FEATURED ACTIVITIES of DERT
October 2009

MEETINGS

Partnering with USEPA and ATSDR to Improve the Use of Superfund Research Program Science
July 28, 2009
Friday Center, Chapel Hill, North Carolina

Introduction/Background: Building on a Superfund Research Program (SRP) research translation workshop held in February, SRP grantees met again in July to exchange ideas of how to build better partnerships with the Superfund programs at EPA and ATSDR. The goals were to better understand the work practices within EPA and ATSDR and their Agencies' science and science communication needs as they relate to the Superfund cleanup program.

Meeting Highlights: Approximately 40 participants attended this one day interactive session. During the first part of the day, a panel comprised of EPA and ATSDR staff discussed their perspectives of the SRP and barriers to working with SRP grantees. They also described how they use science and where, when, and why they seek innovative science findings. Breakout groups then brainstormed on how the SRP can be more responsive to these needs and considered opportunities for increasing communications. The afternoon focused on resources: what does the SRP have and what are points of entry into EPA and ATSDR. In the afternoon breakout sessions ideas were shared on specific mechanisms for collaboration.

Recommendations/Outcomes: NIEHS and SRP-funded universities could 1) convene a "relevancy" group to begin to strategize about connecting universities with USEPA and ATSDR; 2) focus on topics that could bring several universities plus USEPA and ATSDR together (e.g., molecular epidemiology, cumulative risk, community based risk assessment, risk based decision making, etc.); 3) develop work groups focused on themes, such as "how to reach out to EPA from SRP" or "how to synthesize research across agencies"; and 4) create an SRP "Adopt-A-Region" program and get it started by sharing knowledge of current, successful efforts among SRP-funded universities.

NIEHS could 1) increase awareness of SRP among the agencies by actively marketing it to agency leadership; 2) create a formal mechanism to accept incoming research and translation suggestions from USEPA and ATSDR and also use this input to connect agency programs with universities with relevant expertise; 3) create an "organizing/oversight" committee to match SRP research with end users with representation from all stakeholders (agencies), including EPA, ATSDR, NIEHS, RTC leaders and pertinent PIs; and 4) facilitate interaction between NIEHS/SRP and USEPA's Superfund Technology and Liaison program annually, such as attending each other's annual meetings.

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Pesticides and Pulmonary Edemagenic Chemicals
NIH Expert Panel Workshop on Toxic Industrial Chemicals
July 22 - 23, 2009
Marriott Bethesda North Hotel & Conference Center
Bethesda, Maryland

Goals: Several goals were identified for this NIH Expert Panel. 1) To define the current state of knowledge on the toxicology and pathophysiology of highly toxic chemicals identified by the Department to Homeland Security as industrial chemical threats of great public health concern; 2) to understand current medical interventions to treat and perhaps prevent permanent injury or death from such chemicals; 3) to identify gaps in knowledge critical to the understanding of chemical injury and recovery; and 4) to identify needs in medical research leading to the development of safe and effective medical countermeasures.

Summary*:* This workshop, titled as an NIH Workshop, was in essence Trans-Agency in nature, included invited representatives from the Department of Health and Human Services (NIH, Office of the Assistant Secretary for Preparedness and Response, Office of Public Health Emergency Medical Countermeasures, Centers for Disease Control and Prevention), Department of Homeland Security (Chemical Security Analysis Center), Department of Defense (Army, Defense Threat Reduction Agency), the Food and Drug Administration, and the Office of Science and Technology Policy, Executive Office of the President, as well as leading experts in the medical response and research areas related to the pulmonary effects of Toxic Industrial Chemicals, with a focus on pesticides. Following an introduction to the meeting by Dr. Ernie Takafuji, Director, Office of Biodefense Research, NIAID, opening remarks were provided by members of the NIH and included Drs. Hugh Auchincloss, Deputy Director, NIAID; Walter Koroshetz, Deputy Director, NINDS, and *Elizabeth Maull, SPHB*, for Steven Kleeberger, Acting Deputy Director, NIEHS. The workshop, co-chaired by Drs. Richard Dart and Steve Dudek, from the University of Colorado Health Sciences Center and the University of Chicago Medical Center, respectively, focused on medical consequences and medical management of a variety of insecticides, rodenticides, avicides, herbicides, and fumigants that have been identified by the Department of Homeland Security as serious chemical threat agents. These discussions transitioned to more focused discussions related to toxic edemagenic industrial chemicals of concern on the second day of the meeting, and included a presentation related to the NIEHS CounterACT Portfolio provided by Dr. Maull. The co-chairs of the meeting will develop a report detailing the recommendations of Expert Panel for future research needs.

Dr. Maull contributed to the organization of the meeting. Drs. Maull and Kleeberger attended the meeting.

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Breast Cancer and the Environment Research Centers Integration Meeting
"Practicing Transdisciplinary Science"
July 8 - 10, 2009
National Institute of Environmental Health Sciences
Research Triangle Park, North Carolina

Goals: The 2009 Breast Cancer and the Environment Research Centers (BCERC) Integration Meeting brought together the spectrum of investigators and advocates to identify and overcome potential roadblocks to progress, as well as provide updates on current research. The overall goal of the meeting was to enhance the projects through better integration of the existing objectives, to facilitate transdisciplinary goals, to discuss and develop appropriate dissemination goals, and to identify new opportunities for scientific collaboration and synergy. The specific objectives of the meeting were to: 1) identify current scientific hypotheses and potential projects from the epidemiology and biology projects that are relevant for cross projects and to collaboratively develop a plan of action; 2) identify additional cross project hypotheses, as well as communication and dissemination research projects that can be developed collaboratively and implemented within the network; and 3) establish mechanisms to ensure that findings emerging from the various components of the network achieve their potential in

influencing scientific or outreach activities in the overall BCERC program and are communicated easily and efficiently.

Summary: Identification of key messages derived from published results from the BCERC and ready for further development was a key focal point for this year's meeting. The Center Community Outreach and Translation Cores (COTC) had an intensive full day meeting to discuss issues related to message development which included a videocast lecture from Dr. Bradford W. Hesse, Chief of NCI's Health Communications and Informatics Branch. Janice Barlow, Bay Area BCERC, provided a number of potential templates for consideration by the COTC and the group as a whole. The COTC was supported by the Biology and Epidemiology projects, which worked in advance of the meeting to provide summary documents of potential messages resulting from their research.

After welcoming remarks and a brief presentation of current activities of interest to the BCERC by *Dr. Gwen Collman, Acting Director, DERT*, the Biology and COTC provided updates on their activities at each Center. Updates on the projects included success on hitting the recruitment targets for all Centers (approximately 1200 girls), early preliminary data on associations of age of onset of puberty with a select set of exposures; genomic and proteomic data from laboratory animals indicating novel candidate genes that activate when exposed to endocrine disruptors; and a surprising characterization of the ontogeny of estrogen and progesterone receptors through the courses of development and puberty. Each of the projects (Biology, Epidemiology, and COTC) met separately on the second day of the meeting to focus specifically on project related results and issues. Finally, in the last group session, the Biology, Epidemiology, and COTC reported back to the group as a whole the directions each project intended to take in the next year of the program.

The meeting was organized by *Drs. Les Reinlib, Caroline Dilworth, and Elizabeth Maull, SPHB*, and Dr. Gary Ellison and Ms. Shannon Lynch, NCI, and attended by *Drs. Claudia Thompson*, Les Reinlib, Elizabeth Maull, Caroline Dilworth, and Gwen Collman.

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Mitochondria Biomarker Meeting
June 25, 2009
Tyson's Corner, Virginia

Introduction: The National Institute of Environmental Health Sciences (NIEHS) sponsored a workshop on June 25 in conjunction with the United Mitochondrial Disease Foundation annual meeting to explore the state of the science and technology with experts in the field of mitochondrial physiology and function with the goal of developing biomarkers of mitochondrial dysfunction related to genetics and environmental exposures. The session was organized by a committee from DERT (*Drs. Daniel Shaughnessy and Kimberly McAllister, SPHB, Dr. Cindy Lawler, COSPB, and Dr. Leroy Worth, SRB*) and DIR (Drs. William Copeland and Matthew Longley).

Summary: The session featured four invited talks on the effects of environmental exposures on mitochondrial function related to neurological diseases; the use of novel technologies for markers of mitochondrial impairment; and current clinical measures of mitochondrial dysfunction related to genetics and exposures. Dr. Copeland introduced the session and articulated a series of discussion questions including: How do we identify the main classes of environmental exposures that lead to mitochondrial dysfunction; What are the primary mitochondrial targets for environmental stressors; What are the emerging technologies for detecting early molecular, cellular or phenotypic effects of

mitochondrial dysfunction; and What new tools or technologies are needed to apply measures of mitochondria dysfunction to human studies?

Dr. Tim Greenamyre (University of Pittsburgh) presented work on genetic and environmental factors associated with Parkinson's disease (PD) related to inhibition of complex 1 in mitochondria. Dr. Bruce Cohen (Cleveland Clinic) presented three case studies of the secondary effects of cancer chemotherapeutic drugs related to mitochondrial impairment. There are over 60 natural and synthetic compounds that affect mitochondria complexes, uncouple oxidative phosphorylation (OXPHOS), or inhibit mtDNA synthesis. Chemotherapy drugs and other synthetic and natural compounds may exert toxic effects in the brain, heart, ears, kidneys, nerves and liver through primary injury to the mitochondria, and genetic susceptibility may play a role in the more severe effects. Dr. Gino Cortopassi (UC Davis) described a number of short-term, intermediate and long-term biomarkers of mitochondrial dysfunction and noted that mitochondria are targets for damage from environmental and endogenous agents due to excessive reactive oxygen species (ROS) generation, limited DNA repair in mitochondria, and from affinity of these compounds for lipophilic membranes of mitochondria. A set of biomarkers that reflect changes in DNA, RNA, proteins and mitochondrial bioenergetics over long and short time scales could be used to identify mitochondrial toxicants and the biological effects of these exposures. Dr. Doug Wallace (UC Irvine) described rapid screening methods for identifying mitochondria haplogroups and somatic mtDNA mutations in susceptible populations. He also described a noninvasive method called diffuse optical spectroscopy (DOS) that detects infrared light patterns in tissues, reflecting changes in total hemoglobin, oxygenated hemoglobin, and lipid content. This can be used to detect oxygen consumption in muscle during rest, exercise and recovery.

Conclusion: The discussion that followed focused on how to develop early screens for mitochondrial dysfunction related to disease, including metabolomics approaches, development of high-throughput oxygen sensing technologies for assessing mitochondrial respiratory function and the development of noninvasive screens, such as the technologies proposed by Doug Wallace. A barrier to developing these tools is that mitochondrial dysfunction is broadly defined and reflects the fact that mitochondria have different physiological functions in different tissues and cell types and respond in numerous ways to physiological changes. There was consensus that both animal models and work with human disease phenotypes are needed to understand effects of genes and environment in mitochondria dysfunction related to disease.

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International Conference on the Environmental Implications and Applications of Nanotechnology
June 9 - 11, 2009
University of Massachusetts Amherst
Amherst, Massachusetts

Introduction/Background: Nanomaterials present new opportunities to improve our ability to detect, monitor, control and remediate pollutants; however, potential new risks to human health and the environment are a concern that deserves attention. EPA's Office of Superfund Remediation and Technology Innovation hosted this environmental nanotechnology meeting, the fourth of a series of environmental nanotechnology meetings led by the agency beginning with a conference in Washington, DC (October 2005), and two in Chicago, Illinois (September 2006 and October 2008). SRP co-sponsored the meeting.

Meeting Highlights: Mr. Jeff Morris, EPA's National Program Director for Nanotechnology (ORD) and leader of the US delegation to the Organization of Economic Cooperation and Development's Working

Party on Manufactured Nanomaterials, initiated the meeting. The conference brought together researchers and remediation practitioners focusing on the uses of nanotechnology for pollution control/site remediation as well as fate, transport, bioavailability and toxicity of nanoparticles. A growing area of interest was green nanotechnology, which, drawing from green chemistry, addresses processes and products highlighting approaches that reduce toxic byproducts, and ensures that the nanomaterials produced are nontoxic. In addition, a growing number of life cycle analysis studies were presented assessing long-term fate and transport of nanomaterials. Detection techniques such as Field-Flow Fractionation (FFF) coupled to ICPMS in an ultra fast scanning mode, and single particle (SP) mode ICPMS were featured as methods to differentiate naturally occurring nanomaterials from engineered nanomaterials. The meeting consisted of approximately 80 speakers and 40 posters presentations.

Outcomes/Recommendations: Similar to previous EPA environmental nanotechnology meetings, there was a continued interest in developing nanomaterials in a biocompatible manner, and continuing development of nanotechnology-based remediation approaches.

The meeting was attended by Dr. Heather Henry, CRIS.

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World Health Organization International Conference on Children's Health and the Environment
June 7-10, 2009
Busan, South Korea

The NIEHS reaffirmed its commitment to supporting global public health issues at the third World Health Organization (WHO) International Conference on Children's Health and the Environment. NIEHS's *Drs. William Suk, CRIS, and Claudia Thompson, SPHB and CRIS*, were among the more than 450 health ministers, non-governmental organization (NGO) representatives and researchers from over 45 countries who attended the conference. NIEHS Council member Nsedu Witherspoon also attended, representing the Children's Environmental Health Network in Washington, D.C.

In collaboration with the WHO, the NIEHS has long been a strong supporter of children's global environmental health. NIEHS has assisted with the development of partnerships among researchers and institutes, particularly seeking to support collaborations between developing and developed countries. Organized by the WHO and hosted by the Korean Ministries of the Environment, Health, and Social Welfare and Family Planning, the conference was a forum for sharing information regarding the reduction of infant mortality and ensuring environmental sustainability. In addition to the primary meeting, a satellite workshop of the Korean Pediatric Association introduced Korean pediatricians to the need to monitor children's exposure to environmental pollutants. Representatives from the International Pediatric Association presented at the workshop. Dr. Suk presented on the need to understand susceptibility to exposures in vulnerable populations such as children.

The conference included several plenary talks as well as well-attended breakout sessions. A session addressing the health effects of nanotechnology session featured presentations from Dr. Suk and Professor Peter Sly, M.D., of the University of Western Australia. A second session that generated a great deal of interest explored the effects of asbestos exposure in children. The conference culminated with the acceptance by all participants of the Busan Pledge, which reaffirmed the need for collaboration and cooperation among NGOs, governments, researchers and communities.

The first WHO/NIEHS-sponsored International Children's Environmental Health Conference, held in Bangkok in 2002, marked the beginning of an increased emphasis on children's health globally. As a

result of this focus, WHO has designated several programs as Collaborating Centres for Research on Children's Environmental Health. The organization published declarations of support for children's environmental health, which were signed by governments and scientific organizations, and advocated for a marked increase in international research. WHO Coordinating Centers to study these exposures are now operating in Thailand, Canada, Western Australia, Singapore, and New York.

The NIEHS provided support to this international conference as did the National Institute for Child Health and Human Development, the Centers for Disease Control and Prevention, the Agency for Toxic Substances and Disease Registry, and the Environmental Protection Agency. Other support was provided by a range of governments and foundations.

DERT PAPERS OF NOTE

HLA-DR4 – Possible Risk Gene for Autism
George Lambert, MD
University of Medicine and Dentistry of New Jersey
P01ES011256

NIEHS-sponsored scientists report the discovery of a gene that may be involved in autism. The gene, known as HLA-DR4, is unique in that it acts in the mothers of children with autism disorder instead of acting in the children themselves. There reports of about 30 such maternally acting or teratogenic genes.

The team genotyped members of 31 families for HLA-DR4. Children with autism were tested using a standard diagnostic psychological exam to confirm their condition. The results of the study lead to the conclusion that HLA-DR4 is indeed a teratogenic gene and support the possibility of an immune component in the pathogenesis of autism. The authors conclude that the gene could contribute to a subset of autism cases by interacting with other risk alleles or environmental factors to perturb pathways affecting brain development. Additional studies are needed to address the causes of the development of autism that could lead to prevention or therapy for the disorder.

Citation: Johnson WG, Buyske S, Mars AE, Sreenath M, Stenroos ES, Williams TA, Stein R, Lambert GH. HLA-DR4 as a risk allele for autism acting in mothers of probands possibly during pregnancy. *Arch Pediatr Adolesc Med*. 2009 Jun;163(6):542-6.

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The Endocrine Society Position Statement on Endocrine Disruptors
Andrea C. Gore, Ph.D.
University of Texas at Austin, et.al.
R01ES007784, etc.

In its first ever position statement, the Endocrine Society released a report outlining the public health concerns of exposure to endocrine disrupting chemicals and proposed a series of recommendations for revising current and generating new public-health related policies. The report states that the Society is concerned that the public may be at risk for exposure to endocrine disruptors because potential health effects are being overlooked in developing guidelines and regulations.

Endocrine disruptors are natural or man-made substances in the environment that interfere with hormone production, action and metabolism resulting in adverse health effects in a host of biological processes and systems in both humans and wildlife. While stressing that it does not support alarmist action, the Society does support information dissemination on sources of exposure, potential health effects, and preventive actions that can be taken to protect the American public from potential harm. Recommendations in the report include centralized regulatory oversight of endocrine disrupting chemicals, policy development and research recommendations by a collaborative group of endocrinologists, toxicologists, epidemiologists, and policy makers. The report also recommends the application of the precautionary principle to endocrine disrupting chemicals and the application of high-throughput research to test and identify many chemicals for endocrine disrupting activity.

Citation: Diamanti-Kandarakis E, Bourguignon JP, Giudice LC, Hauser R, Prins GS, Soto AM, Zoeller RT, Gore AC. Endocrine-disrupting chemicals: an Endocrine Society scientific statement. *Endocr Rev*. 2009 Jun;30(4):293-342.

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Bisphenol A Study Shows Reproductive Health Effects
Heather B. Patisaul, Ph.D.
North Carolina State University
R01ES016001

New research results suggest that bisphenol A (BPA) significantly affects reproductive health at levels that are the same or lower than those considered to be too low to produce adverse effects. The research was conducted by Heather B. Patisaul, Ph.D., an NIEHS Outstanding New Environmental Scientist grantee.

BPA is a chemical used to harden many plastics in everyday food and beverage containers such as baby bottles, food can liners, water bottles, and many other products. It is widely suspected of being an endocrine disrupting chemical.

The research team exposed female laboratory rats to 50 micrograms per kilogram of body weight in their first four days of life. The rats entered puberty earlier than their unexposed litter mates, developed significant ovarian malformations and showed premature loss of estrus. The dose is significant on a policy level because the EPA considers 50 micrograms per kilogram to be the human no effect level.

Many states and municipalities have banned BPA totally or in products designated for children. Canada has announced plans to completely ban the chemical and has labeled it a toxin. Currently there are bills in the U.S. House of Representatives and the Senate to ban the chemical in all food and beverage containers. This research may add evidence to support banning the chemical or restricting its use.

Citation: Patisaul HB, Adewale HB. Long-term effects of environmental endocrine disruptors on reproductive physiology and behavior. *Front Behav Neurosci*.2009;3:10.

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New Method May Accelerate Drug Discovery for Parkinson's
Guy C. Caldwell, Ph.D.
University of Alabama
R21ES14426

A multi-center collaborative research effort partially funded by NIEHS has developed a rapid, inexpensive drug-screening method that could be used by drug developers to target Parkinson's as well as other debilitating diseases. The technique uses yeast to screen potential compounds, cutting the testing time to a few weeks.

Drug discovery is a long difficult process requiring identification and synthesis of potential compounds, screening of compounds with expensive assays, and defining the structure of the compounds. Typically at the end of this months-long process, less than one per cent of the original compounds are deemed worthy for further testing in living cells.

The new method takes advantage of cyclic peptides which are capable of targeting the protein-protein interactions found in almost all cellular processes. Cyclic peptides are able to bind to proteins in smaller spaces where traditional drugs cannot. Using a yeast model of Parkinson's, the research team identified two cyclic peptides that were able to prevent dopaminergic neuron loss in the model. Once these peptides were sequenced, the team found that only the first four amino acids were necessary for the peptide to work. This four amino acid motif is similar to some important biochemical structures including molecules with oxidation or reduction properties and molecules that bind to metals.

According to the authors, the technique is not limited to yeast or just to Parkinson's disease. It could be used in mammalian cells and to a host of diseases. The study was also funded by the National Institute of Neurological Disorders and Stroke, the Morris K. Udall Centers of Excellence for Parkinson's Disease Research, the Michael J. Fox Foundation, and the American Parkinson's Disease Association.

Citation: Kritzer JA, Hamamichi S, McCaffery JM, Santagata S, Naumann TA, Caldwell KA, Caldwell GA, Lindquist S. Rapid selection of cyclic peptides that reduce α-synuclein toxicity in yeast and animal models. *Nature Chem Biol*, doi:10.1038/nchembio.193.

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Dioxins in Food Chain May Cause Poor Milk Production

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University of Rochester School of Medicine and Dentistry
R01ES013958, K02ES012409 and P30ES001247

An NIEHS-funded research team at the University of Rochester Medical Center reports that exposure to dioxins during pregnancy harms rapidly growing and dividing epithelial cells in breast tissue which may explain why some women have trouble breastfeeding or have poor milk production.

The studies were performed using laboratory mice and show that early administration of dioxin caused mammary cells to stop proliferating as early as six days into the pregnancy and lasted through mid-pregnancy. The researchers also determined that dioxin inhibited the induction of genes involved in milk-production and decreased the number of ductal branches and mature lobules in mammary tissue. The studies show that induction of the Ah receptor was crucial in producing the effect and that timing of the exposure was important.

Estimates suggest that three to six million worldwide are unable to breastfeed or are unable to produce enough milk to nourish their babies. Breastfeeding has been shown over and over again to have positive benefits for mother-child bonding and for the overall health of the child. Further research is necessary to find a link between dioxin exposure and problems with breastfeeding in women.

Citation: Lew BJ, Collins LL, O'Reilly MA, Lawrence BP. Activation of the pregnancy alters mammary epithelial cell proliferation and differentiation. *Toxicol Sci*. 2009 Jun 5.

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Genome-Wide Association Study Identifies Asthma Gene
Frank D. Gilliland, MD, Ph.D. and W. James Gauderman, Ph.D.
Keck School of Medicine, University of Southern California
P01ES011627 and P30ES007048

A multi-center study identified two single nucleotide polymorphisms of a gene known as phosphodiesterase 4D or PDE4D as an asthma susceptibility gene in a large genome-wide association study. PDE4D is a regulator of airway smooth muscle contractility and medications targeted towards inhibition of the enzyme have been developed to treat asthma.

Over 300 million people, or approximately one out of 20, in the world are affected by asthma. Over 20 million people in the U.S. alone have asthma. The economic impact of this disease from lost work productivity as a result of the disease or from caring for a child with asthma is staggering. Previous studies have identified over 40 genes associated with asthma.

A genome-wide association study is an approach that involves scanning markers across the complete genome of many people to find genetic variations they have in common associated with a particular disease. Once the genetic associations are identified, the information is used to develop better strategies to detect, treat, and prevent disease. These studies have proven particularly useful in finding genetic variations that contribute to complex diseases such as asthma, cancer, diabetes, heart disease, and mental illnesses.

Two single nucleotide polymorphisms proved to be highly statistically significant with respect to asthma in a combined population of over 18,000 white and Hispanic subjects. Further study of the polymorphisms of PDE4D will lead to an improved understanding of the gene's role in asthma and the efficacy of PDE4D inhibitors in treating asthma.

Citation: Himes BE, Hunninghake GM, Baurley JW, Rafaels NM, Sleiman P, Strachan DP, Wilk JB, Willis-Owen SA, Klanderman B, Lasky-Su J, Lazarus R, Murphy AJ, Soto-Quiros ME, Avila L, Beaty T, Mathias RA, Ruczinski I, Barnes KC, Celedón JC, Cookson WO,Gauderman WJ, Gilliland FD, Hakonarson H, Lange C, Moffatt MF, O'Connor GT, Raby BA, Silverman EK, Weiss ST. Genome-wide association analysis identifies PDE4D as an asthma-susceptibility gene. *Am J Hum Genet*. 2009 May;84(5):581-93.

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Glutathione S-Transferase P**olymorphism Increases Risk of Second Primary Malignancy**
Guojun Li, M.D., Ph.D.
University of Texas M.D. Anderson Cancer Center
R01ES011740

A large prospective cohort study suggests that people with certain polymorphisms of the glutathione S-transferase (GST) genes are more likely to develop a second primary malignancy after first developing squamous cell carcinoma of the head and neck. The study reports a 1.7-fold increase for people with the GSTP1 Ile105Val polymorphism and an even greater risk for multiple GST risk genotypes.

Most squamous cell carcinomas of the head and neck area are attributable to tobacco and alcohol. Cigarette smokers are at about a 10-fold higher risk of developing the cancer than people who have never smoked. Alcohol consumption is known to contribute to the risk, but most smokers and drinkers never develop squamous cell carcinoma suggesting that genetic susceptibility plays a significant role in

the development of the cancer. Traditional cancer therapies cure many squamous cell carcinomas, but a significant proportion of patients go on to develop a second primary malignancy.

GSTs are known to detoxify many carcinogens in tobacco smoke. The research team hypothesized that variations in the genes coding for GSTs might alter a person's risk for developing a second malignancy. Identifying markers of risk for later malignancies among cancer survivors could greatly enhance secondary cancer prevention efforts. By screening patients for these genetic variations, physicians could identify those patients more likely to develop additional cancers and target them for more stringent intervention regimens and closer follow-up to prevent additional cancers or identify them at earlier stages.

Citation: Zafereo ME, Sturgis EM, Aleem S, Chaung K, Wei Q, Li G. Glutathione S-transferase polymorphisms and risk of second primary malignancy after index squamous cell carcinoma of the head and neck. *Cancer Prev Res* (Phila Pa). 2009 May;2(5):432-9.

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PCBs may Alter *in utero* Neonatal Brain Development

Isaac N. Pessah, Ph.D.
University of California Davis
P01ES011269, Ro1ES014901, and P42ES004699

In three new studies, NIEHS grantees at the University of California Davis provide evidence of how low-level exposure to polychlorinated biphenyls (PCBs) alters the normal development of brain cells. These findings could help to explain the relationship between PCB exposure and neurodevelopmental and behavioral disorders in children.

Although banned 30 years ago, researchers have never understood the mechanism by which PCBs produce neurological problems in children. The researchers exposed laboratory rats to low levels of two structurally different PCBs and examined the hippocampus, a region of the brain involved in memory and learning. They found that PCB exposure locks ryanodine receptors, a class of intracellular calcium channels that control the electrical excitability of neurons, into the "on position" thus altering their excitability. Additional in vitro studies confirmed the results.

The team plans to conduct additional studies in mice that carry some of the same genetic variations of the ryanodine receptors that humans exhibit. Those studies will be important to determine whether there are people who are genetically susceptible to PCB toxicity.

Citation: Kim KH, Inan SY, Berman RF, Pessah IN. Excitatory and inhibitory synaptic transmission is differentially influenced by two ortho-substituted polychlorinated biphenyls in the hippocampal slice preparation. *Toxicol Appl Pharmacol*. 2009 Jun 1;237(2):168-77.

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Alzheimer's Disease Linked to Mitochondrial Damage

Stuart A. Lipton, M.D., Ph.D.
Burnham Institute for Medical Research
P01ES016738

New research findings suggest that preventing S-nitrosylation of the mitochondrial protein Drp1 by the free radical nitric oxide may reduce or even prevent neurodegeneration in Alzheimer's patients. This

finding comes from NIEHS-supported scientists at the Burnham Institute for Medical Research in La Jolla, California.

The research team found that S-nitrosylated Drp1 facilitates mitochondrial fragmentation which leads to synaptic injury and eventual nerve cell death. This finding helps to explain how beta-amyloid protein causes neurodegeration. Beta-amyloid protein is the source of the nitric oxide which reacts with Drp1. By identifying Drp1 as the protein responsible for the synaptic injury, the investigators have discovered a new target for developing drugs that may stop or slow the progression of Alzheimer's.

Drp1 is an enzyme that mediates fission or fragmentation of mitochondria. The team showed that excessive nitric oxide production caused damage to Drp1 which lead to excessive mitochondrial fragmentation in cultured nerve cells. Elevated levels of S-nitrosylated Drp1 were also found in the brains of Alzheimer's patients, but not in those with Parkinson's disease or controls who didn't have neurodegenerative disease, adding additional evidence to the *in vitro* findings.

Finally, experiments to decrease Drp1 activity, either using RNA interference or a mutation that prevented Drp1 activity, inhibited excess mitochondrial damage and protected the neurons. These findings suggest that drugs or interventions to prevent damage to Drp1 could prove to be effective prevention or treatment strategies for Alzheimer's disease.

Citation: Cho DH, Nakamura T, Fang J, Cieplak P, Godzik A, Gu Z, Lipton SA. S-nitrosylation of Drp1 mediates beta-amyloid-related mitochondrial fission and neuronal injury. *Science*. 2009 Apr 3;324(5923):102-5.

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Swine Flu Linked Susceptibility Linked to Arsenic Exposure

Josh Hamilton, Ph.D.
Marine Biological Laboratory and Dartmouth Medical School
P42ES007373

Low-level exposure to arsenic at concentrations found commonly in U.S. drinking water compromises the initial immune response to H1N1 or swine flu infection according to NIEHS-supported scientists. The study, conducted in laboratory mice, suggests that people exposed to arsenic in their drinking water may be at increased risk for more serious illness or death in response to infection from the virus.

Laboratory mice were exposed to arsenic at a concentration of 100 parts per billion in their drinking water. The mice initially showed a weak immune response to the virus, and when the immune response fully developed, it was "too robust and too late" according to the study's senior author, Josh Hamilton. The late influx of immune cells to the lung and the inflammatory response caused lung damage and bleeding not seen in the control animals. Over the course of the infection, the death rate in arsenic exposed animals was much higher than the non-exposed mice.

The current U.S. E.P.A. drinking water standard is 10 parts per billion; however, 100 parts per billion levels are commonly found in well water in areas where arsenic is geologically abundant such as New England, Florida, large portions of the Midwest, the Southwest, and the Rocky Mountains. The study authors also point out that high levels of arsenic in drinking water are common in the areas of Mexico where swine flu was initially reported.

Citation: Courtney D. Kozul, Kenneth H. Ely, Richard I. Enelow, and Joshua W. Hamilton. Low Dose Arsenic Compromises the Immune Response to Influenza A Infection in vivo. *Environ Health Perspect*. doi: 10.1289/ehp.0900911

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Gene May Be Linked to Lung Cancer
Marshall Anderson, Ph.D.
University of Cincinnati
P30ES006096

Recent research from the Environmental Health Sciences Center at the University of Cincinnati indicates that a gene found on chromosome 6 known as RGS17 may be a lung cancer susceptibility gene. The researchers found a significant association between three single nucleotide polymorphisms in the gene and lung cancer susceptibility. These results were confirmed in two separate familial lung cancer populations with a combined total of 380 lung cancer cases and 638 controls.

In addition to the human studies, transgenic mouse experiments were conducted as well. The animal studies showed inhibition of lung tumor cell proliferation and the development of tumors in mice when RGS17 gene expression was decreased.

Cigarette smoking is the number one cause of lung cancer. However, only 15-18% of heavy smokers develop lung cancer and some people who never smoke develop lung cancer. These studies point to a genetic link that may help to explain both phenomena and could lead to new prevention strategies to decrease the occurrence of lung cancer and to identify people who are at increased risk of developing the disease.

Citation: You M, Wang D, Liu P, Vikis H, James M, Lu Y, Wang Y, Wang M, Chen Q, Jia D, Liu Y, Wen W, Yang P, Sun Z, Pinney SM, Zheng W, Shu XO, Long J, Gao YT, Xiang YB, Chow WH, Rothman N, Petersen GM, de Andrade M, Wu Y, Cunningham JM, Wiest JS, Fain PR, Schwartz AG, Girard L, Gazdar A, Gaba C, Rothschild H, Mandal D, Coons, T, Lee J, Kupert E, Seminara D, Minna J, Bailey-Wilson JE, Amos CI, Anderson MW. Fine mapping of chromosome 6q23-25 region in familial lung cancer families reveals RGS17 as a likely candidate gene. *Clin Cancer Res*. 2009 Apr 15;15(8):2666-74.

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Phthalate Exposure may Extend Pregnancy
Robin M. Whyatt, Dr. P.H.
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R01ES013543

A multi-state epidemiologic study funded in part by NIEHS reports that women at the upper range of exposure to the plasticizing agent di-(2-ethylhexyl) phthalate, also known as DEHP, had a two day longer gestation length than women at the lower range of exposure. The highly exposed women also had higher odds for caesarian section delivery and delivery at 41 weeks of gestation or later, and decreased odds for preterm delivery. These findings suggest that DEHP may interfere with the hormonally controlled signaling that initiates birth.

Phthalates are used in a wide variety of products including enteric coatings of food and beverage containers, pharmaceutical pills and nutritional supplements, gelling agents, personal care products, medical devices, detergents, children's toys, nail polish, and many other applications. As of 2004,

manufacturers produced 800 million pounds of phthalates each year. By weight, phthalates contribute 10-60% of plastic products. When added to plastics, phthalates allow the long polyvinyl molecules to slide against one another. Phthalates are easily released into the environment because there is no covalent bond between the phthalates and plastics in which they are mixed. As plastics age and break down, the release of phthalates accelerates. Phthalates in the environment are subject to biodegradation, photo-degradation, and anaerobic degradation; therefore, they do not generally persist in the outdoor environment.

This study adds to the body of knowledge that phthalates and other agents in plastics are hormonally active and act as endocrine disruptors affecting a variety of physiological processes.

Citation: Adibi JJ, Hauser R, Williams PL, Whyatt RM, Calafat AM, Nelson H, Herrick R,Swan SH. Maternal urinary metabolites of Di-(2-Ethylhexyl) phthalate in relation to the timing of labor in a US multicenter pregnancy cohort study. *Am J Epidemiol*. 2009 Apr 15;169(8):1015-24.

PAPERS by DERT STAFF

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Deroo BJ, Rodriguez KF, Couse JF, Hamilton KJ, *Collins JB*, Grissom SF, Korach KS. 2009. Estrogen receptor beta is required for optimal cAMP production in mouse granulosa cells. *Molecular Endocrinology.* 23(7):955-965.

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Liebow E, Phelps J, Van Houten B, Rose S, Orians C, Cohen J, Monroe P, Drew CH. 2009. Toward the assessment of scientific and public health impacts of the National Institute of Environmental Health Sciences Extramural Asthma Research Program using available data. *Environmental Health Perspectives*. 117(7): 1147-54.

GRANTEE HONORS and AWARDS

Two long-standing NIEHS grantees received awards at the International Society of Environmental Epidemiology annual meeting, which was held in Dublin, Ireland, August 25-29:

Dr. Allan Smith, Professor Epidemiology, School of Public Health, University of California Berkeley, is this year's winner of the Goldsmith Award, for important contributions he has made to the field of environmental epidemiology. He was President of ISEE from 1994 to 1995. Among his many contributions to environmental epidemiology, and their impacts on public health thinking and practice, Dr. Smith is best known for his work over several decades in unraveling the health effects of environmental arsenic exposure - especially the risks of cancer. Indeed, his careful multi-country research on the epidemiological relationship of this ubiquitous metal to human cancer paved the way for toxicologists and laboratory science to then identify the underlying biological mechanisms. Dr Smith

has conducted studies on arsenic and health in Bangladesh, Argentina, Chile, and elsewhere, working tirelessly, meticulously and effectively with many local collaborators. The upshot of this definitive work has been to prompt national regulatory agencies to impose stricter standards on arsenic levels in drinking water. Meanwhile, running through Allan's career in epidemiology has been his constant interest in, and publication of, critical issues in methodology.

Dr. Steve Wing, of the Department of Epidemiology, School of Public Health, University of North Carolina at Chapel Hill, is this year's Research Integrity Award winner. Steve has resisted heavy pressure from several strong special interest groups and continued with research that he believed would serve the public good, in particular that of disadvantaged communities. His research on politically sensitive issues includes studies of the community health effects of concentrated animal feeding operations (CAFOs) and of exposure to land-applied sewage sludge in rural communities. His work on CAFOs in North Carolina was challenged by industry lawyers, and he effectively resisted this intimidation. Indeed, this work had subsequent policy impact, contributing to a continuing moratorium on building new hog-waste lagoons. He has also conducted and published investigations into radiation exposure effects, including results unfavorable to the U.S. Department of Energy and other powerful interests. Dr Wing has typically worked in partnership with communities, striving for community-driven socially useful research. He has co-organized a statewide conference on how corporations and foundations influence university decisions, and how faculty can protect the mission of higher education and research.

An article on epigenetic research conducted by NIEHS principal investigators, Drs. Andrea Gore and David Crews (University of Texas, Austin), Michael Skinner (Washington State University, Pullman), Randy Jirtle (Duke University) and others won first prize for explanatory print journalism from the Society of Environmental Journalists. The article, written by Ms. Valerie Brown and printed in Miller-McCune Magazine, explained how "environmental contaminants can turn genes 'on' and 'off,' triggering serious diseases that are handed down through generations." (For the full article, see: http://www.miller-mccune.com/science_environment/environment-becomes-heredity-489)

STAFF HONORS and AWARDS

On Monday, July 8, the Society of Toxicology held a reception at the Capitol Visitor's Center in Washington, D.C. to welcome Dr. Linda Birnbaum as the Director, NIEHS.

On Thursday, June 4, at Bohrer Park in Gaithersburg, Maryland, Ms. Pam Clark and Mr. Aaron Nicholas received the following awards:

Ms. Pam Clark, GMB, received Letters of Appreciation for her work on two NIH Grants Management Advisory Committees (GMAC). The first is in recognition for her work on the preliminary planning of the upcoming Seminar, "Dealing With Stress" in support of grants management initiatives as well as for her active participation in the majority of the subcommittee meetings during the past year. The second is "For significant contributions to SBIR/STTR Vision Subcommittee activities and participation in the majority of subcommittee meetings during the past year".

Mr. Aaron Nicholas, GMB, received a Special Recognition Award for Preparing the flyer that was sent to the Grants Management community to announce the Awards Ceremony and to generate enthusiasm to participate and in appreciation of significant contributions to Vision Award Subcommittee activities and participation in the majority of the subcommittee meetings during the past year.

On July 29 at Natcher Hall on the NIH Campus in Bethesda, Maryland, Mr. Liam O'Fallon and Dr. Terry Nesbitt, received the following NIH Director Awards:

Mr. O'Fallon, SPHB, received the NIH Director's Award, "In recognition of exceptional service in the implementation of outreach and education in support of Environmental Public Health."

Dr. Teresa Nesbitt, *SRB,* received the NIH Director's Award as part of the trans-NIH Early Stage Investigator Workgroup, "For conceiving, developing and implementing NIH policy encouraging biomedical scientists and their institutions to accelerate postdoctoral training completion and early application for independent research support."

STAFF ACTIVITIES

Ms. Beard, WETB, facilitated and presented at a session on "Funding Sources for Job Training and Workforce Development" at the EPA Brownfields Job Training Grantee Meeting on August 26-27 in Alexandria, Virginia.

Dr. Heindel, OSTB, gave an invited presentation, "Health effects of environmental chemicals: need for green chemistry," at a plenary symposium, Green Chemistry: Integrating Environmental Health Research and Chemical Innovation. This was a satellite workshop and symposium to the Planetary Emergencies Conference, which was held in Erice Sicily, August 17-25.

Dr. Humble, OSTB, organized and hosted the 3rd Annual Grantee Meeting for the NIEHS Obesity and the Built Environment program, August 13-14 at NIEHS. The 30 attendees included representatives from the OBE projects, student travelers, and representatives from the various NIH and CDC funding partners. Scientific presentations were given on ten of the fourteen projects funded through this program.

Drs. Heindel and Humble, OSTB, gave invited presentations on the NIH R15 program, NIEHS research interests and principles of grantsmanship on August 3 at the University of North Carolina-Greensboro. The meeting was attended by scientists from numerous local universities interested in applying for the ARRA R15 awards.

Dr. Humble, COSPB, participated in the "Chemicals, the Environment and You" teacher workshop held at NIEHS on July 13. The workshop was sponsored by the North Carolina Association for Biomedical Research (NCABR) and was attended by approximately 24 North Carolina middle and high school science teachers. Dr. Humble was the moderator for the morning and afternoon training sessions and introduced the environmental health science curriculum and activities developed by NCABR and NIH/NIEHS.

Drs. Nadadur, OSTB, and George Leikauf, University of Pittsburgh, chaired a session at the International Conference of the American Thoracic Society on May 20 in San Diego, California. The session, entitled "Translational Research Efforts on Pulmonary Disease and Genetic Susceptibility to Air Pollution," featured research supported by NIEHS in this area. The session included presentations from Dr. Andrew Fontenot, National Jewish Hospital, Denver; Dr. John Hollingsworth, Duke University; Dr. Nadadur, and Dr. Leikauf.

Dr. Heindel, OSTB, was invited to give a presentation, "Obesity: Developmental Origins and Environmental Influences", at a post graduate course on endocrine disruptors in Copenhagen Denmark.

The postgraduate course was followed by the 5th Copenhagen Workshop on Endocrine Disruptors, where Dr Heindel chaired a session on endocrine disruptors and obesity. These events took place May 18-22.

Ms. Anderson, CRIS, represented the NIEHS Superfund Research Program (SRP) at the EPA National Association of Remedial Project Mangers Annual Training Conference, June 2-5 in Atlanta, Georgia. Ms Anderson worked with colleagues from EPA Region 7 in organizing a session "Working together: Getting the Best Results through Partnerships (Everybody Wins!)".

Dr. Heindel, OSTB, was a member of the planning committee for the Teratology Society Continuing Education Course at the 49th annual meeting in Puerto Rico June 27-July 1. He also presented an invited talk, "Historical perspectives of developmental origins of health and disease: a paradigm change with a split personality," at the Continuing Education Course.

Dr. Heindel, OSTB, was invited to give the keynote address at the 2nd Endocrine Society Forum on Endocrine Disruptors: Best Science for Risk Management and Policy. The meeting was held in Washington D.C., June 10. His talk was titled, "Government and Public Health Protection".

Dr. Caroline Dilworth, SPHB, gave an oral presentation at the International Society for Environmental Epidemiology annual meeting in Dublin, Ireland on August 29. The purpose of the presentation, entitled " Benefits of Community Engagement: Communicating Research Findings," was to introduce the new NIEHS Partnership for Environmental Public Health (PEPH) program and present a case example of how study results were reported back to families of participants in the Breast Cancer and the Environment (BCERC) when unexpectedly high levels of a biomarker were found among a subgroup of girls from a particular community. The presentation was part of a larger session on risk communication and policy that also included a group discussion on ethics in environmental epidemiological research.

UPCOMING MEETINGS and WORKSHOPS

The NIEHS Worker Education and Training Program will cosponsor a grantee meeting and workshop, "Global Safety and Health Activities," October 21-22, in Chapel Hill, North Carolina. The focus will be on the implications of REACH, Global Harmonization and other international policies on worker training. The WETP will also use this opportunity to share the international training activities of some of its awardees.

The Superfund Research Program's annual meeting is scheduled for November 3-4 and will be held at Columbia University, New York City, New York.

STAFF CHANGES

Arrivals:

Ms. Rachel Gross, DERT/OD, comes to NIEHS through the NIH Administrative Fellows Program. Rachel earned a BS in Youth Ministries and Physical Education from Toccoa Falls College in Northeast Ga. She recently earned a Masters Degree in Public Administration focused on policy and environmental management from North Carolina State University.

Mr. Wesley Brinson is the new Supervisor for DEAS (Division of Extramural Activities Support). Wes comes to us from Cherry Hill Hospital in Goldsboro, North Carolina, where he was the Continuous

Quality Improvement Coordinator. He has a BS in Communications and Broadcasting and an AA in Applied Science.

Mr. Dwight Dolby and Ms. Carolyn Winters, both formerly with GMB came out of retirement to lend GMB a hand with ARRA.

Ms. Barbara Gittleman and Ms. Natasha Hurwitz are temporary hires to help GMB make ARRA awards.

Ms. Laura McGrew, Research Contracts Branch, and *Mr. Jerry Phelps, PAB*, are both on temporary detail to GMB to help make awards.

Departures:
Dr. Ethel Jackson, DERT OD, retired on July 31 after 37 years of government service. She spent the past 15 years in the Division of Extramural Research and Training as the Chief of the Scientific Review Branch and as a special assistant to the Director, DERT.

Promotions:
Claudia Thompson, Ph.D., was promoted to Acting Branch Chief, Susceptibility & Population Health Branch effective June 22.

Christina Drew, Ph.D., was promoted to Branch Chief, Program Analysis Branch effective August 3.