Winter 2017

Your Health & The Environment

News from the University of Rochester Environmental Health Sciences Center

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E-cigarettes and human health

Courtesy of USA Today

Electronic cigarettes ("E-cigs") started growing in popularity about a decade ago as a "smokeless" alternative to cigarettes. E-cigs work by using an electronic current to vaporize a fluid containing, in most cases, nicotine and flavorings. The general term "vaping" is commonly used to refer to the practice of inhaling such vaporized liquids through a wide range of electronic devices. E-cigarettes were largely unregulated until 2016, when the FDA issued regulations that covered all tobacco products, including e-cigarettes. There are now over 8,000 vaping flavors on the market, most of which have not been evaluated for safety.

Vaping has been promoted as a "healthier" alternative to smoking and as an aid to quitting cigarette use. However, e-cigarettes have become popular with non-smokers, particularly young people. The FDA reported that e-cigarette use rose from 1.5 percent to 16.0 percent among high school students and from 0.6 percent to 5.3 percent among middle school students between 2011 and 2015 . According to the CDC's *HealthStyles* survey, "between 2010 and 2013, the percent of adults who had ever used e-cigarettes more than doubled from 3.3 percent to 8.5 percent ."

As the number of devices, flavorings, and prevalence of vaping has increased, particularly among young people, questions about the potential health effects of the largely unregulated products have grown. University of Rochester researchers have been involved in studies to answers these questions. In this newsletter, we highlight two EHSC members who have been involved in research on the human health effects of e-cig use.

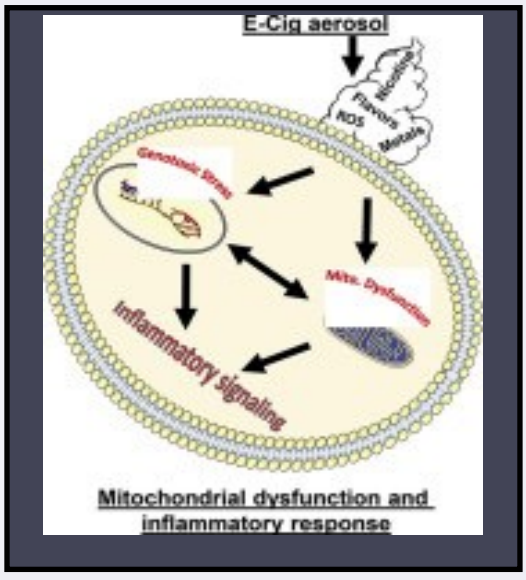
E-Cigs have many forms tailored to their target users. C*ourtesy of the FDA*

E-cigarettes' toxicological effects on lung disease and oral health

Irfan Rahman, PhD, Professor of Environmental Medicine, has formed several research partnerships to explore the health effects of e-cigarettes. Below, we briefly summarize three different areas of his work related to characterizing exposures from e-cigs, impacts on lung cells, and on implications for oral health.

Rahman's team collaborated with researchers from the Rochester Institute of Technology on a study funded by the National Heart Lung and Blood Institute (U.S. Food and Drug Administration, Center for Tobacco Products) to identify the components of e-cigarette vapors. They purchased a range of e-liquids from local vaping shops and tested the chemical composition of the liquids and resulting aerosols. Characterizing the exposures from e-cigs is an essential step toward understanding the potential human health effects. The goal of this study was to test electronic cigarettes for toxic chemicals in e-liquid flavorings (including cinnamon, vanilla, candy, fruits, butter, and coffee) on lung cellular responses. The research team then exposed human lung cells to the aerosols/chemicals from different vaping fluids and found that many flavorings caused inflammation and cellular leakiness in cultured cells, suggesting that they could damage human lungs (Gerloff et al, Applied In Vitro Toxicology 2017).

Another aspect of the Rahman lab's work on e-cigs explores the effects of vaping aerosols/vapors on human lung cells. In research supported by a National Heart Lung and Blood Institute training grant, the group conducted a series of experiments using an air-liquid interface to expose cells in vitro to a range of e-cig vapors. An article published in *Biochemical and Biophysical Research Communications* (Lerner et al, 2016) reported that mitochondria are sensitive to aerosols and metal nanoparticles from e-cigs, which caused nuclear DNA fragmentation and pro-inflammatory responses.



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E-cigarettes' toxicological effects on lung disease and oral health (continued)…

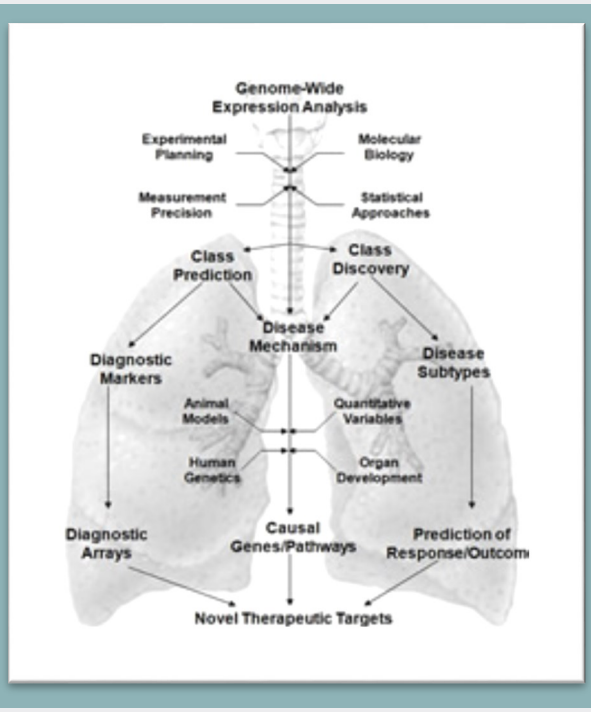
The Rahman lab also partnered with dental researchers to investigate the potential oral health impacts of e-cigs. Rahman teamed with Isaac K. Sundar, PhD, UR Department of Environmental Medicine, Fawad Javed, BDS, PhD, Eastman Institute of Oral Health, and Georgios E. Romanos, D.D.S., Ph.D, Department of Periodontology, School of Dental Medicine, Stony Brook University to explore the oral health effects of e-cigs. "We showed that when the vapors from an e-cigarette are burned, it causes cells to release inflammatory proteins, which in turn aggravate stress within cells, resulting in damage that could lead to various oral diseases," explained Rahman. "How much and how often someone is smoking e-cigarettes will determine the extent of damage to the gums and oral cavity." This research was recently published in *Oncotarget* (Sundar et al , 2016).

1. Gerloff J, Sundar IK, Freter R, Sekera ER, Friedman AE, Robinson R, Pagano T, and Irfan Rahman. 2017. Inflammatory Response and Barrier Dysfunction by Different e-Cigarette Flavoring Chemicals Identified by Gas Chromatography–Mass Spectrometry in e-Liquids and e-Vapors on Human Lung Epithelial Cells and Fibroblasts. *Applied In Vitro Toxicology* 3(1): DOI: 10.1089/aivt.2016.0030
2. Lerner CA, Rutagarama P, Ahmad T, Sundar IK, Elder A, Rahman I (2016) Electronic cigarette aerosols and copper nanoparticles induce mitochondrial stress and promote DNA fragmentation in lung fibroblasts. *Biochem Biophys Res Commun*. Sep 2;477(4):620-5. doi: 10.1016/j.bbrc.2016.06.109.
3. Sundar IK, Javed F, Romanos GE, Rahman I (2016) E-cigarettes and flavorings induce inflammatory and pro-senescence responses in oral epithelial cells and periodontal fibroblasts. *Oncotarget.* Nov 22;7(47):77196-77204. doi: 10.18632/oncotarget.12857.

E-cigarettes effects in the pediatric lung

Thomas Mariani, PhD, is Professor of Pediatrics, Biomedical Genetics and Environmental Medicine, and Director of the Pediatric Molecular and Personalized Medicine Program. When Mariani came to the University of Rochester Medical Center eight years ago, he began his work in Pediatrics focusing on diseases related to lung development. This led him to his current collaboration on the developing lung molecular atlas program (LungMap) with Gloria Pryhuber, MD. As part of LungMAP, they are developing tools and models useful for investigating the effects of environmental exposures on different types of infant and pediatric lung cells, with implications for children's lung development.

In 2014, Mariani's team was awarded a five-year, $2.1 million grant from the National Institutes of Health to look for biomarkers of exposure to tobacco-related products (Comparative Transcriptomic Signatures of Inhaled Tobacco Smoke, 1 R01 DA037447). The project is taking a three-pronged approach to studying the effects of e-cigarettes and other nontraditional tobacco products on humans, in rodents, and on the cellular level. The studies focus on how these products affect lung development in newborns and children.



As part of this effort, Qian Wang, PhD, a postdoctoral fellow in Mariani's lab, used the cell tools from LungMAP to investigate the effects of e-cig vapor on pediatric lung epithelial cells. Using a new apparatus she has developed that allows her to expose cells directly to this vapor and analyze the effects, she found pediatric cells displayed robust increases in oxidative stress and cytochrome P450 enzyme expression. These data indicate e-cig vapor stresses, and may be toxic to, pediatric lung cells.

Wang also found that e-cig vapor exposure can modify the way epithelial cells communicate with the immune system. In prior work, Mariani's lab studied the effects of e-cig liquid on epigenetic gene regulation in adult lung epithelial cells. This work was led by Siva Solleti, PhD, Staff Scientist, and Soumyaroop Bhattacharya, M.Ed., M.S.,Senior Associate in Pediatrics (Under Revision, Scientific Reports). Future work will attempt to more thoroughly define the health effects of e-cig vapor exposure in pediatric cells, how they differ from adult cells, and whether expression of specific genes and/or non-coding RNAs contribute to risk for inflammatory lung disease.

Concerns over lead resurface

Despite the tremendous reductions in childhood lead poisoning in the U.S. since the 1970's, lead exposure remains a health risk for many children. The crisis of lead contamination in Flint, Michigan's public water supply has reawakened the public to the presence of lead in older housing stock, water pipes, and contaminated soil. At the same time, studies by EHSC researchers and others continue to document health effects of lead at lower levels than previously known. Recent EHSC research has provided strong evidence of interactions between lead and other exposures, susceptibility to diseases later in life, and intergenerational impacts.

The EHSC's Community Outreach and Engagement Core (COEC) has a long history of working with community groups in Rochester to support efforts to reduce lead poisoning, disseminate research results, and learn lessons from these ongoing efforts to share with others. The resurgent concern about lead nationwide has increased other communities' interest in learning from Rochester's experiences.

Rochester's local lead law, implemented in 2006, has been of particular interest to other cities contemplating how to reduce lead hazards in private rental housing. Over ten cities from across the U.S. have recently consulted with the COEC, the Coalition to Prevent Lead Poisoning, or the City of Rochester. The Rochester partners stay in close contact about such "consultations" to share the workload, coordinate responses, and encourage each city to seek a combination of government, community, and academic perspectives on "lessons learned." These partners emphasize the importance of community engagement and a multi-sectored process to design and implement locally-appropriate solutions.

An example of lead paint on porches

Source: www.FLSHA.org

Rochester-based research bore fruit this January, when the US Department of Housing and Urban Development announced new policy guidance for its lead hazard control grantees. This policy guidance lowers risk assessment action levels and clearance standards after lead hazard control work is done in publicly assisted housing. National advocates have been urging the federal government to support more protective dust lead standards since 2009. This new guidance for the first time sets a porch dust lead clearance standard for HUD's grant programs (40 micrograms per square foot). The porch standard was in part based on research inspired by a community-identified need in Rochester.

Concerns over lead resurface (continued)…

When it was first passed in 2005, Rochester's lead law included a porch dust lead standard of 250 micrograms per square foot. The Rochester Coalition to Prevent Lead poisoning had insisted on this provision because many of the participants in its 2004 "Get the Lead Out" initiative reported that their children frequently played on outdoor porches. The city removed the porch dust standard from the lead law in 2006, citing lack of evidence or a federal standard as reference. The COEC then facilitated a research collaboration between the City of Rochester, Action for a Better Community, and the National Center for Healthy Housing (NCHH), which obtained a HUD grant to study and analyze porch dust lead levels post-renovation and over time. NCHH presented the study findings at a meeting for staff of the HUD Office of Lead Hazard Control and Healthy Homes, which inspired them to take action on porches.

Source: National Center for Healthy Housing
www.NCHH.org

At the national level, COEC director Katrina Korfmacher, PhD has been involved in a number of efforts to synthesize research and local experiences to inform the national lead policy agenda. In October 2016 she participated in the National League of Cities' "convening" on health and housing hazards. Throughout 2016, she was also involved in the "National Roundtable" developing the "Find it, Fix it, Fund it" campaign, a collaborative effort to analyze the existing federal framework for lead poisoning and inform future federal actions to eliminate childhood lead poisoning. (http://www.nchh.org/Policy/FindItFixItFundIt.aspx)

NEW EHSC STAFF

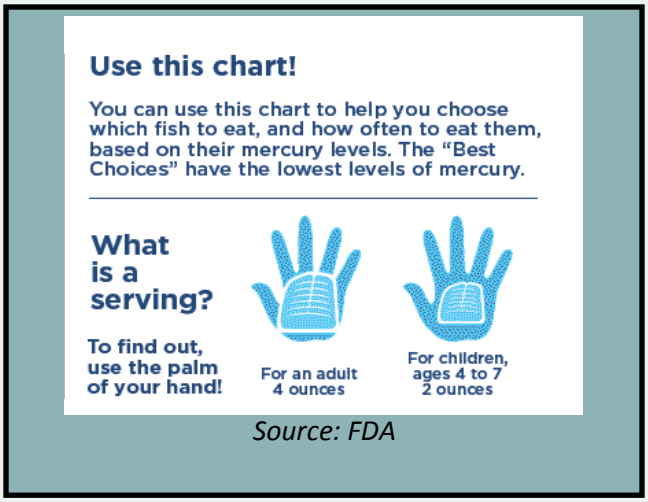
Cait Fallone, MA joined the COEC as program manager January 2016**.** She is a medical anthropologist who is interested in improving the health of local communities by understanding their culture and environment. She joins the Environmental Health Sciences Center from the Department of Pediatrics, Division of Neonatology, where she was a Clinical Research Coordinator for the NIH Neonatal Research Network grant.

Her graduate work was through the University at Buffalo School of Medicine, Department of Family Medicine Primary Care Research Institute conducting research for Independent Health's *Good for the Neighborhood* community outreach program. Her master's thesis, "A Study of Lifestyle Diseases and Lifestyle Behaviors in Three Underserved Communities in Buffalo, NY" focused on the role of diet, exercise, alcohol consumption, and smoking habits in correlation with type-2 diabetes, hypertension, heart attack, and stroke.

Cait has worked as an informal educator, clinical research coordinator and health & sanitation program manager for a number of local organizations.

Fish consumption: New FDA/EPA guidelines announced

Fish consumption is the primary source of human methyl mercury exposure. For over four decades EHSC investigators have investigated the potential neurotoxicity of methyl mercury, and the risks and benefits of fish consumption. Recent center research has highlighted the importance of considering the role of genes and nutrients. The COEC has worked to integrate these research findings, national advisories and local guidelines to help community members make safe fish choices. In January 2017, the US Food and Drug Administration and US Environmental Protection Agency released a new fish consumption advisory for pregnant women and children, the first update since 2004. This revision was intended to reflect new research on the health effects of mercury. The advisory aims to help consumers choose fish that is lower in mercury, while also promoting the health benefits of nutrients found in fish. Balancing these factors within a clear and simple message is an ongoing challenge for environmental health educators. In June 2014, the EPA released a draft revision of its fish consumption advisory for pregnant women and children. The EPA received over 200 comments from the scientific community, nongovernmental organizations, and the general public, which they synthesized into the final advisory message. The resulting advisory lists different types of fish as "Best Choices: eat 2-3 servings a week," "Good Choices: eat one serving a week," and "Choices to Avoid" for pregnant women (separate advice is provided for children).



Source: FDA

The new federal advice has the potential to encourage pregnant women to eat more fish, and some women may respond by eating more locally-caught fish. For that reason, the COEC plans to focus on promoting public awareness of both the new federal advisory and existing local fish consumption advisories in our region, which are not based on mercury, but rather PCB and other contaminants that may pose a risk to those eating fish caught in Lake Ontario. Fish consumption advisories are by their nature very complex, so different groups of consumers in different geographic areas may need assistance in understanding how these multiple messages relate to their fish consumption choices .

The new advisory and public information materials may be found at:
http://www.fda.gov/Food/FoodborneIllnessContaminants/Metals/ucm393070.htm

NYU and Rochester NIEHS centers collaborate on air pollution exposure research

Judith Zelikoff, PhD
Environmental Medicine
New York University

Judith Zelikoff , PhD, Professor of Environmental Medicine at New York University, and Deborah Cory-Slechta, PhD, Professor of Environmental Medicine at the University of Rochester, have interacted around their common research interests for many years. Recently, their labs collaborated on a project that leveraged the complementary resources of the New York University and University of Rochester NIEHS Core Centers. Both centers have inhalation facilities for exposure to ambient air pollution. Work associated with a doctoral thesis at NYU had exposed mice prenatally to particulate air pollution to look at impacts on the developing brain. The researchers wondered whether these animals would have similar brain development patterns to those recently found in postnatally exposed mice in Rochester.

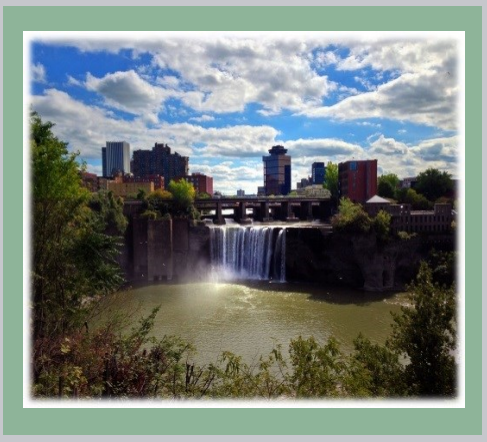
In order to make sure the methodology was consistent, a team from Cory-Slechta's lab travelled to NYU to teach Zelikoff's lab how they conducted brain dissections, then brought the samples to Rochester for analysis. Toxicology trainee Carolyn Klocke analyzed the samples and found evidence of damage to the central nervous system; results were published in *Toxicological Sciences* in January 2017 (Klocke et al, 2017). As Klocke reported: "Among our findings, we showed that gestational exposure to air pollution dramatically changes the size of certain brain regions, activates inflammatory cells in the brain, and causes an excess production of myelin, a component of the CNS that helps neurons propagate signals. One of the most interesting and novel findings was that we saw iron inclusions in a major myelinated region of the brain, indicating that air pollution exposure is altering metal homeostasis and may be an underlying mechanism driving excess myelination."

Through this inter-Center partnership, the two research groups produced comparable changes in neurodevelopment using different air pollution sources and exposure patterns, demonstrating that early life exposure to particulate air pollution can alter neurodevelopment. From her perspective as a doctoral student involved in the project, Klocke reflected that "the team at NYU has been excellent in this collaboration, fielding my never-ending emails about the exposures. I'm lucky to have Dr. Zelikoff on my thesis advisory committee to advise me on the finer points of their exposure system, which is different than what we have at Rochester. Overall, I would say this has been a very successful collaboration, one that has generated even more collaborations at other universities as the findings become more interesting and complex."

Klocke C, Allen JL, Sobolewski M, Mayer-Pröschel M, Blum JL, Lauterstein D, Zelikoff JT, Cory-Slechta DA. 2017. Neuropathological Consequences of Gestational Exposure to Concentrated Ambient Fine and Ultrafine Particles in the Mouse . *Toxicological Sciences.* 2017 kfx010. doi: 10.1093/toxsci/kfx010

AHR conference:

August 3-6th 2016, the Department of Environmental Medicine hosted an international conference bringing together researchers from many fields who all study the aryl hydrocarbon receptor (AHR). This conference was co-organized by EHSC Deputy Director Paige Lawrence, PhD, and Alvaro Pugo, PhD, from the University of Cincinnati. Lawrence said, "My motivation to organize the conference was driven by a desire to bring the field together.



There has been tremendous growth in research on the AHR, but at larger conferences the research on the AHR is present but diffuse and in disciplinary silos. Consequently, the people who are studying it did not have a chance to get together in the same place."

40 years ago, two University of Rochester researchers, Dr. Alan Poland and Dr. Andrew Kende, played a major role in the discovery of the AHR. Since this time, University of Rochester scientists from many departments have remained involved in various aspects of AHR research. In part because of this history, Lawrence thought it would be appropriate to hold a meeting in Rochester to celebrate the 40th anniversary of the AHR and to develop an agenda for future research. In addition, as Lawrence said, "I was so very pleased that the conference was here, showcasing the University of Rochester and the City of Rochester. I suppose that was the second reason why I was happy to have it here—it showed a lot of people how wonderful Rochester is."

Over 160 scientists and trainees from multiple disciplines who work all over the world came together for the conference. With 105 presentations in three days, researchers shared the research their institutions are doing in their respective fields of study. Linda Birnbaum, PhD, Director of the NIEHS, gave the keynote presentation on "Dioxin and the aryl hydrocarbon receptor: Synergy of discovery." The conference also provided opportunities for attendees to discuss connections between their diverse areas of research and formulate an agenda for future research directions.

The AHR conference was sponsored by the University of Rochester, University of Cincinnati, and the NIEHS, as well as many other supporters.

The aryl hydrocarbon Receptor (AHR):

The AHR has long been recognized as a ligand-activated transcription factor responsible for the induction of xenobiotic metabolizing enzymes (molecules that interact with drugs, environmental toxicants, etc. and determine how the body is affected by these chemicals). Much of the early attention given to this receptor focused on anthropogenic ligands, many of which are known or suspected carcinogens. Through this work, it has become widely accepted that the AHR is the primary mediator of the toxic effects of many persistent environmental contaminants, including dioxins and innumerable halogenated and polycyclic aromatic hydrocarbon ligands. Yet, more recently, other functions of this fascinating protein have been recognized, and it is becoming clear that the AHR functions in pathways outside of its initially discovered role in metabolic enzyme induction and toxicant metabolism.

The emerging diversity of pathways implicates the AHR in the regulation of multiple developmental and homeostatic biological processes, such as immune responses, growth factor and hormone signaling, cell cycle progression, oxidative stress, inflammation, differentiation, development, and apoptosis. Literally hundreds of genes have been shown to be regulated either directly or indirectly by the AHR, and some of the underlying regulatory mechanisms may involve the interaction of the AHR with other cellular effectors. It has become evident that the AHR is a key environmental sensor that drives the biological outcome resulting from the molecular dialogue established between genes and the environment.

Summary from: AHR Conference 2016: **The aryl hydrocarbon Receptor as a Central Mediator of Health and Disease** www.urmc.rochester.edu/center-experiential-learning/cme/types-of-activities/ahr-conference-2016.aspx

TOXICOLOGY TRAINING PROGRAM ANNUAL RETREAT

The annual retreat was held May 26, 2016. The event featured a keynote address by Ilona Jaspers, PhD platform presentations and posters by students

- **Elissa Wong** won the William F. and Margaret W. Neuman Award for exemplary scholarship and citizenship in the Toxicology Training Program
- **Amanda Croasdell** won the (student) Robert F. Infurna Award for publishing the best research paper in toxicology
- **Lisbeth Boule, PhD,** won the (postdoc) Robert F. Infurna Award for publishing the best research paper in toxicology
- **Carolyn Klocke** won the (student) Weiss Toxicology Scholar Award
- **Luisa Caetano-Davies, PhD,** won the (Postdoc) Weiss Toxicology Scholar Award
- **Jasmine Reed** won best poster for a 1st year grad student
- **Brian Palmer** won the "Question Award" for consistently asking thoughtful questions in the student research-in-progress seminar series

TOXICOLOGY TRAINING PROGRAM ANNUAL RETREAT KEYNOTE LECTURE

The keynote speaker for the June 2016 Toxicology Training Program Annual Retreat was Ilona Jaspers, PhD, Professor of Pediatrics at the University of North Carolina at Chapel Hill and Director of the UNC Chapel Hill Curriculum in Toxicology.

Jaspers' talk presented her work on how vaping e-cigarettes may modify immune responses in the respiratory mucosa. The effects of new and emerging tobacco products, such as e-cigarettes, on the immune status of the respiratory mucosa are largely unknown. Jaspers' data suggests a similarity between smoking traditional tobacco cigarettes and vaping e-cigarettes, in that they both reduce the expression of immune-related genes in the nasal mucosa.

Toxicology Trainee News

· Congratulations to Claire McCarthy, the recipient of the Spring 2016 Medical Faculty Council UR-SMD Trainee/ Student Travel Award.

· Lisa Prince, Carrie Klocke and Brian Palmer won Travel Awards to attend the annual Society of Toxicology meeting in Baltimore, MD (March 2017).

· Parker Duffney won 1st place Best Poster at the Annual Lung Research and Trainee Day for Graduate Students.

· Anthony Franchini, PhD won 1st place Poster at the Annual Lung Research and Trainee Day for Postdocs.

Thesis Defenses held in 2016 (Received their PhD in Toxicology):

- Emily Resseguie, PhD, went on to a Toxicologist position at Envigo CRS, Inc
- Amanda Croasdell, PhD, went on to Postdoctoral Fellow position at the University of Edinburgh

Students who received their Masters in Toxicology:

- Shannon Lacy, Denise Herr, Keith Morris-Shaffer, Sarah Phelan, Kelly Hanson, Candace Wong, and Katrina Jew

WELCOME NEW TOXICOLOGY GRADUATE STUDENTS

The Toxicology Training program welcomed four new graduate students in 2016
From left to right (Front Row): Ashley Rackow, Ashley Fields, Kadijah Abston
Back Row: Keegan Vaughan

DR. CORY-SLECHTA AWARDED DISTINGUISHED NEUROTOXICOLOGIST AWARD

The Society of Toxicology (SOT) Neurotoxicology Specialty Section (NTSS) Awards Committee has selected Deborah Cory-Slechta, PhD, as the recipient of the 2017 Distinguished Neurotoxicologist Award.

Cory-Slechta has demonstrated a life-long commitment to neurotoxicology. She has been a pioneer in championing neurotoxicology and behavioral science, and in exploring the interactions of chemical and non-chemical stressors to understand the complex etiology of behavioral diseases. This research is highlighted, for example, in experimental work confirming that low-level lead exposure alters neurodevelopment, which was highly influential in setting federal guidelines for developmental lead exposures. Her more recent research including that on the interactions between air pollution exposure and socioeconomic stress on neurodevelopment also promises to be highly influential. In addition, Cory-Slechta has served extensively in a variety of administrative roles including as Department Chair, Institute Director, and Dean for Research at two prominent academic programs on occupational and environmental health. She also has served on numerous federal advisory panels and as an Officer and President of the NTSS. This overall record of research accomplishments and service marks a singularly distinguished career in neurotoxicology that is recognized by this award.