

Environmental Etiologies of Neurological Disorders

Modifiers of Risk: Genes, Age, Gender, Nutrition, Simultaneous Exposures, Socio-Economic Issues

NOVEMBER 11 - 14, 2007

Holiday Inn RIVERWALK

SAN ANTONIO, TEXAS

Sunday 11 November 2007 1:00 – 2:30 PM

9:00 AM REGISTRATION OPENS

- All Conference functions will be held in the Holiday Inn Riverwalk Hotel
- Posters on display starting Sunday
- NEUROTOXICOLOGY 24 Registrants are invited to attend the LDDI Pre-Conference Workshop

1:00 PM CONFERENCE OPENS

Sunday Early Afternoon 11 November 2007 1:00 – 2:30 PM

Opening

SESSION I: OPENING OF THE 24TH CONFERENCE

Conference Chair: **Joan Cranmer**

1:00 – 1:30 PM

Welcome, Acknowledgements & Overview

Joan Cranmer ~ *University of Arkansas for Medical Sciences*

1:30 – 2:15 PM

Keynote Address



“Science and the Public Interest”

KENNETH OLDEN, PH.D.

Dr. Kenneth Olden is the former Director of the NIEHS and the National Toxicology Program. At present, he is a Yerby Professor, Harvard University, School of Public Health, and Chief of the Metastasis Section, NIEHS.

In this presentation, Dr. Olden will describe his views about how research and development priorities are established in the United States Government. He will argue (1) that we have a fragmented priority setting process; (2) that we are making important investment decisions without adequate forethought and planning at the national level; and (3) that we lack adequate metrics to determine how our investments are performing. He will conclude (1) that the United States needs a National Commission to develop a rational science policy; (2) that we need a mechanism to analyze our investment portfolio with respect to impact; and (3) that translation of scientific discoveries into technologies to prevent or treat chronic diseases will require community participation.

2:15 – 2:30 PM

Rationale for Theme

Deborah Cory-Slechta ~ *University of Rochester School of Medicine*

Sunday Late Afternoon 11 November 2007 2:30– 5:15 PM

Plenary Session

SESSION II: COGNITIVE DYSFUNCTION LINKED TO LEAD EXPOSURE: MODIFIERS OF EFFECT: Socioeconomic Status, Stress, Gender, Genetic Background and Aging

Session Chair: **Deborah Cory-Slechta**

Co-Chair: **David Bellinger**

Theme and Rationale: After the removal of lead, a well known neurotoxicant, from paint and gasoline in many countries, blood lead levels of the general population declined, easing the burden of lead exposure in corresponding populations. However, new concerns have arisen over the residual lower levels of exposure, as accumulating evidence documents effects on cognitive function and other health outcomes even at levels below the currently defined level of concern for children. Moreover, lead exposures remain a significant public health problem in particular for inner city minority children living in old housing with residual lead paint. Although much of the focus of research on lead has concerned the confirmation of its impact on cognitive function, it is becoming increasingly evident that these effects can be significantly modified by other environmental and host risk factors. Among these modifiers are socioeconomic status, gender, genetic background, nutrition and aging. Older members of the population had higher level exposures that may now impact the nervous system. In addition, new findings suggest that some effects of lead exposure may be transgenerational. Understanding how these other risk factors influence the impact of lead on the nervous system allows the development of more refined experimental animal models and more directed cohort studies. In addition, it should provide a sounder basis for the determination of behavioral or other directed therapeutic strategies for attenuation of lead effects, as well as increasing precision and reducing uncertainties related to redefining blood lead levels of concern.

2:30 – 3:00 PM

Interactions of Lead Exposure, Stress and Gender: Implications for Cognitive Disorders

Deborah Cory-Slechta ~ *University of Rochester School of Medicine & Dentistry*

Every individual experiences stress in their lifetime. High and chronic levels of stress have been linked to the increased incidences of various diseases and dysfunctions in low socioeconomic status populations, the same groups that are subjected to the highest levels of exposure, making these co-occurring risk factors. This talk will describe the combined effects of Pb with stress in experimental models, effects that show notable differences in relation to gender, as well as the implications of these findings for human populations and for public health blood lead screening programs.

3:00 – 3:30 PM

Socioeconomic Status as a Modulator of the Behavioral Toxicity of Lead

David Bellinger ~ *Harvard Medical School*

This talk will address ways in which a deeper understanding of the social, political, and economic contexts in which environmental chemical exposures occur can produce a deeper understanding of individual susceptibility and patterns of disease occurrence. Most studies include measurement of individual-level factors, such as host characteristics or the immediate family, but rarely consider more macro-level factors such as neighborhood, community, and cultural characteristics. Even more rarely are such factors evaluated as risk modifiers as well as potential confounders.

3:30 – 3:45 PM Break

3:45 – 4:15 PM

Developmental Lead and Late Onset Alzheimer’s Disease Pathology

Nasser Zawia ~ *University of Rhode Island, Kingston*

The authors have recently reported that developmental exposure of rats to lead resulted in a delayed overexpression (20 months later) of the amyloid precursor protein (APP) and its amyloidogenic Abeta product. Similarly, aged monkeys exposed to Pb as infants also responded in the same way. These data suggest that environmental influences occurring during brain development predetermine the expression and regulation of APP later in life, potentially influencing the course of amyloidogenesis, and argue for both an environmental trigger and a developmental origin of Alzheimer’s Disease. This talk will present evidence for the developmental basis of neurodegeneration and discuss mechanisms that may explain how perturbations during development can have long-term or delayed consequences in the aging brain.

4:15 – 4:45 PM

Low-Level Human Equivalent Gestational Lead Exposure Produces Gender-Specific Motor and Coordination Abnormalities and Late-Onset Obesity in Year-Old Mice

Donald A. Fox ~ *University of Houston*

Low-level developmental lead exposure is linked to cognitive and neurological disorders in children. However, the long-term effects of gestational lead exposure (GLE) have received little attention. Our goals were to establish and validate a murine model of human equivalent GLE and to determine dose-response effects on body weight, motor functions and dopamine neurochemistry in year-old offspring. A study in mice was conducted to help answer these questions. Our novel results show that GLE produced permanent male-specific deficits. The nonmonotonic dose-dependent responses showed that low-level GLE produced the most adverse effects. These data reinforce the idea that lifetime measures of dose-response toxicant exposure should be a component of the neurotoxic risk assessment process.

4:45 – 5:15 PM

Panel Discussion and Q&A:

- Can gender differences in the behavioral consequences of Pb exposure be used to assist in diagnosis of specific

behavioral disorders and in the development of appropriate behavioral therapeutic strategies?

- Do permanent Pb-induced changes in HPA axis function from even maternal only Pb exposure mean that screening for Pb exposure should include pregnant women?
- How should future cohort studies and experimental animal models be refined in future studies to more precisely estimate risks arising from even current levels of Pb exposure?

Sunday, November 11th

5:15 PM – 7:00 PM

“MEET & GREET”

No Host Bar

Dinner on your own

Sunday Evening 11 November 2007 7:00PM – 9:30PM

Thought Provokers

SESSION III: CROSS-CUTTING ISSUES: HOT NEW TOPICS

Session Chair: **Richard LoPachin**
Co-Chair: **William Atchison**

7:00 – 7:30 PM

From Trees to Forest: Using Bibliometrics for Synthesizing and Prioritizing Biology, Toxicology and Exposure Topics in the Research Literature on Autism

Martha Herbert ~ *Harvard Medical School*

There is a growing awareness of the need for better approaches to setting strategic priorities across potential avenues of research. The rapidly expanding literature related to autism shows that a great deal of research is underway, but keeping track of so much new literature is daunting. Autism research seems to be expanding in emphasis beyond behavior and genetics to include more physiology and molecular biology. Objective metrics describing the areas of emphasis and apparent shifts would be helpful. We will describe a bibliometric assessment of the research literature, highlighting topics that have been heavily studied or understudied. We focus here in particular on chemical substances, including risk factors, markers of exposure, and markers of effect. We will review the state of biological research in autism as revealed by these methods, identify horizons highlighted by this approach, and discuss methodological challenges. Describing the state of the literature through patterns of keywords and other useful groupings can quickly summarize useful information and generate new insights into areas needing further research attention. For example, a greater emphasis on the exposure biology and intermediary metabolism domains may be critical for understanding this complex, heterogeneous set of conditions that appear to involve gene-environment interactions. This could be helpful to individual researchers, research programs and the NIH, which is increasingly expected to produce comprehensive research roadmaps that document plans and progress in various areas, including the autism research matrix.

7:30 – 7:40 PM **Q&A**

7:40 – 8:10 PM

Type-2 Alkene-Induced Nerve Terminal Damage Represents a Unified Mechanism for Neurodegenerative Diseases (Alzheimer's Disease, Parkinson's Disease, ALS)

Richard M. LoPachin ~ *Albert Einstein College of Medicine*

Growing evidence indicates that Alzheimer's disease (AD), amyotrophic lateral sclerosis (ALS), Parkinson's disease (PD) and other neurodegenerative conditions (stroke, ischemia) involve initial oxidative stress-induced lipid peroxidation and subsequent generation of endogenous conjugated type-2 alkenes such as acrolein and 4-hydroxy-2-nonenal (HNE). The purpose of this symposium is to present evidence supporting the hypothesis that the early stages of many neurodegenerative diseases are characterized by oxidative generation of type-2 alkenes in specific brain regions. We propose that cumulative protein adduction by these chemicals inhibits neurotransmission and, thereby, causes synaptic toxicity and eventual nerve terminal degeneration. Since type-2 alkenes such as acrolein, acrylamide and methylvinyl ketone are prevalent pollutants, it is possible that environmental exposure to these and other electrophilic chemicals accelerates the onset of neurodegenerative diseases like AD and ALS. Understanding the molecular mechanism of type-2 alkene-induced nerve terminal damage could provide insight into the development of pharmacotherapeutic approaches to these debilitating diseases.

8:10 – 8:40 PM

Amino Acid Neurotransmission: It's Role in Neurodegenerative Diseases and Neurotoxicity

William Atchison ~ *Michigan State University*

The amino acids glutamate and GABA are the predominant excitatory and inhibitory transmitters, respectively, in the mammalian brain. Evidence is accumulating that glutamate, in addition to its well described role in stroke and ischemic brain damage, also may contribute to Parkinson's and Alzheimer's Disease, and it appears to play a dominant role in amyotrophic lateral sclerosis. Disruptions in GABAergic transmission, in turn, are well recognized as playing crucial roles in seizurigenic disorders, but are increasingly recognized as playing a significant role in Huntington's disease, and may also be important contributors to the actions of ethanol.

The interaction of these two transmitter systems may play a role in neurotoxicity or some environmental agents as well.

8:40 – 9:10 PM

Ketamine-Induced Neuronal Cell Death in Perinatal Rhesus Monkeys

William Slikker ~ *National Center for Toxicological Research /FDA*

An increase (~20-150%) in the percentage of damaged brain cells was observed in the frontal cortex of monkey fetuses from ketamine-treated pregnant animals and five-day-old infant monkeys compared with non-treated controls. These findings are of interest because ketamine is used as a pediatric anesthetic in children. Previous studies have shown that ketamine is neurotoxic (causes brain damage) in the developing rat but these results needed to be confirmed or ruled out in an appropriate primate model with greater similarity to developing humans. Results of a study in rhesus monkeys will be presented. Many questions remain to be answered: 1) will the observed cell death affect overall brain function 2) can the injured brain tissue recover with no loss of normal function, and 3) are there preventive treatments that will ameliorate the anesthetic-induced neuronal cell death?

9:10 – 9:30 PM

Panel Discussion and Q&A:

- How can primary nerve terminal damage lead to generalized neurodegeneration?
- How does the relative electrophilicity of the type-2 alkenes determine nervous tissue vs. systemic toxicity?
- What pharmacotherapeutic approaches can be developed based on the role of protein adduction in type-2 alkene neurotoxicity?
- Are type-2 alkene adducts other than cysteine relevant to nerve terminal toxicity?

Monday Early Morning 12 November 2007 8:00 – 10:15 AM

Plenary Session

SESSION IV. COGNITIVE DISORDERS LINKED TO METHYL MERCURY EXPOSURE: MODIFIERS OF EFFECT: Chemical Co-Exposures and Nutrition

Session Chair: **Deborah C. Rice**

Co-Chair: **M. Christopher Newland**

Theme and Rationale: It has been known for decades that methyl mercury is a potent neurotoxicant, and that the developing brain is more susceptible to impairment as a result of methyl mercury exposure than is the adult. Epidemiological and experimental studies documented the constellation of effects produced by environmental exposure to methyl mercury. Developmental exposure may produce a constellation of adverse effects, including decreased cognitive function; deficits in attention, memory, and ability to inhibit inappropriate or non-adaptive behavior; and sensory and motor deficits. Some of these effects may be mediated through interference with dopaminergic neurotransmitter function. Exposure to methyl mercury is exclusively through consumption of fish and marine mammals. In recent years, the potential for protection against methyl mercury toxicity by nutrients present in fish, particularly omega-3 fatty acids and selenium, has received increasing attention. In addition, the potential for methyl mercury to interact with other chemicals present in marine food, including PCBs and pesticides, is of vital importance. These issues have important implications for risk assessment and risk management. This session will focus on potential interactions between methyl mercury and potential protective nutrients in humans and an animal model, as well as potential effect modification by other chemicals.

8:00 – 8:30 AM

Overview of Issues for Risk Assessment of Methyl Mercury Toxicity

Deborah Rice ~ *Maine Center for Disease Control*

Experimental studies have contributed much to our understanding of the neurotoxic effects of developmental exposure to methyl mercury. However, laboratory studies typically do not mimic the complexities of the many factors that influence the expression of methyl mercury toxicity. An understanding of the interactions of the multiple factors that determine the final behavioral outcome of exposure to methyl mercury is crucial to risk assessment and risk management.

The presentations in this session will address the influence of nutritional elements present in abundance in fish in modifying methyl mercury neurotoxicity in children, the interaction of multiple chemicals present in fish and marine mammals on neuropsychological outcome in children, and the interaction of methyl mercury and various dietary constituents in an animal model of methyl mercury neurotoxicity.

8:30 – 9:00 AM

Interactions of Neurotoxic Contaminants in the Arctic

Joseph Jacobson ~ Wayne State University

Many pollutants are transported into the Arctic environment from the northern hemisphere, including mercury, PCBs and other halogenated pollutants, and pesticides. These may be bioconcentrated up the food chain and are consumed by residents eating locally-caught fish and sea mammals. These chemicals may interact with each other in complex ways in analyses of associations between exposures and neurotoxic effects, as well as with nutritional constituents of the foods containing these pollutants. Specific factors in the social environment may also interact with toxicant exposure in determining the ultimate expression of toxicity. This presentation will focus on results from studies Arctic populations on the interactions between various contaminants present in the marine food chain.

9:00 – 9:30 AM

Neurodevelopmental Effects of Maternal Nutritional Status and Exposure to Methylmercury from Eating Fish during Pregnancy

Phil Davidson ~ University of Rochester

The Seychelles Islands Nutritional Study is designed to study the interaction of multiple nutritional components and methyl mercury exposure on the cognitive function of children. Blood and tissue levels of multiple nutrients are being measured, including omega-3 and omega-6 fatty acids, selenium and other essential trace elements, and vitamin and antioxidant status. There is a complex interaction of various nutritional elements with regard to protection against behavioral changes associated with increased body burden of methyl mercury. This presentation will present ongoing analyses of these complex interactions.

9:30 – 10:00 AM

Fish Nutrients and Methyl Mercury: A View from the Lab

M. Christopher Newland ~ Auburn University

Fish are a main source of both methyl mercury and important nutrients such as selenium and n-3 fatty acids. We have been studying the extent to which dietary levels of these important nutrients modify the expression of methyl mercury's neurotoxicity in a rodent model of low-level developmental and adult-onset exposure. A key strength of laboratory models of nutrient-toxicant interactions is the ability to exert precise control over dietary levels of the mix of nutrients. Developmental exposure to methyl mercury results in perseveration, behavioral rigidity, and enhanced sensitivity to reinforcing stimuli, and enhanced sensitivity to dopamine agonists. Both n-3 PUFAs and selenium exert behavioral effects of their own but do little to modify the expression of developmental exposure to methyl mercury. Selenium, however, can significantly protect against the more severe consequences of adult-onset exposures.

10:00 – 10:15 AM

Panel Discussion and Q&A:

- What is the evidence for protective effects of nutrients or additive effects of chemical co-exposure?
- How do we use that information in risk assessment?

10:15 – 10:30 AM Break

Monday Late Morning 12 November 2007 10:30 – NOON

Roundtable Discussion

SESSION V. TRANSLATING RISK ASSESSMENT INTO THE REAL WORLD

Session Chair: Bernard Weiss

Co-Chair: Kevin Crofton

Theme and Rationale Neurological diseases and disorders are rarely unidimensional or unifactorial. Even those whose etiologies seem closely linked to genetic predispositions tend to be the product of multiple and intertwined risk factors, of which environmental chemical exposures may serve as one component. Factors such as genetic background, age, dietary status, immune status, obesity, stress, socioeconomic status, sex, and intercurrent disease state, as well as current and past chemical exposures, must also be considered.

Despite these complexities, traditional risk assessment practices fail to capture this reality. Instead, they focus on exposures to single chemicals in isolation from other risk factors. Animal studies often examine effects of a single chemical in young adult, mostly male rodents, ignoring, for instance, the potential importance of age, sex, and early environment. Epidemiological and clinical studies tend to emphasize main effects of environmental exposures, stripping away interactions by allegedly controlling for confounders. The result is a wide gulf between current models of diseases and disorders and the actual conditions under which they emerge.

The vulnerability of an organism to disease results from a combination of environmental stressors and modifiers. Advances in our ability to interdict threats to neurobehavioral integrity require us to take into account xenobiotic exposures, life stage, socio-economic factors, nutritional status, and genetics. We already possess substantial evidence of the health impact of single environmental factors. *We lack the data required to model the interactions between these risk modifiers and to translate them into risk policy.* This session is designed to examine the multifaceted nature of neurotoxic risk.

Questions for the Roundtable Discussants:

- We are supposed to be part of a science whose framework was constructed by the mantra that The Dose Makes the Poison. Is it now time to bid farewell to the NOAEL as it is currently applied? (Schettler, Rice, Mergler)
- We agree that exposures take place in a complex societal setting whose features help determine how the consequences of those exposures will be expressed. So what does all this mean for what is labeled as translational research? Does it mean viewing disease as an astute clinician might see it? Such a clinician would not

undertake to diagnose and treat a patient without knowing the patient's home environment, his or her workplace, dietary practices, family situation, economic status, and other components of the individual's life. Is our situation parallel? (Cory-Slechta, C. Miller)

- Conversely, despite the immense volume of literature demonstrating connections between environmental exposures and clinical diseases and disorders, they still are accorded a relatively minor role in diagnosis, treatment, and, especially, prevention. How do we promote awareness of these connections among health professionals and health agencies? (E. Miller, Gilbert)
- Finally, how do we embed these new perspectives into our research, especially for those of us whose primary efforts lie in the laboratory? Who can we convince to pay for them? (Crofton, Newland)

Speakers and Roundtable Discussants:

Deborah Cory-Slechta ~ *University of Rochester*

Kevin Crofton ~ *US Environmental Protection Agency*

Steven Gilbert ~ *Inst. for Neurotoxicology and Neurological Disorders*

Donna Mergler ~ *University of Quebec at Montreal*

Elise Miller ~ *Learning and Developmental Disabilities Initiative*

Claudia Miller ~ *Univ. of Texas Health Science Center at San Antonio*

M. Christopher Newland ~ *Auburn University*

Deborah Rice ~ *Maine Center for Disease Control*

Ted Schettler ~ *Science and Environmental Health Network*

Bernard Weiss ~ *University of Rochester*

cytokines, are the link between developmental exposures to neurotoxicants and late-onset neurodegenerative disease will be examined. The speakers will discuss data obtained from in vivo and in vitro models by means of numerous techniques, including, imaging, neurochemical and hormonal analysis, immunocytochemistry, electrophysiology, and behavioral testing. This session would be of interest to neuroscientists who are investigating disease etiologies, particularly given the increased emphasis in recent years on environmental factors in the etiology of Parkinson's and Alzheimer's Diseases.

1:00 – 1:05 PM

Introduction

Evelyn Tiffany-Castiglioni ~ *Texas A&M University*

1:05 – 1:25 PM

CNS Mechanisms of Manganese in the Stimulation of Precocious Puberty

W. Les Dees ~ *Texas A&M University*

Manganese (Mn) is an important element for normal growth and reproduction. Dr. Dees will present evidence that Mn from slightly elevated dietary exposures accumulates in the hypothalamus and stimulates precocious puberty in female rats. The principal mechanisms of action in the hypothalamus will be discussed.

1:25 – 1:45 PM

Developmental Exposure to PCBs Alters the Response of the Adult Brain to Stress

Pamela Lein ~ *Oregon Health & Science University*

Emerging evidence suggests that developmental exposure to PCBs influences the response of the adult brain to various stressors. Dr. Lein will present evidence obtained using well defined rodent models of stroke and seizure that developmental exposure to PCBs alters the response of the adult brain to focal cerebral ischemia, and enhances seizure susceptibility.

1:45 – 2:05 PM

Developmental Basis for Parkinson's Disease

Mona Thiruchelvam ~ *Environmental and Occupational Health Sciences Institutes, Rutgers and UMDNJ*

Compelling recent evidence from animal models has shown that exposure during development to the common pesticides paraquat and maneb can directly reduce the number of dopamine neurons, or cause an increased susceptibility to their degeneration with subsequent environmental insults or with aging alone. To begin to determine critical pathways of paraquat + maneb neurotoxicity, the functions of cell death-inducing and protective mechanisms were analyzed. Results suggest that protective mechanisms involve modulation of the level of reactive oxygen species and alterations of the functions of specific signaling cascades.

2:05 – 2:25 PM

Lead Effects on Molecular Chaperones: A Link to Neurodegenerative Diseases?

Evelyn Tiffany-Castiglioni ~ *Texas A&M University*

Molecular chaperones are highly conserved proteins that assist the folding of nascent proteins into their correct conformations. Chaperone are sensitive to environmental stress and a deficiency in their function may underlie neurodegenerative diseases that exhibit protein accumulation or misfolding. Evidence from in vitro studies will be presented that Pb disrupts the function of the chaperone glucose regulated protein 78 (GRP78).

Monday Early Afternoon 12 November 2007 1:00 – 3:00 PM

Parallel Session

Symposium

SESSION VI-A. FETAL BASIS OF ADOLESCENT AND ADULT DISEASES

Session Chair: **Evelyn Tiffany-Castiglioni**

Co-Chair: **Pamela J. Lein**

Theme and Rationale: During the past 30 years, research on mechanisms of developmental neurotoxicity has focused primarily on the impact on children's health. However, compelling evidence from animal models published within the past few years has shown that developmental exposures to neurotoxicants and other environmental stressors may also adversely affect adult health and cognitive function during aging. Much less recognized is the vulnerability of the adolescent to toxic exposures prior to the onset of puberty. Both topics deserve focused attention as neuroscientists attempt to understand gene-environment interactions in lifelong health. This session will focus on recent progress in understanding how exposure to neurotoxicants early in life may affect neural function in the adolescent and adult. Examples include the effects of manganese on the onset of puberty through actions on the hypothalamic-gonadal axis and the association of early exposures to lead and pesticides on neurodegenerative disease in aging. In addition, the hypothesis that molecular targets, such as chaperones and

2:25 – 2:45 PM

Developmental Pesticide Exposure: A New Risk Factor for ADHD?

Jason R. Richardson ~ *Robert Wood Johnson Medical School*

Attention deficit hyperactivity disorder (ADHD) is a complex disorder with significant genetic contributions. However, no single gene has been linked to a significant percentage of cases, suggesting that environmental factors or gene-environment interactions may contribute to the etiology or clinical manifestation of ADHD. Dr. Richardson will present data from both animal and epidemiological studies that point to development pesticide exposure as an environmental risk factor for ADHD.

2:45 – 3:00 PM

Panel Discussion

Monday Early Afternoon 12 November 2007 1:00 – 3:00 PM

Parallel Session

Roundtable / Open Forum

SESSION VI-B. CELL DEATH IN THE NERVOUS SYSTEM: FACTS AND ARTIFACTS

Session Chair: **David Dorman**

Co-Chair: **Jack Harkema**

Theme and Rationale: This round table discussion session will address a number of key issues concerning the delineation of neuronal cell death by histopathology. Specifically, roundtable discussants will examine key questions related to this important area of research. **It is hoped that attendees of this session with experience in these issues will also participate in an open discussion of these important topics.**

Topics include:

- What are the accepted morphological, biochemical, and/or other cellular changes that may serve as criteria for neuronal cell death?
- What types of stains / staining techniques are most appropriate and reliable for directly or indirectly (e.g., glial responses) recognizing neuronal cell death in *in vivo* studies
- What are known morphological artifacts that may interfere with evaluating tissues for neuronal cell death?
- How do these artifacts occur, and how can they be minimized or avoided by tissue processing or staining techniques?

Roundtable / Open Forum Discussants:

David Dorman ~ *North Carolina State University*

Hassan El Fawal ~ *Mercy College*

Jack Harkema ~ *Michigan State University*

Kenneth Reuhl ~ *Rutgers University and UMDNJ*

Conference Participants

Monday Late Afternoon 12 November 2007 3:15– 5:15PM

Parallel Session

Platform Session

SESSION VII-A. DEVELOPMENTAL NEUROTOXICITY; NEUROPROTECTION

Session Chair: **DMG DeGroot**

Co-Chair: **Nikolay Filipov**

3:15 – 3:40 PM

Role of oxidative stress and free radicals in Methamphetamine, MPTP or FeSO₄-induced Neurotoxicity

Eden Tareke ~ *National Center for Toxicological Research/FDA.*

3:40 – 4:05 PM

Important Role for the Early Growth Response Factor 1 (EGR1) in the Potentiation of Microglial Proinflammatory Cytokine Production by Manganese Exposure

Nikolay M. Filipov ~ *Mississippi State University*

4:05 – 4:30 PM

Functional Imaging of Developmental Neurotoxicity

DMG de Groot ~ *TNO Quality of Life, Zeist, the Netherlands.*

Student Presentations ~ 15 minutes each (also presenting from poster)

4:30 – 4:45 PM

Developmental Phencyclidine (PCP) or Ketamine Treatment Increases the Frequency of Abnormal Activity in Sprague-Dawley Rat Pups

Sherin Y Boctor ~ *National Center for Toxicological Research/FDA and University of Arkansas for Medical Sciences*

4:45 – 5:00 PM

Paraquat Induces Oxidative Stress, Neuronal Loss and Parkinsonism in Rats: Neuroprotection by Water-Soluble COQ₁₀

Mallika Somayajulu-Nitu ~ *University of Windsor, Windsor, ON, Canada.*

5:00 – 5:15 PM

Prenatal LPS Exposure Alters the Fate of Developing Dopamine Projections

Angela J. Monahan ~ *Rush University*

Monday Late Afternoon 12 November 2007 3:15– 5:15 PM

Parallel Session

Symposium

SESSION VII-B: THE OLFACTORY SYSTEM: AN OFTEN FORGOTTEN TARGET

Session Chair: **David Dorman**

Theme and Rationale: The olfactory system is unique in that it forms a direct interface between the air and the central nervous system (CNS). There is growing evidence that metals and other xenobiotics deposited within the nose can be absorbed at this site and then undergo transport along the olfactory nerve, thus bypassing the blood-brain-barrier. One metal of special concern to be discussed in this symposium is manganese, a neurotoxic metal shown to be able to cross synapses in the olfactory bulb and migrate via secondary

olfactory neurons to more distant nuclei of the brain. This symposium will also discuss inter-species differences in nasal anatomy that may play a role in olfactory uptake and transport and responses. The olfactory neuron is also an important target for many xenobiotics with both functional and structural changes of concern and will be addressed by two speakers during the symposium.

3:15 – 3:40 PM

The Olfactory System: Anatomy and Overview

David Dorman ~ North Carolina State University – College of Veterinary Medicine

3:40 – 4:05 PM

Olfactory Transport of Xenobiotics

Melanie Struve ~ CIIT

4:05 – 4:30 PM

Toxicologic Pathology of Olfactory Sensory Neurons

Jack Harkema ~ Michigan State University

4:30 – 4:55 PM

Odor Perception

Pamela Dalton ~ Monell Chemical Senses Center

4:55 – 5:15 PM

Discussion

5:15 – 7:00 PM *Break for dinner on your own*

Monday Evening 12 November 2007 7:00PM – 9:30PM

SESSION VIII. POSTER SESSION

No-Host Bar & Refreshments

Session Chair: **Darryl Hood** (invited)
Co-Chairs: **Joseph Jacobson** (invited)

Poster abstracts are numbered from P-58 to P-104 and can be found on pages 15 - 18.

The Poster Session is a highlight of this conference series. It has proven to be an effective venue for informal, in-depth discussion and collaboration building -- as well as an important networking opportunity for all participants. Papers on any aspect of neuroscience, toxicology, children's environmental health, public health & policy are welcome!

Posters may be put up as early as 9:00 AM on Sunday and should remain up for the duration of the conference for maximum exposure. Posters should be taken down by 1:00 PM on Wednesday.

STUDENT AWARD COMPETITION

Chair: **Jason Richardson**

Judging will be done between 7:15 PM – 8:30 PM. Students please stand by your poster during this time.

The Student Award Competition is divided into two groups: one for post-doctoral competition and one for pre-doctoral competition. Awards will consist of a cash prize, plaque or certificate, plus a one year subscription to the international

journal *NeuroToxicology*. A winner(s) will be chosen from each group. Competing students are expected to give an overview of their work in 2-3 minutes to the judges followed by a brief set of questions and answers. Originality, significance, hypothesis, presentation material and style, as well as knowledge of the subject, will be considered in selecting the winners. All papers in competition for the Student Awards must be presented from poster.

GROUP 1: POST-DOCTORAL COMPETITION

Chair: **Kenneth Reuhl**

Post-Doctoral Student Award Committee

1. Kenneth Reuhl, *Chair*
2. Richard LoPachin
3. Kevin Crofton

Post-Doctoral Students (5)

- | | |
|------------------------|-------------------------------------|
| Joan Garey, Ph.D. | <i>Mentor:</i> Merle Paule, Ph.D. |
| Olga Pakhomova, Ph.D. | <i>Mentor:</i> P.J. Hart, Ph.D. |
| Jesse Rodriguez, Ph.D. | <i>Mentor:</i> Merle Paule, Ph.D. |
| Fuyong Song, Ph.D. | <i>Mentor:</i> Xie Keqin, Ph.D. |
| TramAnh Ta, Ph.D. | <i>Mentor:</i> Robert Berman, Ph.D. |

GROUP 2: PRE-DOCTORAL COMPETITION

Chair: **Jason Richardson**

Pre-Doctoral Student Award Committee

Sub-Group A

1. Merle Paule, *Co-Chair (Group A)*
2. Pam Lein
3. Darryl Hood

Sub-Group B

4. Anumantha Kanthasamy, *Co-Chair (Group B)*
5. Mona Thiruchelvam
6. Richard Nass

Sub-Group C

7. Gary Miller, *Co-Chair (Group C)*
8. Syed Imam
9. Nikolay Filipov

Pre-Doctoral Students (12)

- | | |
|-------------------------|---------------------------------------|
| Rebecca Alyea | <i>Mentor:</i> Cheryl Watson, Ph.D. |
| Sherin Boctor | <i>Mentor:</i> Sherry Ferguson, Ph.D. |
| Daniel Braunschweig | <i>Mentor:</i> Judy Van de Water, PhD |
| Josh Harrill | <i>Mentor:</i> Kevin Crofton, Ph.D. |
| Ravikumar Hosamani | <i>Mentor:</i> M. Muralidhara, PhD |
| Chia-Jung Hsieh | <i>Mentor:</i> Pau-Chung Chen, PhD |
| Ahmed Ismail | <i>Mentor:</i> Diane Rohlman, Ph.D. |
| Ebany Martinez | <i>Mentor:</i> Andrea Allan, Ph.D. |
| Angela Monahan | <i>Mentor:</i> Paul Carvey, Ph.D. |
| Wang QingShan | <i>Mentor:</i> Xie Keqin, Ph.D. |
| Pallavi Sethi | <i>Mentor:</i> Deepak Sharma, Ph.D. |
| Mallika Somayajulu-Nitu | <i>Mentor:</i> Siyaram Pandey, PhD |

Tuesday Morning 13 November 2007 8:30AM - Noon

Plenary Session

SESSION IX. MODIFIERS OF DISEASE DEVELOPMENT IN PARKINSON'S DISEASE: ROLE OF ENVIRONMENTAL TOXICANTS

Session Chair: Donato A. Di Monte
Co-Chair: Gary Miller

Theme and Rationale: Investigations into factors and mechanisms that predispose to Parkinson's disease (PD) are directly relevant to our understanding of the pathogenesis of the disease and provide important clues for the development of preventive strategies and neuroprotective intervention. Epidemiological and clinical evidence points to an unequivocal risk factor for PD, i.e. aging, as well as putative predisposing and protective conditions. The former include pesticide and metal exposure, inflammation and polymorphism of the alpha-synuclein promoter, whereas an example of protective factors is cigarette smoking. Modeling PD in experimental animals though toxic or genetic manipulation provides a tool for validating the role of specific risk factors and studying the mechanisms underlying their action. Results of these studies support a role of environmental toxicants in the pathogenesis of PD and have suggested, for example, that: **Aging** is not associated *per se* with progressive dopaminergic cell degeneration, but it causes nigrostriatal dysfunction and increased susceptibility to injury by environmental toxicants. Neuromelanin accumulation and loss of tyrosine hydroxylase immunoreactivity are markers of these age-related changes within nigral dopaminergic neurons. Furthermore, recent work has revealed increasing levels of alpha-synuclein with age in the substantia nigra of humans and non-human primates, suggesting an additional mechanism for age-related enhanced susceptibility to neurodegenerative processes. **Pesticides** such as paraquat, maneb, dieldrin and rotenone reproduce pathological aspects of PD in animal models. Interesting features of these models include synergistic interactions, the formation of alpha-synuclein-positive deposits and signs of oxidative damage. Neuronal injury by putative environmental toxicants triggers an up-regulation of **alpha-synuclein**. This effect provides an intriguing mechanism by which genetic (polymorphism within the gene promoter) and environmental (toxic exposures) factors may cooperate to induce alpha-synuclein-related pathology (a hallmark of PD). **Polychlorinated biphenyls (PCBs)** are widespread environmental and occupational neurotoxicants. Although the majority of PCB research has dealt with the consequences of developmental exposure, a growing body of literature has shown that the adult CNS is also a target. PCBs reduce: (i) the number of tyrosine hydroxylase positive neurons in the substantia nigra; (ii) dopamine (DA) concentrations in basal ganglia and (ii) in common with some pesticides, both vesicular monoamine and dopamine transporter function. The putative role of PCBs as an etiologic factor in Parkinson's Disease warrants further investigation.

A pre-existing **inflammatory process** and, in particular, microglial activation can dramatically enhance the susceptibility of dopaminergic cells to toxic injury. This "priming" effect could be mediated by oxidative reactions catalyzed by enzymes such as NADPH-oxidase and inducible nitric oxide synthase. Early-in-life conditions, such as increased neonatal **iron** intake, can have long-term consequences and lead to neurodegenerative changes in aged animals. These changes appear to

selectively affect the dopaminergic nigrostriatal system. The decreased incidence of PD in smokers, which has been reported by a large number of epidemiological studies and is not a mere consequence of decreased life expectancy, could be mediated at least in part through neuroprotection by **nicotine**. Data suggest that injury caused by environmental toxicants may be alleviated by co-exposure with nicotine.

These important modifiers of PD pathogenesis will be discussed in this symposium with particular emphasis on (i) translational information from clinical/epidemiological studies to laboratory research and vice versa, and (ii) how environmental toxicants may act as risk factors for PD and interact with other PD modifiers in disease pathogenesis. For this reason, the lectures and discussions should be of significant interest to a broad audience of neurotoxicologists, neuroscientists, epidemiologists, clinicians and patient advocates.

8:30 – 9:00 AM

Interactions Between Alpha-Synuclein and Environmental Toxicants in the Pathogenesis of Parkinson's Disease

Donato A. Di Monte ~ The Parkinson's Institute

Increased expression of the protein α -synuclein is associated with familial parkinsonism in humans with genomic multiplication of the α -synuclein gene. In sporadic (i.e. non-familial) Parkinson's disease (PD), non-genetic factors could account for enhanced α -synuclein levels and augmented vulnerability to α -synuclein pathology, including exposure to environmental toxicants and aging. Observations in the non-human primate brain reveal that treatments with the herbicide paraquat or the parkinsonism-inducing agent MPTP cause a marked increase in α -synuclein at both the mRNA and protein levels. This toxicant-induced up-regulation is accompanied by post-translational modifications of the protein in the form of phosphorylated and nitrated α -synuclein that resemble changes seen in PD. Increased protein expression is also followed by the accumulation of insoluble α -synuclein aggregates that are particularly evident within dystrophic neurites and are therefore reminiscent of PD Lewy neurites. Another factor associated with enhanced α -synuclein levels is normal aging. Both α -synuclein mRNA and protein are significantly elevated in the brain of old humans as well as old non-human primates. Interestingly, this finding contrasts with observations in rodents in which α -synuclein levels decline rather than increase with age. Taken together, evidence indicates that α -synuclein may be a critical target for PD-relevant environmental toxicants and that aging may act as a risk modifier by enhancing α -synuclein expression in the primate brain.

9:00 – 9:30 AM

Environmental Risk Factors for PD Identified Through Epidemiological Studies

Caroline Tanner ~ The Parkinson's Institute

Epidemiological studies have identified many factors associated with Parkinson's disease (PD) risk. Increasing age and male gender are the most frequently observed nongenetic risk factors for PD. Many other risk factors have been described inconsistently. These include certain occupations, pesticide exposure, head injury and dietary factors. Lower risk of PD has also been associated with many factors, including tobacco use, especially cigarette smoking, drinking coffee or tea and nonsteroidal anti-inflammatory drug use. Family history of PD is associated with increased risk, but purely genetic causes of PD likely constitute no more than 10% in

most populations. Twin studies, including a recent large prospective follow-up of twin pairs discordant for PD, do not find greater concordance for PD in monozygotic twins with typical age at onset, suggesting that environmental determinants are of primary importance in typical-onset PD. However, in twins with onset before age 50, concordance is greater in monozygotic twins, supporting a genetic cause in this small young-age-at-onset group. The majority of parkinsonism in the community most likely has complex determinants, involving one or more environmental and/or one or more genetic factors. Investigation of the pathophysiologic mechanisms of the toxicants and genes known to cause parkinsonism can provide insight into other likely candidates, alone or in combination.

9:30 – 10:00 AM

The Influence of Gender and Aging on the Effects of Environmental Toxicants in Parkinson's Disease

Richard Seegal ~ *Wadsworth Center*

Polychlorinated biphenyls (PCBs) are widespread environmental and occupational neurotoxicants shown to reduce dopamine (DA) concentrations and the number of tyrosine hydroxylase positive neurons in the substantia nigra (SN) of both adult laboratory rodents and non-human primates. To determine whether PCB-induced changes in central DA are also seen in humans, we measured the density of dopamine transporters (DAT) in the basal ganglia of male and female former capacitor workers using β -CIT imaging. The mean age of the workers at time of examination was 63.5 years. Women constituted approximately 44% of the population and were exclusively postmenopausal. Although mean current serum PCB concentrations were similar between men and women (mean for men = 7.9 ppb; mean for women = 6.7 ppb; $F=0.94$, $p=0.336$), a significant negative relationship was observed between serum PCB concentrations and β -CIT measures of DAT density for women ($r^2=0.18$, $p\leq 0.01$, $N=37$), but not for men ($r^2=0.01$, $p=0.46$, $N=41$). Control for potential confounders including age, body mass index, smoking, alcohol consumption, caffeine consumption, bone lead body burden and the use of cardiovascular medicines did not alter the above relationship. These results suggest that reductions in circulating ovarian hormones following menopause may increase the risk for reduction in central DA following exposure to PCBs and similar neurotoxicants. Our findings gain further support when one considers the recent findings of Steenland et al. (2006) who reported increased PD mortality only in highly exposed female former capacitor workers. In summary, these findings highlight the potential importance that ovarian hormones play in altering basal ganglia DA following toxic insult. Supported by U.S. Army grant # DAMD17-02-0173 to RFS.

10:00 – 10:30 AM Break

10:30 – 11:00 AM

Cyclodiene Insecticides and Parkinson's Disease: Evidence from Mice and Men

Gary Miller ~ *Emory University*

The pathogenic processes in Parkinson's disease (PD) occur over several decades ultimately leading to the loss of dopamine neurons in the substantia nigra pars compacta.

Epidemiological studies support an association between pesticide exposure and PD, but have been unable to identify specific compounds or classes associated with the disease. Our laboratory has hypothesized that the compounds most likely to be associated with PD are lipophilic compounds that persist in the environment and bioaccumulate in brain tissue. To test this hypothesis we performed GC/MS analysis on the brains of nearly 100 patients in the Emory University Brain Endowment Bank, including controls and those with PD and Alzheimer's disease. Our results show that there is a significant association between the concentration of cyclodiene insecticides and the neuropathological diagnosis of PD. Furthermore, we have identified two plausible mechanisms by which this class of compounds may contribute to the development of PD, namely, increased expression of alpha-synuclein and altered sequestration of dopamine. Increased alpha-synuclein expression via gene duplication or triplication has been implicated in human cases of PD and we have recently shown that reduced vesicular storage of dopamine causes progressive nigrostriatal dopamine neuron degeneration in mice. These data suggest that cyclodiene insecticides should be considered suspects in the continued mystery of environmental causation of Parkinson's disease.

11:00 – 11:30 AM

The Role of Inflammation in Toxicant-Induced Injury in Parkinson's Disease

Jau-Shyong Hong ~ *NIHES*

Microglia, the predominant cell type in the central nervous system expressing the major histocompatibility complex class II molecule, play an important role in immune surveillance. However, during in certain pathological conditions, over-activated and dys-regulated microglia secrete neurotoxic substances, such as proinflammatory cytokines or free radicals, which kill neurons and have been proposed to be the major causes of neurodegenerative diseases, such as Parkinson's disease. Because neurodegeneration is a common sequela for patients exposed to a variety of environment-related neurotoxins, information generated from this line of research should further our understanding of the mechanisms of action for neurotoxicants. In this presentation, I will discuss the following two aspects:

1. Role of microglia in inflammation-related neurodegeneration. Using both primary midbrain neuron/glia co-cultures and *in vivo* study, we have developed an inflammation-induced rodent Parkinson's disease model by employing different inflammagens such as endotoxin, LPS, α -amyloid peptides, and the pesticide, rotenone. We have studied the molecular mechanisms underlying microglia-mediated neurotoxicity through the investigation of pro-inflammatory factors released from microglia and how these factors exert their toxic effects on neurons.

2. Development of potential therapeutic interventions in inflammation-related diseases. Based on our understanding of the microglia-mediated neurotoxic effects in inflammation-related neurodegeneration, effort has been made to develop novel anti-inflammatory drugs, which have potential therapeutic use for Parkinson's disease. These compounds are different from the current available anti-inflammatory drugs in their mode of action and safe for long-term clinical usage.

TWENTY-FOURTH INTERNATIONAL NEUROTOXICOLOGY CONFERENCE

11:30 – 12:00 NOON

Panel Discussion and Q&A:

- How strong is the association between toxicant exposure and PD risk?
- Is there a concordance between epidemiological and experimental findings related to environmental toxicants and other modifiers of PD development?
- How well do animal models reproduce the “multiple hits” hypothesis of PD pathogenesis involving environmental toxicants?
- What are the most relevant modifiers of the effects of neurotoxicants in PD?
- How does knowledge of PD modifiers influence our view of disease prevention and treatment?

3:00 – 3:20 PM

Vascular and membrane pathology in neurodegenerative disorders: red cells as target and biomarker

Donald E. Schmechel ~ *Falls Neurology and Memory Center, Granite falls, NC*

3:20 – 3:40 PM Break

Tuesday Late Afternoon 13 November 2007 3:40 – 5:45 PM

Symposium

SESSION XI: AN ECOSYSTEM APPROACH TO EXPOSURE TO NEUROTOXIC SUBSTANCES IN LATIN AMERICA

Session Chair: Donna Mergler

Co-Chair: Maryse Bouchard ~ *Harvard University*

Theme and Rationale: Although exposure to neurotoxic exposure has been extensively studied in occupational and environmental settings in industrialized societies, fewer studies have been carried out in lesser industrialized countries where exposure profiles may be very different with respect to source, pathways and effects, modulated by different biogeophysical, social, cultural and nutritional realities. Using an ecosystem approach to human health, which integrates research in the natural, social and health sciences, with a view to proposing prevention intervention strategies, several studies are currently being carried out in Latin America on neurotoxic agents and their effects on adults and children.

Tuesday Early Afternoon 13 November 2007 1:00 – 3:30 PM

Platform

SESSION X: ENVIRONMENTAL LINKS TO NEUROLOGICAL DISEASES (PARKINSON'S, ALZHEIMER'S)

Session Chair: Anumantha Kanthasamy

Co-Chair: Syed Imam

1:00 – 1:20 PM

Humoral Neuroimmunity in Neurological Disorders and Neurotoxicity: Parallels, Mechanisms and Biomarkers. A review of the Literature

Hassan El-Fawal ~ *Mercy College*

1:20 – 1:40 PM

JNK Mediates Lactacystin-Induced Dopamine Neuron Degeneration

Weidong Le ~ *Baylor College of Medicine*

1:40 – 2:00 PM

Neurotoxic Insults Modulate Oxidative Stress-sensitive PKC δ Gene Promoter Activity in Neuronal Cells: Implications for Gene-Environment Interactions in Neurodegeneration

Anumantha Kanthasamy ~ *Iowa State University*

2:00 – 2:20 PM

Human Range Dietary Aluminum Equivalents Cause Cognitive Deterioration in Aged Rats

Judie Walton ~ *Australian Institute for Biomedical Research, Australia*

2:20 – 2:40 PM

Neuroprotective Effects of Cannabinoids in MPTP-Treated Mice: Role of CB1 and CB2 Receptors

Andrea Giuffrida ~ *University of Texas Health Science Center at San Antonio*

2:40 – 3:00 PM

Chemo Brain: A Translational Challenge for Neurotoxicology

Bernard Weiss ~ *University of Rochester School of Medicine and Dentistry*

3:40 – 4:00 PM

Neurotoxic Effects of Mercury in the Brazilian Amazon: An Ecosystem Approach to Exposure Reduction and Effects

Donna Mergler ~ *University of Quebec at Montreal*

4:00 – 4:20 PM

An Ecosystem Approach to Neuropsychological Effects of Manganese Exposure on Children Living in Communities Near to Processing Plants in Mexico.

Rodolfo Solís ~ *National Institute of Public Health, Mexico*

4:20 – 4:40 PM

An Ecosystem Approach to Environmental Pesticide Exposure and Neurological Effects in Children

Berna van Wendel de Joode ~ *Central American Institute for Studies on Toxic Substances, Universidad Nacional, Costa Rica*

4:40 – 5:00 PM

Pesticide Exposure and Neurobehavioral Development in Ecuadorian Infants and Children: An Ecohealth Approach

Alexis Handal ~ *National Institute for Child Health and Human Development, NIH*

5:00 – 5:20 PM

Feasibility for Studying Parkinson's Disease in Relation to Pesticide Exposure in Costa Rica

Ana Mora ~ *Central American Institute for Studies on Toxic Substances, Universidad Nacional, Costa Rica*

5:20 – 5:45 PM

Discussion

*Hosted
Social Evening
Dinner & Recognition Ceremonies*

Entertainment by Jalapeño Honey!

“Six Flags over Texas - Neurotox Style!”

Calling all NEUROTOX 24 musicians:

**You are cordially invited to sit in with
the Jalapeño Honey band
at the NEUROTOX banquet,
TUESDAY NIGHT, NOVEMBER 13.**

Jalapeño Honey is a contra dance band based in College Station, Texas. Our main repertory is Celtic, Old Time American, and New England dance music, but for this occasion we will also play tunes from Mexico, Latin America, and Western Europe. Texas was governed at various times under six different flags: France, Spain, Mexico, The Republic of Texas, The Confederate States of America, and the United States of America. Many other countries and cultures are also represented in Texas, so our playlist will be wide, varied & fun.

If you play a portable instrument and want to bring it (flute, clarinet, mandolin, violin, guitar, tin whistle, kazoo, concertina, small percussion, etc.), please let me know. I will send you the music by email.

A message from,

~ Evelyn

Evelyn Tiffany-Castiglioni

Chair of Music & Entertainment for “Six Flags Over Texas - Neurotox Style!”

Ecastiglioni@cvm.tamu.edu

Whether you want to dance the Cotton-Eyed Joe, shake your maracas, or listen to Mark Noble sing the blues about being a scientist, the NEUROTOX 24 banquet will be the place to be. Music will be played by Jalapeño Honey, the #1 contra dance band in southeastern College Station. There will be two accordions (TWO!), a flute, guitars, a Celtic harp, and maybe a bandolin (you'll see). If you missed the invitation to join the band, there is still time! Email me for music and bring your instrument (penny whistle, clarinet, didgeridoo, mandolin, concertina, kazoo, bongos, whatever you can carry; sorry, no banjos). Our program will be the music of the six sovereign nations that governed Texas, plus whatever else we want to play. Just kidding about the banjos. See you there!

~ Evelyn

Ecastiglioni@cvm.tamu.edu

Plenary Session

SESSION XII: OXIDATIVE STRESS IN AUTISM - CAUSE OR CONSEQUENCE?

Session Chair: **Isaac Pessah**

Co-Chair: **Jill James**

Theme and Rationale: Autism is among the most complex neurodevelopmental disorders with potential susceptibility genes spread across the entire genome. Concordance between monozygotic twins for autism is significantly less than unity and phenotypic presentation can vary broadly between sibs. Autism therefore presents unique opportunities and challenges to study interactions among multiple susceptibility genes, and how epigenetic factors and exposure to environmental modifiers may contribute to variable expression of autism, and autism-related traits. Markers of oxidative stress have been recently detected at higher levels in autistic individuals compared to those that are not autistic. Whether oxidative stress is an etiological determinant of autism, biomarker of environmental susceptibility, or simply and epiphenomenon has been hotly debated.

In the first presentation, Dr. James will discuss the metabolic pathways that have been found to be abnormal in many autistic children (and their parents) with focus on the interdependent pathways of folate, methionine, and glutathione metabolism and related genetic polymorphisms. She will present evidence for plasma, intracellular and mitochondrial redox imbalance that suggests many autistic children may be under systemic oxidative stress with a reduced capacity to buffer pro-oxidant environmental exposures.

The second presentation (Pratico) will focus on new evidence that children with a clinical diagnosis of autism have significantly higher urinary levels of lipid peroxidation biomarkers that correlate with markers of platelet and vascular endothelium activation. These imbalances in fatty acid metabolism, possibly mediated by oxidative stress, may contribute to autism, since recent data indicates that supplementation with omega-3 fatty acids may be an effective treatment. Of particular importance to the etiology of autism is identification of critical cellular signaling pathways that may be common cell of the central nervous and immune systems that particularly sensitive to shifts in antioxidant defenses and redox signaling.

One such redox sensitive receptor tyrosine kinase (RTK) signaling pathway is required for cell division in central nervous system (CNS) progenitor cells. Local chemically induced changes in redox status have been associated with Fyn kinase activation that leads to activation of c-Cbl ubiquitin ligase. Sequential Fyn and c-Cbl activation, with consequent pathway-specific suppression of RTK signaling, is induced by levels of methylmercury and paraquat. Dr. Noble (3rd talk) will present results of studies that identify a novel regulatory pathway of oxidant-mediated Fyn/c-Cbl activation as a shared mechanism of action of chemically diverse toxicants at environmentally relevant levels, and as a means by which increased oxidative status may disrupt mitogenic signaling. He will discuss a predictive framework of broad potential relevance to the

understanding of pro-oxidant-mediated disruption of normal development.

Dr. Ashwood will describe new evidence that NK and CD8+ immune cells isolated from autistic children exhibit altered patterns of activation and cytokine secretion compared to those isolated from typically developing children and discuss possible mechanisms leading to inflammation. Calcium is a universal signaling molecule in virtually all cellular systems that regulate activation, metabolism, growth, and differentiation.

The final talk by Dr. Pessah will describe molecular mechanisms by which Ca²⁺ channels are deregulated in autism and how such mutation can confer increased susceptibility to chemically induced oxidative stress and abnormal Ca²⁺ signaling. The implications of Ca²⁺ channel mutations in conferring susceptibility to environmental triggers will be discussed.

8:30 – 8:40 AM

Introduction

Isaac Pessah ~ *University of California, Davis*

8:40 – 9:10 AM

Redox Imbalance and the Metabolic Pathology of Autism

S. Jill James ~ *University of Arkansas for Medical Sciences*

9:10 – 9:40 AM

Lipid Biomarkers of Enhanced Oxidative Stress: Relationship to Platelet and Vascular Endothelium Activation

Domenico Pratico ~ *Temple University*

9:40 – 10:10 AM

Regulation of CNS Progenitors by Redox State: Implications for Autism and Understanding the Interplay Between Genes and Environment

Mark Noble ~ *University of Rochester*

10:10 – 10:20 AM Break

10:20 – 10:50 AM

The Relationship Between Oxidative Stress, Immune Cells and Inflammation in Autism.

Paul Ashwood ~ *The UC Davis M.I.N.D. Institute*

10:50 – 11:20 AM

Redox Sensing of Calcium Channels – A Convergence of Genes and Environment

Isaac Pessah ~ *University of California, Davis*

11:20 – NOON

Panel Discussion and Q&A:

- How do nutritional factors influence autism? Does diet (supplements) mitigate autistic phenotypes and/or co-morbidities?
- What are the sources of heavy metal exposure (mercury, lead, cadmium, arsenic)?
- What are the sources of organic quinones and epoxides
- Household chemicals as pro-oxidants; what are they?
- What are the new pesticides of particular concern to autistic children?

Wednesday Afternoon

14 November 2007

1:00 – 3:00PM

Platform

SESSION XIII: AUTISM SPECTRUM DISORDERS

Session Chair: **Cindy Lawler**

Co-Chair: **Martha Herbert**

1:00 – 1:20 PM

An Emerging Gene-Environment Interaction Model: Autism Spectrum Disorder Resulting From Exposure to Environmental Contaminants During Gestation

Darryl B. Hood ~ *Meharry Medical College*

1:20 – 1:40 PM

Divergent Effects of PBDE-47 on T Cell Immune Responses in Autistic and Typically Developing Children

Judy Van de Water ~ *University of California, Davis*

1:40 – 2:00 PM

Brain Levels of Oxidative Stress Markers, Mercury and Selenium in Autism

Elizabeth M. Sajdel-Sulkowska ~ *Harvard Medical School and BWH*

2:00 – 2:20 PM

The Autistic Phenotype Exhibits a Remarkable Localized Modification of Brain Proteins by Products of Free Radical-Induced Lipid Oxidation

George Perry ~ *University of Texas at San Antonio*

Student Presentation ~ (also presenting from poster)

2:20 – 2:35 PM

Autism: Maternally Derived Antibodies Specific for Fetal Brain Proteins

Daniel Braunschweig ~ *The M.I.N.D. Institute, University of California at Davis. NIEHS Center for Children's Environmental Health*

Wednesday Afternoon

14 November 2007

3:15 – 5:30PM

Roundtable Discussion / Consensus Building

SESSION XIV: WHAT IS THE WEIGHT OF EVIDENCE THAT ENVIRONMENTAL CONTAMINANTS AND/OR GENETIC FACTORS INFLUENCE THE ETIOLOGY OF NEUROLOGICAL DISORDERS?

Focus on Cross-Cutting Issues of Environmental Exposures related to Autism, Alzheimer's and Parkinson's

Discussion Leaders: **Richard Seegal**

Isaac Pessah

Ted Schettler

Theme and Rationale: The etiologic factors responsible for the neurological diseases and disorders discussed this week (*i.e.*, Alzheimer's disease, Attention Deficit Disorder, Autism Spectrum Disorders, and Parkinson's disease) are complex, multi-factorial and thought to involve interactions between environmental factors and genetic predispositions. However, the relative importance of these major risk factors and the mechanisms by which they may interact are poorly understood. Hence, progress in identifying susceptible individuals or developing therapeutic interventions has not yet resulted in a reduction in the incidence or consequences of these diseases.

Participants from each plenary session will discuss, using criteria set forth by the Institute of Medicine for the strength of association(s), the evidence that environmental contaminants, lifestyle and genetic factors play in each disease/disorder. Are there certain disorders that are more likely to be induced by environmental contaminants; are there some disorders that are primarily genetic in nature? Finally, despite the emphasis on the role(s) of environmental contaminants in the etiology of cognitive dysfunctions, is it useful to ask whether genetic susceptibilities also contribute to the cognitive deficits seen following developmental exposure to lead, mercury and PCBs?

The success of this roundtable is based not only on comments made by members of the Roundtable but, perhaps more importantly, on questions and discussion from an active audience.

The following questions will be addressed by the Roundtable members for each of the focus diseases. Discussion by conference participants is enthusiastically invited!

1. Question on **Gender**
2. Question on **Environment**
3. Question on **Genetics/ Epigenetics**

Discussion Leaders: **Richard Seegal
Isaac Pessah
Ted Schettler**

Roundtable Discussants and Disease Focus:

Autism
S. Jill James
M. Christopher Newland

Alzheimer's
Donald Schmechel
Judie Walton

Parkinson's
Syed Imam
Anumantha Kanthasamy
Caroline Tanner

IOM Criteria. USING THE CRITERIA DEVELOPED BY THE IOM, WHAT DEGREE OF CERTAINTY/ASSOCIATION CAN BE ASSIGNED TO THE ROLE OF ENVIRONMENTAL CONTAMINANTS IN THE ETIOLOGY OF AUTISM, AD, PD?

Sufficient Evidence of a Causal Relationship

Evidence from available studies is sufficient to conclude that a causal relationship exists between exposure to a specific agent and a specific health outcome in humans, and the evidence is supported by experimental data. The evidence fulfills the guidelines for sufficient evidence of an association (below) and satisfies several of the guidelines used to assess causality: strength of association, dose-response relationship, consistency of association, and a temporal relationship.

Sufficient Evidence of an Association

Evidence from available studies is sufficient to conclude that there is a positive association. A consistent positive association has been observed between exposure to a specific agent and a specific health outcome in human studies in which chance and bias, including confounding, could be ruled out with reasonable confidence. For example, several high-quality studies report consistent positive associations, and the studies are sufficiently free of bias, including adequate control for confounding.

Limited/Suggestive Evidence of an Association

Evidence from available studies suggests an association between exposure to a specific agent and a specific health outcome in human studies, but the body of evidence is limited by the inability to rule out chance and bias, including confounding, with confidence. For example, at least one high-quality study reports a positive association that is sufficiently free of bias, including adequate control for confounding. Other corroborating studies provide support for the association, but they were not sufficiently free of bias, including confounding. Alternatively, several studies of less quality show consistent positive associations, and the results are probably not due to bias, including confounding.

Inadequate/Insufficient Evidence to Determine Whether an Association Exists

Evidence from available studies is of insufficient quantity, quality, or consistency to permit a conclusion regarding the existence of an association between exposure to a specific agent and a specific health outcome in humans.

Limited/Suggestive Evidence of No Association

Evidence from available studies is consistent in not showing a positive association between exposure to a specific agent and a specific health outcome after exposure of any magnitude. A conclusion of no association is inevitably limited to the conditions, magnitudes of exposure, and length of observation in the available studies. The possibility of a very small increase in risk after exposure studied cannot be excluded.

Consensus Not Reached on Category of Association

If the entire committee did not agree on a conclusion, then the association was not assigned a category.

Posters may be put up as early as 9:00 AM on Sunday. For maximum exposure posters should remain throughout the conference

Posters should be taken down by 1:00 PM on Wednesday.

The poster board is 4 feet high x 6 feet wide.

Poster Presentations:

Monday Evening 12 November 2007 7:00 – 9:30PM

SESSION VIII. POSTER SESSION

No-Host Bar & Refreshments

Session Chair: **Darryl Hood** (invited)
Co-Chairs: **Joseph Jacobson** (invited)

Poster abstracts are numbered from P-58 to P-104.

The Poster Session is a highlight of this conference series. It has proven to be an effective venue for informal, in-depth discussion and collaboration building - as well as an important networking opportunity for all participants. Papers on any aspect of neuroscience, toxicology, children's environmental health, public health & policy are welcome!

STUDENT AWARD COMPETITION

Chair: **Jason Richardson**

Judging will be done between 7:15 PM – 8:30 PM

The Student Award Competition is divided into two groups: one for post-doctoral competition and one for pre-doctoral competition. Awards will consist of a cash prize, plaque or certificate, plus a one year subscription to the international journal *NeuroToxicology*

A winner(s) will be chosen from each group. Competing students are expected to give an overview of their work in 2-3 minutes to the judges followed by a brief set of questions and answers. Originality, significance, hypothesis, presentation material and style, as well as knowledge of the subject, will be considered in selecting the winners. All papers in competition for the Student Awards must be presented from poster.

PAPERS PRESENTED FROM POSTER

P-58

THE COMBINED EFFECT OF TRANSCULTURAL MARRIAGE AND BREAST FEEDING ON CHILDREN'S NEUROBEHAVIORAL DEVELOPMENT AT 6 AND 18 MONTHS OF AGE. Li-Ching Chu, Pau-Chung Chen. *Institute of Occupational Medicine and Industrial Hygiene, National Taiwan University College of Public Health, Taipei, Taiwan*

P-59

LEAD IN UMBILICAL CORD BLOOD, VDR-FokI POLYMORPHISM AND CHILDREN'S NEURODEVELOPMENT AT THE AGE OF TWO YEARS. Chen-Chung Ko,¹ Yaw-Huei Hwang,¹ Hua-Fang Liao,² Wu-Shiun Hsieh,³ Suh-Fang Jeng,² Yi-Ning Su,⁴ Hui-Chen Wu,¹ Pau-Chung Chen¹. ¹*Institute of Occupational Medicine and Industrial Hygiene, National Taiwan University College of Public Health, Taipei,* ²*School and Graduate Institute of Physical Therapy, National Taiwan University College of Medicine, Taipei,* ³*Department of Pediatrics, and* ⁴*Department of Medical Genetics, National Taiwan University Hospital and National Taiwan University College of Medicine, Taipei, Taiwan*

P-60 Pre-Doc Award Competition

COTININE IN UMBILICAL CORD BLOOD, GENETIC POLYMORPHISMS, AND NEURODEVELOPMENT AT THE AGE OF TWO YEARS. Chia-Jung Hsieh,¹ Hua-Fang Liao,² Kuen-Yuh Wu,³ Wu-Shiun Hsieh,⁴ Yi-Ning Su,⁵ Suh-Fang Jeng,² Shih-Ni Yu,¹ Pau-Chung Chen¹. ¹*Institute of Occupational Medicine and Industrial Hygiene, National Taiwan University College of Public Health, Taipei,* ²*School and Graduate Institute of Physical Therapy, National Taiwan University College of Medicine, Taipei,* ³*Division of Environmental Health and Occupational Medicine, National Health Research Institutes, Miaoli,* ⁴*Department of Pediatrics, and* ⁵*Department of Medical Genetics, National Taiwan University Hospital and National Taiwan University College of Medicine, Taipei, Taiwan*

P-61

PRENATAL AND POSTNATAL EXPOSURE TO ENVIRONMENTAL TOBACCO SMOKE AND CHILDREN'S NEUROBEHAVIORAL DEVELOPMENT AT 6 TO 18 MONTHS OF AGE. Shan-An Chou, Pau-Chung Chen. *Institute of Occupational Medicine and Industrial Hygiene, National Taiwan University College of Public Health, Taipei, Taiwan*

P-62

PRENATAL EXPOSURE TO MANGANESE AND PSYCHOMOTOR DEVELOPMENT AT 6 AND 24 MONTHS OF AGE. Feng-Chiao Su,¹ Hua-Fang Liao,² Yaw-Huei Hwang,¹ Wu-Shiun Hsieh,³ Hui-Chen Wu,¹ Suh-Fang Jeng,² Yi-Ning Su,⁴ Pau-Chung Chen¹. ¹*Institute of Occupational Medicine and Industrial Hygiene, National Taiwan University College of Public Health, Taipei, Taiwan,* ²*School and Graduate Institute of Physical Therapy, National Taiwan University College of Medicine, Taipei, Taiwan,* ³*Department of Pediatrics, and* ⁴*Department of Medical Genetics National Taiwan University Hospital and National Taiwan University college of Medicine, Taipei, Taiwan.*

P-63 Pre-Doc Award Competition

AUTISM: MATERNALLY DERIVED ANTIBODIES SPECIFIC FOR FETAL BRAIN PROTEINS. D. Braunschweig,^{1,7,8} P. Ashwood,^{2,7,8} P. Krakowiak,^{3,7,8} I. Hertz-Picciotto,^{3,7,8} R. Hansen,^{4,7,8} L. Croen,^{5,7,8} I.N. Pessah,^{6,7,8} and J. Van de Water^{1,7,8} ¹*Division of Rheumatology, Allergy and Clinical Immunology, University of California at Davis.* ²*Department of Medical Microbiology and Immunology, University of California at Davis.* ³*Department of Public Health Sciences, Division of Epidemiology, University of California at Davis,* ⁴*Department of Pediatrics, University of California at Davis.* ⁵*Division of Research, Kaiser Permanente Northern California, Oakland, CA.* ⁶*Department of Veterinary Molecular Biosciences, University of California at Davis* ⁷*The M.I.N.D. Institute, University of California at Davis.* ⁸*NIEHS Center for Children's Environmental Health, University of California, Davis. Davis, CA 95616 USA*

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ADDRESSING NEUROINFLAMMATION IN AUTISM AND PDD WITH IV LIPID THERAPY. Kane PC, Braccia D, Cartaxo, A, Kane E. Haverford Wellness Center Havertown, PA and Kinnelon, NJ USA

Life Sciences, Jawaharlal Nehru University, New Delhi, 1110067. ² Department of Biosciences, Jamia Millia Islamia, New Delhi, India.

P-65 Pre-Doc Student Award

NEUROBEHAVIORAL EFFECTS AMONG ADOLESCENT PESTICIDES APPLICATORS IN EGYPT. AA Ismail^{1,2}, DS Rohlman², ME Abou Salem¹, AA Mechael¹, OM Hendy³, GM Abdel Rasoul¹. ¹Community, Environmental and Occupational Medicine Department, Faculty of Medicine, Menoufiya University, Shebin Elkom, Egypt; ²Center for Research on Occupational and Environmental Toxicology, Oregon Health & Science University, Portland, OR, USA; ³Clinical Pathology Department, National Liver Institute, Menoufiya University, Shebin Elkom, Egypt.

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MOLECULAR AND GENETIC ANALYSIS IN NOVEL MODELS OF METHYLMERCURY NEUROTOXICITY Grimes, KA.¹, Henry, TB.², Braun, K.³, Nass, R.¹. Depts. of Pediatrics and Pharmacology¹, Vanderbilt University Medical Center, Nashville, TN, USA; Center for Environmental Biotechnology², The University of Tennessee, Knoxville, TN, USA; Dept. of Zoology/Developmental Neurobiology³, Otto von Guericke University Magdeburg, Germany

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NEUROANTIBODIES IN POPULATIONS EXPOSED TO PESTICIDES. HAN EL-Fawal¹, NAN El-Fawal², NMB El-Fawal³ and MY Shamy⁴. ¹Neurotoxicology Laboratory, Mercy College, Dobbs Ferry, NY, ²Faculty of Dentistry, University of Alexandria, Alexandria, Egypt, ³Purchase College, SUNY, Purchase, NY, ⁴High Institute of Public Health, University of Alexandria, Alexandria, Egypt.

P-74

METHYLMERCURY EXPOSURE INDUCES HYPERACTIVITY AND NEURONAL LOSS IN THE CAUDATE PUTAMEN IN MICE. Masumi Sawada, Masatake Fujimura and Akira Yasutake. National Institute for Minamata Disease, 4058-18 Hama, Minamata, Kumamoto 867-0008, JAPAN

P-67 Pre-Doc Award Competition

MODERATE PERINATAL ARSENIC PERTURBS THE HPA AXIS AND HAS LONG-TERM EFFECTS ON LEARNING AND MEMORY BEHAVIOR. Ebany J. Martinez, University of New Mexico Health Sciences Center Department of Neurosciences and College of Pharmacy Department of Toxicology and Andrea Allan, PhD, University of New Mexico Health Sciences Center Department of Neurosciences, Albuquerque, New Mexico, USA

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SELENIUM PREVENTION & TREATMENT OF MERCURY TOXICITY NVC Ralston and LJ Raymond. Energy & Environmental Research Center, University of North Dakota, Grand Forks, ND, U.S.A.

P-68 Pre-Doc Award Competition

PRENATAL LPS EXPOSURE ALTERS THE FATE OF DEVELOPING DOPAMINE PROJECTIONS. Angela J.Monahan, Zaodung Ling, and Paul M. Carvey. Rush University Chicago, IL 60605

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METHYLMERCURY, DIETARY FISH OILS, AND BRAIN FATTY ACIDS MC Craig-Schmidt¹, CA Teodorescu¹, EE Eckley¹, A Inniss¹, and MC Newland² Departments of Nutrition and Food Science¹ and Psychology², Auburn University, Auburn, AL USA

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PERINATAL EXPOSURE TO 2,2',3,5'-PENTACHLOROBIPHENYL (PCB95) ALTERS SEIZURE SENSITIVITY AND PERSISTENTLY CHANGES HIPPOCAMPAL CA1 EXCITABILITY. Kyung Ho Kim¹, Salim Yalcin Inan², Robert F. Berman², and Isaac N. Pessah¹. ¹Departments of Molecular Biosciences, School of Veterinary Medicine and ²Department of Neurological Surgery, School of Medicine, University of California, Davis, California, USA

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AIR POLLUTION, OXIDATIVE STRESS AND NEUROTOXICITY. Arezoo Campbell¹, Sheba M. J. MohanKumar² and Bellina Veronesi³ ¹Department: of Pharmaceutical Sciences, Western University of Health Sciences, Pomona, CA., ²Department of Pharmacology and Toxicology, Michigan State University, E. Lansing, MI and ³Neurotoxicology Division, NHEERL, US. EPA, RTP, NC.

P-70 Post-Doc Award Competition

PERINATAL EXPOSURE TO 2,2',4,4'-TETRABROMODIPHENYL ETHER (PBDE-47) RETARDS GROWTH AND DELAYS NEURODEVELOPMENT OF C57BL/6J MICE. TramAnh N. Ta, Pavel Aronov, Mari S. Golub, Jozsef Lango, Isaac N. Pessah, Robert F. Berman. Center for Children's Environmental Health, University of California Davis, Davis, California 95618, USA.

P-78 Pre-Doc Award Competition

PARAQUAT INDUCES OXIDATIVE STRESS, NEURONAL LOSS AND PARKINSONISM IN RATS: NEUROPROTECTION BY WATER-SOLUBLE COQ₁₀. Mallika Somayajulu-Nitu¹; T. S. Sridhar¹, Anca Matei², Vera Parameswarann³; Jerome Cohen²; Jagdeep Sandhu¹; Henryk Borowy-Borowski³; Marianna Sikorska³ and Siyaram Pandey¹. 1. Chemistry & Biochemistry, University of Windsor, Windsor, ON, Canada. 2. Psychology, University of Windsor, Windsor, ON, Canada. 3. Institute for Biological Sciences, National Research Council of Canada, Ottawa, ON, Canada. *Current address: St John's Medical College, Bangaluru. India.

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COMPARATIVE GENE EXPRESSION ANALYSIS IN DEVELOPING RAT BRAIN EXPOSED TO MIXTURES OF METHYL MERCURY, POLYCHLORINATED BIPHENYLS AND ORGANOCHLORINE PESTICIDES. B.K. Padhi¹, G. Pelletier¹, A. Williams², C. Yauk¹, W.J. Bowers¹. ¹Environment and Occupational Toxicology Division, ²Biostatistics and Epidemiology Division, HECSB, Health Canada, Ottawa, Canada, K1A 0K9.

P-79

EXACERBATION OF PARKINSON'S DISEASE WITH EXPOSURE TO NEUROTOXINS MAY BE RESPONSIVE TO LIPID THERAPY. Kane PC, Braccia D, Kane E. Haverford Wellness Center, Havertown, PA USA

P-72 Pre-Doc Award Competition

ALUMINUM INDUCED ELECTROPHYSIOLOGICAL, BIOCHEMICAL AND COGNITIVE MODIFICATIONS IN THE HIPPOCAMPUS OF AGING RATS. Pallavi Sethi^{1,2}, Amar Jyoti¹, Rameshwar Singh¹, Ejaz Hussain² and Deepak Sharma¹. ¹Neurobiology Laboratory, School of

P-80 Pre-Doc Award Competition

PROTECTIVE EFFICACY OF BACOPA MONNIERI EXTRACT AGAINST ROTENONE INDUCED NEUROTOXIC EFFECTS IN DROSOPHILA. Ravikumar Hosamani, K.N Chandrashekar and Muralidhara. Biochemistry & Nutrition, Central Food Technological Research Institute, Mysore, India

P-81 Post-Doc Award Competition

STRUCTURAL STUDIES OF WORM CU/ZN SUPEROXIDE DISMUTASE. O. N. Pakhomova¹, J. P. Schuermann¹, L. T. Jensen², V. Cizewski Culotta², P. J. Hart¹. ¹Department of Biochemistry, University of Texas Health Science Center, San Antonio, USA,

²Department of Environmental Health Sciences, John Hopkins University Bloomberg School of Public Health, Baltimore, USA.

P-82 UTILIZATION OF DROSOPHILA SYSTEM TO UNDERSTAND THE EMERGING ROLE OF PHYTOCHEMICALS AS NEUROMODULATORS. Dr. Muralidhara. *Biochemistry & Nutrition, Central Food Technological Research Institute, Mysore, Karnataka, India*

P-83 Pre-Doc Award Competition
SPLICE VARIANT SPECIFIC UPREGULATION OF CA+2/CALMODULIN DEPENDENT PROTEIN KINASE 1G BY PYRETHROID INSECTICIDES IN VIVO. J.A. Harrill¹, K.M. Crofton².
¹Curriculum in Toxicology, UNC-CH, Chapel Hill, NC, ²Neurotoxicology Division, NHEERL, ORD, USEPA, RTP, NC.

P-84 EFFECT OF 1-BROMOPROPANE EXPOSURE ON GENE EXPRESSION OF NEUROTRANSMITTER RECEPTORS AND EXPLORATION OF BIOMARKERS FOR THE CENTRAL NERVOUS SYSTEM TOXICITY. S. Sahabudeen and G. Ichihara. *Department of Occupational & Environmental Health, Nagoya University Graduate School of Medicine, Nagoya, Japan*

P-85 Pre-Doc Award Competition
EXPRESSIONS CHANGES OF CYTOSKELETAL PROTEIN AND RELATED PROTEIN KINASES IN CEREBRUM CORTEX OF 2,5-HEXANEDIONE SUBCHRONIC TREATED RATS. Wang QingShan Student and Xie KeQin Advisor. *Institute of Toxicology, Shandong University, Jinan, ShanDong, China.*

P-86 INVOLVEMENT OF CALPAINS IN THE PERIPHERAL AXONOPATHY INDUCED BY 2,5-HEXANEDIONE. Song Fuyong and Xie KeQin. *Institute of Toxicology, Shandong University, Jinan, ShanDong, China.*

P-87 Post-Doc Award Competition
THE REVERSIBILITY OF NEUROFILAMENTS DECLINE INDUCED BY 2,5-HEXANEDIONE IN RAT SCIATIC NERVES. Song Fuyong and Xie KeQin. *Institute of Toxicology, Shandong University, Jinan, ShanDong, China.*

P-88 Post-Doc Award Competition
CHRONIC LOW-DOSE ACRYLAMIDE EXPOSURE REDUCES APPETITIVE MOTIVATION IN FISHER 344 RATS BETWEEN 8 TO 12 MONTHS OF AGE. J. Garey and M.G. Paule. *Division of Neurotoxicology, National Center for Toxicological Research/FDA, Jefferson, AR, USA.*

P-89 EFFECTS OF CHRONIC ORAL ACRYLAMIDE EXPOSURE ON INCREMENTAL REPEATED ACQUISITION (LEARNING) PERFORMANCE IN ADULT FISCHER 344 RATS. M.G. Paule and J. Garey. *Division of Neurotoxicology, National Center for Toxicological Research/FDA, Jefferson, AR, USA*

P-90 THE ROLE OF NMDA RECEPTOR REGULATION IN PCP-INDUCED CORTICAL APOPTOSIS. Cheng Wang¹, Natalya Sadovova², Xiaoju Zou¹, Sherry Ferguson¹, Merle Paule¹ and William Slikker¹. ¹Division of Neurotoxicology, NCTR, FDA and ²Toxicologic Pathology Associates, Jefferson, Arkansas

P-91 PROTECTIVE EFFECTS OF 7-NITROINDAZOLE ON KETAMINE-INDUCED NEUROTOXICITY IN RAT FOREBRAIN CULTURE. N. Sadovova¹, C. Wang², T.A. Patterson², X. Zou², X. Fu³, J.P. Hanig⁴,

M.G. Paule², S.F. Ali² and W. Slikker, Jr.² ¹Toxicologic Pathology Associates, Jefferson, AR; ²Division of Neurotoxicology and ³Division of Biochemical Toxicology, National Center for Toxicological Research/U.S. Food & Drug Administration, Jefferson, AR; and ⁴Center for Drug Evaluation and Research/U.S. Food & Drug Administration, Silver Spring, MD

P-92 Pre-Doc Award Competition
DEVELOPMENTAL PHENCYCLIDINE (PCP) OR KETAMINE TREATMENT INCREASES THE FREQUENCY OF ABNORMAL ACTIVITY IN SPRAGUE-DAWLEY RAT PUPS. SY Boctor^{1,2}, N Sadovova³, X Zou², C Wang², SA Ferguson²; ¹Dept. of Interdisciplinary Biomedical Science, UAMS, Little Rock, AR, USA; ²Div. of Neurotoxicology, National Center for Toxicological Research/FDA, Jefferson, AR, USA; ³Toxicologic Pathology Associates, Jefferson, AR, USA

P-93 CO-EXPOSURE OF HEAVY METALS AND PSYCHOSTIMULANTS ALTER DOPAMINE TRANSPORTER (DAT) DENSITY WITHOUT CHANGES IN DAT FUNCTION. AN Hood and DR Wallace. *Department of Forensic Science, Oklahoma State University Center for Health Sciences, Tulsa, Oklahoma, USA*

P-94 Pre-Doc Award Competition
EFFECTS OF ESTRADIOL AND XENOESTROGENS ON DOPAMINE TRANSPORT. Rebecca A. Alvea¹, Kathryn A. Cunningham², and Cheryl S. Watson¹. *Department of Biochemistry & Molecular Biology, Univ. of Texas Medical Branch, Galveston TX 77555-0645; ² Department of Pharmacology & Toxicology, Univ. of Texas Medical Branch, Galveston TX 77555-1031*

P-95 Post-Doc Award Competition
THE EFFECTS OF METHYLPHENIDATE ON RHESUS MONKEY PERFORMANCE IN AN OPERANT TEST BATTERY. JS Rodriguez^a, SM Morris^b, CE Hotchkiss^c, DR Mattison^d and MG Paule^e. ^aDivision of Neurotoxicology, ^bDivision of Genetic and Reproductive Toxicology, and ^cThe Bionetics Corporation; National Center for Toxicological Research, FDA, Jefferson, AR, and ^dObstetric and Pediatric Pharmacology Branch, National Institute of Child Health and Human Development, NIH, Bethesda, MD

P-96 USING OPERANT RESPONSE ACQUISITION TO ASSESS MOUSE MODELS OF ALZHEIMER'S PATHOLOGY. TJ Zarcone³, A Sagare¹, R Deane¹, RD Bell¹, N Paquette¹, D Carbonari³, R Pendu², PJ Lenting², Z Wu¹, & BV Zlokovic¹. ¹ Frank P. Smith Laboratory for Neuroscience and Neurosurgical Research, Department of Neurosurgery, University of Rochester Medical School, Rochester, New York 14642, USA. ² Laboratory for Thrombosis and Haemostasis, Department of Hematology, University Medical Center Utrecht, 3584 CX Utrecht, The Netherlands. ³ Neurobehavioral Facility Laboratory, Department of Environmental Medicine, University of Rochester Medical School, Rochester, New York, USA.

P-97 ASSESSING THE EFFECTS OF CHRONIC DOPAMINERGIC (D3) AGONIST ADMINISTRATION ON COMPLEX BRAIN FUNCTIONS IN JUVENILE RHESUS MONKEYS USING THE NCTR OPERANT TEST BATTERY. T.A. Patterson¹, M. Li¹, C.E. Hotchkiss², A. Mauz³, M. Eddie³ and M.G. Paule¹. ¹Division of Neurotoxicology, National Center for Toxicological Research/U.S. FDA, Jefferson, AR, ²The Bionetics Corporation, Jefferson, AR and ³Boehringer Ingelheim Pharma GmbH & Co. KG, Biberach/Riss, Germany

P-98 RACE-GENE-ENVIRONMENT INTERACTIONS AND NEUROTOXICOLOGY: MULTIPLE ENVIRONMENTAL AND GENETIC VULNERABILITIES TO TOXINS. Roger D. Masters. *Department of Government, Dartmouth College, Hanover, NH 03755, USA*

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TOXICOLOGY IN THE KITCHEN: POLYHEDRAL GRAPHIC MODELING IN FOOD TOXICOLOGY, ENVIRONMENTAL NEUROSCIENCE AND NUTRITION. BW Whitman, *Mental Health and Behavioral Sciences Services, Carl T. Hayden VA Medical Center, Phoenix, Arizona*

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FROM SCIENCE TO POLICY: THE LEARNING AND DEVELOPMENTAL DISABILITIES INITIATIVE. Elise Miller, MEd, *Executive Director, Institute for Children's Environmental Health, Freeland, Washington, USA.*

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TOXIPEDIA: CONNECTING SCIENCE AND PEOPLE. SG Gilbert, *Institute of Neurotoxicology and Neurological Disorders, Seattle, Washington, USA*

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ALTERNATIVE COMMUNITY BASED APPROACH - PRECAUTIONARY ASSESSMENT. SG Gilbert, *Institute of Neurotoxicology & Neurological Disorders, Seattle, WA, USA*

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NEUROTOXICITY OF ARSENIC ON EXPOSED WORKERS L. Fat¹ and M. Ghita². ¹*Occupational Health Department, Institute of Public Health, Cluj-Napoca, Romania,* ²*Neurological Department, County Hospital, Baia Mare, Romania*

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SERUM FLUORIDE LEVEL AND CHILDREN'S INTELLIGENCE QUOTIENT IN TWO VILLAGES IN CHINA. Xiang Quanyong^a, Liang Youxin ^b, Chen Bingheng^b, Chen Liansheng ^a, Wang Caisheng ^a, Chen Xiaodong ^a, Zhou Mingsheng ^c. ^a *For correspondence: Xiang Quanyong, Department of Environmental Health, Jiangsu Province Centers for Diseases Control and Prevention. 172 Jiangsu Road, Nanjing, Jiangsu Province, 210009, P.R. China.* ^b *Department of Occupational Health, School of Public Health, Fudan University, P.R. China.* ^c *Center for Disease Control and Prevention, Sihong County, Jiangsu Province, Nanjing, P.R. China. 210009 P.R. China*