A recent study conducted by Center members Pam Factor-Litvak, Xinhua Liu, Frederica Perera, and Robin Whyatt looked at the association between maternal and prenatal urinary phthalate metabolite concentration and its effect on IQ in school aged children. Previous work by this group looked at maternal urinary phthalate metabolite concentrations and found an inverse association with the mental and motor development of pre-school aged children. This study hoped to see if these past findings persisted into school aged children as well.

The study followed up 328 inner-city mothers and their children and measured five prenatal urinary metabolites in late pregnancy: did-n-butyl phthalate (Danby), butyl benzyl phthalate (Bebop), did-isobutyl phthalate (Dip), di-2-ethylhexyl phthalate and diethyl phthalate. Urine samples were taken from mothers while the children were followed up with testing at age 3, 5, and 7. To measure IQ, the 4th edition of The Wechsler Intelligence Scale for Children was used to evaluate four areas of cognitive function that associate with IQ: Verbal Comprehension Index, the Perceptual Reasoning Index, the Working Memory Index, and the Processing Speed Index.

Results of the study showed that there is in fact an inverse relationship between child IQ in school aged children and prenatal urinary metabolites concentrations of the following two phthalates—Danby and Dip. When looking at the mothers with the highest concentration of Danby and Dip metabolites, their children had IQs that were 6.7 (95% CI = 1.9, 11.4) and 7.6 (95% CI = 3.2, 12.1) points lower than children whose mothers had the lowest concentrations, respectively. These associations remained unchanged after control for cognition at age 3 years. Researchers found that there were significant inverse associations for these two phthalates in the areas of perceptual reasoning, working memory and cognitive processing speed. The presence of maternal prenatal urinary metabolite concentrations in late pregnancy for the phthalates Danby and Dip are significantly associated with deficits in children's IQ development at 7 years of age. The importance of this finding is that while we do not know the mechanisms by which phthalates directly affect child health, we do know that the magnitude of their effect is troubling and significant.

(Continued on Page 3)
Welcome to Our Newest EHS Faculty Member!

Center member Diane Re has had a noteworthy journey in our Center. Diane was appointed in October 2014 as the newest Assistant Professor in the Department of Environmental Health Sciences (EHS). Before coming to EHS, she was an Associate Research Scientist in the Dept. of Neurology and later Pathology and Cell Biology. She was a Career Development awardee in the Center from 2010 to 2012. In 2011, she became an Associate Center member, and finally in October 2014, she became a full Center member with her own grant from the Department of Defense. When asked about her time as a new Center member, Diane replied: “I feel very welcome in this highly dynamic Center. I am already actively collaborating with three other labs from the Center and I hope it is just the beginning of an exciting scientific journey that will hopefully have an impact on people suffering from neurodegenerative diseases.” Diane recently received a pilot award from the Center (the abstract can be found on page 7 of the newsletter). Welcome, Diane!!

WE ACT For Environmental Justice Healthy Homes Success

The WE ACT for Healthy Homes Campaign is an initiative by WE ACT for Environmental Justice to use community organizing, partnerships, advocacy, and policy to implement positive change for New Yorkers and their housing. The goal of this campaign is to improve indoor environmental health for low and moderate income New Yorkers by ensuring that all of these New Yorkers have healthy and affordable housing. The first step in this campaign was WE ACT’s NYC Healthy Homes Summit.

This 2-day event provided opportunities to share knowledge and develop a policy platform to sustain, preserve, and create healthy housing for low and moderate income New Yorkers that is safe, affordable and energy efficient. The U.S. Environmental Protection Agency Administrator, Gina McCarthy, headlined the event that had a strong discussion focus on indoor air pollution and its link to asthma rates.

The event featured panel discussions, workshops and a plenary style session that included:
  - Manhattan Borough President, Gale Brewer
  - New York City Public Advocate, Letitia James
  - Deputy Commissioner from the Department of Health and Mental Hygiene, Daniel Kass
  - New York City Council Housing and Buildings Committee Chair, Jumaane Williams

The NYC Healthy Homes Summit had a remarkable turnout. Around 320 people were in attendance--from tenants and researchers, to advocates and policy makers. WE ACT has and will continue to develop and pass a suite of healthy housing policies by the end of 2015 through coalition partnerships and the introduction of a bill at the city council.
(Continued from Page 1)

Table 2. Distribution of Phthalate metabolites (ng/ml) in maternal spot urine during the third trimester of pregnancy (n=328).

<table>
<thead>
<tr>
<th>Metabolite</th>
<th>Mean (95% CI)</th>
<th>LOD*</th>
<th>%&lt;LOD</th>
<th>Range</th>
<th>25%</th>
<th>Median</th>
<th>75%</th>
</tr>
</thead>
<tbody>
<tr>
<td>MnBP</td>
<td>37.6 (33.5, 42.3)</td>
<td>0.6</td>
<td>0</td>
<td>1.2–1,110</td>
<td>19.4</td>
<td>38.0</td>
<td>79.8</td>
</tr>
<tr>
<td>MBzP</td>
<td>13.4 (11.6, 15.4)</td>
<td>0.22</td>
<td>0.3</td>
<td>ND–550.4</td>
<td>5.8</td>
<td>14.4</td>
<td>30.0</td>
</tr>
<tr>
<td>MEHHP</td>
<td>22.3 (19.4, 25.5)</td>
<td>0.7</td>
<td>0</td>
<td>1.1–1,750</td>
<td>10.6</td>
<td>21.8</td>
<td>47.2</td>
</tr>
<tr>
<td>MEHP</td>
<td>4.95 (4.2, 5.7)</td>
<td>1.2</td>
<td>16.2</td>
<td>ND–613</td>
<td>1.9</td>
<td>4.9</td>
<td>12.4</td>
</tr>
<tr>
<td>MEP</td>
<td>160.5 (140.4, 183.4)</td>
<td>0.53</td>
<td>0</td>
<td>7.8–604.5</td>
<td>69.9</td>
<td>141.5</td>
<td>334.1</td>
</tr>
<tr>
<td>MiBP</td>
<td>9.1 (8.1, 10.2)</td>
<td>0.3</td>
<td>0.3</td>
<td>ND–374.4</td>
<td>5.0</td>
<td>9.2</td>
<td>19.0</td>
</tr>
</tbody>
</table>

Table 3. Estimated adjusted regression coefficients relating to maternal phthalate concentrations and IQ

<table>
<thead>
<tr>
<th>Metabolite (log base e)</th>
<th>Total (n=328)</th>
<th>Girls (n=173)</th>
<th>Boys (n=155)</th>
<th>Difference</th>
<th>p-value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>MBnBP</td>
<td>−2.69 (−4.33, −1.05)**</td>
<td>−3.15 (−4.22, −1.16)**</td>
<td>−2.92 (−5.17, −0.67)</td>
<td>0.46 (−4.34, 0.56)</td>
<td>0.73</td>
</tr>
<tr>
<td>MiBP</td>
<td>−2.69 (−4.22, −1.16)**</td>
<td>−2.38 (−4.50, −0.26)*</td>
<td>−2.92 (−5.17, −0.67)</td>
<td>0.46 (−4.34, 0.56)</td>
<td>0.73</td>
</tr>
<tr>
<td>Perceptual Reasoning</td>
<td>MnBP</td>
<td>−2.58 (−4.40, −0.76)**</td>
<td>−3.55 (−5.96, −1.14)**</td>
<td>−1.50 (−4.36, 1.35)</td>
<td>0.28 (−4.36, 1.35)</td>
</tr>
<tr>
<td></td>
<td>MiBP</td>
<td>−2.41 (−4.11, −0.71)</td>
<td>−2.39 (−4.64, −0.14)</td>
<td>−2.41 (−5.05, 0.23)</td>
<td>0.99 (−5.05, 0.23)</td>
</tr>
<tr>
<td>Processing Speed</td>
<td>MnBP</td>
<td>−2.01 (−3.91, −0.11)</td>
<td>−1.29 (−4.04, 1.45)</td>
<td>−2.85 (−5.63, 0.08)</td>
<td>0.43 (−5.63, 0.08)</td>
</tr>
<tr>
<td></td>
<td>MiBP</td>
<td>−1.94 (−3.72, −0.17)</td>
<td>−1.94 (−4.46, 0.58)</td>
<td>−2.10 (−4.70, 0.50)</td>
<td>0.93 (−4.70, 0.50)</td>
</tr>
<tr>
<td>Verbal Comprehension</td>
<td>MnBP</td>
<td>−1.52 (−3.06, 0.02)</td>
<td>−1.06 (−3.29, 1.16)</td>
<td>−1.64 (−3.90, 0.62)</td>
<td>0.72 (−3.90, 0.62)</td>
</tr>
<tr>
<td></td>
<td>MiBP</td>
<td>−2.08 (−3.51, −0.65)**</td>
<td>−1.05 (−3.10, 1.00)</td>
<td>−3.04 (−5.11, −0.98)**</td>
<td>0.18 (−5.11, −0.98)**</td>
</tr>
<tr>
<td>Working Memory</td>
<td>MnBP</td>
<td>−2.57 (−4.55, −0.59)**</td>
<td>−4.73 (−7.53, −1.93)**</td>
<td>−0.07 (−2.92, 2.78)</td>
<td>0.02 (−2.92, 2.78)</td>
</tr>
<tr>
<td></td>
<td>MiBP</td>
<td>−1.98 (−3.84, −0.12)</td>
<td>−2.53 (−5.16, 0.11)</td>
<td>−1.27 (−3.92, 1.38)</td>
<td>0.51 (−3.92, 1.38)</td>
</tr>
</tbody>
</table>

http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4262205/
“Domestic Airborne Black Carbon Levels and 8-isoprostane in Exhaled Breath Condensate Among Children in New York City”

Center member Matt Perzanowski and his colleagues worked on a study that looked at mechanisms by which airborne black carbon (BC) exposure impacts lung/respiratory function using non-invasive collected exhaled breath condensation (EBC) to check for biomarkers. The airway lining fluids collected from the EBC were used to check for an oxidative stress biomarker, 8-isoprostane. Through this, the researchers sought to verify associations between 8-isoprostane in EBC and domestic airborne BC.

The study participants were seven- and eight-year-old children who were enrolled in a NYC asthma case-control study. This study used air samples collected from visits to the participants’ homes as well as participants’ EBC levels. Seven day averages of domestic PM levels of <2.5μm (PM$_{2.5}$), environmental tobacco smoke (ETS) and breath condensation were measured. 8-isoprostane, along with urea were measured in EBC by the use of liquid chromatography tandem mass spectrometry.

The results showed that the BC and PM$_{2.5}$, but not ETS, had significant associations with “increases in 8-isoprostane in the EBC (β=0.006 and β=0.106, respectively, p<0.05 for both)”. After adjustments for covariates, the associations between PM$_{2.5}$ and BC measurements remained statistically significant. In a different model using PM$_{2.5}$, ETS, and BC, only BC remained a statistically significant predictor of 8-isoprostane (p<0.05). The findings showed that the BC fraction of particulate matter may actually contain exposure that is relevant to increased oxidative stress in these children’s airways.


“Temperature, Ozone, and Mortality in Urban and Non-urban Counties in the Northeastern United States”

Citing the need to look at data outside of urban areas, the 2015 study of Environmental Health Sciences student Jaime Madrigano and Center members Darby Jack and Patrick Kinney looked at the health of effects of temperature and ozone in over 90 urban and non-urban areas. They collected ozone measurements, meteorological data, and observed data from national data sources and archives. They first used the data to estimate each county’s increase in mortality risk from ozone and temperature. Next, they examined these county-level associations by population density and compared the urban and non-urban counties. Lastly, they used these data to then rule out county-level characteristics that could lead to variations in these associations. They found that there are increased health risks associated with ozone and temperature and that most importantly, these results are not limited to just urban areas.

“Early-life Lead Exposure Recapitulates the Selective Loss of Parvalbumin-Positive GABAergic Interneurons and Subcortical Dopamine System Hyperactivity Present in Schizophrenia”

The study of Career Development awardee, Kirstie Stansfield, and Center member, Tomás Guilarte, on the brains of rats exposed to lead has uncovered striking similarities with what is known about the brains of human schizophrenia patients, adding compelling evidence that lead is a factor in the onset of schizophrenia.

The researchers found that lead had a detrimental effect on cells in three brain areas implicated in schizophrenia: the medial prefrontal cortex, the hippocampus, and the striatum of rats exposed to lead before birth and in the early part of their lives. Density of brain cells known as Parvalbumin-Positive GABAergic interneurons, or PVGI, declined by approximately a third—roughly the same percentage decline seen in schizophrenia patients. The researchers also identified higher levels of a dopamine receptor called D2R. Again, the magnitude of the increase matched what has been documented in human schizophrenia patients, and in a previous study of genetically engineered mice.

“The similarities in the brain structure and neuronal systems between what we see in lead-exposed rats and human schizophrenia patients are striking, and adds to a growing body of literature suggesting that early lead exposure primes the brain for schizophrenia later in life,” says senior author, Dr. Guilarte, Chair of Environmental Health Sciences at the Mailman School.

Cocaine Insights

In a related finding, the researchers found that rats exposed to lead had a much stronger reaction to cocaine than healthy rat controls. In the experiment, lead-exposed rats that were injected with cocaine ran around in their cages twice the distance of lead-free control rats. The rat behavior is meaningful because it mirrors what is seen in schizophrenia patients, who are known to have a heightened response to the drug.

Schizophrenia is not the only possible consequence of lead exposure. A follow-up experiment will allow the rats to self-administer cocaine in order to test whether lead exposure plays a role in addiction.

“We are currently assessing the impact of lead exposure on both the rewarding and reinforcing properties of addictive drugs like cocaine while exploring the biological underpinnings of how lead exposure plays a role in addiction,” says first author, Dr. Stansfield, Associate Research Scientist at the Mailman School.

Two New Pilot Projects Funded in 2014-15!

Ellen A. Lumpkin, PhD, Associate Professor, Departments of Dermatology & Physiology & Cellular Biophysics
Co-Investigator: David M. Owens, PhD, Associate Professor, Departments of Dermatology & Pathology; “Naturally Occurring Terpenes as a Therapeutic Strategy for Cutaneous Squamous Cell Carcinoma”  Award: $35K

Abstract: Non-melanoma skin cancers are the most common tumors in humans. Concerns over the striking increase in skin cancer incidence have recently led to the Surgeon General’s Call To Action To Prevent Skin Cancer. Cutaneous squamous cell carcinomas (cSCC) are invasive lesions, 10% of which carry a high propensity for metastasis. cSCC causes ~2,500 deaths annually in the US. One of the primary risk factors for cSCC is exposure to ultraviolet radiation (UVR). The current standard of care for cSCC is surgical excision followed by adjuvant radiation or chemotherapy; however, a subset of cSCC termed high risk can recur following surgery and are typically unresponsive to adjuvant therapy. This is particularly problematic in immunocompromised patients, whose incidence of high-risk cSCC is increased 60-100 fold. Epidermal growth factor receptor (EGFR) inhibitors have been recently FDA-approved for cSCC treatment; however, they show inconsistent efficacy and severe skin toxicity. Thus a major unmet medical need is novel therapeutic approaches for high risk cSCCs. Our preliminary studies identify camphor oil, a mixture of structurally related terpenes, as a potent cSCC suppressor. Daily treatment with camphor oil slows malignant progression and causes dramatic regression of pre-malignant tumors in a pre-clinical murine model of cSCC. Importantly, skin tumor regression induced by camphor oil is associated with a marked decline in the incidence of cSCC tumors. Here we aim to identify novel constituents of camphor oil that are effective in attenuating cSCC growth and are available at low cost to patients. We propose to 1) identify naturally derived, bioactive compounds in camphor oil that mediate tumor regression and 2) determine whether these common environmental chemicals reduce tumor burden by acting directly on keratinocytes or by altering aspects of the skin microenvironment. If successful, this pilot study will provide the basis for a novel and low-cost therapeutic method to treat cSCC.
Abstract: Manganese (Mn) is a metal vital to human health as it is absolutely necessary for development, metabolism and antioxidant defenses. However, excessive Mn exposure or intake can cause a disorder of the nervous system called "manganism". This condition usually starts with psychiatric symptoms, such as compulsive behavior and emotional outbursts, before it progresses to a Parkinson's Disease-like syndrome, exhibiting difficulties in movement initiation and motor control. However, other symptoms of manganism, such as muscle weakness and impairment in fine motor control are more reminiscent of Lou Gehrig’s Disease, also known as Amyotrophic Lateral Sclerosis (ALS). Recently, brain imaging studies in young drug users injecting a home-made drug called ephedron, that contains high levels of Mn, revealed abnormalities close to those observed in ALS. In addition, exposure to high Mn levels has previously been suspected to contribute to the development of an inexplicably high number of patients affected by an ALS-parkinsonism-dementia syndrome in Guam and in the Kii Peninsula of Japan. In animals chronically exposed to Mn, it was shown to accumulate preferentially in areas of the brain that are selectively affected in Parkinson’s disease and in the spinal cord. So far, Mn has been shown to cause neuronal death in diverse regions of the brain. However, the neurotoxicology of Mn in the spinal cord has never been investigated.

Dr. Guilarte, the co-investigator of this proposal, has been studying the neurological effects of chronic exposure of Mn in non-human primates for over 10 years. **Drs. Guilarte and Re hypothesized that Mn may cause injury to the spinal cord and its connection to muscles, which could explain some of the ALS-like symptoms that were previously observed in animal models and humans. Accordingly, in specific aim 1 of this project, we will carry out the first investigation of the pathological effects of Mn in the spinal cord of macaques chronically exposed to Mn.** Parenthetically, we should note that the spinal cord of control and Mn-exposed animals have already been collected and are available for immediate use. Specifically, we will assess Mn-induced neuronal death, inflammation, and protein aggregation in the spinal cord. These endpoints have been observed in other brain regions of Mn-exposed macaques, but this will be the first study of the spinal cord. Another common interest of Drs Re and Guilarte which is related to the second objective of this proposal pertains to a protein called Amyloid Precursor-Like Protein 1 (APLP1). In 2008, Dr. Guilarte described increased APLP1 levels in the brains of macaques treated with Mn. Independently, Dr. Re found that APLP1 was necessary for the induction of neuronal death when she was modeling ALS in a dish. More precisely, Dr. Re showed that astrocytes, brain cells which are normally supportive to neuron survival, become neuronal killers when the level of APLP1 increased. Thus, **a natural question is whether or not increased APLP1 levels are also responsible for neuronal death upon Mn exposure. This hypothesis will be tested in specific aim 2, by treating brain astrocytes in a dish with Mn and assess their level of APLP1 and toxicity to neurons.**
Upcoming Summer and Fall Seminars and Meetings

**July 9:** **Tony Fletcher,** PhD, Senior Lecturer at the London School of Hygiene and Tropical Public Health and Adjunct Research Professor in Environmental Health at Boston University SPH; Title: “The health risks of PFOA and PFOS: biomarkers vs. exposure assessment”; 722 W. 168th Street, 11th floor, Rm. 1101, 1:30-2:30pm. Host: Pam Factor-Litvak

**October 22:** **Kari Nadeau,** MD, PhD, Associate Professor of Pediatrics (Allergy & Clinical Immunology), Stanford University, Stanford, CA; Title: TBD (Topic: Allergy and Immunology); Place TBD; 12-1pm. Hosts: Rachel Miller and Matt Perzanowski

**Other Pending Speaker:** **John Greally,** MB, BCh, PhD, Professor, Departments of Genetics, Medicine (Hematology) and Pediatrics, Albert Einstein College of Medicine of Yeshiva University, Bronx, NY; Date and Title: TBD (Epigenomics)

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**SAVE THE DATE:**

**Annual NIEHS Center Retreat/External Advisory Meeting**

**Friday, June 5th**

Faculty House  
W. 116th St. and Amsterdam Ave

**9:00-4:00pm**

Continental breakfast and lunch will be served! Join us!

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**Johns Hopkins Talent**

The CEHNM will host a one-day Science and Technology program for 7-10th grade academically talented students and their parents on

**Saturday, October 24th, 2015**

**9:00-4:00pm**

Sponsored by  
The Johns Hopkins Center for Talented Youth

More details to come.