**Council Meeting Highlights Mission Accomplishments**

Throughout the September 15–16 meeting of the National Advisory Environmental Health Sciences Council (NAEHSC) at NIEHS, the discussions were upbeat. [read more]

**Fellows Recognized at Regional Showcase in Cincinnati**

The University of Cincinnati (UC) Center for Environmental Genetics (CEG) joined with other NIEHS-supported training programs, Centers and Superfund Research Programs to celebrate the first Environmental Health Sciences Regional Showcase of Fellows on September 18 at UC. [read more]

**2009 ONES Awardees Named**

NIEHS announced the selection of six early-stage tenure-track investigators as 2009 Outstanding New Environmental Scientist (ONES) awardees. [read more]

**Beijing Green Science Policy Symposium on Fire Retardants**

NIEHS played an important role in the August 22 Green Science Policy Symposium on “The Fire Retardant Dilemma in China” with two distinguished speakers on the five-lecture agenda — NIEHS and NTP Director Linda Birnbaum, Ph.D., D.A.B.T., A.T.S., and NIEHS grantee Tom Webster, D.Sc., of Boston University (BU). [read more]

**NIEHS Director Gives Distinguished Lecture**

NIEHS and National Toxicology Program (NTP) Director Linda Birnbaum, Ph.D., D.A.B.T., A.T.S., presented the first seminar of the 2009 – 2010 NIEHS Distinguished Lecture Series on September 8 titled “Halogenated Flame Retardants: Does the Benefit Justify the Risk?” [read more]

**NIEHS Microarray Group Hosts Genomics Day**

NIEHS Genomics Day, held on September 1, offered scientists at NIEHS and visitors an afternoon of talks by investigators and trainees, a poster session, and an opportunity to learn more about the NIEHS Microarray Laboratory. [read more]

**Genome-Wide Association Study Focuses on Asthma in Children**

A new genome-wide association study (GWAS) published August 28 in *PLoS Genetics* identified the chromosome 9q21.31 region as a novel candidate region for childhood asthma. [read more]

**Investigators Show Protective Role of DNA Repair Protein**

A new NIEHS-supported study reports that human cells deficient in a singularly resourceful DNA repair enzyme, known as Werner syndrome protein (WRN), exhibit more replicative stress and DNA damage after exposure to the industrial pollutant hexavalent chromium — Cr(VI) — than do cells with normal WRN levels. [read more]
### NIEHS Spotlight

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### Science Notebook

**Study Links Same-Day CO to Risk of Hospitalization for CVD**

An NIEHS- and U.S. Environmental Protection Agency (EPA)-funded epidemiological study published in the September 2009 issue of Circulation presents strong evidence of an association between daily low-level carbon monoxide (CO) exposure and an increased risk of same-day hospitalization for cardiovascular disease (CVD) among an older population. ...read more

**Electronic Nose Sniffs Out Toxins**

Imagine a polka-dotted postage stamp-sized sensor that can sniff out some known poisonous gases and toxins and show the results simply by changing colors. ....read more

**Imaging the Effects of Childhood Lead Exposure on Neuronal Circuitry**

In a recent NIEHS-funded study published in Neurotoxicology, imaging research scientist Kim M. Cecil, Ph.D. describes the long-term effects of childhood lead exposure on brain microstructure. According to her research, neurotoxic insults caused by childhood lead exposure are associated with changes in myelination and axonal integrity in brain white matter that persist into adulthood. ...read more

**Speaker Explores Gene-Environment Interactions in Acute Lung Injury**

On September 17, Professor George Leikauf, Ph.D., of the University of Pittsburgh, presented the first in a series of talks in the Keystone Seminar Series hosted by the Division of Extramural Research and Training (DERT). ....read more
Extramural Update

The American Reinvestment and Recovery Act has been a challenge for the extramural staff at the National Institutes of Health (NIH). With $10 billion extra dollars to spend in approximately seven months, NIH had to develop, announce, review and make awards — at the same time ensuring the best science was funded and appropriately distributed geographically ...

Extramural Papers of the Month

- Natural Food Products Can Treat Cancer
- Carbon Monoxide and Cardiovascular Disease in the Elderly
- Diesel Exhaust Linked to Cancer Development Through Blood Vessel Growth
- Maternal Exposure to Air Pollution Lowers Children’s IQ
Intramural Research

Intramural Papers of the Month

- Novel p38 MAPK-RhoA Signaling Pathway Involved in Cell Adhesion
- Copper Exposure Leads to HepG2 Cell Transcriptome Changes
- Risk of Amyotrophic Lateral Sclerosis is Higher in Affected Families
- Coherent Co-Expression Biclustering Analysis Can Identify Hepatotoxic Pathways Through the Overrepresentation of Co-Expressed Genes

Inside the Institute

Lobbyist Speaks on Equal Access for People with Disabilities

A small but engaged audience of people from NIEHS and neighboring Environmental Protection Agency that included NIEHS and National Toxicology Program Director Linda Birnbaum, Ph.D., gathered on September 8 to hear guest speaker and civil rights lobbyist Julia Leggett. ...read more

RTP Toll Road Advances Beside NIEHS-EPA Campus

As recently as August, the right-of-way for the new Triangle Parkway was still scrub pine and new growth hardwood. A rutted dirt road plunged into the property adjacent to the NIEHS-EPA campus and wound its way along the border near the First Environments daycare center. ...read more

Calendar of Upcoming Events

- **October 1 (Offsite Event)**, at the University of Wisconsin - Milwaukee — NIEHS Townhall Meeting - Community Environmental Health: Making Milwaukee a Sustainable City with Director Linda Birnbaum, Ph.D.
- **October 1**, in Rall Building D450, 10:00–11:00 — Thomas Kunkel, Ph.D. speaking on “Determinants of Leading and Lagging Strand DNA Replication Fidelity”
- **October 5 (Offsite Event)**, at the Friday Center in Chapel Hill — Genetics and Environmental Mutagenesis Society Fall Meeting, “Dissecting genome structure, genetic traits, and basis for complex diseases”
- **October 8–9**, in Rodbell Auditorium, 9:00–5:00 — Centers for Neurodegeneration Science Annual Meeting
- **October 15**, in Rall Building D450, 10:00–11:00 — “Environmental exposure to engineered nanomaterials as a potential cause of lung inflammation, fibrosis, and cancer,” with James Bonner, Ph.D.
- **October 21–22 (Offsite Event)**, at the Sheraton Chapel Hill — NIEHS Worker Education and Training Program Awardee Meeting and Workshop: Global Safety and Health Activities
- **October 26**, in Rodbell Auditorium, 11:00–12:00 — Distinguished Lecture with Teresa Wang, Ph.D., speaking on “The Perils of Bad DNA Polymerases: Chromosome Chaos.”
- **October 26–27 (Offsite Event)**, at the NIH Natcher Conference Center in Bethesda — Partners in Research Grantee Workshop
- **October 28–30**, in Rodbell Auditorium, 8:00–5:00 —NIEHS/Health and Environmental Sciences Institute (HESI) Epigenetics Meeting
- **November 2–4 (Offsite Event)**, at the Hilton in RTP, 8:30–4:00 — NTP/RoC Expert Panel Meeting on Formaldehyde
- View More Events: NIEHS Public Calendar
Throughout the September 5–6 meeting of the National Advisory Environmental Health Sciences Council (NAEHSC) at NIEHS, the discussions were upbeat. Each speaker on the agenda presented evidence of steady advancement toward meeting the priorities that Director Linda Birnbaum, Ph.D., has articulated in the course of her eight-month tenure at the head of NIEHS and the National Toxicology Program (NTP).

The meeting opened with a report by Birnbaum featuring an impressive catalogue of accomplishments and budgetary developments. In the area of finance, she noted that more than 86% of the $195 million NIEHS American Recovery and Reinvestment Act (ARRA) funds had been awarded for some 290 grants — “thanks to the heroic efforts of our extramural program, review, and grants management staff.” She also observed that there is every indication NIEHS will enjoy what is proportionately the largest increase in its FY 2010 budget of any NIH institute or center (IC).

Turning to the topic of scientific excellence, Birnbaum highlighted some of the top papers of the last quarter. Then, she announced, with justifiable pride, that two veteran grantees — Leona Samson, Ph.D., of the Massachusetts Institute of Technology, and Sarah Tishkoff, Ph.D., of the University of Pennsylvania — will be the first NIEHS-supported scientists to receive the prestigious NIH Director’s Pioneer Awards in the NIH program’s six-year history.

Birnbaum outlined progress on recruiting a permanent leadership team as she urged the Council members to spread the word about the Institute’s “wide open” searches for permanent heads of the two research divisions — a scientific director to lead the Division of Intramural Research (DIR) and a director to head the Division of Extramural Research and Training (DERT) — as well as the deputy director, education director and four liaison positions for the NIEHS Bethesda office.

Referring to her several meetings with new NIH Director Francis Collins, M.D., Ph.D., Birnbaum also touched on progress in meeting another of her goals for NIEHS — the enhanced integration of resources and efforts on every level of operation. Several of the other speakers also returned to the theme in their own reports.
NIEHS Acting Deputy Director Steve Kleeberger, Ph.D., described his ongoing efforts to restructure the Office of the Deputy Director and his office’s activities in finalizing a Memorandum of Understanding (MOU) between the NIEHS and U.S. Environmental Protection Agency (EPA) to further enhance research collaborations.

NTP Associate Director John Bucher, Ph.D., reported on interagency efforts in relation to the Tox 21 MOU and alternative testing.

In his report, NIEHS Acting Clinical Director Darryl Zeldin, M.D., outlined key collaborations within NIEHS, NIH and NTP, with other agencies, especially EPA and the Centers for Disease Control and Prevention (CDC), and with institutional partners, including Duke University and the University of North Carolina at Chapel Hill.

Leading up to the meeting’s scientific presentation by NIEHS Principal Investigator Paul Wade, Ph.D., NIEHS Acting Scientific Director John Pritchard, Ph.D., reported on DIR activities. He discussed staffing initiatives, training accomplishments and future collaborations with graduate schools at area universities, as well as research milestones, such as the Grand Opening of the NIEHS Clinical Research Unit and the completion of enrollment for the 50,000-person cohort of the Sister Study.

The theme of collaboration among agencies and principal investigators ran through a series of presentations on activities of DERT — reports by Superfund Research Program External Advisory Panel Member William McFarland, Ph.D., NIEHS Center for Risk and Integrated Sciences Director William Suk, Ph.D., and Acting DERT Director Gwen Collman, Ph.D. Although Collman’s presentation focused on the outstanding performance of her DERT staff in processing, reviewing and approving ARRA grants, her written report highlighted the division’s impressive series of collaborative and partnership-building efforts, in addition to noting accomplishments of grantees and staff.

The open session of Council concluded with reports by NIEHS Health Science Administrators Jerry Heindel, Ph.D., and Sri Nadadur, Ph.D., (see text box) on two innovative initiatives.
BPA and Nano — Helping Keep Investigators on the Same Page

Heindel and Nadadur presented reports on the new ARRA-funded Grand Opportunities (GO) initiatives on bisphenol A (BPA) and engineered nano-materials (ENMs) health and safety that are structured to foster productive collaborations and platform compatibility within their respective groups of investigators. While the specific challenges facing investigators working on each initiative may be distinctive, Heindel and Nadadur obviously collaborated on overall project design for the innovative two-year RC2 grants.

Both initiatives include provisions for ensuring their research will have the greatest impact possible:

- Meetings of grantees at NIEHS during October to coordinate research design and goals from the outset their projects
- Ongoing coordination of protocols, models, endpoints, diets/exposure routes and dosages, measurements and data validation across different laboratories
- Collaboration and sharing of tissues among animal researchers and epidemiologists
- Emphasis on collaborations with Food and Drug Administration (FDA) and NTP research programs

The goals of both initiatives are ambitious — in the case of BPA, to produce “primary data sets for use in regulatory assessment,” and in the case of ENMs, to “develop guidelines for environmental health effects and safety.” Enabling objectives address the shortcomings of current research on BPA and ENMs with an injunction to strive for the development of “reliable and reproducible methods to assess exposure and biological response/toxicological endpoints.”

During his presentation, Pritchard touted the success of this year’s Summers of Discovery program and the performance of the postdoctoral fellows in the NIH Fellows Award for Research Excellence (FARE) competition. “We had more candidates apply for this than any other IC except Cancer,” he said.

Following his report, Zeldin, foreground right, took Council members on a tour of the Clinical Research Unit. Zeldin is shown responding to a question from member Hillary Carpenter, Ph.D., foreground left. (Photo courtesy of Steve McCaw)
The science talk by molecular biologist Paul Wade, above, gave NIEHS a chance to showcase the excellence of its science. Wade focused on the role of chromatin remodeling in breast cancer. (Photo courtesy of Steve McCaw)

ENMs present a special challenge to researchers, Nadadur explained, because of the lack of uniformity in production and surface configuration. Past research has produced conflicting results from the different assays used. (Photo courtesy of Steve McCaw)

Heindel, above, has been on the cutting edge of the Institute’s BPA initiatives. He wants the newly funded investigators to take a major step forward by producing high-quality data that can be extrapolated to human beings. (Photo courtesy of Steve McCaw)

Reflecting on the presentations by Heindel and Nadadur, member Stefani Hines, above, commented, “This seems to be a very well-coordinated effort beforehand... very interesting and exciting.” (Photo courtesy of Steve McCaw)
The University of Cincinnati (UC) Center for Environmental Genetics (CEG) joined with other NIEHS-supported training programs, Centers and Superfund Research Programs to celebrate the first Environmental Health Sciences Regional Showcase of Fellows on September 18 at UC. The event provided an opportunity for early career scientists to present their work while networking with other environmental health scientists in the Ohio-Kentucky-Michigan region.

On hand to show the Institute’s support for this novel initiative were NIEHS Program Administrators David Balshaw, Ph.D., of the Center for Risk and Integrated Sciences, and Carol Shreffler, Ph.D., who oversees the Institute’s training grants.

Seven NIEHS-supported T32 training program directors and the CEG Career Development Core each invited an Exemplary Fellow to represent their programs, while thirty other NIEHS-supported trainees presented posters describing their research (see text box). The expertise of the fellows spanned the career development range, from graduate students to junior faculty, including NIEHS K99 and K22 early-career support recipients.

Students from the Health Technologies Program at Cincinnati’s Woodward Career Technical High School, under the direction of Tracy Greeley and Sarah Woodward, were invited to the Showcase as part of the UC Department of Environmental Health initiative, which works to encourage interest in environmental health sciences research among students at every level. Organizers hope that exposing this group to environmental health sciences research will inspire some of them to pursue a career in the field.

Kicking off the morning session, which was co-chaired by UC Professor and NIEHS-funded Principal Investigator Grace LeMasters, Ph.D., and trainee Nicholas Newman, D.O., Balshaw presented a keynote address on “Use of Emerging Technologies to Build Capacity in Exposure Biology and Gene, Environment, and Health Interactions.” He presented an overview of NIH and NIEHS to
the standing-room-only crowd and described several new methods under development for more accurately characterizing personal exposure to environmental toxicants.

The event’s poster session was designed to encourage introductions and networking experiences. CEG staff made every effort to assign each poster presenter at least one judge who was an established investigator from a different university with appropriate expertise to discuss the fellow’s research, and perhaps give some insight into future collaborations. This was possible thanks to support from participating senior investigators, such as David Hein, Ph.D., and Rong Wan, M.D., Ph.D., of the University of Louisville, and Young Lin, D.V.M., Ph.D., of The Ohio State University.

The afternoon session was co-chaired by Mary Vore, Ph.D., and Donna Coy, both from the University of Kentucky (UK). Shreffler chaired a career development panel discussion that included NIEHS-funded investigators Vore, Ranjan Deka, Ph.D., Erin Haynes, Dr.PH., and Michael Borchers, Ph.D., an NIEHS Outstanding New Environmental Scientist (ONES) awardee. Each panelist added his or her unique point of view on career development and the future of environmental health research. Shreffler reviewed employment statistics to assure the crowd that there will be jobs available in environmental health sciences in coming years.

Evaluations collected at the end of the day confirmed that the majority of attendees intend or prefer to remain in the region — underscoring the need for more center activities designed to provide networking opportunities for environmental health scientists in the Midwest. Future events will be organized to offer time for more extensive interaction among established investigators and early career fellows.

(Elizabeth Kopras is a junior research associate in the Department of Environmental Health and program coordinator for the Center for Environmental Genetics at UC.)
Oral Presentations

- Eric Brandt, Ph.D., Cincinnati Children’s Hospital Medical Center, *Impact of Early Life Diesel Exposure on Immune Patterning, Lung Development, and Function*

- Erica Sparkenbaugh, Michigan State University (MSU), *The cytotoxic interaction of hypoxia and elastase in a murine hepatoma cell line*

- Stephen Adjei, M.D., UC, *Cerium pneumoconiosis: A case report*

- Deanna Edwards, UK, *Chronic cisplatin treatment accelerates premature senescence of normal human fibroblasts*

- Erica Rogers, University of Louisville, *Curcumin Regulates Cell Cycle Progression in Response to DNA Damage*

- Elisia Tichy, Ph.D., UC, *Suppressing Mutation in Embryonic Stem Cells*

- Devon Graham, Ph.D., Cincinnati Children’s Hospital Medical Center, *Effects of developmental lead (Pb^{2+}) and barren cage rearing in rats on corticosterone levels and monoamines*

- Greg Motz, UC, *NK Cell Activation in Mouse Model of COPD*

Poster winners, as judged by students from Woodward

- Best poster design: Pamela Heckel, PhD, UC. “Novel approaches to estimate ambient mercury exposures“

- Best research description: Wan-yee Tang, Ph.D., UC, “Early developmental exposures to estrogens/bisphenol A impact a specific prostate epigenome“

- Best overall poster and presentation: Fedoria Rugless, UC, “Airborne Manganese Exposure and Postural Balance in Children.”

Poster Winners, as judged by fellows and established investigators

#1 Elisabet Johansson, Ph.D., UC, “Quantitative PCR analysis of Streptomyces in household dust from homes in the Cincinnati area”

#2 Nicholas Newman, D.O. UC, “Is Ultrafine Particle Exposure Associated with Attention Deficit/Hyperactivity Disorder in Children?”

#3 Aaron M. Fullerton, Michigan State University, “TCDD enhances inflammatory liver injury in response to concanavalin A administration.”

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2009 ONES Awardees Named

By Eddy Ball

NIEHS announced the selection of six early-stage tenure-track investigators as 2009 Outstanding New Environmental Scientist (ONES) awardees. The highly competitive, five-year ONES grants will total $3.6 million for the first year, and the awardees, like their predecessors in the four-year-old program, will visit NIEHS to present talks about their research projects.

The new awardees are Jesus Araujo, M.D., Ph.D., Michelle Block, Ph.D., Yu Chen, Ph.D., Dana Dolinoy, Ph.D., James Luyendyk, Ph.D., and Scott McCulloch, Ph.D.

The 2009 group of ONES awardees will make their presentations at a meeting in the NIEHS Rodbell Auditorium in January, date and time to be announced. Videos of their talks will be posted afterwards on the Grant Program Events archive online.

Established in 2006, the ONES program identifies outstanding scientists who are in the early, formative stages of their careers and who intend to make a long-term career commitment to research in the mission areas of the NIEHS. The program assists them in launching an innovative research program focusing on problems of environmental exposures and human biology, human pathophysiology and human disease.

“This grant is designed to serve as the foundation of a successful research career,” said NIEHS Training and Career Programs Health Science Administrator Carol Shreffler, Ph.D. “The program strives to build a long-term relationship between the awardees and NIEHS.”

“We indeed have made this a very competitive process,” Shreffler noted, “and we look forward to having these awardees make some very seminal contributions to the future of our Institute.”

Applications for the 2010 ONES Awards (RO1) will be accepted beginning October 4 and be due November 3, 2009.

Stories about previous ONES recipients appeared in the November 2006, December 2007 and January 2009 issues of the Environmental Factor.
Epidemiologist Yu Chen, Ph.D., is an assistant professor in the Departments of Environmental Medicine and Medicine in the Langone Medical Center at New York University. She intends to continue her investigation into the interactions between arsenic exposure from drinking water and genetic susceptibility related to inflammation and oxidative stress in cardiovascular disease. (Photo courtesy of Yu Chen)

Geneticist Dana Dolinoy, Ph.D., is an assistant professor in Environmental Health Sciences in the University of Michigan School of Public Health, where she also holds the Searle Assistant Professorship in Public Health. She will be investigating effects on the fetal epigenome of in utero exposure to bisphenol A. (Photo courtesy of Dana Dolinoy)

James Luyendyk, Ph.D., is an assistant professor in the Department of Pharmacology, Toxicology and Therapeutics at the University of Kansas Medical Center. His research goal is to understand the mechanisms of xenobiotic-induced biliary inflammation and fibrosis. (Photo courtesy of James Luyendyk)

Toxicologist Scott McCulloch, Ph.D., is an assistant professor in the North Carolina State University Department of Environmental and Molecular Toxicology. He plans to continue his investigations into the role of human DNA polymerase eta (pol η) in the mutagenic response to oxidative stress. (Photo courtesy of Scott McCulloch)
Beijing Green Science Policy Symposium on Fire Retardants

By Eddy Ball

NIEHS played an important role in the August 22 Green Science Policy Symposium on “The Fire Retardant Dilemma in China” with two distinguished speakers on the five-lecture agenda — NIEHS and NTP Director Linda Birnbaum, Ph.D., and NIEHS grantee Tom Webster, D.Sc., of Boston University (BU). The meeting in Beijing was sponsored by the Berkeley, Calif.-based Green Science Policy Institute, an organization dedicated to mobilizing scientists, industry, government, non-governmental organizations and consumers worldwide to reduce toxic exposures in the environment.

According to the Green Science Policy Institute, the fire retardant dilemma is “How can we achieve fire and environmental safety as well as protect public health?” The issue is global, but also increasingly pertinent in China. As speakers at the meeting explained, production levels of the more toxic halogenated flame retardant (HFR) chemicals are nearly three times those in the U.S. and the European Union and each year the country receives an estimated 70 percent of the world’s electronic waste — an important source of HFRs now in use as well as those banned elsewhere.

As her contribution to the discourse about HFRs, Birnbaum, who also delivered an NIEHS Distinguished Lecture on HFRs in September, presented “An Overview of Halogenated Fire Retardant Research.” Birnbaum’s presentation focused on the human health effects, especially from early exposure, ecotoxicity, regulatory status and policy developments related to the three most common HFR chemicals — Tetrabromobisphenol A (TBBPA), Hexabromocyclododecane (HBCD) and Polybrominated Diphenyl Ethers (PBDEs). Fittingly, she concluded her talk with a review of green science and sustainability principles that scientists should bear in mind as they search for safer alternative and next-generation flame retardants.

In his presentation, Webster, who is associate chairman of Environmental Health in the BU School of Public Health, spoke on the topic “From Product to Person: How to Measure Human Exposure to Persistent Halogenated Chemicals.” Webster reviewed findings from the literature on HFRs to trace the complete pathway from the source to the microenvironment that results in personal exposure, usually by inhalation or ingestion of HFRs in dust or food, and the ultimate internal dose, which has most commonly been measured in blood and breast milk. His talk ended on a disturbing note as he speculated that PBDEs still in the environment long after production has ceased may one day be the target of a “Superfund of the future.”

Also featured at the symposium were three other experts on the issue of HFRs and their health risks. Arlene Blum, Ph.D., founder and executive officer of the Green Science Policy Institute and a visiting scholar in chemistry at the University of California, Berkeley, opened the symposium with her talk on “The Fire Retardant Dilemma in China: Human Health and the Global Environment.” Susan Shaw, Dr.PH., founder and director of the U.S. Marine Environmental Research Institute, explored “A Comparison Of Fire Retardant Levels And Known
Health Effects in Wildlife and Humans.” The final speaker was Eddy Zeng, Ph.D., director of the State Key Laboratory of Organic Geochemistry at the Guangzhou Institute of Geochemistry, who offered the audience “A big picture view of halogenated chemical exposures in China.”

At the panel discussion that followed their talks, Birnbaum and Webster joined their colleagues for a consideration of “How to protect human health and the environment from halogenated flame retardant chemicals.”

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By Eddy Ball

Two long-term NIEHS grantees were recognized at the joint British-Irish 21st Annual Conference of the International Society for Environmental Epidemiology 2009 (ISEE) at the University College Dublin August 25–29. Their awards are the highest honors presented each year at the ISEE conference.

During an awards plenary session at the conference on August 26, former ISEE President Allan Smith, M.D., Ph.D., of the University of California at Berkeley (UCB), was presented the John Goldsmith Award for Outstanding Contributions to Environmental Epidemiology, and Steve Wing, Ph.D., of the University of North Carolina at Chapel Hill (UNC-CH) received the ISEE Research Integrity Award. Smith and Wing gave talks on their research as a part of the awards ceremony.

“We have supported Allan Smith continuously since the 1990s,” said NIEHS Division of Extramural Research and Training Acting Director Gwen Collman, Ph.D. “He is one of the pioneer researchers in the field of arsenic and an innovative collaborator who has uncovered international trends of arsenic’s effects on human health.”

“Steve Wing is both an outstanding scientist and an outspoken advocate,” Collman continued, “and his work has been very influential in the area of environmental justice issues. He has taken significant personal and professional risks to protect the integrity and confidentiality of his research.”

Smith, a professor of Epidemiology in the UCB School of Public Health and an NIEHS grantee for more than 20 years, was honored for his important contributions to the field of environmental epidemiology and their significant impact on public health thinking and practice. Smith is best known for his pioneering work spanning several decades in unraveling the health effects of environmental arsenic exposure — especially the risks of cancer. 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 identify underlying biological mechanisms.
Smith has conducted studies on arsenic and health in India, 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 Smith’s long and distinguished career in epidemiology has been his constant interest in, and publication of, critical issues in methodology.

Wing, of the Department of Epidemiology in the UNC-CH School of Public Health was honored for his resistance to heavy pressure from several strong special interest groups for 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.

Although Wing’s work on CAFOs in North Carolina was challenged by industry lawyers, he effectively resisted this intimidation. This work had subsequent policy impact, contributing to a continuing moratorium on building new hog-waste lagoons. Wing has also conducted and published investigations into radiation

According to Collman, Wing “really sees the world as an activist-scientist. It’s a very different perspective than people in basic science generally have.” (Photo courtesy of Steve Wing and UNC-CH)
exposure effects, including results unfavorable to the U.S. Department of Energy and other powerful interests. 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 responsible research.

“These scientists are an important part of the fabric of NIEHS,” Collman said. “We have made a major, decades-long investment in their work, and it’s wonderful to see the value their contributions to the field recognized by an organization of the stature of ISEE.”

Heinz Awards Go to NIEHS Grantees

By Eddy Ball

On September 15, Teresa Heinz and the Heinz Family Foundation announced the recipients of the 15th annual Heinz Awards, which this year honor ten individuals whose achievements have helped bring about a cleaner, greener and more sustainable planet. Two of the awards, which bestow $100,000 on each winner, were given to long-time NIEHS grantees — Beverly Wright, Ph.D., executive director of the Dillard University Deep South Center for Environmental Justice (DSCEJ) in New Orleans; and Kirk Smith, Ph.D., professor of Global Environmental Health at the University of California, Berkeley.

“At this unique time in history, when the environment is more important than ever to our lives, our economy, our national security and our future, it is only fitting that we focus exclusively on this critical topic,” said Teresa Heinz, chairman of the Heinz Family Foundation. The 2009 Heinz Awards, established in 1993 to honor her late husband, U.S. Senator John Heinz of Pennsylvania, commemorate the senator’s long-standing commitment to the environment.

According to the foundation, Wright was honored for “her work as an environmental justice advocate” on behalf of communities, especially those in Louisiana’s “Cancer Alley.” As head of the Deep South Center for Environmental Justice at Dillard University in New Orleans, the Foundation’s press release said, “She has been tackling issues of environmental racism and working to raise the profile of environmental issues in poor and minority communities nationwide.”

For more than two decades, Wright has directed numerous grassroots, community-initiated programs, including ones funded by NIEHS grants. These programs have provided opportunities for communities, scientific researchers and decision makers to collaborate on programs and projects that promote the rights of everyone to be free from environmental harm.
The foundation recognized Smith for “exposing the relationships among household air pollution, fuel use, climate and health.” In its press release, the foundation observed, “Smith was the first to recognize and quantify the magnitude of the pollution exposure received by the poorest women and children in developing countries as a result of cooking indoors with solid (wood, coal or other biomass) fuels.”

Aided by support from NIEHS grants, Smith has pioneered ways to measure and compare the effects, showing both the tremendous costs of ignoring the problems of indoor air pollution and pointing the way to inexpensive solutions for protecting health and climate. Throughout his career, Smith has advised major international organizations, such as the World Health Organization, and is routinely cited by other scientists who use his work as a standard.

With their awards, Wright and Smith join an elite group of individuals recognized for their exceptional leadership and accomplishments in areas of special interest to Senator Heinz, who once said, “The most important investments — and the most profitable — are investments in people.”

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NIH Announces 2010 Grants for “Risky Science”

By Eddy Ball

In September, NIH announced that it will accept applications through October 2009 for at least 40 grants in the area of what it describes as “transformative research” — “exceptionally innovative, high-risk, original and/or unconventional research projects that have the potential to create or overturn fundamental paradigms.” NIH will fund the projects as part of the NIH Roadmap for Medical Research under the 2010 Director’s Pioneer Awards and New Innovator Awards programs.

Applications under the Pioneer Awards (RFA-RM-09-010) announcement, which provides up to $2.5 million in direct costs over five years, are due October 20. The awards are open to investigators at any career stage, and NIH expects to make at least seven such awards.

Applications under the New Innovator Awards (RFA-RM-011) announcement are due October 27, and NIH anticipates making at least 33 awards in this category. New Innovator Awards target early stage investigators who have not received a regular research (RO1) or similar NIH grant, providing up to $1.5 million in direct costs over a five-year period.
Awards under both programs are made annually. Pioneer Awards applicants are open to scientists who are at an institution in the United States and agree to commit at least 51 percent of their research effort to the project. New Innovator Awards are open to scientists who hold an independent research position at an institution in the United States, have received a doctoral degree or completed a medical internship and residency within the past 10 years, and agree to commit at least 25 percent of their research effort to the project.

The awards are part of the Transformative R01 (T-RO1) program funded through the NIH Common Fund. According to the announcement, “these programs cut across the missions of individual NIH Institutes and Centers (ICs) and are intended to accelerate the translation of research to improvements in public health.”

Launched in 2004, the NIH Roadmap for Medical Research initiatives are intended to address fundamental knowledge gaps, develop transformative tools and technologies, and foster innovative approaches to complex problems.

Applicants can visit the new innovator website for more information and e-mail questions about the announcements.

**Search Opens for Extramural Director**

*By Eddy Ball*

During an open-discussion meeting on September 17, the NIEHS launched another “wide open” search for a key member of the Institute’s leadership team — the head of the NIEHS extramural program. The search committee (see text box), chaired by Robert T. Croyle, Ph.D., of the National Cancer Institute, attended the meeting to discuss the recruitment process and listen to comments from employees, most of them veteran members of the DERT staff.

The director of the NIEHS Division of Extramural Research and Training (DERT) will oversee the Institute’s Extramural Research Program, which is organized into seven branches and centers and is composed of 56 full-time federal employees. Each year, DERT is responsible for awarding approximately 874 research grants for a total of $388 million.

The deadline for job applications is January 5, 2009. Interested individuals should contact Stephanie Jones in the Office of Human Resources. The announcement will be posted online at the NIEHS Web site and will be broadly advertised in journals and trade publications.

NIEHS and National Toxicology Program Director Linda Birnbaum, Ph.D., opened the meeting by saying she considers the DERT
director “one of the top five leadership positions” at NIEHS. She explained that she wants “someone who has a national and international reputation as a science leader, but is also an experienced manager [with outstanding leadership skills] and knows something about the extramural program.” As she did with the search for a scientific director, she took the occasion to “urge everyone to encourage qualified applicants to apply.”

Birnbaum also discussed “our whole new procedure” for recruiting candidates for key leadership positions. “When we’re hiring for these very, very important positions at the top leadership level,” she explained, “I want to get as much input from everybody and afford you numerous opportunities to do that.”

Many of the DERT staff in the audience took Birnbaum up on her offer to provide input and suggestions about the kind of person NIEHS needs as director of DERT. Several speakers offered their thoughts about what they would like to see in the new director:

- A leader who can work effectively in the small-team atmosphere among staff in the NIEHS DERT program, who work closely together on one floor with open-door access to their colleagues.
- Someone who can lead by example.
- A quick learner with long-term vision capable of understanding the potential of early-stage research areas.
- An approachable manager with real people skills.

The committee members expressed their appreciation for employee input at the meeting. Croyle reiterated Birnbaum’s call for help reaching potential candidates. “Everybody is encouraged, as the official announcements and deadlines [for the search] go out, to post on listserves [and] send it to people you think would be good,” Croyle told his audience. “The search committee really depends on the whole group to help get the word out and encourage people you know and respect to apply so that we get the strongest possible applicant pool.”

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NIH Funds Grantees Focusing on Epigenomics of Human Health and Disease

By Robin Mackar

The NIH announced on September 6 that it will fund 22 grants on genome-wide studies of how epigenetic changes — chemical modifications to genes that result from diet, aging, stress, or environmental exposures — define and contribute to specific human diseases and biological processes.

The awards will build on the important work undertaken as part of the NIH Roadmap for Medical Research’s Epigenomics Program. Approximately $62 million will be awarded over the next five years to study the epigenome in a number of diseases and conditions, including tumor development, hardening of the arteries, autism, glaucoma, asthma, aging, and abnormal growth and development.

“Epigenomics represents the next phase in our understanding of genetic regulation of health and disease,” said NIH Director Francis Collins, M.D., Ph.D. “These awards will address the extent to which diet and environmental exposures produce long lasting effects through changes in DNA regulation.” The initiative was launched through the NIH Director’s Office and, as part of the Roadmap, is expected to profoundly alter the way we understand, diagnose, and treat disease.

“This is the largest effort to date to apply epigenetics on a genome-wide scale to specific diseases,” said James F. Battey, M.D., Ph.D., director of the National Institute on Deafness and Other Communication Disorders (NIDCD), one of the lead NIH institutes for this Roadmap program.

The Roadmap Epigenomics Program was designed to characterize epigenetic modifications and to correlate the presence or absence of specific modifications with disease status. DNA methylation is a fundamental epigenetic modification that regulates gene expression and chromosome stability. This and other epigenetic modifications control gene activity by changing the three-dimensional structure of chromosomes.

“The new grantees being announced will join a larger collaborative research effort that is working together to understand epigenetics and how it affects human health and disease,” said Nora D. Volkow, M.D., director of the National Institute on Drug Abuse (NIDA).

This health and disease-focused component of the NIH Roadmap Epigenomics Program builds on the previous four interrelated initiatives, but is the first to tackle questions related to diseases. The other four initiatives include the establishment of four epigenome mapping centers, the funding of an epigenomics data analysis and coordination center, the development of innovative technology in epigenetics, and the discovery of novel epigenetic changes.

“These studies will help increase our understanding of how factors such as environmental exposures, alcohol, drug abuse and stress can modify the effect of epigenetics on diseases,” said Linda S. Birnbaum, Ph.D., director of the National Institute of Environmental Health Sciences.
The awards are funded by 11 NIH institutes and the NIH Office of the Director. The Epigenomics Program is part of the National Institutes of Health’s (NIH) Roadmap for Medical Research funded through the NIH Common Fund and is managed by the NIEHS, the NIAD, the NIDCD, the National Institute of Diabetes and Digestive and Kidney Diseases, and the Office of Strategic Coordination. The Roadmap is a series of initiatives designed to pursue major opportunities and gaps in biomedical research that no single NIH institute could tackle alone, but which the agency as a whole can address to make the biggest impact possible on the progress of medical research.

Note: A complete list of grantees and participating NIH institutes and centers is available online in the full NIEHS press release.

(Robin Mackar is the news director in the NIEHS Office of Communications and Public Liaison and a regular contributor to the Environmental Factor.)

**Suk Seeks Input on Superfund Advisory Panel Report**

*By Eddy Ball*

As follow-up to the meeting of the NIEHS National Advisory Environmental Health Sciences Council (NAEHSC) September 15–16, NIEHS Superfund Research Program Director William Suk, Ph.D., expressed the Program’s gratitude for the thoughtful analyses and recommendations by the members of its 2009 External Advisory Panel chaired by William Farland, Ph.D. Suk also invited grantees, stakeholders and partners to provide input on the findings in the Panel’s report.

The report is the outcome of a series of teleconferences, a two-day meeting and preparation of a final report. McFarland presented a summary of the findings at the National Advisory Environmental Health Sciences Council meeting.

The Panel, which was convened to provide input for the development of a framework for the future direction of the Superfund Research Program (SRP), stated that the Program’s activities fill an important niche in the science needs for site assessment and remediation and have had a positive impact on public health. The Panel strongly endorsed the Program’s long-term commitment to supporting
multidisciplinary research and encouraged continued efforts to provide effective and sensitive community outreach to communities directly impacted by Superfund sites. The recommendations also included the development of strategies to establish and maintain effective interactions among the Superfund Agencies and key stakeholders likely to increase the impact of this Program.

Interested parties may submit comments by email to SRP Program Analyst Beth Anderson or send comments to the following address:

Beth Anderson, Program Analyst  
NIEHS Superfund Basic Research Program  
Mail Drop K3-04  
P.O. Box 12233  
RTP, NC 27709

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NTP Provides Updates on Cell Phone Studies

By Robin Mackar

On September 14, 2009, toxicologists from the National Toxicology Program (NTP) traveled to Washington to present updates on research supported by NTP and NIEHS related to exposure to radiofrequency energy from the use of cellular telephones. Wireless communication devices are used by more than 270 million Americans, yet there is little known about the potential health effects of long-term exposure to these devices.

In the morning, NTP toxicologist Michael Wyde, Ph.D., presented an overview of the NTP cell phone radiofrequency radiation studies at an “Expert Conference on Cell Phones and Health: Science and Public Policy Questions.” The international conference was organized largely by Devra L. Davis, Ph.D., professor of Public Health at the University of Pittsburgh, and supported in part by NIEHS. Chris Portier, Ph.D., associate director at NIEHS, served on the Steering Committee. According to organizers, the goal of the three-day conference was to propose a U.S. research agenda.

Wyde updated the attendees about the three phases of the NTP rodent studies. The three phases of the studies include: (1) a series of pilot studies to establish field strengths that do not excessively raise body temperature; (2) subchronic toxicology studies where rodents are exposed to various non-thermal field strengths for up to two months; and (3) chronic toxicology and carcinogenicity studies where rodents will be exposed for 24 months. Wyde also discussed how the NTP worked with experts from the National Institute of Standards and Technology to design special reverberation chambers for the studies. Cell phone radiation will be administered in 10-minute on/off cycles for up to 20 hours per day. The NTP anticipates the completion and reporting of all phases of the studies by 2014.
In the afternoon, conference participants were invited to attend a U.S. Senate hearing on cell phones and health at the nearby Dirksen Building. NTP Associate Director John Bucher, Ph.D., had the opportunity to represent NIEHS, NTP and the NIH at the hearing. "While the current scientific evidence has not conclusively linked cell phone use with any health problems, we and other scientific organizations evaluating the available studies have concluded that better data are needed to establish any potential health risks from the low-level radiofrequency radiation exposures associated with their use," Bucher said.

Bucher provided an overview of the NTP studies, which he pointed out are designed to clarify any potential hazards, including cancer risk, from exposure to cell phone radiation. He also responded to numerous questions from Senators Tom Harkin and Arlen Specter. Bucher’s testimony can be found online. NTP has also prepared a fact sheet on cell phones.

(Robin Mackar is the news director in the NIEHS Office of Communications and Public Liaison and a regular contributor to the Environmental Factor.)

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Sharon Finds the Environment Down Under

By Eddy Ball

As it turns eight years old this year, the popular NIEHS read-along story, Sharon Finds the Environment (NIH Publication #01-4922), continues to edify young readers worldwide. Sharon’s latest incarnation combines author Tom Hawkins’ original 2001 text and the story’s Web-version clipart graphics with minor revisions by teacher and writer Fiona Brown of Brisbane, Queensland, Australia — most notably replacing Herman, the talking squirrel in the original, with a talking frog named Francis for readers in Australia where squirrels are not indigenous.

Sharon relates the adventures of the title character as she discovers the many aspects of her environment — from the dust under her bed and the factory in town to the sky above her and the air she breathes — as part of her quest to understand how to keep the environment clean. With the help of her insightful companions Herman and his Australian counterpart Francis, Sharon gains new awareness of the world around her:

"‘Wow!’” Sharon said, standing up and slowly turning around and around. ‘The environment is everywhere! It is the sun, sky and air. It’s the ground, water, plants and trees. It’s my house and even under my bed!’’
As a government publication, Sharon is not copyright protected and has always been in the public domain with no restrictions on use by others. Although a Google search using the title turns up page after page of hits for Sharon, Hawkins and others at NIEHS have no way of knowing exactly how many times the story has been republished for new audiences.

Now and then publishers, like Brown in Australia and Tripti Sachdev with India’s Allied Publishing, will contact NIEHS before bringing out a new version of Sharon. Hawkins said he is also aware of its reproduction in a text for environmental education in the United Kingdom and adaptation as a puppet show script in Canada.

Wherever it appears in print or on the Web, Sharon’s message at the conclusion of the story remains just as relevant today as it was in 2001:

“Sharon said, ‘Gosh, that’s an awfully big job to clean the whole environment.’”

“‘That’s why it takes nearly everyone, everywhere, all the time,’ Herman said.”

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NIEHS and National Toxicology Program (NTP) Director Linda Birnbaum, Ph.D., D.A.B.T., A.T.S., presented the first seminar of the 2009 – 2010 NIEHS Distinguished Lecture Series on September 8 titled “Halogenated Flame Retardants: Does the Benefit Justify the Risk?” The lecture focused on halogenated flame retardants (HFRs), particularly brominated flame retardants (BFRs), which are widely used in consumer products to reduce fire-related injury and property damage. Birnbaum, a board-certified toxicologist who has spent several years of her research career studying these toxic chemicals, suggested that their health and environmental effects may outweigh their fire-prevention benefits.

Introducing the speaker was NTP toxicologist Michelle Hooth, Ph.D., who represented the lecture host, the NIEHS Women’s Scientist Assembly (WSA).

According to Birnbaum, HFRs are heavily used in electronics, building and wire insulation, polyurethane foam, carpet padding, computer casings and televisions, just to name a few. Although there are many classes of HFRs, she said that BFRs are the largest class because they are cheap and extremely effective. One of these brominated molecules, tetrabromobisphenol A (TBBPA), doesn’t escape into the environment easily because it chemically binds with the product matrix, but when the matrix does break down, it could have devastating consequences. “TBBPA can eventually generate bisphenol A (BPA), and we all know about BPA and its endocrine disrupting properties,” Birnbaum said.

She also discussed another concern regarding TBBPA. “When TBBPA burns, it generates brominated dioxins. TBBPA also disturbs the homeostasis of the thyroid system,” she explained. “It does so by binding with a higher affinity to transthyretin, a major thyroid transport protein in mammals, than to the natural ligand T4. This process could interrupt a key step during development in rodents and humans.”
Birnbaum’s current studies involve hexabromocyclododecane (HBCD), another BFR that poses a threat to wildlife. Since HBCD is mixed with the product matrix rather than being bound to it chemically, HBCD easily escapes into the environment. *In vitro* studies have demonstrated that HBCD is an anti-androgen and an aromatase inhibitor, specifically binding to several steroid hormone receptors.

The commercial mix of HBCD is composed of three stereoisomers, alpha, beta and gamma, with gamma making up 70 – 80 percent of the mixture. Birnbaum and her colleagues noticed that soil sediments from a particular location tended to resemble the commercial mix, but the biota — the plants and animals living in that environment — had more of the alpha isomer than gamma. The phenomenon, known as an HBCD diasteriomer shift intrigued Birnbaum, and she wanted to understand what was happening.

“Our collaborators labeled alpha and gamma with $^{14}$C, and we did a dose-dependent study in which we exposed mice to a single dose and looked at the elimination,” she explained. “With gamma there is no dose effect in elimination, but much less alpha is coming out in the urine than gamma, which suggests that alpha is more persistent.”

Birnbaum ended her talk with polybrominated diphenyl ethers (PBDEs), compounds that changed behaviors and caused deficits in cognitive and sensory function in rat and mouse studies. Since many products contain PBDEs, people in the U.S. and U.K., for example, are exposed to the chemical through the air and dust in their homes and offices. However, these groups may not be at the highest risk.

“Kids in poor countries who live and work in garbage dumps have the highest levels of PBDE, and these levels are comparable to the upper five percent of the American population,” Birnbaum noted. She concluded by saying that researchers must find an alternative for HFRs. The material should have low toxicity and minimize the potential for hazard and exposure.

Hooth commented afterwards that the information Birnbaum presented helped those in the audience who were not toxicologists better understand the field. “Dr. Birnbaum’s lecture highlighted a number of principal concepts in toxicology, including the importance of evaluating low dose effects, the metabolism and distribution of compounds, sensitive life stages and a variety of relevant endpoints.”

(Note: This issue also includes a *story* about Birnbaum’s talk at the August 22 Green Science Policy Symposium on “The Fire Retardant Dilemma in China.”)

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NIEHS Microarray Group Hosts Genomics Day

By Laura Hall

NIEHS Genomics Day, held on September 1, offered scientists at NIEHS and visitors an afternoon of talks by investigators and trainees, a poster session, and an opportunity to learn more about the NIEHS Microarray Laboratory. Attendees also had a chance to talk to vendors about new microarray products and instrumentation. In his opening remarks, moderator Kevin Gerrish, Ph.D., technical laboratory manager, said the Microarray Group organized this event to ensure that intramural researchers were aware that “we do more than gene expression.”

There have been many changes since the last Genomics Day in 2004. Rapid technological advances in microarray capabilities and the acquisition of three commercial platforms have greatly expanded the types of research that can be done through the facility. Gone are the days when the group made its own microarray slides. “We found that it was much more efficient to just buy the commercially available arrays,” observed Gerrish.

Scientists no longer need to worry about limited choices in microarrays. Agilent, Affymetrix and now Illumina, the three platforms available, are able to provide microarrays that cover analyses from “plant species to Caenorhabditis elegans to bacteria to even zebrafish – almost every model organism that I’ve run across here,” said Gerrish. He explained that in the rare situation that an investigator needs a custom array, most of the suppliers will work with the scientist to create one.

According to Gerrish, the types of studies that can be done with microarrays have expanded as well. The traditional gene expression studies allow screening across an entire genome for disease biomarkers or effects of environmental agents. Now, researchers who use the Microarray facility can explore the mechanisms that regulate gene expression utilizing array-based techniques.
Investigators can assay protein-DNA interactions with chromatin immunoprecipitation (ChIP-chip), genetic variation with array-based comparative genomic hybridization, a method that surveys DNA copy-number across an entire genome, and single nucleotide polymorphisms (SNPs). SNPs can affect disease susceptibility and effectiveness of drug therapies. SNPs can also be used to study loss of heterozygosity (LOH), an allelic imbalance in which there is a complete loss of one allele or an increase in copy number of one allele relative to the other. LOH occurs in many human cancers.

Arrays can be used in studies of epigenetics, looking at heritable changes not in the DNA sequence, and microRNAs (miRNAs) — short non-coding RNAs that regulate gene expression.

Research using microarrays generates vast quantities of data requiring bioinformatic software for analysis. Biostatistician Pierre Bushel, Ph.D., talked about the Microarray and Genome Informatics (MGI) service provided to NIEHS scientists to help with analyzing microarray data. The MGI uses commercial and in-house custom software and can assist the researcher in data processing and database management.

To give the audience a sampling of the types of research projects utilizing microarrays, Gerrish invited four trainees to discuss their research (see text box). The poster session following the talks gave NIEHS scientists an opportunity to have in-depth discussions about microarray techniques and applications. Other members of the Microarray Group — Rick Fannin, Danica Andrews, Stella Sieber and Laura Wharey — were on hand during the poster session to answer questions.

(Laura Hall is a biologist in the NIEHS Laboratory of Pharmacology currently on detail as a writer for the Environmental Factor.)
Trainees’ Presentations Showcase the Value of Microarrays in Research

- Brian Chorley, Ph.D., used ChIP-chip to identify novel genomic binding locations for a transcription factor of interest, nuclear factor erythroid-derived 2-like 2 (NRF2). NRF2 senses and responds to oxidative stress by binding to antioxidant response elements (AREs), many of which are unknown. Chorley found many genes displayed both NRF2 binding in their promoter and gene induction by NRF2 — over half of these genes had not previously been described as being regulated by NRF2.

- Lindsay Smith’s studies on glucocorticoid-induced apoptosis led her to use microarrays to discover that miRNAs were differentially regulated by glucocorticoids in rat thymocytes. Cells treated with dexamethasone, a glucocorticoid receptor agonist, had widespread downregulation of miRNAs.

- Matthew McElwee, a graduate student in the Comparative Genomics Group, examined the molecular mechanisms of mercury toxicity comparing the effects of inorganic mercuric chloride (HgCl₂) to organic mercury, methyl mercury chloride (MeHg), in the gene expression pattern of Caenorhabditis elegans using microarrays. He found some similarities, but more often very different transcriptional responses between the two forms of mercury.

- Stephanie Lahousse compared the gene expression of normal mouse liver and oxazepam-induced liver tumors using microarrays. Lahousse found differences in over 1500 genes, including genes involved in oxidative stress, the wnt signaling pathway, DNA methylation, and histone modification.
A new genome-wide association study (GWAS) published August 28 in *PLoS Genetics* identified the chromosome 9q21.31 region as a novel candidate region for childhood asthma. Researchers from the NIEHS, the National Institute of Public Health (Mexico) and their collaborators at universities in the U.S. and the U.K. looked at over 500,000 variants across the genome in 492 Mexican children with asthma and their parents to identify genes that may influence asthma development.

“We know that asthma is a chronic childhood disease that is influenced by both genetic and environmental factors, but so far no genes have been definitively shown to influence asthma development, “ said Stephanie London, M.D., Dr.P.H., principal investigator at NIEHS and senior author of the study. “By using new approaches that have emerged in the past two years, such as genome-wide association studies, we’re able to home in on specific regions that might be involved in the disease process.”

To date, there have been only a handful of genome-wide association studies, commonly called GWAS, focused on asthma. Genetic studies of asthma are very few in Hispanic populations, making this the first GWAS in Mexicans and one of the first to look at genetic variation in an asthma GWAS in any Hispanic population. The GWAS approach involves scanning for markers across the complete genome of many people to find genetic variations they have in common that are associated with a particular disease.

“This is a small study by GWAS standards, but it adds to the growing body of research in this area,” said Dana Hancock, Ph.D., a postdoctoral fellow who worked with London to author the paper. The researchers add that NIEHS is now part of a consortium with other researchers on studies funded by the NIH who are using GWAS data to look at asthma. “Being part of the NIH consortium known as EVE allows us to combine information from individuals across many studies, and this larger sample size is a more powerful approach to identify genetic risk factors and their interactions with environmental risk factors and to characterize how they may influence susceptibility to disease,” Hancock observed.

The paper also included an analysis that looked at ancestry in this Mexican population. The data suggest that chromosome 9q21.31 may underlie some of the differences in childhood asthma. Other studies have shown that different major ethnic groups have different rates of disease, but it remains unclear why Mexicans are more protected from asthma than other groups.
The chromosome 9q21.31 variants associated with childhood asthma in this study are located near the TLE4 gene, but London points out that further work is needed to decipher whether TLE4 or a nearby gene explains the signals from the chromosome 9q21.31 region.

“These studies are helping to increase our understanding of the gene-environment interactions and biological pathways that lead to disease, which provides new insights into prevention, as well as treatment interventions,” said NIEHS Director Linda Birnbaum, Ph.D.


(Robin Mackar is the news director in the NIEHS Office of Communications and Public Liaison and a regular contributor to the Environmental Factor.)

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Investigators Show Protective Role of DNA Repair Protein

By Brian Chorley

A new NIEHS-supported study reports that human cells deficient in a singularly resourceful DNA repair enzyme, known as Werner syndrome protein (WRN), exhibit more replicative stress and DNA damage after exposure to the industrial pollutant hexavalent chromium — Cr(VI) — than do cells with normal WRN levels. The findings were published in Toxicological Sciences by Assistant Professor Patricia Opresko, Ph.D., — a recipient of an NIEHS Outstanding New Environmental Scientist (ONES) award — and her research team in the Department of Environmental and Occupational Health at the University of Pittsburgh.

While the role of WRN malfunction in premature aging and cancer predisposition in individuals suffering from Werner syndrome is well documented, this study provides the first molecular evidence of the protective effects of this DNA repair protein in Cr(VI) toxicity — as well as further evidence that Cr(VI) induces replicative stress and replication-associated DNA breaks. In their conclusion, the authors point to persistent public health concern about occupational exposure to Cr(VI) at levels below the permissible limit as reason why a complete understanding of its genotoxicity and carcinogenicity is so critical.

Cr(VI) is a chemical compound used commonly as an anti-corrosive agent and pigment in paint, dyes and other surface coatings. Melting metal chromium, which is a component of stainless steel, results in chromium...
oxidation and conversion to a hexavalent state. Industrial workers and others in the vicinity of these materials without protective gear can inhale and expose sensitive lung tissue to Cr(VI). Acute inflammation in nasal passages and conducting airways can result from high levels of short-term exposure. Chronic long-term exposure has been shown to significantly increase lung cancer risk.

The researchers explain that this increased cancer risk is thought to result from the reduced forms of Cr(VI) that are generated after cellular uptake of Cr(VI), which readily create DNA adducts and subsequent interference with DNA replication machinery. This interruption can lead to double-strand breaks, which contribute to genomic instability via chromosomal rearrangements, genomic deletion and other potentially detrimental mutational events.

Cells have evolved recovery mechanisms to resist genomic instability. WRN is a DNA helicase, which allows for proper DNA access and processing by DNA replication and repair enzymes. This role is underscored by the observation that individuals who lack the ability to produce WRN are predisposed to cancer development and premature aging, a condition known as Werner syndrome.

Opresko and her research team reasoned that WRN, given its role in DNA repair, would likely protect cells from Cr(VI)-induced toxicity. They demonstrated that WRN-deficient cells were hypersensitive to Cr(VI) and exhibited markers of double-strand breaks and stalled DNA replication machinery. While these markers of genomic instability were also observed in cells with normal levels of WRN protein, recovery occurred much later in WRN-deficient cells.

Opresko’s observation is one of the few that describe how cells mechanistically resist Cr(VI) toxicity. Importantly, this information creates a more complete picture of how Cr(VI) contributes to cancer etiology. While the Cr(VI)-induced double-strand DNA breaks have been well described, exposure also overwhelms the processes of recovery and repair. This suggests that individuals with attenuated production of WRN, whether genetic or chemically altered, may be more susceptible to the detrimental effects of Cr(VI) exposure.

University of Pittsburgh Postdoctoral Associate Fu-Jun Liu, Ph.D., was first author on the study. It was also co-authored by University of Pittsburgh Associate Professor Aaron Barchowsky, Ph.D. Funding for the study was provided by the Ellison Medical Foundation and an NIEHS grant for studies on “Mechanisms of Telomeric DNA Loss and Repair.”


(Brian Chorley, Ph.D., is a postdoctoral fellow in the NIEHS Laboratory of Molecular Genetics Environmental Genomics Group.)
Study Links Same-Day CO to Risk of Hospitalization for CVD

By Dixie Ann Sawin

An NIEHS- and U.S. Environmental Protection Agency (EPA)-funded epidemiological study published in the September 2009 issue of Circulation presents strong evidence of an association between daily low-level carbon monoxide (CO) exposure and an increased risk of same-day hospitalization for cardiovascular disease (CVD) among an older population. Associate Professor Michelle Bell, Ph.D., of the Yale School of Forestry and Environmental Studies and a recipient of the NIEHS Outstanding New Environmental Scientist (ONES) Award, was lead author and principal investigator on the multi-site, time-series study.

Bell and her colleagues analyzed a cohort of 9.3 million Medicare enrollees, aged 65 and over, in one of the first national-scale, population-based investigations of the health effects of low ambient CO levels. The study assessed subjects from 126 urban counties in 41 states across the U.S. over a seven-year period from 1999 to 2005. The findings underscore the importance of re-evaluating daily exposure limits, relative to air pollution components such as CO and particulate matter with an aerodynamic diameter of 2.5 µm or less (PM$_{2.5}$).

According to the study’s authors, the primary source of CO in urban centers is traffic exhaust. Although the mechanism involved remains unclear, CO is known to bind hemoglobin — forming carboxyhemoglobin, which decreases its affinity for oxygen and affects vital downstream cellular processes implicated in such outcomes as ischemic heart disease, heart rhythm disturbances, heart failure and cerebrovascular disease.

The most compelling laboratory evidence of an association between CO and CVDs has come from controlled exposure studies on CO inhalation at levels that simulate the urban environment. However, the findings from these studies and previous epidemiological studies have been inconclusive.

In their seminal study, Bell and her co-authors provide much needed information. They report that the current outdoor CO level for an average 1-hour daily maximum exposure was 1.6 ppm in most counties included in the study — significantly below the health-based National Ambient Air Quality Standard of 5 ppm set by the U.S. EPA in 1994. This regulatory threshold was based largely on studies of volunteers with coronary artery disease who were exposed to CO concentrations capable of raising their blood carboxyhemoglobin from the typical non-smoker (basal) level of one to six percent.

The researchers found that the CO levels currently present in ambient air were associated with increased risk of cardiovascular

“We found a positive and statistically significant association between same-day carbon monoxide levels and an increased risk of hospitalization for cardiovascular disease in general, as well as for multiple, specific cardiovascular disease outcomes,” Bell explained. (Photo courtesy of Michelle Bell and Yale University)

Before moving to the University of Southern California last year, Samet was a professor and chairman of the Department of Epidemiology at Johns Hopkins, where Bell received her doctorate and collaborated on previous studies with Samet, Peng and Dominici. (Photo courtesy of Jonathan Samet)
hospitalizations in an older population, and this association persisted even at very low CO levels. The authors note that it is difficult to disentangle the health effects of CO from other traffic-related pollutants. Interestingly, they also found that the association retained statistical significance, although the effect estimate was attenuated, when they adjusted for possible confounding effects of other traffic-related pollutants, such as nitrogen dioxide, PM2.5 and elemental carbon.

A limiting factor of their study, the authors acknowledge, is a possible misclassification of the personal exposure of city dwellers because of the study’s reliance on stationary outdoor monitors. This misclassification could lead to reduced estimates, possibly underestimating the risk of CVD hospitalization associated with CO exposure. “Understanding the public health consequences of multiple pollutants is an area needing further research,” the researchers emphasize in their discussion.

Bell receives support from an NIEHS grant for “National Assessment of the Mortality and Morbidity Effects of Tropospheric Ozone.” Co-author Jonathan Samet, M.D., of the Keck School of Medicine at the University of Southern California, is renowned for his work on the effects of particulate matter on health, in particular the roles of air pollution, ozone and smoking in lung cancer epidemiology. The two other co-authors, biostatisticians Roger D. Peng, Ph.D., of Johns Hopkins University Bloomberg School of Public Health, and Francesca Dominici, Ph.D., of Harvard University School of Public Health, provided critical analytical support for the data-rich study.


Extramural Papers of the Month summary

(Is Air Conditioning an Answer for Modifying the Effects of Air Pollution?)

In a brief report appearing in the September 2009 issue of Epidemiology, Bell and her colleagues present findings that air conditioning (AC) significantly attenuated the effects of PM$_{2.5}$ on the health of 65-year-olds from 168 US counties, assessed from 1999-2005. This study was based on their earlier finding that risk of hospitalization for CVD or urgent respiratory illness differed by community. There, they assessed whether the between-community effect was due to AC prevalence, that is, the fraction of households with AC. In summary, they showed that AC prevalence lowered the short-term effects of PM$_{2.5}$ on CVD hospitalizations.

Although similar findings have been suggested by others, this study was the first to confirm that the presence of central AC, as opposed to solitary units, can significantly impact individual health by filtering outdoor allergens, preventing them from entering indoor areas. However, the researchers acknowledged that this association might be lessened by a number of factors including inadequate maintenance of AC systems. The increasing numbers of households with central AC, coupled with increased energy use by these systems, could also subsequently contribute to greenhouse gas emission and decreased overall health. Thus, they emphasized that future research on the overall health benefit of AC on PM-related health issues should incorporate climate change considerations.


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Electronic Nose Sniffs Out Toxins

By Robin Mackar

Imagine a polka-dotted postage stamp-sized sensor that can sniff out some known poisonous gases and toxins and show the results simply by changing colors.

Support for the development and application of this electronic nose comes from a grant from NIEHS. The new technology is discussed in a study in this month’s issue of Nature Chemistry and exemplifies the types of sensors that are being developed as part of the NIH Genes, Environment and Health Initiative (GEI).

Once fully developed, the sensor could be useful in detecting high exposures to toxic industrial chemicals that pose serious health risks in the workplace or through accidental exposure. While physicists have radiation badges to protect them in the workplace, chemists and workers who handle chemicals do not have equivalent devices to monitor their exposure to potentially toxic chemicals. The investigators hope to be able to market the wearable sensor within a few years.

“The project fits into the overall goal of a component of the GEI Exposure Biology Program that the NIEHS has the lead on, which is to develop technologies to monitor and better understand how environmental exposures affect disease risk,” said NIEHS and National Toxicology Program Director Linda Birnbaum, Ph.D. “This paper brings us one step closer to having a small wearable sensor that can detect multiple airborne toxins.”

The paper’s senior author is Kenneth S. Suslick, Ph.D., the M.T. Schmidt Professor of Chemistry at the University of Illinois at Urbana-Champaign (UIUC). Suslick and his colleagues in the Suslick Research Group at UIUC have created what they refer to as an optoelectronic nose, an artificial nose for the detection of toxic industrial chemicals (TICs) that is simple, fast, and inexpensive and works by visualizing colors.

“We have a disposable 36-dye sensor array that changes colors when exposed to different chemicals. The pattern of the color change is a unique molecular fingerprint for any toxic gas and also tells us its concentration,” said Suslick. “By comparing that pattern to a library of color fingerprints, we can identify and quantify the TICs in a matter of seconds.”

The researchers say older methods relied on sensors whose response originates from weak and highly non-specific chemical interactions, whereas this new technology is more responsive to a diverse set of chemicals.
The power of this sensor is its ability to identify so many volatile toxins stems due to the increased range of interactions that are used to discriminate the response of the array.

To test the application of their color sensor array, the researchers chose 19 representative examples of toxic industrial chemicals. Chemicals such as ammonia, chlorine, nitric acid and sulfur dioxide at concentrations known to be immediately dangerous to life or health were included. The arrays were exposed to the chemicals for two minutes. Most of the chemicals were identified from the array color change in a number of seconds and almost 90 percent of them were detected within two minutes.

The laboratory studies used inexpensive flatbed scanners for imaging. The researchers have developed a fully functional prototype handheld device that uses inexpensive white LED illumination and an ordinary camera, which will make the whole process of scanning more sensitive, smaller, faster and even less expensive. It will be similar to a card-scanning device.

“One of the nice things about this technology is that it uses components that are readily available and relatively inexpensive,” said David Balshaw, Ph.D., a program administrator at the NIEHS. “Given the broad range of chemicals that can be detected and the high sensitivity of the array to those compounds, it appears that this device will be particularly useful in occupational settings.”

Citation: Lim SH, Feng L, Kemling JW, Musto CJ, Suslick KS. 2009. An Optoelectronic Nose for Detection of Toxic Gases. Nature Chemistry. Published Online in Advance of Print. DOI: 10.1038/NCHEM.360.

(Robin Mackar is the news director in the NIEHS Office of Communications and Public Liaison and a regular contributor to the Environmental Factor.)

All of the compounds tested to date have their own pattern of response indicated by signature color patterns, allowing identification of volatile chemicals in an individual’s environment. (Photo courtesy of Ken Suslick and UIUC)
Imaging the Effects of Childhood Lead Exposure on Neuronal Circuitry

By Negin Martin

In a recent NIEHS-funded study published in *Neurotoxicology*, imaging research scientist Kim M. Cecil, Ph.D. describes the long-term effects of childhood lead exposure on brain microstructure. According to her research, neurotoxic insults caused by childhood lead exposure are associated with changes in myelination and axonal integrity in brain white matter that persist into adulthood. These findings add to the understanding of how lead alters brain development and present a detailed, quantitative assessment to supplement the known adverse neurophysiological effects of childhood lead exposure.

Cecil is a Professor of Radiology, Pediatrics and Neuroscience at the University of Cincinnati (UC) College of Medicine. She uses magnetic resonance (MR) spectroscopy and state-of-the-art imaging techniques to evaluate the effects of environmental neurotoxicants on brain function.

In this study, 91 adults ranging in age from 20-26 years who had previously participated in the Cincinnati Lead Study (CLS) underwent diffusion tensor imaging (DTI), a recently developed MR imaging technique. The CLS was a longitudinal birth cohort study designed to determine the effects of low to moderate lead exposure on children. From late 1979 to early 1984, the CLS enrolled pregnant women in their first or early second trimester and collected blood samples from their children prenatally, at birth and until the children were almost seven years old. Scientists on Cecil’s team accessed these and relevant demographic records for their study.

Knowing the childhood lead exposure levels, Cecil’s group used a sensitive microscopic imaging technique to evaluate water-diffusion properties in the white matter of the subjects’ brains. Mean diffusivity (MD), axial diffusivity (AD), radial diffusivity (RD) and fractional anisotropy (FA) — indicators of the degree of freedom in the water-diffusion process — were measured and calculated from the brain images of all subjects.

The analysis revealed an inverse association between FA and the mean childhood blood lead levels. The observed decrease in FA in participants with higher lead exposure can be interpreted as a general measure of disorganization within the specific areas of white matter in brain.

Further analysis of diffusion parameters such as MD, AD and RD points to significant neurological insults. Damage was evident in the corona radiata, where axon sheets in white matter carry all neuronal traffic to and from the cerebral cortex. Increased water diffusion...
in all directions in the corona radiata suggests axonal injury and myelination damage in individuals with childhood lead exposure. The corona radiata develops over a long period of time extending beyond infancy and requires prolonged maturation of cortical connections.

Abnormalities in myelination were also observed in the corpus callosum and the superior longitudinal fasciculus of exposed individuals. The corpus callosum connects the two hemispheres of the brain, and the superior longitudinal fasciculus connects the front and the back of the cerebrum. The myelination of these structures is completed within the first year of life. The increased myelination of the corpus callosum and superior longitudinal fasciculus may have served as a measure of protection or compensation against the early lead insult.

Despite altered brain circuitry, none of the individuals in Cecil’s study presented with the typical clinical symptoms of white matter damage found in predominately white matter diseases such as multiple sclerosis. The mean of the childhood blood lead levels of participants in this study averaged approximately 13 µg/dl, but ranged from 5-37 µg/dl. Therefore, the majority of participants had moderate childhood lead exposures by contemporary standards. Combining imaging findings with differences in the cognitive, behavior and motor skills of this group may help define a set of sub-clinical characteristics for low-level early childhood lead exposure.


(Negin Martin, Ph.D., is a biologist in the NIEHS Laboratory of Neurobiology Viral Vector Core Facility and a 2009 Science Communication Fellow with Environmental Health Sciences. She recently completed a postdoctoral fellowship with the NIEHS Membrane Signaling Group.)

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Speaker Explores Gene-Environment Interactions in Acute Lung Injury

By Dixie-Ann Sawin

On September 17, Professor George Leikauf, Ph.D., of the University of Pittsburgh, presented the first in a series of talks in the Keystone Seminar Series hosted by the Division of Extramural Research and Training (DERT). Hosted by Health Science Administrators Sri Nadadur, Ph.D., and Liz Maull, Ph.D., Leikauf’s lecture, “Gene-Environment Interactions: Utility and Uncertainty,” surveyed his recent research supported by a five-year grant from the NIEHS under the NIH Countermeasures Against Chemical Threats (CounterACT) Research Network for “Functional Genomics of Chemical-Induced Acute Lung Injury.”

Leikauf is searching for more effective ways to treat survivors of a possible terrorist act involving chemical agents. With a widely applicable, survival-based approach, he is assessing the effects of chemical-induced acute lung injury (CIALI) on gene pathways. CIALI has a complex etiology and a poor prognosis. Current therapies are by and large palliative and of limited efficacy.

Leikauf hopes to identify genetic determinants and molecular mechanisms involved in CIALI from exposure to five leading hazardous chemicals — chlorine, phosgene, sulfuric acid, ammonia and acrolein. He also plans to develop a preliminary chemical-specific database based on the selective signatures of these chemicals.

He began his talk with a broad overview of genes and environment interactions and the impact of these parameters on human variability. When considering any human population, Leikauf noted that there is always concern about the uncertainty factor incorporated into any risk assessment to account for inter-individual variability, including age, weight, sex, physical condition, medications, nutrition, and last but not least, genetic heritability and environmental factors.

Genetic heritability and environmental factors should be seen as two interacting components that result in a specific event, Leikauf insisted. As an example, he pointed to mortality trends that relate to solely genetic diseases compared to complex diseases. From the global perspective, purely genetic diseases account for approximately 5000 deaths per year, while almost 1.5 million deaths per year are caused by complex diseases, such as heart disease, cancer and cardiovascular diseases.

There is an environmental component to most “genetic” diseases, Leikauf maintained, and a genetic component involved in most “environmental” disease. “There isn’t any barrier to environmental health,” he said.
The question then becomes, how can one apply gene and environmental interactions to daily situations? Understanding how genetic pathways are altered in response to environmental toxicants may improve genetic risk assessment. Nonetheless, there are caveats. For instance, there is no one enzyme that metabolizes a single chemical, and there is an “array of genetic variation” among the population that cumulatively contributes to the variability in the risk assessment.

Two of the chemicals that Leikauf addressed in his talk are acrolein and chlorine.

Acrolein is a 3-carbon aldehyde formed during combustion and is an irritant even at doses as low as 0.06 ppm. Leikauf has developed a mouse model for studying acrolein exposure that exhibits increased levels of pro-inflammatory cytokines, such as IL-6 and TNFα, and decreased neutrophil infiltration. His approach includes genome-wide and single-nucleotide polymorphism analyses to identify candidate genes and biochemical pathways. For acrolein, he identified several possible candidates and concluded that acrolein exposure is not associated with changes at the transcriptional level, but instead affects protein function. For chlorine, he found associations with a different complex of genes, but these can be viewed as members of the same pathway.

Leikauf’s overall aim is to combine the data from acrolein and chlorine, ultimately including the three other chemicals that he plans to test, and scrutinize for proteins of interest involved in common, exposure-related cell survival pathways — leading to the development of new and improved “medical countermeasures” to quickly and effectively treat conditions caused by the chemical agents of terrorism or accidents due to natural disasters and transportation, leakage or storage of these chemicals.

(Dixie-Ann Sawin, Ph.D., is a post-doctoral research fellow in the NIEHS Laboratory of Neurobiology Neurotoxicology Group on detail as a writer for the Environmental Factor.)
involved in maintaining genome stability — what trans-acting factors are involved and how they function in the process. According to Wang, the major focuses of her group are to investigate mutator phenotypes induced by aberrant chromosome replication and identify the genetic and biochemical elements that maintain the DNA replication checkpoint.

The group is ultimately striving to characterize the replication mechanisms involved in chromosome instability and the development of cancer — specifically, the replication mutants that have an elevated mutation frequency in deletion or duplication of genomic sequences and the carcinogenic effects of mutations of the S-phase checkpoint gene products in mammalian homolog genes.

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This Month in EHP

By Eddy Ball

The October issue of *Environmental Health Perspectives (EHP)* highlights “Children’s Health 2009” with a Focus story on “Environmental Factors in Birth Defects: What We Need to Know” and a Spheres of Influence feature on “Learning Curve: Putting Healthy School Principles into Practice.”

Highlights from the issue include several studies exploring aspects of children’s environmental health:

- **National Children’s Study (NCS): Environmental Exposures** — Reviewing information sources that will be used to determine exposures in Queens, New York, one of seven NCS pilot study locations. The authors note that data collection efforts at each NCS site will need to be customized to account for local characteristics and data sources.

- **Chemical Concentrations During Lactation** — Analyzing changes in persistent organic chemicals in breast milk samples collected one, two and three months postpartum and at the end of lactation from a convenience sample of ten women from Pennsylvania. The study finds evidence challenging the general assumption that concentrations of lipophilic chemicals decrease during lactation.

- **Variation in PON1 Enzyme Activity in Young Children** — Examining age- and genotype-related variation in activity of the paraoxonase 1 (PON1) enzyme, which detoxifies activated organophosphorus pesticides (OPs) and reduces oxidative stress. The authors note that children with low-activity genotypes may be particularly vulnerable to OPs compared with other children because of lower PON activity overall and a slower increase in activity with age.

- **Mass Lead Intoxication in Senegal** — Describing an investigation prompted by the unexplained deaths of 18 children in the NGagne Diaw suburb of Dakar, Senegal. The study’s findings highlight the need to strengthen national and international efforts to address this global public health problem.
Extramural Update

Grants Management Branch and ARRA – How All Those Awards Got Made?

The American Reinvestment and Recovery Act has been a challenge for the extramural staff at the National Institutes of Health (NIH). With $10 billion extra dollars to spend in approximately seven months, NIH had to develop, announce, review and make awards — at the same time ensuring the best science was funded and appropriately distributed geographically. Working on a September deadline, the NIEHS Division of Extramural Research and Training (DERT) asked staff to take on additional duties, and the DERT Grants Management Branch (GMB) worked quickly to bring in six extra temporary staff.

At NIEHS, GMB had the Herculean task of making all the awards. The task was made more difficult because three experienced employees had recently left and their positions were not all filled. To accomplish the extra workload, Dorothy Duke, chief grants management officer for NIEHS, recruited two DERT employees from sister branches to details at GMB, filled two temporary positions with former federal employees and lured two former employees out of retirement (see text box).

While NIH current and would-be grantees were busy planning and writing applications for ARRA opportunities, much was taking place behind the scenes as the work came in waves. NIH and DERT management were busy developing initiatives, and the Center for Scientific Review and Institute review groups planned strategies for reviewing applications in a well-conceived and timely manner. Program staff juggled the myriad duties associated with program management, while other staff developed systems for tracking everything that was going on, and the budget office helped strategize on the allocation of funds.

The hard work has paid off, however, and GMB expected to award the final ARRA contracts by October 1. Each day, NIEHS gets closer to its goal of completing ARRA funding, and grantees, new and old, are getting the stimulus they need to preserve and create jobs while pursuing high-quality environmental health sciences research.
Recognizing Temporary Staff at GMB

• Jerry Phelps, Extramural Program Analysis Branch, offered to be detailed to GMB because it would be an interesting way to learn what specialists do on a daily basis that would help him in his regular job and would give GMB another pair of hands during this busy time.

• Laura McGrew, Research Contracts Branch, took great pleasure assisting to spend ARRA funds to improve the U.S. Economy. She said, “The process gave me a chance to learn about grants and work with the great people in the DERT Grants Management Branch.”

• Dwight Dolby, a former NIEHS grants management specialist, had only a brief taste of retirement before accepting Duke’s request to help out after he retired on January 2 of this year. It took some convincing, but he eventually agreed because Duke told him how much she needed experienced people. He said that although he enjoys being retired, “it was harder than he expected.” Now he sees his friends, but has the luxury of knowing he can leave when ARRA is over.

• Carolyn Winters received a letter of invitation from NIH asking her whether she had an interest in coming back as a re-employed annuitant. At the time she retired from NIEHS in 2006, Winters still loved her job, but decided it was time to do other things. She remains active with other granting organizations as a volunteer. She had to think about it, but with no immediate big plans, Winters took this opportunity as a challenge – could she still do the old job? She likes that it is for a short period, and while helping out, she gets to spend time with old friends.

• Natasha Hurwitz, a former NICHD grants specialist, was looking for part-time work following the birth of her second child. She was happy to accept a position that has allowed her to use her skills on a part-time basis while working from her home in the DC metro area.

• Barbara Gittleman is a former government employee with OMB and the Office of Food and Nutrition in the Department of Agriculture. As a recent transplant to North Carolina from Washington with a Master’s degree in Public Policy and experience with budgets and programs, Barbara describes this opportunity as her dream job and loves helping implement the President’s plan to stimulate the economy.
Extramural Papers of the Month

By Jerry Phelps

- Natural Food Products Can Treat Cancer
- Carbon Monoxide and Cardiovascular Disease in the Elderly
- Diesel Exhaust Linked to Cancer Development Through Blood Vessel Growth
- Maternal Exposure to Air Pollution Lowers Children’s IQ

Natural Food Products Can Treat Cancer

Combinations of natural food compounds and chemotherapy drugs provide promise as powerful and potentially less toxic chemotherapeutic treatment strategies, according to researchers at the Linus Pauling Institute. A recent study supported by NIEHS found that chlorophyllin, a derivative of chlorophyll, was 10 times more potent in killing colon cancer cells than the commonly used chemotherapeutic agent hydroxyurea.

The study, carried out in human colon cancer cell lines, found that chlorophyllin kills cancer cells by causing a disruption in cell division. The cells tend to be stalled in the S-phase of cell division when DNA replication occurs. The compound then induces apoptosis in a cytochrome c-independent manner resulting in cell death.

Chlorophyllin is inexpensive and has been proven in other NIEHS-funded research to be an effective treatment for aflatoxin-induced liver cancer. It can be ingested at relatively high levels without causing toxicity; however, it is poorly absorbed in the gut. Levels needed for therapeutic purposes as well as delivery systems are currently under study.

The researchers point out that other dietary cancer fighters also show promise. Organic forms of selenium have shown promise in targeting colon and prostate cancers.


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Carbon Monoxide and Cardiovascular Disease in the Elderly

Low-dose exposure to the acutely poisonous gas carbon monoxide, even at levels far below national exposure limits, is associated with increased risk of adverse cardiovascular outcomes in elderly persons requiring hospitalization. This report comes from NIEHS grantee, Michelle Bell of Yale University, who is the recipient of an Outstanding New Environmental Scientist award from NIEHS.

The research team conducted an epidemiologic investigation of 126 urban communities across the U.S. The study results show that with each one part per million increase in the maximum daily one-hour exposure to carbon monoxide, the risk of hospitalization due to cardiovascular disease increases about one percent in people over age 65.
This evidence suggests that the currently accepted regulatory level of carbon monoxide may still be posing a health risk at least for this vulnerable population. The study indicates that as carbon monoxide levels rose, the risk of hospitalization increased. The findings were based on the analysis of hospital records for more than 9 million Medicare recipients matched to data on air pollution levels and weather from 1999 through 2005.

Although additional research is necessary to determine if the observed effect is due to exposure to carbon monoxide alone or in combination with other traffic-related pollutants, this study points toward a “positive and statistically significant association” between same-day carbon monoxide levels and increased risk for hospitalization for multiple cardiovascular diseases.


Diesel Exhaust Linked to Cancer Development Through Blood Vessel Growth

NIEHS-supported scientists have identified a way that exposure to diesel exhaust stimulates the growth of cancerous tumors. Using a laboratory mouse research model, the research team determined that exposure to diesel exhaust particles stimulates the growth and formation of new blood vessels necessary for solid tumors to grow. The studies were carried out at exposure levels similar to those found in urban areas with heavy commuting traffic.

Most inhaled diesel exhaust particles are less than 0.1 micrometers in diameter, which enables them to penetrate the circulatory system and other organs and cause damage in just about any tissue in the body.

The researchers implanted small platforms embedded with normal endothelial cells, the cells that line blood vessels, under the skin of a group of healthy mice. In another set of mice, the researchers surgically created an ischemic condition in the hind limbs, resulting in a severe lack of oxygen.

Exposure to diesel exhaust for six hours per day caused a six-fold increase in new blood vessel formation in the ischemic limbs at eight weeks and a four-fold increase in the non-ischemic limbs compared to mice breathing normal air. Similar effects were seen in the mice with the implanted cells.

The team determined that exposure to diesel particles activates vascular endothelial growth factor, a chemical signal associated with new blood vessel development, and lowers activity for an enzyme involved in tumor suppression. The researchers are now conducting experiments to determine whether exposure to diesel exhaust influences metastasis of tumors as well.

Maternal Exposure to Air Pollution Lowers Children’s IQ

Public health experts at Columbia University report that a mother’s exposure to polycyclic aromatic hydrocarbons (PAHs) can lower her child’s IQ. PAHs are widely found in urban air and result from the combustion of coal and automotive fuel. They are also found in tobacco smoke.

Non-smoking pregnant women of African-American or Dominican-American descent living in the South Bronx and Harlem were enrolled in the study. They wore personal air monitors during pregnancy and provided additional information about their work and home environments. The women were split into high- and low-exposure groups based on whether their PAH exposure was above or below the median of 2.26 nanograms per cubic meter of air. Their children were monitored from the perinatal period until age five when they were given a standard intelligence exam. On average, the IQ scores of children in the high exposure group were about four points lower than children in the low exposure group.

An IQ deficit in the range of four points is believed to affect how well children perform in school and how well they score on standardized tests. These deficits are similar to those seen in children with significant lead exposure.


Story

(Jerry Phelps is a program analyst in the NIEHS Division of Extramural Research and Training. Each month, he contributes summaries of extramural papers to the Environmental Factor.)

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Intramural Papers of the Month

By Laura Hall and Dixie-Ann Sawin

• Novel p38 MAPK-RhoA Signaling Pathway Involved in Cell Adhesion
• Copper Exposure Leads to HepG2 Cell Transcriptome Changes
• Risk of Amyotrophic Lateral Sclerosis is Higher in Affected Families
• Coherent Co-Expression Biclustering Analysis Can Identify Hepatotoxic Pathways Through the Overrepresentation of Co-Expressed Genes

Novel p38 MAPK-RhoA Signaling Pathway Involved in Cell Adhesion

NIEHS researchers have shown that arachidonic acid (AA) induces cell adhesion by activating a novel RhoA GTPase (RhoA) pathway involving a p38 mitogen activated protein kinase (MAPK) dependent complex including a guanine nucleotide exchange factor (p115RhoGEF) and heat shock protein 27 (HSP27).
Their findings reveal that AA may promote certain steps in metastasis through RhoA and that HSP27 is critical to activate RhoA. That activation leads to changes in cellular adhesion and cytoskeleton supporting the idea that small heat shock proteins may have the potential for therapeutic use in the disruption of tumor cell metastasis.

Western diets have high levels of linoleic acid, a type of fatty acid that in animal models enhances tumor progression and metastasis through changes in cell adhesion, invasion and migration. Linoleic acid is metabolized to AA in the body. The authors utilized MDA-MB-435 cells, a highly metastatic human cancer cell line, to study AA induced cell adhesion to type IV collagen, an extracellular matrix protein.

In the signaling pathway following AA exposure, MAPK was upstream of RhoA activation which required association of HSP27 and p115RhoGEF followed by p115RhoGEF binding to and activation of RhoA. Rho Kinase isoform II (ROCKII) signaling was downstream of RhoA activation and necessary for MDA-MB-435 cell adhesion to collagen IV.


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Copper Exposure Leads to HepG2 Cell Transcriptome Changes

Analysis of microarray data from HepG2 cells exposed to 100, 200, 400 and 600 uM of copper at 4, 8, 12 and 24 hours showed these levels of exposure induced adaptive physiological and toxicological changes in the HepG2 transcriptome with 2,257 differentially expressed genes. High copper levels in humans may occur after environmental exposure from drinking water, human genetic diseases like Wilson’s disease, pathological conditions like hepatitis and some neoplastic diseases.

Copper is physiologically essential as a cofactor in enzymes. Previous studies from other laboratories determined that normal human serum concentrations range from 18.1-31.5 uM. At higher concentrations, copper can cause damage by generating reactive oxygen species, binding to proteins causing structural and functional changes, and binding to DNA. Copper also induces developmental abnormalities in invertebrates, and this study’s results show that copper has the potential to affect vertebrate development by modulating multiple gene signaling pathways.

The NIEHS scientists found that the primary response to the lower experimental copper concentrations were in transition metal binding upregulation and responses to stress stimuli. At higher concentrations, the cells showed cell signaling disruption, transcriptional suppression and increased cell death.

The authors used principal component, cluster, interactome and pathway mapping analysis to determine the global and molecular mechanisms involved in copper exposure.

Citation: Song MO, Li J, Freedman JH. 2009. Physiological and toxicological transcriptome changes in HepG2 cells exposed to copper. Physiol Genomics 38(3):386-401.

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Risk of Amyotrophic Lateral Sclerosis is Higher in Affected Families

Amyotrophic Lateral Sclerosis (ALS) is a neurodegenerative disorder characterized by motor neuron dysfunction. The majority of cases are sporadic, but approximately 10 percent of cases are familial. Researchers from the NIEHS, Sweden’s Karolinska Institute and the University of Milano-Biocca, Italy found that ALS risk was 10-fold higher (95 percent CI: 7.21–2.8) among relatives from affected compared to unaffected families. This study highlighted the importance of genetics in the etiology of ALS.

Using nationwide Swedish registers from 1961–2005, the researchers conducted the first large, prospective, population-based study of familial ALS risk. They studied 1,901 full siblings, 13,947 children and 5,405 spouses of 6,671 ALS patients. They found that the risk for ALS was increased 17-fold among siblings and 9-fold among children of ALS patients, compared to siblings and children from unaffected families. Thus, siblings may be at greater risk than children because they are more likely to share two recessive genes or because they also share early life experiences. Children of a mother with ALS were at greater risk than children of an affected father. The relative risk was greater when either the relative or the original patient was diagnosed at a younger age, suggesting that younger onset ALS is more likely to have a familial component.


Coherent Co-Expression Biclustering Analysis Can Identify Hepatotoxic Pathways Through the Overrepresentation of Co-Expressed Genes

In a new NIEHS-funded study, researchers at NIEHS showed that specific hepatotoxic mechanisms could be identified through the over-representation of co-expressed genes using the Coherent Co-expression Biclustering approach.

Drug-induced hepatotoxicity is a major reason for withdrawing a drug from the market or restricting its use. Thus, understanding and determining chemical-induced hepatotoxic mechanisms is an important research focal point.

The researchers previously demonstrated that gene expression data could be used to identify the severity of injury to the liver. Building on this, the team analyzed 318 liver samples from rats individually exposed to one of eight known chemical hepatotoxicants, in time- and dose-dependent manners, by gene expression profiling and gene clustering. Hierarchical clustering of genes is based on similarity of gene expression patterns across all samples. Biclustering, however, identifies subsets of genes and samples that are coherently and homogeneously co-expressed.

Using alanine aminotransferase (ALT) as the phenotypic marker (elevation of ALT indicates liver injury), they identified subsets or biclusters of genes that were over-represented and co-expressed in response to alterations in pathways presumably involved in hepatotoxicity. Of the chemicals tested, they concluded that effects due to 1,4-dichlorobenzene may not be genotoxic at low doses; however, the seven other chemicals used — bromobenzene, diquat dibromide, galactosamine, monocrotaline, 1,2-dichlorobenzene, thioacetamide or N-nitrosomopholine — were more toxic and showed over-representation of genes involved in inflammation, glycolysis/gluconeogenesis and apoptosis.
Citation: Chou JW, Bushel PR. 2009. Discernment of possible mechanisms of hepatotoxicity via biological processes over-represented by co-expressed genes. BMC Genomics 10:272.

(Laura Hall is a biologist in the NIEHS Laboratory of Pharmacology currently on detail as a writer for the Environmental Factor. Dixie-Ann Sawin, Ph.D., is a post-doctoral research fellow in the NIEHS Laboratory of Neurobiology Neurotoxicology Group also on detail as a writer for the Environmental Factor.)

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A small but engaged audience of people from NIEHS and neighboring Environmental Protection Agency that included NIEHS and National Toxicology Program Director Linda Birnbaum, Ph.D., gathered on September 8 to hear guest speaker and civil rights lobbyist Julia Leggett. Her seminar, “Disability, Access and Why it Matters,” was sponsored by the NIEHS Disability Advocacy Committee (DAC) and hosted by DAC Chair Alicia Moore.

Leggett is the policy coordinator and chief lobbyist for The Arc of North Carolina — the state chapter of a national advocacy group with a 50-year history of working to secure for all people with intellectual and developmental disabilities the opportunity to choose and realize their goals of where and how they learn, live, work and play.

Continuing in the Arc tradition, Leggett works with members of the North Carolina General Assembly on legislation to improve equal opportunities for people under the laws of the state of North Carolina. She also authors the Arc of North Carolina Policy Blog, where she provides regular updates on the group’s legislative agenda and the status of specific bills.

As Leggett reviewed the history of the disability rights movement, she underscored the central theme of her presentation. “In the United States, even though we passed the Americans with Disabilities Act (ADA) in 1996,” she explained, “we have a very long way to go toward full and complete inclusion for people with disabilities.”

Although she envisions the ADA as “one of the last stages of a very long civil rights fight that started many, many years ago,” Leggett emphasized that there will continue to be obstacles to overcome, as well as new challenges that will emerge in the future for the estimated 41.2 million Americans with some kind of disability.

Working to overcome these obstacles, argued Leggett, is important for people who now have disabilities, but guarantees of full access to citizenship and participation should also be of concern to everyone. “Access means much more than handicapped parking…, [and] if you live long enough,” Leggett reminded the audience, “you’ll have a disability at some point in your life.”

Reflecting on her own experiences in the N.C. General Assembly, Leggett related examples of the barriers faced by people with disabilities that limit their access. Some of these barriers are due to obviously inadequate planning and facility design affecting physical access to the legislative chambers for people such as Leggett who use wheel chairs. Others, she noted, are more subtle and perhaps less visible, but still significantly impact full participation by people with disabilities in significant ways.
One of Leggett’s most recent lobbying efforts, for example, focused on the Parent and Student Involvement Act, which contains new provisions for students recommended for expulsion or suspension and their families. As she explained, children with cognitive and developmental disabilities often experience emotional and behavioral conditions that can lead to disciplinary action, so that legislation ostensibly about discipline in school also affects full participation in the educational process for students with disabilities.

In the course of her talk, Leggett pointed to recent accomplishments — the disability provision in the federal Health Insurance Portability and Accountability Act of 1996 (HIPAA), the Help American Vote Act (HAVA) of 2002 and the ADA Amendments Act of 2008. She also praised state legislation in 2007 for designating October as Disability History and Awareness Month and cited current good-faith efforts on the part of bill-drafting staff at the General Assembly to incorporate nonrestrictive “People First” wording into state legislation where possible.

However, Leggett returned several times to her great disappointment over the N.C. Legislative session that concluded recently, which the Arc describes as “the most difficult legislative session in decades.” According to Leggett, the extreme budget cuts on the state level have affected people with disabilities disproportionately and threaten to set back hard-won advances in the area of community-based services. “The budget cuts this year,” she commented, “were horrific for people with developmental disabilities.”

RTP Toll Road Advances Beside NIEHS-EPA Campus

By Eddy Ball

As recently as August, the right-of-way for the new Triangle Parkway was still scrub pine and new growth hardwood. A rutted dirt road plunged into the property adjacent to the NIEHS-EPA campus and wound its way along the border near the First Environments daycare center. The tract was empty except for power lines, an unauthorized dump, the occasional drink container or snack wrapper, and storm water drains.

In September, crews cleared trees and underbrush for the earth moving equipment that will construct the roadbed for the 3.4-mile freeway between NC 540 and I-40. As early as next year, the six-lane, median-divided toll road could be carrying automobile and truck traffic.
By September 24, the right-of-way was cleared along the entire length of the campus. (Photo by Eddy Ball)

On September 4, some of the first signs of progress and profit were evident alongside Hopson Road just a few hundred yards away from the Keystone Building and the rear entrance to the NIEHS-EPA campus. (Photo by Eddy Ball)

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