

Sunday Afternoon 11 Sept 2005 4:00 – 6:00 PM

4:00 PM Conference Opens

SESSION I. Welcome, Overview and Goals of the Conference

Conference Chair: Joan Cranmer

Plenary Session:

SESSION II: Neurotoxicants and Learning and Developmental Disabilities: Translating the Science into Education and Public Policy

Session Chairs: Elise Miller and TBA

Theme: Scientists are often reluctant to become involved in educating the general public about technical subjects, or becoming involved with the intersections of science and public policy, for fear that such activities will take them away from more important work or raise questions about their objectivity. This plenary session will provide an overview of the latest science on neurotoxicants in relation to learning and developmental disabilities and discuss the role of translating science in order to educate health-affected constituencies and guide stronger policy to protect children's environmental health. In addition, case studies as to how the precautionary principle can be applied to reduce exposures to neurotoxicants will be highlighted. Panelists will also describe model environmental health programs initiated by learning and developmental disabilities groups.

Monday Morning 12 Sept 2005 8:30 AM – 12:00 N

Symposium

SESSION III-A. PBPK/PD Models for Developmental Neurotoxicology: Risk Assessment Strategies and Research Recommendations

Session Chairs: Bill Slikker and Don Mattison

Theme: Over the past decade regulatory agencies in developed countries have recognized that infants, children, and adolescents handle chemicals differently than adults (indeed, adults are not pharmacologically homogeneous). While recognizing those pharmacological differences has led to increased attention to preclinical and clinical data gaps, the information needed to fill those gaps can not be simply addressed by testing chemicals in pediatric populations. The concepts of efficacy and safety must be reformulated in the context of development, and new approaches for preclinical and clinical testing (including clinical trial designs) developed and validated in immature animals and humans. These testing methods, especially for the nervous system, must be grounded on an understanding of healthy developmental trajectories as well as the impact of disease and treatment on healthy development. Clearly this constraint suggests that there is little of relevance from adult pharmacology and it is necessary to develop preclinical and clinical testing for pediatric pharmacology and developmental neurotoxicology.

Monday Morning 12 Sept 2005 8:30 AM – 12:00 N

Workshop

SESSION III-B. Developmental Effects on the Immune System: Implications for the Nervous System

Session Chairs: Jean Harry and TBA

Theme: In recent years, evidence for the role of infectious and inflammatory processes as mediators of brain injury has been growing. The immune response within the brain as well as linkages between the immune and nervous system are becoming well documented. With regards to development, clinical correlations between fetal plasma cytokines and neurological outcomes in the premature infant have been established. Recent work suggests that maternal infection and inflammatory responses in the offspring are associated with increased risk for diseases such as schizophrenia and autism. In addition, the immunological status of the developing organism during a period of toxicant exposure has recently been identified as a potential susceptibility factor in neurological disease processes. The following sessions will focus on work underlying these hypotheses in both the human clinical setting as well as the establishment of experimental animal models. The translation of adverse effects as the result of an innate immune response in the brain following exposure to environmental agents and the contribution of the immunological competence as a factor determining susceptibility will be addressed.

Monday Afternoon 12 Sept 2005 1:30 – 5:30 PM

Workshop - continued

SESSION III-B. Environmental Perturbations of the Immune System: Implications for Autism and other Neurodevelopmental Disorders

Session Chairs: Cindy Lawler and TBA

Theme: Several studies have reported systemic immunologic aberrations in autism spectrum disorders (ASD) that are associated with both autoimmunity and with dysfunctional immunity such as abnormalities or deficits of function in immune cell subsets. The relationship between these abnormalities and the development of neuropathologic changes is not yet known. There has been speculation, however, that aberrant immune system activation occurring during critical periods of nervous system development and maturation may significantly contribute to the susceptibility of the organism to environmental exposure. Such interactions may contribute to the phenotypic differences of diseases seen in the human population.

Monday Afternoon 12 Sept 2005 1:30 – 3:25 PM

Symposium

SESSION IV-A. Neurotoxicant Exposures in Military Deployments and Putative Associations with Neurodegenerative Diseases

Session Chairs: TBA

Theme. Topics presented in this session will include epidemiologically focused research on neurotoxicant exposures and putative associations with neurodegenerative diseases. This session will feature presentations of on-going projects sponsored by the US Army Military Research and Materiel Command, Military Operational Medicine Research Program and the US Army Research Institute of Environmental Medicine.

Monday Afternoon 12 Sept 2005 3:45 – 5:30 PM

Platform Session

SESSION IV-B. Talks Selected from Abstracts

Session Chairs and Theme: To be determined after abstracts are received

Tuesday Morning 13 Sept 2005 8:30 AM – 12:00 N

Plenary Session

SESSION V. Molecules to (Wo)man: I. Animals

Dissecting the Dysfunction to Look at the Whole Picture

Session Chairs: Isaac Pessah and Rich Seegal

Theme: Session V will present an integrated overview of the multidisciplinary approaches needed to understand risk factors contributing to childhood disorders and aging. Goal: To provide mechanistic data that will aid in the interpretation of epidemiological data and in understanding the role that environmental agents play in inducing central nervous system dysfunctions. Identifying the principal molecular targets that are responsible for producing toxicosis has been a cornerstone of risk assessment. Prominent examples include the activity of dioxins at the AhR, anticholinesterase activity of organophosphates and carbamates, and the interaction of pyrethroids with sodium channels. Understanding the relationship among low level exposure to environmentally persistent chemicals, their critical molecular targets, ensuing cellular dysfunction, and defining often subtle consequences on animal and human neurodevelopment is perhaps one the most challenging goals of modern toxicology.

Tuesday Afternoon 13 Sept 2005 1:30 – 3:30 PM

Plenary Session

SESSION V: Molecules to (Wo)man: II. Humans

Dissecting the Dysfunction to Look at the Whole Picture

Session Chairs: Sue Schantz and Elaine Faustman

Tuesday Afternoon 13 Sept 2005 3:30 – 5:30 PM

Poster Session

SESSION VII: General Poster Session

Session Chairs: Ken Reuhl and Toshio Narahashi

Pre-Doctoral Student Award Committee: Ken Reuhl and TBA after abstracts are received

Post-Doctoral Student Award Committee: Toshio Narahashi and TBA after abstracts are received

The poster session is a highlight of this conference series and provides an ideal opportunity for one-on-one personal exchange of research information and ideas in an informal setting with a unique consortium of participants expert in various aspects of the theme and neurotoxicology in general. The General Poster Session has proven to be a wonderful venue for informal, in-depth discussion, collaboration building, and mentoring of young scientists. It is an important networking opportunity for students. Judging and selection of Pre – and Post-Doctoral Student Awardees will be made during the session. All papers on neuroscience plus toxicology are invited. Posters do not need to address the theme; they can be on any aspect of toxicology.

Tuesday Evening 13 Sept 2005 7:00 – 9:00 PM

Platform Session

SESSION VIII-A. Talks Selected from Abstracts

Session Chairs and Theme: To be determined after abstracts are received

Tuesday Evening 13 Sept 2005 7:00 – 9:00 PM

Symposium

SESSION VIII-B. Endocrine Active Compounds and their Effects on Brain Development: Integration of Methods and Approaches

Session Chairs: Eva Polston and Robert Handa

Theme: Throughout an animal's lifetime, steroid hormones have profound effects on brain function. Because the brain is sensitive to low concentrations of steroids and steroid-like compounds, there is growing concern that low levels of endocrine-active compounds (EACs) in the environment may exert toxicological effects in the brain. In contrast to necrosis-inducing neurotoxins that cause histopathological damage, the effects of EACs are likely to result in subtle and specific alterations of neuronal function. This workshop will present a multifaceted approach through which changes in the developing and adult brain can be assessed. Talks will focus on cellular/molecular, neuroanatomical, and functional approaches for detecting perturbations in hormone-sensitive neuronal systems.

Wednesday Morning 14 Sept 2005 8:30 AM – 12:00 N

Symposium

SESSION X-A. Contemporary Health Issues Associated with Over Exposure to Manganese

Session Chairs: Michael Aschner and Thomas Gunter

Theme: This multidisciplinary session will address contemporary research issues associated with the health effects of manganese (Mn) both in humans and animal models. Speakers will discuss recent findings on the specific cellular, molecular, and physiologic mechanisms by which manganese mediates its adverse effects. Speakers will also note factors, such as age, pre-existing disease, and genetics, as conditions that might predispose individuals to enhanced susceptibility to manganese toxicity. The session will span studies in various tissue culture models to non-human primates, incorporating diversity of techniques, from molecular biology to imaging.

Timely Topics to be Addressed:

- Consideration of the relevant health issues associated with over exposure to manganese.
- Characterization of exposures
- Development of appropriate biomarkers of exposure.
- Quantifying the relationships between exposure and ill health, including pharmacokinetics.
- Understanding the mechanisms of transport, damage and repair.
- Understanding and utilizing invertebrate models such as the *c. elegans* to probe for mechanisms of Mn neurotoxicity

Wednesday Afternoon 14 Sept 2005 1:30 – 4:00 PM

Symposium - continued

SESSION X-A. Contemporary Health Issues Associated with Over Exposure to Manganese

Session Chairs: Tomas Guilarte and Anumantha Kanthasamy

Wednesday Morning 14 Sept 2005 8:30 AM – 12:00 N

Platform Session

SESSION IX-B. Talks Selected from Abstracts

Session Chairs and Theme: To be determined after abstracts are received

Wednesday Morning 14 Sept 2005 8:30 AM – 12:00 N

Note: Attendance at this Technical Workshop is limited to 50 registrants. Pre-registration is required. Results will be presented and discussed in Open Plenary Session X.

Developmental Toxicology Technical Workshop

SESSION IX-C. Optimizing the Design and Interpretation of Epidemiological Studies for Assessing Neurodevelopmental Effects from in utero Chemical Exposure

Session Chair: Roger Ladda

Description: While many epidemiologic studies of children's environmental health have been completed, and more are being planned, a comprehensive critical examination of the methodologies commonly used in past studies has not been conducted. In fact, in some of the completed studies (e.g., those related to pharmaceuticals and environmental chemicals such as lead, methylmercury, and PCBs), the authors have acknowledged the limitations of existing methods. Currently, there is a great deal of interest in conducting additional epidemiologic investigations into environmental chemicals and children's health. For example, the proposed National Children's Study (NCS) is likely to investigate environmental and other factors influencing the health and development of children *in utero*, through birth, childhood, and into young adulthood.

Therefore, as new studies are being planned, this is an appropriate time to determine whether existing methods as they have been practiced will serve future studies, especially those designed to assess the potential impacts at current exposures. In short, such an examination serves to identify the key methodological factors that ultimately determine the value and strength of future research. Thus, investigators designing new studies will benefit from this thoughtful examination as they develop future study designs and analyze resulting study data. The outcome of this session will provide valuable input not only to the design of future investigations, but also metrics whereby scientists and others can judge the adequacy of reported studies. However, the scope of the session will focus only on scientific methodological issues (i.e., the development of 'best practices' for future study design, conduct, reporting and interpretation); that is, specifically, it will not include an evaluation of conclusions or findings from previous epidemiological studies of environmental health.

The Expert Panel assembled for this session will address a series of topics with related questions prior to, and during, the session. These topics and questions include:

Study Design:

? What is the best experimental design and methodology to assess the likelihood that *in utero* exposure to an environmental chemical can result in adverse neurodevelopmental effects in newborns that continue into childhood?

? What are the statistical issues that must be addressed to conclude with adequate confidence that an *in utero* exposure to a specific environmental chemical can result in adverse neurodevelopmental effects?

Measurement Tool:

? What specific measurement tools/tests are best suited and validated for assessing the variety of potential neurodevelopmental and behavioral deficits? What is the known sensitivity, specificity and predictive value of each

endpoint being measured? How reproducible is/are the measurement(s)?

? Are there particular sampling strategies or data collection methods that are especially relevant to detecting potential neurodevelopmental effects from *in utero* exposure? What sampling and analysis strategies can be employed to avoid Type II (failure to detect a real effect) errors?

? What is the relationship between the estimated window of exposure and the *nature* of a potential effect, and how might this affect the selection of tests?

? How might data and methods from the field of molecular epidemiology be used to enhance traditional epidemiologic approaches?

Exposure Assessment:

? Which specific measurement tools and biomarkers are best suited and validated for assessing the nature, extent, and patterns of *in utero* exposure to a particular environmental chemical? How might these differ from tools and biomarkers used to assess post-natal exposure?

? To avoid exposure misclassification or misleading estimates when assessing potential exposure, how frequently should exposure be estimated (i.e., what temporal units should be used for serial exposure measurements)? If appropriate temporal units are chemical- or tissue-specific, what data or criteria should be used to determine the optimal units? How should critical timeframes – critical windows of vulnerability in neurodevelopment - be taken into account when designing an exposure assessment approach?

? How should potential aggregate exposure from multiple routes (inhalation, ingestion, dermal) be addressed? How should potential cumulative exposure to multiple chemicals be addressed? How can trends in exposure and trends in neurodevelopmental outcomes be assessed?

? How long should the subject be followed with appropriate studies (e.g., school age, puberty, reproductive ages)?

Participant Selection:

? What is the most appropriate and valid way to select and follow exposed and control groups for studies attempting to demonstrate an association between *in utero* exposure to a specific environmental chemical and adverse neurodevelopmental effects?

Confounders:

? What guidance can be offered with respect to selecting and measuring potential confounders? What criteria should be applied when selecting control variables for inclusion in a multivariate analysis? How should potential mediating factors be identified and analyzed?

? Are there cultural aspects to neurodevelopmental tests that should be considered before use?

Reporting:

? How is clinical significance versus population significance defined and reported?

? How do researchers address the issue of labeling of children based on study results and how should the study results be reported to parents?

Research Needs and Recommendation:

? What are the key needs for future research? What are the primary uncertainties and gaps in our knowledge that should be addressed with future research?

Wednesday Afternoon 14 Sept 2005 4:00 – 6:00 PM

Plenary and Closing Session

SESSION X. Translational Research

- **Research Recommendations by Session.**
- **Current Status of The National Children's Study.**
- **Presentation of Student Awards**

Session Chairs: TBA

Wednesday Evening 14 Sept 2005 6:00 – 10:00 PM

Conference Social Evening

6:00 – 7:00 PM

Cocktails on Outside Terrace

7:00 - 10:00 PM

North Carolina Pig Pickin'

Entertainment & Dancing

Thursday Day 15 Sept 2005 9:00 AM – 3:30 PM

9:00 AM - 3:00 PM

Post-Conference Tours of CIIT Centers for Health Research and EPA

(Included in Registration)

9:00 AM

Buses to CIIT

CIIT Demonstrations and Tours

- *Inhalation Toxicology*
- *Neuropathology*

12:00 NOON

Buses to EPA

Lunch in EPA Cafeteria

Tour EPA Laboratories