *Eli Lilly*
- 2:05 p.m. Aquatic Environmental Risk Assessment of Pharmaceutical and Personal Care Product Ingredients**
Versteeg, Donald J., Ph.D., *Procter & Gamble*
- 2:30 p.m. Potential Exposure to Human Prescription Pharmaceutical Residues from Wastewater**
Kostich, Mitchell, Ph.D., *U.S. EPA, Office of Research and Development, National Exposure Research Laboratory*
- 3:00 p.m. Break**
- 3:30 p.m. Illicit and Legal Drugs and Biomarkers in Municipal Wastewater Influent: A New Tool for Drug Epidemiology**
Field, Jennifer A., Ph.D., *Oregon State University*
- 3:55 p.m. Field Analysis of Methamphetamine in Clandestine Labs: Direct Reading Methods for the Detection of Surface Contamination**
Snawder, John E., Ph.D., D.A.B.T., *National Institute for Occupational Safety and Health*
- 4:20 p.m. Panel Discussion**

2B. Behavioral Toxicology

Co-Chairs:

Hess-Ruth, Amanda (Amy), M.S., *U.S. Army Center for Health Promotion and Preventive Medicine*

CDR Chapman, Gail D., M.B.A., Ph.D., *U.S. Navy, Naval Health Research Center Detachment, Environmental Health Effects Laboratory*

Many neurological deficiencies are not detected under routine cage-side observations or neuropathology. By assessing behavioral functions such as motor activity, startle response, and measurements of learning, behavioral toxicology addresses this data gap and adds to the array of tests available to toxicologists.

This session will provide an overview of behavioral toxicology, as well as including case studies highlighting the importance of this growing field. Subjects of discussion would include behavioral endocrinology, rodent and avian behavioral tests within neurotoxicity, developmental neurotoxicology, as well as current standards of behavioral tests in toxicology.

- 1:00 p.m. Introduction**
CDR Chapman, Gail D., M.B.A., Ph.D., *U.S. Navy, Naval Health Research Center Detachment, Environmental Health Effects Laboratory*
- 1:10 p.m. Neurobehavioral Toxicity Testing for Risk Assessment**
Moser, Virginia C. (Ginger), Ph.D., D.A.B.T., *U.S. EPA, Office of Research and Development, National Health and Environmental Effects Research Laboratory*

- 1:40 p.m. The Startle Response and Toxicology: Methods, Use and Interpretation**
Crofton, Kevin M., Ph.D., *U.S. EPA, Office of Research and Development, National Health and Environmental Effects Research Laboratory*
- 2:25 p.m. Behavioral Measures for Toxicity Tests in the Japanese Quail**
Quinn, Michael, Ph.D., *U.S. Army Center for Health Promotion and Preventive Medicine*
- 3:00 p.m. Break**
- 3:30 p.m. Sodium Tungstate Effects on Neurobehavioral, Reproductive and Systemic Organs in Sprague-Dawley Rats**
Gunasekar, Palur, Ph.D., *U.S. Navy, Naval Health Research Center Detachment/ Environmental Health Effects Laboratory*
- 4:00 p.m. Mn Neurotoxicity: A Behavioral and Neuroimaging Perspective**
Guilarte, Tomás R., Ph.D., *John Hopkins Bloomberg School of Public Health, Department of Environmental Health Sciences*
- 4:30 p.m. Lead Neurotoxicity: Behavioral Effects and Therapeutic Strategies**
Dziedzic, Jennifer, M.S., *John Hopkins Bloomberg School of Public Health, Department of Environmental Health Sciences*

2C. EPA's Four Lab Study Integrating the Toxicity and Chemistry of Complex Disinfection By-Product Mixtures

Co-Chairs:

Speth, Thomas F., Ph.D., P.E., *U.S. EPA, Office of Research and Development, National Risk Management Research Laboratory*

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

Chemical disinfection of drinking water reduces concentrations of potentially pathogenic microorganisms but also forms complex mixtures of disinfection byproducts (DBPs), which may be reproductive and developmental toxicants or carcinogens. Because of the widespread human exposures to DBP mixtures, the U.S. EPA undertook a comprehensive toxicological evaluation of DBP concentrates. Dubbed the "Four Lab Study" because planning and execution required the collaboration of four Laboratories in the EPA's Office of Research and Development, the study examined the toxic potential of the concentrates (~100-fold higher than found in treated waters) using *in vitro* and *in vivo* toxicity assays. This session opens with an overview of the study. Presentations follow describing the preparation of the concentrates using a newly developed reverse osmosis procedure and the chemical analysis of the concentrates that were produced. Two *in vitro* assays are described, assessing the mutagenicity of these concentrates, and the effects on trophoblast cells obtained from full term human placentas. In the second half of the session, the first three presentations will discuss the developmental, reproductive, neurotoxic, and immunotoxic outcomes in a multigenerational rodent bioassay conducted using the drinking water concentrates. The final presentation discusses the risk assessment implications of the Four Lab Study for complex mixtures of DBPs.

- 1:00 p.m. The Integrated Disinfection By-Product Mixtures Project (the 4-Lab Study): An Overview**
Simmons, Jane Ellen, Ph.D., *U.S. EPA, Office of Research and Development, National Health and Environmental Effects Research Laboratory*
- 1:30 p.m. Concentration and Treatment of Drinking Waters in the Four Lab Study**
Pressman, Jonathan, Ph.D., *U.S. EPA, Office of Research and Development, National Risk Management Research Laboratory*

- 1:55 p.m. Chemical Analysis of Drinking Water Concentrates in the Four Lab Study**
Miltner, Richard J., P.E., *U.S. EPA, Office of Research and Development, National Risk Management Research Laboratory*
- 2:20 p.m. Pregnancy Outcome in a Multi-Generational Rat Bioassay of Drinking Water Concentrates in the Four Lab Study**
Narotsky, Michael G., Ph.D., *U.S. EPA, Office of Research and Development, National Health and Environmental Effects Research Laboratory*
- 3:00 p.m. Break**
- 3:30 p.m. Reproductive Development in a Multi-Generational Rat Bioassay of Drinking Water Concentrates in the Four Lab Study**
Hunter, E. Sidney, Ph.D., *U.S. EPA, Office of Research and Development, National Health and Environmental Effects Research Laboratory*
- 3:55 p.m. Neurotoxicity and Immunotoxicity Outcomes Following Gestational Exposure to Four Lab Drinking Water Concentrates**
Luebke, Robert, Ph.D., *U.S. EPA, Office of Research and Development, National Health and Environmental Effects Research Laboratory*
- 4:20 p.m. The Effect of Four-Lab-Study Concentrated Mixtures of Drinking Water Disinfection By-products on Human Term Trophoblast Cell Differentiation**
Chen, Jiangang, Ph.D., *University of California-Davis*
- 4:45 p.m. Implications of the Four Lab Study Results for Evaluating Risks posed by Disinfection By-products**
Teuschler, Linda K., M.S., *U.S. EPA, Office of Research and Development, National Center for Environmental Assessment*

Tuesday, April 15, 2008

5:30 p.m. – 7:30 p.m.

Evening Session

Poster Session/Reception

Poster Session Co-Chairs:

Mattie, David R., Ph.D., D.A.B.T., *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 16, 2008

8:00 a.m. – 11:45 a.m.

Morning Session

8:00 a.m. – 11:45 a.m.

Sessions 3A, 3B and 3C

9:45 a.m. – 10:15 a.m.

Break

3A. Challenges in Assessing Risks from Low Dose Exposures

Co-Chairs

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

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

Most experimental data from animal studies are conducted at high doses, shorter time period and to single chemicals. However, humans are exposed to lower doses, for longer durations and to multiple chemicals. Therefore, estimation of human health risk due to long-term exposures to very low doses of chemicals in the environment poses a number of biological and statistical challenges. Biological challenges include lack of positive response at very low doses due to shorter duration of exposure, availability of data in animal studies and not in human studies etc. One of the statistical problems is to extrapolate the animal dose-response relation from the high dose levels where data are available to low dose, which humans might encounter. The purpose of this symposium is to illustrate a number of these issues through a discussion of the available information at low doses using specific examples of chemicals.

8:00 a.m. Introduction: Challenges in Assessing Risk from Low-Dose Chemical Exposures – a Brief Overview

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

8:05 a.m. Low Dose Extrapolation: New Approaches to Old Problems

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

8:40 a.m. The Use of Mode of Action Information to Inform Low Dose Estimates of Cancer Risk: A Case Study Involving Carbon Tetrachloride

Eastmond, David A., Ph.D., *University of California, Environmental Toxicology and Department of Cell Biology*

9:10 a.m. From Genomics to Mechanistic Insight: A Perspective on Molecular Deficits Induced by Environmental Agents

Ramos, Kenneth S., Ph.D., *University of Louisville, Department of Biochemistry and Molecular Biology*

9:45 a.m. Break

10:15 a.m. Roles of Heme Biosynthetic Biomarkers in Evaluating Lead, Cadmium, Arsenic Mixture Exposures at LOEL Dose Levels

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

10:45 a.m. Mode of Action and Mixtures Risk Assessment: Paying Attention to Details

Lambert, Jason, Ph.D., D.A.B.T., *U.S. EPA, Office of Research and Development, National Center for Environmental Assessment*

11:15 a.m. Panel Discussion – Mode of Action and Low Dose Extrapolation: Research Needs to Improve Risk Assessment

3B. Updates on Reproductive/Developmental Toxicology and Risk Assessment

Co-Chairs:

Makris, Susan L., M.S., *U.S. EPA, Office of Research and Development, National Center for Environmental Assessment*

Hooth, Michelle J., Ph.D., D.A.B.T., *National Institute of Environmental Health Sciences, National Toxicology Program, Toxicology Branch*

EPA scientists have many years of practical experience in the application of guidelines in the areas of reproductive and developmental toxicology to hazard characterization and human health risk assessment. Nevertheless, as with any other scientific discipline, advances in the sciences and in the approaches to screening and testing have yielded a wealth of new considerations and information that have the potential to further influence and/or refine the use of these data in risk assessment. This session will provide an informative review of recent activities and information in several relevant topic areas.

8:00 a.m. Introduction

Makris, Susan L., M.S., *U.S. EPA, Office of Research and Development, National Center for Environmental Assessment*

8:05 a.m. Developmental Neurotoxicity Testing: Past, Present and Future

Crofton, Kevin M., Ph.D., *U.S. EPA, Office of Research and Development, National Health and Environmental Effects Research Laboratory*

8:55 a.m. Developmental Immunotoxicity

Luebke, Robert W., Ph.D., *U.S. EPA, Office of Research and Development, National Health and Environmental Effects Research Laboratory*

9:45 a.m. Break

10:15 a.m. An Update on the Progress of the Extended One-Generation Reproductive Protocol

Cooper, Ralph L., Ph.D., *U.S. EPA, Office of Research and Development, National Health and Environmental Effects Research Laboratory*

10:45 a.m. Update on the Mammalian Tier 1 Endocrine Disruptor Screening Protocols

Stoker, Tammy E., Ph.D., *U.S. EPA, Office of Research and Development, National Health and Environmental Effects Research Laboratory*

11:15 a.m. An Introduction to: "Terminology of Developmental Abnormalities, Version 2"

Solomon, Howard M., Ph.D., *GlaxoSmithKline Pharmaceuticals*

3C. Identification, Ecology, and Risk Assessment of Emerging Cyanobacterial and Harmful Algal Toxins

Co-Chairs:

Zimba, Paul V., Ph.D., *U.S. Department of Agriculture, Agricultural Research Service*

de la Cruz, Armah, Ph.D., *U.S. EPA, Office of Research and Development, National Exposure Research Laboratory*

Up to 48% of lakes in North America are eutrophic and greater reliance on surface water sources is expected as groundwater can not supply drinking water needs. Eutrophic water conditions can stimulate algae to grow in dense (bloom) concentrations. Most blooms have high concentrations of cyanobacteria (blue-green algae) or eukaryotic algae that can produce a wide array of bioactive toxic compounds responsible for human health problems and animal disease and death. Algal toxins are often grouped by their functional activities based on their toxicological targets: neurotoxins, cytotoxins, dermatotoxins and hepatotoxins. Additionally, haptophytes such as *Prymnesium parvum* as well as euglenoid algae (*Euglena sanguinea*) are also known to cause fish kills. This session will provide current information on freshwater cyanobacteria, haptophyte, and euglenoid toxins and a risk assessment to animals and humans.

- 8:00 a.m. Overview of Session and Recent Evidence for *Cylindrospermopsis* Occurrence in U.S. Potable Water Sources**
Zimba, Paul V., Ph.D., *U.S. Department of Agriculture, Agricultural Research Service*
- 8:15 a.m. An Overview of Freshwater Toxins**
Burkholder, JoAnn M., Ph.D., *North Carolina State University*
- 8:45 a.m. Isolation of Novel Toxins: Case Studies**
Moeller, Peter, Ph.D., *National Oceanic and Atmospheric Administration*
- 9:15 a.m. Harmful Algal Blooms in Multi-Use Reservoirs**
Walker, David B., Ph.D., *University of Arizona*
- 9:45 a.m. Break**
- 10:15 a.m. Toxic Cyanobacteria in the Laurentian Great Lakes – An Overview of the Past and a Looking Glass to the Future**
Wilhelm, Steven W., Ph.D., *The University of Tennessee*
- 10:45 a.m. Cyanobacterial Toxins: Toxicity and Human Health Risk**
Hawkins, Belinda S., Ph.D., D.A.B.T., *U.S. EPA, Office of Research and Development, National Center for Environmental Assessment*
- 11:20 a.m. Panel Discussion and Questions**

11:45 a.m. – 1:00 p.m. Lunch

Wednesday, April 16, 2008

1:00 p.m. – 5:00 p.m.

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. Uncertainty in Epidemiologic Evaluations of Environmental and Occupational Exposures

Co Chairs:

Bateson, Thomas, Sc.D., M.P.H., *U.S. EPA, Office of Research and Development, National Center for Environmental Assessment*

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, Education and Information Division*

Uncertainty in epidemiologic studies arises under two circumstances: (1) when the results of an epidemiologic study may be biased, or (2) when internally valid results derived from one study population are not validly applied to another study population. The presence or methodologically justifiable suspicion of bias in an epidemiologic study increases uncertainty in the study results. Bias-related uncertainty can be related to information bias, confounding, and selection bias. Separate from the issues of bias-related uncertainty, uncertainty also arises when internally valid results derived from one study population are not

applicable to another study population. This may be characterized as susceptibility or effect modification, for example, when data suggest differential effects by life stage or genetic predisposition.

In this session, a series of presentations will highlight challenges related to uncertainty in epidemiologic evaluations of environmental and occupational exposures and showcase methodologies to characterize and potentially minimize those uncertainties.

- 1:00 p.m. Sources of Uncertainty in Environmental Epidemiological Data**
Wright, J. Michael, Sc.D., *U.S. EPA, Office of Research and Development, National Center for Environmental Assessment*
- 1:15 p.m. Sources of Uncertainty in Occupational Epidemiological Data**
Park, Robert M., M.S., *National Institute for Occupational Safety and Health, Education and Information Division*
- 1:30 p.m. Quantitative Analysis of Nonrandom Error in Epidemiologic Studies**
Jurek, Anne M., Ph.D., *University of Minnesota, Department of Pediatrics, Division of Epidemiology and Clinical Research*
- 2:15 p.m. Sensitivity Analysis and Meta-analysis of Published Epidemiologic Studies in Quantitative Risk Assessment: Methods and Challenges**
Van Wijngaarden, Edwin, Ph.D., *University of Rochester Medical Center, Department of Environmental Medicine*
- 3:00 p.m. Break**
- 3:30 p.m. The Role of Chrysotile Asbestos Fiber Demension on the Risk of Respiratory Disease in South Carolina Textile Workers**
Gilbert, Steven J., M.S., *National Institute for Occupational Safety and Health, Education and Information Division*
- 4:00 p.m. Correction for Classical Measurement Error in Drinking Water Disinfection By-products Studies Using Multiple Surrogate Exposures**
Bateson, Thomas, Sc.D., M.P.H., *U.S. EPA, Office of Research and Development, National Center for Environmental Assessment*
- 4:30 p.m. Panel Discussion**

4B. Toxicology and Risk Assessment of Jet Fuel and Alternative Fuels

Co-Chairs:

Mattie, David R., Ph.D., D.A.B.T., *Air Force Research Laboratory, Applied Biotechnology Branch*

LT Wagner, Dean, *U.S. Navy, Environmental Health Effects Laboratory*

Hinz, John P., Ph.D., *Air Force Institute of Operational Health*

The Air Force has initiated a major alternatives fuels program and is conducting the Toxicity Testing Program for an alternative jet fuel called F-T or S-8. The effort has highlighted old as well as new questions and emerging issues about the toxicity and risk assessment of jet fuels. Issues and research will be reviewed for synthetic fuels, JP-8, Jet A and S-8. This session will discuss emerging issues, hazard and exposure assessment, environmental impacts and the current risk assessment for jet fuel.

- 1:00 p.m. Past, Present and Emerging Toxicity Issues for Jet Fuel**
Mattie, David R., Ph.D., D.A.B.T., *Air Force Research Laboratory, Applied Biotechnology Branch*
- 1:40 p.m. Alternative Fuels**

Jarnot, Bruce, Ph.D., *American Petroleum Institute*

- 2:20 p.m. Toxicity Assessment of F-T Jet Fuel**
LT Wagner, Dean, *U.S. Navy, Environmental Health Effects Laboratory*
- 3:00 p.m. Break**
- 3:30 p.m. Exposure Assessment in Occupational Epidemiology: Issues Related to Jet Fuels**
Proctor, Susan P., D.Sc., *U.S. Army Research Institute of Environmental Medicine*
- 4:00 p.m. Environmental Impacts and Restoration Implications**
Becvar, Erica, M.S., *Department of the Air Force, Air Force Center for Engineering and Environment*
- 4:30 p.m. Jet Fuel Exposure Guidelines & Risk Assessments**
Hinz, John P., *Air Force Institute of Operational Health*

4C. Common Mechanisms across Species, Diseases and Toxicity: What Can We Infer from Oxidative Stress

Co-Chairs

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

Gunasekar, Palur, Ph.D., *U.S. Navy, Naval Health Research Center Detachment/ Environmental Health Effects Laboratory*

Survival of aerobic organisms is dependent on one essential element, Oxygen. Almost all of the oxygen that enters the mitochondrion of a cell is utilized, where it is reduced to water and small percentage (~1%) of electrons leaked from mitochondria leads to generation of reactive oxygen species (ROS). In addition to this, various metabolic reactions of endogenous/exogenous substances also contribute to the formation of ROS. To be protected from the deleterious effects of ROS, aerobic organisms have evolved enzymatic and non-enzymatic antioxidant defense mechanisms. Under normal physiological conditions homeostatic mechanisms protect the cell and its essential components. A tilt in this balance occurs in various disease conditions or under stress conditions such as exposure to xenobiotic/environmental agents, resulting in oxidative stress. Oxidative stress is recognized as a major etiologic factor for numerous human diseases including atherosclerosis, cancer and neurodegenerative disorders, some of which are resultant of environmental insult. The core biochemical and molecular mechanisms that govern oxidative stress appear to be conserved across the tissues and species and common across disease or toxic insult. This overview talk will attempt to enhance our current understanding on some of the newer insights into the mechanisms underlying oxidative stress, the diversity and commonality among different species, diseases and environmental stressors.

- 1:00 p.m. Introduction**
Mudipalli, Anuradha, Ph.D., *U.S. EPA, Office of Research and Development, National Center for Environmental Assessment*
- 1:10 p.m. The Role of Oxidative Stress and Oxidative Damage in Chemical Carcinogenesis**
Klaunig, James E., Ph.D., *Indiana University School of Medicine, Center for Environmental Health*
- 1:50 p.m. Oxidative Stress Signaling in Environmental Neurotoxicants Induced Dopaminergic Toxicity**
Kanthasamy, Anumantha, Ph.D., *Iowa State University, College of Veterinary Medicine*
- 2:25 p.m. SKN-1 (Nrf1/2), Systemic Detoxification and Aging in *C. elegans***

Blackwell, T. Keith, M.D., Ph.D., *Harvard Medical School, Harvard Stem Cell Institute*

3:00 p.m. Break

3:30 p.m. Oxidative Stress and Inflammation in the Pathogenesis of COPD
Rahman, Irfan, Ph.D., *University of Rochester Medical Center*

4:00 p.m. Oxidative Stress and Determining its Measurement Parameters – Mode of Action Studies with Arsenic and LC-MS/MS as an Analytical Tool
Kitchin, Kirk T., Ph.D., D.A.B.T., *U.S. EPA, Office of Research and Development, National Health and Environmental Effects Research Laboratory*

4:30 p.m. Oxidative Stress as a Key Event in or an Inevitable Consequence of the Chemical Carcinogenesis Process
Preston, R. Julian, Ph.D., *U.S. EPA, Office of Research and Development, National Health and Environmental Effects Research Laboratory*

5:00 p.m. Wrap-up
Gunasekar, Palur, Ph.D., *U.S. Navy, Naval Health Research Center Detachment, Environmental Health Effects Laboratory*

Thursday, April 17, 2008

8:00 a.m. – 4:00 p.m.

Workshops

Workshop Chair:

Zwayer, Bette, C.P.M., *U.S. EPA, Office of Research and Development, National Center for Environmental Assessment*

8:00 a.m. – 12:00 p.m. Discussion Session

8:00 a.m. – 4:00 p.m. Workshop W-4, W-5 and W-6

10:00 a.m. – 10:20 a.m. Break

2:10 p.m. – 2:30 p.m. Break

1 hour 15 minute Lunch Break

Discussion Session — Chemicals and Substances of Common and Emerging Concern

Presenters:

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

Attendance Open

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 are 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-4. Dosimetric Adjustment Methods and Application in Dose Response Assessment (6 hours)

Presenter:

Zhao, Q. Jay, M.P.H., Ph.D., D.A.B.T., *U.S. EPA, Office of Research and Development, National Center for Environmental Assessment*

This workshop is designed to provide basic training in methods used for the dosimetric adjustments required for completing dose-response assessments derived from animal toxicology data. The topics will include interspecies oral dose adjustment for noncancer and cancer assessment, cancer unit risk or slope factor conversion, inhalation exposure concentration unit conversion, and human equivalent concentration (HEC) calculation for particle and vapor exposure using various modeling approaches. Applications of the results of physiologically-based pharmacokinetic (PBPK) modeling will also be introduced. The participant will be provided with sufficient working knowledge of the various techniques to conduct all the necessary dosimetric adjustment in typical noncancer and cancer risk assessments.

W-5. 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., M.P.H., *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 day 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. Effect (measure) modification as well as the impact of bias and confounding on relative risk estimates will also be examined. The first half of the workshop will conclude with a section on drawing causal inference from epidemiological data.

The second half of the workshop will be devoted to an introductory statistical analysis section. 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. In addition, a section on descriptive health statistics and cluster identification will be included. The second half of the workshop

will conclude with a practical exercise in assessing study validity and drawing causal inferences from observational epidemiologic data.

W-6. Evaluation of the Human Relevance of Modes of Action in Animals

Presenters:

Olin, Stephen S., Ph.D., *ILSI Research Foundation*

Lipscomb, John C., Ph.D., D.A.B.T., *U.S. EPA, Office of Research and Development, National Center for Environmental Assessment*

Understanding the toxic mode of action of a chemical improves the scientific basis for choosing methods for low-dose and interspecies extrapolation. This full-day workshop presents a systematic approach to characterizing the mode(s) of action (MOA) of toxicants and will give participants “hands-on” experience in the application of a framework for evaluating the relevance of an animal mode of action in assessing human risk. The framework, developed over the past several years, has already been widely adopted and used by government agencies and international organizations. The workshop will use a combination of lecture and interactive case studies with group participation to demonstrate the framework. An opening tutorial will introduce workshop participants to basic concepts and walk them through a model case study. This leads into a series of facilitated interactive case studies in which participants analyze examples of varying complexity, drawn from recent peer reviewed publications involving “real world” chemicals. Participants are provided with background materials, copies of the presentations, and other materials specially developed for the case studies. Case studies are worked through in small breakout groups, each guided by a speaker/facilitator. The speaker/facilitators for this workshop have been leaders in the development of MOA human relevance analysis and have extensive experience in its practical use.