Children's Environmental Health Research Roadmap Fiscal Year 2016 Annual Report

DRAFT October 12, 2016

U.S. ENVIRONMENTAL PROTECTION AGENCY
OFFICE OF RESEARCH AND DEVELOPMENT

Contents

Authors and Contributors

Roadmap Lead

John Cowden
Office of Research and Development

Lead Author

Benjamin Zukowski
Office of Research and Development

Contributors (in alphabetical order)

Tina Bahadori
Office of Research and Development

Susanna Blair
Office of Research and Development

Michael Firestone
Office of Children's Health Protection

William Fisher
Office of Research and Development

Lynn Flowers
Office of Research and Development

Jill Franzosa
Office of Research and Development

Dayna Gibbons
Office of Research and Development

Annette Guiseppi-Elie
Office of Research and Development

Monica Linnenbrink
Office of Research and Development

Nica Louie
Office of Research and Development

Kelsey Maloney
Office of Research and Development

Nicolle Tulve
Office of Research and Development

Valerie Zartarian
Office of Research and Development

Children's Environmental Health Implementation Working Group Members

Working Group Leads

Jill Franzosa
Office of Research and Development, U.S. EPA
Nicolle Tulve
Office of Research and Development, U.S. EPA

Working Group Members (in alphabetical order)

Marcus Aguilar Region 9	**Annette Guiseppi-Elie** Office of Research and Development	**Edward Ohanian** Office of Water
Daniel Axelrad Office of Policy	**Maureen Gwinn** Office of Research and Development	**Kathleen Raffaele** Office of Land and Emergency Management
Tina Bahadori Office of Research and Development	**Intaek Hahn** Office of Research and Development	**Santhini Ramasamy** Office of Water
Kim Bartels Region 8	**Ronald Hines** Office of Research and Development	**John M. Rogers** Office of Research and Development
Wayne Cascio Office of Research and Development	**Kristen Keteles** Region 8	**Jason Sacks** Office of Research and Development
Elaine Cohen Hubal Office of Research and Development	**Thomas Knudsen** Office of Research and Development	**LaTonya Sanders** Region 7
John Cowden Office of Research and Development	**Nica Louie** Office of Research and Development	**Gretchen Stewart** Region 10
Michael Firestone Office of Children's Health Protection	**Mark Maddaloni** Region 2	**Maryann Suero** Region 5
Stiven Foster Office of Land and Emergency Management	**Kelsey Maloney** Office of Research and Development	**Siobhan Tarver** Region 4
Andrew Geller Office of Research and Development	**Jacquelyn Menghrajani** Region 9	**Prentiss Ward** Region 3
Dayna Gibbons Office of Research and Development	**Becky Ofrane** Region 2, U.S. EPA	**Benjamin Zukowski** Office of Research and Development

Abbreviations and Acronyms

ACE	Air, Climate, Energy National Research Program
ADHD	Attention Deficit Hyperactivity Disorder
ATSDR	Agency for Toxic Substances and Disease Registry
BBDR	Biologically Based Dose Response
BPA	bisphenol A
CEH	children's environmental health
CEH IWG	Children's Environmental Health Implementation Working Group
CSS	Chemical Safety for Sustainability National Research Program
DDT	dichlorodiphenyltrichloroethane
EDSP	Endocrine Disruptor Screening Program
EPA	Environmental Protection Agency
FIFRA	Federal Insecticide, Fungicide, and Rodenticide Act
FY16	Fiscal Year 2016
HHRA	Human Health Risk Assessment National Research Program
HS	Homeland Security National Research Program
NHANES	National Health and Nutrition Examination Survey
NIEHS	National Institute of Environmental Health Sciences
NIH	National Institutes of Health
NRC	National Research Council
OCM	Organotypic Culture Models
OCSPP	Office of Chemical Safety and Pollution Prevention
OW	Office of Water
ORD	Office of Research and Development
PAH	Polycyclic Aromatic Hydrocarbon
PBDE	polybrominated diphenyl ethers
PCB	Polychlorinated biphenyl
PEHSU	Pediatric Environmental Health Specialty Unit
PFC	Perfluorinated Compound
SHC	Sustainable and Healthy Communities National Research Program
SmARTI	Smart Acceleration of Research Through Investment
SSWR	Safe and Sustainable Water Resources National Research Program
STAR	Science to Achieve Results
SVOC	Semivolatile Organic Compound
TSCA	Toxic Substances Control Act

Executive Summary

Purpose of the Children's Environmental Health Research Roadmap

Protecting children's health from environmental risks remains a critical and enduring part of the U.S. Environmental Protection Agency's (EPA's) mission. EPA conducts and supports children's environmental health (CEH) research to inform regulatory decisions and to support community decision-making that promotes sustainable, healthy environments for children. In October 2015, EPA's Office of Research and Development (ORD) released the *Children's Environmental Health (CEH) Research Roadmap*, which describes the Agency's strategic vision for CEH research. The CEH Research Roadmap provides EPA and stakeholders with scientific understanding, information, and tools required to address early-lifestage sensitivity, susceptibility, and vulnerability[1] to chemical and nonchemical stressors.

The CEH Research Roadmap is not a research program. Rather, it integrates children's health research activities across ORD's six Strategic Research Action Plans (https://www.epa.gov/research/strategic-research-action-plans-2016-2019) developed by the ORD National Research Programs: Air, Climate, and Energy (ACE); Chemical Safety for Sustainability (CSS); Human Health Risk Assessment (HHRA); Safe and Sustainable Water Resources (SSWR); Sustainable and Healthy Communities (SHC), and Homeland Security (HS). The CEH Research Roadmap describes crosscutting research needs that have two important attributes: (1) they are "owned" by a National Research Program in a near-term timeframe; and (2) they should enable EPA/ORD to take a transformative leadership role.

Purpose of the Annual Report

This *CEH Research Roadmap Annual Report* summarizes progress made during the fiscal year on research goals and activities described in the Research Roadmap; it also demonstrates EPA's commitment to continue integrating and advancing this critical area of crosscutting research. This report highlights successes and challenges of implementing ORD's CEH research during Fiscal Year 2016 (FY16; October 1, 2015 to September 30, 2016). The report also identifies emerging issues or data needs that could inform future research efforts.

Summary of FY16 CEH Research Progress

ORD is investing heavily in CEH research—intramurally, extramurally, and through strategic partnerships. Through each National Research Program research portfolio, ORD is collecting and compiling data on children's exposures and providing access to information on exposure factors, human

[1] Sensitivity – Differences in toxic response resulting from toxicodynamic differences, toxicokinetics differences, or both. These differences can arise due to numerous biological factors such as lifestage (windows of enhanced sensitivity), genetic polymorphisms, gender, disease status, and nutritional status.
Susceptibility – Differences in risk resulting from variation in both toxicity response (sensitivity) and exposure (due to gender, lifestage, and behavior).
Vulnerability – Differences in risk resulting from the combination of both intrinsic differences in susceptibility and extrinsic social stress factors such as low socioeconomic status, crime and violence, lack of community resources, crowding, access to healthcare, education, poverty, segregation, and geography.
Lifestage – A distinguishable period in an individual's life characterized by unique and relatively stable behavioral or physiological (or both) characteristics that are associated with development and growth.
Source: EPA/NCER 2013 RFA re: Susceptibility and Variability in Human Response to Chemical Exposure

behavior, chemical use, and developmental toxicity. Complex systems models of tissues and multi-organ development are being constructed, and studies are being implemented that combine epidemiological and laboratory-based approaches, to provide a holistic understanding of the relationship between early-life environmental exposures and well-being across the lifespan. ORD is developing tools and models that can be used to access data, forecast exposures for thousands of chemicals, and evaluate dosimetry of chemicals in the developing organism. ORD is also developing decision-support tools to help States, local governments, and community organizations consider potential impacts of environmental exposures in the context of decisions designed to protect and promote children's health. Selected of FY16 research products are highlighted here. Complete references for FY16 peer-reviewed publications and for the citations in the body of this report are presented in Appendix A.

In FY16, ORD CEH research resulted in the development of pharmacokinetic models of vasculogenesis (El-Masri et al. 2016), computational models of estrogen receptor activity (Mansouri et al. 2016), and in silico models of reproductive development (Leung et al. 2016a, 2016b). These predictive models are part of a larger research effort on development health. ORD continued developing novel screening approaches for developmental neurotoxicants in FY16 (Druwe et al. 2016). Research also furthered progress on adverse outcome pathways for developmental neurotoxicity, including investigations on epigenetic modifications (Perumal-Kuppusamy et al. 2015; Vidal et al. 2015) and the lasting impacts of prenatal thyroid hormone disruption (Gilbert et al. 2016; Spring et al. 2016). A systematic scoping review synthesized evidence of both chemical and nonchemical stressors, reporting prenatal growth, sleep health, lead, water pollutants, breastfeeding, and social interactions as factors associated with childhood cognitive ability (Ruiz et al. 2016). Consideration of both chemical and nonchemical stressors, organized by common adverse outcomes and biological targets, is a first step towards understanding the cumulative impact of the environment on the developing nervous system (e.g., Kraft et al. 2016).

ORD's systems approach to hazard and exposure integrates a variety of data streams (e.g., *in vitro*, *in vivo*, and *in silico*) to inform complex risk decisions, such as lead contamination in drinking water. Risk decisions require understanding both hazard and exposure. In FY16, ORD researchers developed methods to directly measure chemical exposure in children (Funk et al. 2015) and built predictive exposure models for perfluorinated compounds (Wu et al. 2015a) and polybrominated diphenyl ethers (Bennett et al. 2015; Wu et al. 2015b; Marchitti et al. 2016).

A fundamental challenge for EPA is evaluating the combined impact of chemical (e.g., Howdeshell et al. 2015; Moser et al. 2015; Paul Friedman et al. 2016) and nonchemical (e.g., Chen et al. 2015; Morgan et al. 2015; Vesper et al. 2015; Arnold et al. 2016; King et al. 2016; Vesper and Wymer 2016) stressors on children's health. ORD's FY16 work demonstrates that coordinated and focused research can provide rapid response to emerging issues of concern, such as indoor air quality. The systems approach outlined in the CEH Research Roadmap, and integrated into ORD's research portfolio, is the first step in characterizing cumulative impacts of the built, natural, and social environments on children's health.

In FY16, EPA and NIEHS awarded five new NIEHS/EPA Children's Center grants. Research supported under these awards includes the interplay of particulate matter and obesity on asthma among inner city

children; prenatal and early childhood pollutant exposure and adverse birth outcomes; polycyclic aromatic hydrocarbons and adolescent cognitive, emotional, behavioral health outcomes; cumulative environmental exposures and increased risk for childhood acute lymphoblastic leukemia; and the effects of environmental contaminants on the microbiome and neurodevelopment.

Summary of FY16 CEH Research Translation

To protect vulnerable lifestages, ORD collaborates with partners and stakeholders to CEH research can be translated into action. In FY16, ORD regularly communicated CEH research at scientific meetings and conferences in the United States and abroad as well as targeted meetings and presentations for ORD partners in Programs and Regions. For instance, ORD researchers partnered with the Endocrine Disruptor Screening Program (EDSP) to develop and evaluate a high-throughput screening assay with over 1,000 chemicals from the ToxCast Phase I and II libraries (Paul Friedman et al. 2016). This work is part of a larger collaborative ORD research effort to develop in vitro high-throughput assays and computational models for detecting receptor activity in endocrine pathways, including androgen and thyroid.

Another effort to translate ORD CEH research is through support to the Zika Interagency Task Force, a cross-Federal government partnership established to address the emerging health issue from the Zika virus. Laboratory studies are underway within ORD, Organotypic Cell Model Science to Achieve Results (STAR) Centers, and other external collaborations to probe maternal viral infection and develop a virtual tissue model for microcephaly. ORD CEH research also is informing the Presidential mandate to investigate potential risk to children from exposure to tire crumbs. In FY16, *Synthetic Turf Fields with Tire Crumb Rubber Infill Research Protocol* was drafted to provide a standard method to evaluate the chemical make-up of tire crumbs. ORD scientists are gathering tire crumb samples from manufacturing plants and fields across the country and will release a draft status report in late 2016.

ORD scientists are providing technical assistance to address the issue of lead in drinking water. In FY16, exposure and dose model predictions, generated with the Stochastic Human Exposure and Dose Simulation-Multimedia and Integrated Exposure Update Biokinetic models, were used to identify key exposure pathways and model inputs, providing health-based values for evaluating lead in drinking water. In another important effort focusing on exposure and dose, ORD developed a novel physiologically based pharmacokinetic approach to inform the derivation of the maximum contaminant level goal for perchlorate in drinking water. This unprecedented effort uses a biologically based dose-response (BBDR) model to estimate the effects of perchlorate exposure on hormone levels in pregnant mothers and fetuses.

Internally, ORD has built a coalition of children's health experts through the CEH Implementation Working Group (IWG). The CEH IWG, whose members are listed at the beginning of this report, is composed of ORD researchers, ORD National Research Program leadership, and EPA Program Office and Regional partners. The group meets monthly to learn about and help translate results of CEH research, facilitate integration, and leverage ongoing efforts to implement the strategic vision of the CEH Research Roadmap.

Summary of ORD CEH Research Impact

In FY16, ORD CEH research substantially contributed to multiple, high-profile Agency efforts. Risk decisions about perchlorate in drinking water and pesticide applicator certifications relied on ORD research to protect vulnerable lifestages. ORD's research on lead was the scientific foundation for EPA's response to drinking water contamination in Flint, Michigan. ORD CEH research provided critical biological context for microcephaly following exposure to Zika virus, and informed EPA's recommendations for combating mosquito vectors. ORD research on endocrine disruptors, including screening compounds and building predictive models, continued to provide critical support to the EDSP. These activities clearly demonstrate that ORD CEH research directly supports the efforts of EPA's Science Advisor and are essential for protecting children's health.

Progress and Emerging Opportunities

FY16 was the first full year the CEH Research Roadmap was implemented. ORD scientists produced an impressive number of peer-reviewed publications (Appendix A), continuing EPA's legacy of scientific leadership in CEH research. ORD CEH research and scientific expertise were applied to critical Agency needs (e.g., contaminated drinking water, tire crumbs, Zika virus, endocrine disruption) through collaborations with partners and stakeholders. Because of these science translation efforts, ORD research was the cornerstone for EPA risk decisions on pesticide application, perchlorate, and lead.

Looking ahead, the focus will remain on translating ORD's research to support EPA's public health mission. Future research will apply complex systems science to integrate the rapidly expanding body of information on children's health. This information will be translated into tools and databases to support Agency decisions that promote and protect children's health and well-being. ORD will apply advanced systems science and integrate diverse emerging data and knowledge in exposure, toxicology, and epidemiology to improve understanding of the role of environmental exposure during early life on health impacts that could occur at any point over the lifecourse.

I. Accomplishments

This section describes the Office of Research and Development's (ORD) efforts to integrate, coordinate, and deliver children's environmental health (CEH) research products and to support several high-priority issues across the U.S. Environmental Protection Agency (EPA) in FY16. In addition to peer-reviewed publications, results of ORD research are regularly communicated through scientific meetings and conferences in the United States and internationally, and at targeted meetings and presentations for ORD partners in EPA Program Offices and Regions. ORD also regularly collaborates with these partners to translate its research for use in EPA actions and decisions, including risk assessments and health advisories. Example impacts of ORD CEH research on EPA decisions are provided. "Research Highlights" boxes showcase a sample of impactful publications, and several research projects are described in the section, *Integration of CEH Research for Impact Delivery*, to demonstrate progress toward integrating this research among the National Research Programs. Appendix A provides a complete list of ORD CEH peer-reviewed manuscripts delivered during the fiscal year.

A. Impacts of ORD CEH Research on EPA Decisions

In FY16, results from ORD's intramural and extramural CEH research were used to inform several pesticide risk assessments and EPA's decisions regarding safe drinking water, contaminants of emerging concern, dietary exposures, and air pollution health. Critical CEH issues addressed by ORD research included certification of pesticide applicators, screening for endocrine disrupting compounds, microcephaly from Zika virus, analysis of exposure effects of tire crumbs, and recommendations for remediating lead contamination in drinking water. These activities directly support the efforts of EPA's Science Advisor and are essential for protecting children's environmental health.

Research Highlight

Exposure to elemental carbon, organic carbon, nitrate, and sulfate fractions of fine particulate matter and risk of preterm birth in New Jersey, Ohio, and Pennsylvania (2000–2005). *Rappazzo et al.; Environmental Health Perspectives 2015 Oct; 123(10):1059–65. doi: 10.1289/ehp.1408953.*

Exposure to particulate matter ≤ 2.5 µm (PM2.5) during pregnancy is associated with preterm birth. There are numerous PM2.5 species, but few studies have examined how the different species contribute to risk of preterm birth. Risk of preterm birth associated with prenatal exposure to changes in ambient concentrations of PM2.5—specifically elemental carbon, organic carbon, nitrate, and sulfate—was the focus of this manuscript.

Using a cohort of approximately 1.8 million pregnancies, the study identified associations between average weekly PM2.5 exposure during gestation and risk of preterm birth. The study reported differences among PM2.5 species, with elemental carbon and sulfate showing consistent association with risk for preterm birth. Differences in windows of exposure and risk of preterm birth at specific gestational ages were also reported for the PM2.5 species. These results suggest diverse periods of action for the PM2.5 species of PM, along with differing windows of susceptibility.

Certification of Pesticide Applicators

Research from the jointly funded EPA/National Institute of Environmental Health Sciences (NIEHS) Children's Environmental Health and Disease Prevention Research Centers (Children's Centers) informed the proposed Certification of Pesticide Applicators rule revision in FY16. EPA is proposing age restrictions and stronger training and certification standards for restricted-use pesticides. EPA risk decisions and data from the Children's Centers were cited in the July 2016 *Economic Analysis of Final Amendments to 40 CFR part 171: Certification of Pesticide Applicators*. In addition, the Scientific Advisory Panel for the Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA) used data generated by the Children's Centers in their review of biomonitoring and epidemiological data for chlorpyrifos (https://www.epa.gov/sap/meeting-materials-april-19-21-2016-scientific-advisory-panel).

Organophosphates – Retention of Safety Factor

In October 2015, EPA's Office of Chemical Safety and Pollution Prevention (OCSPP) proposed to revoke all food residue tolerances for the insecticide, chlorpyrifos. The proposed rule retained the statutory 10X Food Quality Protection Act Safety Factor for infants, children, youths, and women of childbearing age for all exposure scenarios (https://www.federalregister.gov/documents/2015/11/06/2015-28083/chlorpyrifos-tolerance-revocations). The rule included data from three Children's Centers: the Columbia Center for Children's Environmental Health, the Mount Sinai Center for Children's Environmental Health and Disease Prevention Research, and the Center for Environmental Research and Children's Health. The review of "Chlorpyrifos - Analysis of Biomonitoring Data" and inclusion of epidemiological data continues as discussed by the 2016 FIFRA Scientific Advisory Panel (https://www.epa.gov/sap/meeting-materials-april-19-21-2016-scientific-advisory-panel).

Endocrine Disruptor Screening Program (EDSP)

In FY15, EPA announced its plans to adopt *in vitro* high-throughput assays and computational models for detecting and measuring estrogen receptor bioactivity as an alternative for three current assays in the EDSP (http://www.epa.gov/endocrine-disruption/use-high-throughput-assays-and-computational-tools-endocrine-disruptor). This "pivot," which will be expanded to other endocrine pathways including androgen and thyroid, was driven largely by ORD's advances in computational toxicology research and successful collaborations with NIEHS. For the androgen pathway, the FY16 focused on approaches to validate high-throughput assays and computational predictive model as a potential alternative for traditional EDSP screens. For the thyroid pathway, significant emphasis was placed on expanding the assay portfolio in ToxCast (https://actor.epa.gov/actor/home.xhtml). For example, ORD researchers developed and tested a high-throughput screening assay and used over 1,000 chemicals in the ToxCast Phase I and II libraries to evaluate its performance further (Paul Friedman et al. 2016). The plan to incorporate these new approaches into the EDSP will be reviewed at upcoming meetings of the FIFRA Science Advisory Panel.

Microcephaly and Zika Virus

Infection from the Zika virus has been associated with devastating effects on prenatal neurological development, including microcephaly and optical or aural anomalies. The Zika virus is spread by the

Aedes aegypti mosquito, and EPA has endorsed an integrated vector management approach for mosquito control. ORD collaborates with EPA Program Office partners and other Federal partners to support the Zika Interagency Task Force. ORD has developed research priorities for the task force and initiated projects to address some of the identified environmental and public health research gaps. A research effort in Brownsville, Texas is gathering spatial and temporal information on *Aedes aegypti* distribution in relation to habitat and developing models to forecast future vulnerabilities to Zika and other mosquito-borne diseases. A project in San Juan, Puerto Rico is investigating potential relationships between wastewater discharge, flooding, and habitat alteration to mosquito population size, viral load, and infections of nearby residents. Laboratory studies are underway to develop a virtual tissue model for microcephaly to understand its various causes, including Zika infection. ORD researchers have collaborated with investigators from two of the Organotypic Cell Model STAR Centers to probe maternal infection and Zika mode of action and have provided a foundation for additional research. ORD will continue to work closely with Federal partners to identify and address emerging research needs for this growing threat.

Recycled Tire Crumbs and Health Risks

Use of recycled tire crumbs in playing fields and playgrounds in the United States has recently raised public safety concerns, and no available studies comprehensively evaluate health risks from exposure to tire crumb. To address these concerns, EPA, the Centers for Disease Control and Prevention/Agency for Toxic Substances and Disease Registry (ATSDR), and the U.S. Consumer Product Safety Commission launched the *United States Federal Research Action Plan on Recycled Tire Crumb Used on Playing Fields* on February 12, 2016 to study key environmental human health questions. The *Synthetic Turf Fields with Tire Crumb Rubber Infill Research Protocol* provides an overview of the peer-review study design for this research. ORD scientists are collecting tire crumb samples from manufacturing plants and from fields across the country to characterize their chemical make-up. Scientists also will gather activity data from people who regularly perform activities on turf fields. This information will help answer some of the key questions that have been raised. By late 2016, the agencies will release a draft status report and outline next steps. For more information about the research, visit the Tire Crumb Research website: www.epa.gov/tirecrumb.

Remediating Lead Contamination in Drinking Water

EPA's Office of Water (OW) requested technical assistance on the Lead and Copper rule, and ORD scientists are responding by conducting multimedia exposure analyses to inform a public health-based value for lead in drinking water. Using a probabilistic modeling methodology and multimedia lead exposure analysis, they are determining drinking water lead levels that would keep children's blood lead level below target concentrations. As part of this analysis, the exposure and dose model predictions from the coupled Stochastic Human Exposure and Dose Simulation-Multimedia and Integrated Exposure Update Biokinetic models have been evaluated using National Health and Nutrition Examination Survey (NHANES) blood lead data to identify key exposure pathways and model inputs. The final analyses will support the development of a health-based value for lead in drinking water.

Perchlorate Dose-Response Modeling

In response to OW's request for technical support on the perchlorate National Primary Drinking Water Regulation, ORD scientists developed a BBDR model to estimate the effect of perchlorate exposure on serum thyroid hormone levels in pregnant mothers and fetuses. The BBDR model predicts thyroid hormone perturbations for lactating mothers, breast-fed infants, and bottle-fed infants resulting from exposure to perchlorate under different intake levels of dietary iodine. The modeling effort is being used to inform the regulatory decisions for perchlorate levels in drinking water. This effort represents the first time that OW will have relied on information that characterizes specific effects on multiple, early lifestages to inform a drinking water regulation.

B. Integration of CEH Research for Impact Delivery

The CEH Research Roadmap outlines integrative research across ORD National Research Programs. In FY16, ORD began implementing CEH Roadmap recommendations through several cross-disciplinary research projects. These projects leverage ORD scientists, EPA Program Office partners, and academic researchers to provide EPA with fundamental research on children's environmental health. Highlights of these projects are provided below.

Virtual Tissues Modeling Research Project – Integrating EPA's Intramural and Extramural Research

Understanding the impact of chemical exposures on the developing embryo is critical to CEH research. The Virtual Tissue Modeling Research Project uses in vitro and in vivo data to build in silico models of human development. These computer simulation models promote systems-level understanding of chemical exposures that could lead to adverse outcomes in development. Ultimately, the in silico models could serve as an analytical tool for predicting effects of chemical exposure on embryogenesis. The project is a collaboration with EPA-funded Science to Achieve Results (STAR) grantees of the Organotypic Culture Models (OCMs) for Predictive Toxicology Centers (OCM Centers; see Table 3). OCM Center researchers participate in project meetings, allowing for real-time flow of science and knowledge and for EPA to incorporate "organ-on-a-chip" research models into EPA's predictive toxicology research and activities.

An example of this integration is the collaborative development of novel models for EPA's developmental neurovascular toxicology research. Although EPA research has had a notable focus on the thyroid, this engagement with academic and biotechnology partners has significantly accelerated EPA's learning curve: This transfer of technology and knowledge is at least 3 to 4 years ahead of expectations. EPA was able to reprioritize and redirect intramural resources to support the neurovascular OCM and its research team. Conversely, engagement with EPA has helped the OCM grantees direct the case studies in their research toward topics that would have relevance to EPA's public and environmental health protection mission. Several new postdoctoral students are being recruited to advance this effort.

Research Highlight

Integration of life-stage physiologically based pharmacokinetic (PBPK) models with adverse outcome pathways (AOPs) and environmental exposure models to screen for environmental hazards. *El-Masri et al.; Toxicological Science (2016) doi: 10.1093/toxsci/kfw082.*

Physiologically based pharmacokinetic (PBPK) models describe what the body does to a chemical and how chemicals are absorbed, distributed, metabolized, and excreted. Because developing fetuses and infants are especially sensitive to chemical exposure, a PBPK model was developed to describe where chemicals end up based on various lifestages: pregnancy, fetal, neonatal, infant, and adulthood.

EPA scientists integrated the lifestage-specific PBPK model with existing data on in vitro high-throughput screening assays using an adverse outcome pathway on embryonic vascular disruption. The universal model takes into consideration important biologically relevant factors and real-life chemical exposure levels to create a framework applicable to chemicals of interest for children's environmental health. This framework can be used to screen and prioritize chemicals for further research or regulatory decision-making.

Developmental Health – Integrating across ORD and with Program and Regional Partners

EPA implements screening, testing, and research programs to gather information for use in evaluating possible endocrine effects associated with chemical use (https://www.epa.gov/endocrine-disruption). The EDSP's chemical screening list contains approximately 10,000 chemicals. The FY15 announcement to incorporate high-throughput technologies to accelerate the pace of EDSP screening, described above, signaled an imminent opportunity to demonstrate the relevance and potential applicability of ORD CEH research to environmental policy in near real time.

Taking advantage of this opportunity and policy focus, ORD also increased its research focus on developmental health, vulnerable lifestages, and susceptible populations. This research supports progress in understanding adverse outcome pathways (AOPs) associated with important developmental health processes and those associated with disease endpoints of concern. Mechanistic toxicology information and epidemiology insights are being assembled within CSS, SHC, and ACE National Research Programs to facilitate model development and analysis of critical knowledge gaps. In FY16, ORD published novel screening approaches for developmental neurotoxicants (Druwe et al. 2016). Research also progressed on AOPs for developmental neurotoxicity, including investigations on epigenetic modifications (Perumal-Kuppusamy et al. 2015; Vidal et al. 2015) and the persistent impacts of prenatal thyroid hormone disruption (Gilbert et al. 2016; Spring et al. 2016). Computational models of estrogen receptor activity (Mansouri et al. 2016) and in silico models of reproductive development (Leung et al.

2016a, 2016b) also have informed this research focus. A systematic scoping review synthesized evidence of both chemical and nonchemical stressors, reporting prenatal growth, sleep health, lead, water pollutants, breastfeeding, and social interactions as factors associated with childhood cognitive ability (Ruiz et al. 2016). Consideration of both chemical and nonchemical stressors, organized by common adverse outcomes and biological targets, is a first step toward understanding the cumulative impact of the environment on the developing nervous system (e.g., Kraft et al. 2016).

Safe Drinking Water – The Lead Example: Integrating across Policy Domains

ORD supports Agency efforts to reduce childhood exposure to lead and characterize associated health impacts through innovative research in SSWR, SHC, and HHRA National Research Programs. ORD research focuses on understanding and characterizing population-level exposures to lead from multiple sources such as soil, dust, and water; furthering the scientific understanding of human health effects of lead exposures, especially on sensitive lifestages; and advancing the science on how best to mitigate lead exposure from different environmental sources. Projects include evaluating water chemistry adjustments to control the leaching of lead from pipes, analyzing lead bioavailability and risk from exposure to lead in soil, and developing improved approaches for remediating lead-contaminated soils. Other areas include drinking water technology research to address the unique needs of small communities in preventing lead contamination of drinking water and community case studies that evaluate the socioeconomic impacts of lead contamination at a large urban Superfund site. ORD's 2013 *Integrated Science Assessment for Lead* is being updated by synthesizing and evaluating the most policy-relevant science in support of National Ambient Air Quality Standards for lead.

Research Highlight

The relationship between environmental relative moldiness index values and asthma. *Vesper & Wymer, International Journal of Hygiene and Environmental Health (2016). doi: 10.1016/j.ijheh.2016.01.006.*

Mold exposure is qualitatively associated with asthma, but efforts to quantify this relationship have been limited. To address this issue quantitatively, the relationship between asthma and a measure of indoor mold was analyzed. The environmental relative moldiness index (ERMI) value, derived from analysis of molds in dust samples, was compared with asthma incidence data from six epidemiological studies in both children and adults. The results show children and adults with asthma were living in homes with significantly higher ERMI values than comparison homes. Based on this study, the ERMI metric could be a useful public health tool to mitigate a factor associated with higher asthma incidences.

Indoor Air and Health – Emerging Area of Integration

An emerging area of research interest among ORD's National Research Programs is indoor air and health, including indoor air and climate (ACE), healthy schools and science to support healthy Tribal environments (SHC), indoor exposures to consumer products (CSS), and the microbiome of built environments (across ORD and with EPA's Office of Radiation and Indoor Air). Components of this research area are addressed through new STAR grants (see Table 4) and intramural research in the National Research Programs. One crosscutting element focuses on nontargeted analyses, based on high-

resolution mass spectrometry platforms, to screen for xenobiotic chemicals in a variety of environmental and biological media and to use these approaches to inform real-world exposures.

C. Outreach to Partners and Stakeholders

This section highlights the interaction between ORD and EPA partners in Program and Regional Offices and ORD and public stakeholders. Such interaction is essential for integrating ORD scientific research into relevant decision contexts and ensuring relevance of ORD research products for users. This section also presents successes in addressing programmatic recommendations from scientific advisory groups.

Scientific and Advisory Bodies

EPA's Science Advisory Board and the Executive Committee of its Board of Scientific Counselors have provided guidance on the development of the CEH Research Roadmap. The Board will continue to monitor progress on the implementation, integration, and impact of EPA's CEH research.

In addition, EPA has commissioned the National Academies of Sciences, Engineering, and Medicine to evaluate the state of the-science and recommend approaches for using emerging science to promote effective, health-protective decisions and actions. Several of these studies will inform ORD's CEH research efforts. Examples of formative studies follow.

Unraveling Low Dose: Case Studies of Systematic Review of Evidence (In progress)

An ad hoc committee under the auspices of the National Research Council (NRC) is developing a strategy for evaluating evidence of low-dose adverse human effects that act through an endocrine-mediated pathway. Systematic reviews of chemicals, populations, and endpoints for human and animal data streams will be performed under the direction of the committee. The committee will evaluate the results of the systematic reviews, demonstrate how human and animal data streams can be integrated, determine whether the evidence supports a likely causal association, and evaluate the nature and relevance of the dose-response relationship(s). The results of the committee's evaluation of low-dose toxicity can be used to inform EPA on the adequacy of its current regulatory toxicity-testing practices. A consensus report is expected in early 2017.

Microbiome of Built Environments

The National Academies of Sciences, Engineering, and Medicine are conducting a consensus study that will examine the formation and function of microbial communities in built environments, the impacts of such microbial communities on human health, and how human occupants shape complex indoor microbiomes. This study is intended to provide an independent, objective examination of the current state of science regarding built environment microbiomes and their impacts on human health. Attempts then will be made to bridge gaps in moving this research to an application stage, in which building materials and architecture will be designed with microbiomes in mind. The consensus report for the study, which is being conducted by a committee of experts, is expected in 2017.

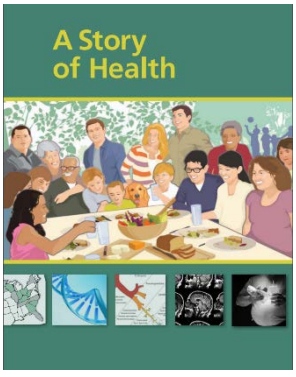
Advancing Understanding of the Implications of Environmental-Chemical Interactions with Human Microbiomes

An ad hoc committee of the NRC will develop a research strategy to improve the understanding of interactions between environmental chemicals and human microbiomes, including the intestinal, skin, and lung microbiomes, and the implications of those interactions on human health risk. The committee will assess the state of science regarding how the microbiome affects, and is affected by, chemical exposures. It will also assess how lifestage or interindividual differences in microbiota, for example, might influence effects. The research strategy will identify the types of studies needed to improve understanding of how various microbiome communities can affect chemical absorption and metabolism, how population variation in microbiome activity might affect individual chemical exposure, and the effect of chemical exposure on microbiome functions and possible implications for human health risk. A consensus report is expected in 2018.

Program Offices and Regions

ORD's CEH research is implemented through the CEH Research Roadmap. A Children's Environmental Health Implementation Working Group (CEH IWG) was established in FY16 to facilitate cross-ORD implementation of the CEH Research Roadmap; enhance communication about CEH research among ORD researchers, partners, and stakeholders; and serve as a resource for EPA leadership on CEH research and science. The CEH IWG provides a forum for communication and collaboration among EPA Program Offices, Regional Offices, and ORD's National Research Programs. The group meets monthly to discuss CEH issues of priority for EPA and progress in ongoing research, creating early and frequent opportunities for engagement, translation, and collaboration.

EPA and ATSDR co-fund Pediatric Environmental Health Specialty Units (PEHSUs; http://www.pehsu.net/), an interconnected system of pediatric medical specialists located throughout North America. The PEHSU network supports translation from healthcare research to practice. These pediatric specialists respond to questions about the impacts of environmental factors on the health of children and reproductive-age adults from public health professionals, clinicians, policy-makers, and the public. The PEHSUs, located in each of EPA's 10 Regions, operate under the umbrella of the American Academy of Pediatrics and the American College of Medical Toxicology.



PEHSUs also partner with the EPA/NIEHS Children's Centers and EPA Regions. Efforts to have the PEHSUs partner with the NIEHS/EPA Children's Centers have increased. Examples include the Story of Health, an award-winning multimedia e-book on environment and health created in collaboration between the Region 9 PEHSU and the University of California – Berkeley Children's Center. In Region 7, the PEHSU program partnered with the Center for Environmental Health at Children's Mercy, a hospital in Kansas City, Missouri, to provide education, consultation, and referrals for children with environmental exposures. Additionally, the Center for Environmental Health has successfully delivered Healthy Homes and Healthy schools training throughout the Region: More than 700 healthcare students and 275 healthcare professionals have been

educated to advocate for home-based environmental changes that can improve children's health. The Center for Environmental Health-PEHSU effort will present 10 more Healthy School trainings and provide at least 2 more training courses to local Tribal communities during FY17 and FY18.

Current List of Products/Peer-Reviewed Publications

In FY16, ORD CEH research resulted in more than 290 abstracts, book chapters, peer-reviewed publications, posters, and presentations. A table of the completed ORD CEH research manuscripts is provided in Appendix A. The list represents ORD's FY16 manuscripts related to CEH that have been accepted by journals for publications. This table presents products of intramural research only. Numerous publications from extramural grants, including STAR Grants, Children's Centers, and others are tracked by the STAR program and reported publicly as required by that program. To facilitate review, the articles in Appendix A are loosely organized by research areas, such as exposure evaluation, or health outcomes, such as asthma, that were identified as high priority in the CEH Research Roadmap. Much of the research, which is crosscutting and transdisciplinary by design, could fall into multiple categories. In addition, articles that are also relevant to an emerging research area—early-life determinants of cancer, the microbiome, thyroid disruption—are listed.

D. Encouraging Innovation

ORD has established a variety of mechanisms to germinate, encourage, and support innovation in science research projects. This section describes ORD's commitment to advancing innovation in CEH research within ORD and through its extramural grants.

Pathfinder Innovation Projects

The **Pathfinder Innovation Projects (PIPs)** program is the "high risk, high reward" component of ORD's research portfolio. PIPs foster development of transformative ideas through a competitive renewal process, with funding awards progressively increasing at each stage. At the final stage of the competition, these innovation projects are incorporated into ORD's strategic research action plans.

> **Stage 1. Explore your Idea:** Applicants propose short-term projects (≤4 months, ≤$30 K, ≤0.5 FTE [full-time equivalent]). The primary resource provided to awardees is time to test an idea's viability, better understand the technical challenges, and scope future work.
>
> **Stage 2. Prove your Concept:** At the end of the exploration period, Stage 1 awardees propose longer-term projects (≤12 months, ≤$100 K, ≤1.5 FTE). Funding is used for proof-of-concept, limited demonstration, or scale-up of the project.
>
> **Stage 3. Scale Up your Project:** Concurrent with Stage 2 review, Stage 2 awardees propose long-term efforts (≥12 months, ≤$250K, ≤1.5 FTE) to expand on their PIP research to date. Researchers must have successfully demonstrated proof-of-concept and have a well-articulated plan to expand the work with NPD support.

Table 1 provides a synopsis of FY16 PIPs related to goals outlined in the CEH Research Roadmap.

Table 1. Pathfinder Innovation Projects (PIPs)		
Title	**Brief Description**	**PIP Stage**
Development of a novel method to estimate children's dust ingestion	Identify candidate compounds that can be used as potential tracers to estimate children's dust ingestion rates using a systematic framework.	Stage 1
Fetal origins of lifestage disease	Develop an embryonic zebrafish model to test whether manufactured chemicals (1) disrupt normal control over fat-cell development and (2) influence fat volume later in life.	Stage 1
Gut microbiome influence on developmental toxicity	Develop multiple zebrafish assays to test whether microbial colonization modifies the developmental toxicity of environmental chemicals.	Stage 2
Use of epigenetic information to transform how EPA identifies susceptible populations	Develop methods to examine and characterize impact air pollutants on chromatin and gene expression for insights on susceptibility.	Stage 2
The "brain on a chip" model for developmental neurotoxicity testing	Develop a rapid method to screen chemicals for developmental neurotoxicity by examining the responses of neuron networks.	Stage 3

Smart Acceleration of Research Through Investment Awards

The FY16 Smart Acceleration in Research Through Investment (SmARTI) Awards provided an opportunity for research proposals supporting strategic collaborations or ideas ready for implementation. Of the three SmARTI Awards funded, two were CEH-relevant:

1. **Identification of potential thyroid hormone-disrupting chemicals that interfere with deiodinase enzymes:** Develop screening assays for deiodinase enzymes responsible for activation and catabolism of thyroid hormones.
2. **A high-throughput examination of the universe of chemicals that might appear in a variety of recycled consumer articles to identify, quantify, and prioritize potential chemical exposure sources in recycled materials (e.g., tire-derived rubber):** Examine the universe of chemicals that might appear in various recycled consumer articles in an innovative, high-throughput manner, in support of identifying, quantifying, and prioritizing potential chemical exposure sources.

Science to Achieve Results (STAR) Grants

The National Center for Environmental Research's STAR program funds research grants and graduate fellowships through a competitive solicitation process and independent peer review. The leading edge of CEH science is driven through transformative research conducted in academia through the STAR program. The centerpiece of this investment is the NIEHS/EPA Children's Environmental Health and Disease Prevention Research Centers (Children's Centers) primarily funded by the SHC research program, which are described in more detail below and in Table 2. Table 3 lists the previously funded NIEHS/EPA Children's Centers that closed in FY16. In addition, over a dozen other STAR grants funded by

the National Research Programs, summarized in Table 4, investigate key issues related to CEH, including exposure to complex mixtures, modeling of developmental health, indoor environments, and Tribal health.

Children's Environmental Health and Disease Prevention Research Centers

The Children's Centers were established to improve understanding of the effects of exposure to chemical and nonchemical stressors on children's health and to explore ways to reduce children's health risks from environmental stressors. Additionally, the Children's Centers promote translation of basic research findings into intervention and prevention methods to prevent or reduce adverse health outcomes.

Table 2 lists the currently funded Children's Centers. Many of these Centers have received funding as part of the Children's Centers program. In FY16, NIEHS and EPA jointly funded five new Centers (italicized below). The Children's Centers publish extensively on the results of their research. For more information about each Center, visit the EPA Children's Centers homepage: https://www.epa.gov/research-grants/niehsepa-childrens-environmental-health-and-disease-prevention-research-centers.

Table 2. NIEHS/EPA Children's Environmental Health and Disease Prevention Research Centers

Center Name	Year Funded	Institution	Research Goals
Center for the Study of Childhood Asthma in the Urban Environment https://cds.johnshopkins.edu/cei/index.cfm?fuseaction=display_program&id=114	2015	Johns Hopkins University	Explore how exposure to air pollution causes high rates of asthma in the inner city. Define the relationship between obesity, asthma, and air pollution in inner city African-American children.
Center for Children's Health, the Environment, the Microbiome, and Metabolomics http://www.nursing.emory.edu/c-chem2/index.html	2015	Emory University	Characterize environmental exposures to African-American women during pregnancy and to their infants. Explore how environmental exposures during pregnancy and infancy, the microbiome, and the immune system work together to influence brain development.
The Columbia Center for Children's Environmental Health http://ccceh.org/	2015	Columbia University	Define the effects of air pollution, specifically polyaromatic hydrocarbons, on brain development, obesity, and inability to regulate thought, emotion, and behavior. Investigate if these changes in brain development can lead to serious cognitive, emotional, and adiposity problems during adolescence.
Center for Research on Early Childhood Exposure and Development in Puerto Rico http://www.northeastern.edu/crece/	2015	Northeastern University	Study the effects of chemical mixtures on child health and development. Focus on an underserved, highly exposed, low-income population in Puerto Rico. Evaluate how social and economic factors could modify the effects of the environment on children's health.

Table 2. NIEHS/EPA Children's Environmental Health and Disease Prevention Research Centers			
Center Name	**Year Funded**	**Institution**	**Research Goals**
Center for Integrative Research on Childhood Leukemia and the Environment http://circle.berkeley.edu/	2015	University of California, Berkeley	Identify the causes of acute lymphoblastic leukemia in an ethnically diverse population. Understand how environmental factors increase risk of acute lymphoblastic leukemia.
UC Davis Center for Children's Environmental Health and Disease Prevention http://www.ucdmc.ucdavis.edu/mindinstitute/research/cceh/index.html	2013	University of California, Davis	Identify risk factors contributing to autism spectrum disorder. Understand early markers of risk to identify children who might develop this disorder.
The UCSF Pregnancy Exposures to Environmental Chemicals Children's Center http://prhe.ucsf.edu/prhe/PEEC_childrens_center.html	2013	University of California, San Francisco	Determine the impacts of in utero exposure to hazardous chemicals, such as polybrominated diphenyl ethers (PBDEs) and perfluorinated compounds (PFCs), on child growth and development. Evaluate how social stress on the mother during pregnancy might modify the effects of these chemicals on children's health.
Novel Methods to Assess Effects of Chemicals on Child Development http://ikids.beckman.illinois.edu/	2013	University of Illinois	Examine the impact of endocrine disrupting chemicals, such as bisphenol A (BPA) and phthalates, on child development. Investigate how these chemicals interact with diets high in saturated fat to influence brain and reproductive system development.
Children's Health and Air Pollution Study – San Joaquin Valley http://chaps.berkeley.edu/	2013	University of California, Berkeley; Stanford University	Investigate how air pollution in the San Joaquin Valley contributes to birth defects, preterm birth, allergies, obesity, diabetes, and other childhood illnesses. Evaluate the role of social and economic factors on the health effects associated with air pollution.
Lifecourse Exposures and Diet: Epigenetics, Maturation, and Metabolic Syndrome https://sph.umich.edu/cehc/index.html	2013	University of Michigan	Understand how early exposure to endocrine disrupting chemicals, such as BPA, lead, and phthalates, produce adverse neurodevelopmental, reproductive, and immunological effects. Explore how early exposure to these chemicals affects growth and sexual development during childhood and adolescence to increase risk of disease in adulthood.
Center for Study of Neurodevelopment and Improving Children's Health following Environmental Tobacco Smoke Exposure http://niches.duke.edu/	2013	Duke University	Investigate the relationship between environmental tobacco smoke and brain function in children. Explain how environmental tobacco smoke increases the risk of attention deficit hyperactivity disorder through epigenetic alterations.

Table 2. NIEHS/EPA Children's Environmental Health and Disease Prevention Research Centers			
Center Name	**Year Funded**	**Institution**	**Research Goals**
Southern California Children's Environmental Health Center http://hydra.usc.edu/cehc/	2013	University of Southern California	Understand the impact of near-roadway air pollution on childhood obesity and diabetes.
Children's Environmental Health and Disease Prevention Research Center at Dartmouth http://www.dartmouth.edu/~childrenshealth/	2013	Dartmouth College	Understand the impact of arsenic in drinking water and food on children's health. Inform the public about how to minimize health risks from arsenic.
Center for Environmental Research and Children's Health http://cerch.org/	2009	University of California, Berkley	Investigate the health effects of pesticides, including DDT and manganese, and PBDE flame-retardants in boys approaching puberty. Explore whether pesticide exposure to children affects development and timing of puberty.

Table 3 lists the previously funded NIEHS/EPA Children's Centers that closed in FY16. Those Centers marked with an asterisk are continuing research under a different grant.

Table 3. NIEHS/EPA Children's Centers CLOSED in FY16			
Center Name	**Year Funded**	**Institution**	**Research Goals**
The Columbia Center for Children's Environmental Health* http://ccceh.org/	2015	Columbia University	Explore the role of polyaromatic hydrocarbons and BPA in the development of obesity, metabolic syndrome, and neurodevelopmental disorders in children. Explore the epigenetic mechanisms that mediate the effects of these chemicals on disease.
Mechanisms of Asthma - Dietary Interventions against Environmental Triggers* https://cfpub.epa.gov/ncer_abstracts/index.cfm/fuseaction/display.abstractDetail/abstract/9218	2009	Johns Hopkins University	Understand how diet influences the asthmatic response to indoor and outdoor airborne pollutants and allergens. Translate findings into practical dietary strategies to improve pediatric asthma health. Explore the mechanisms related to airway inflammation, oxidative stress, and respiratory morbidity in inner-city African-American children.
Center for Integrative Research on Childhood Leukemia and the Environment* http://circle.berkeley.edu/	2015	University of California, Berkeley	Examine the interplay of environmental, genetic, and epigenetic factors related to the risk of leukemia in children. Evaluate the effects of exposures to chemicals such as pesticides, polychlorinated biphenyls, and PBDEs on childhood leukemia.
Center for Child Environmental Health Risks Research https://www.epa.gov/research-grants/niehsepa-cehcs-center-child-environmental-health-risks-research-university	2003	University of Washington	Understand factors that increase susceptibility to the adverse effects of pesticides. Improve understanding of critical pathways of exposure to pesticides for children. Identify mechanisms for the adverse developmental neurotoxicity of pesticides.

* Research is continuing under a different grant.

Children's Center Publications

The Children's Centers published at least 135 papers in 2015 and 69 papers in 2016 (to date). A few publications from the Children's Centers are highlighted below.

Highlighted publications

Children Exposed to Organophosphate Pesticides Early in Life Showed Decreased Lung Function

Findings from the NIEHS/EPA Children's Center at the University of California, Berkeley, link organophosphate pesticide metabolites in the urine of 279 children living in California's Salinas Valley that have decreased lung function. This decrease in lung function is similar to the decrease seen in response to a child's exposure to secondhand smoke. The findings are the first to link chronic, low-level exposures of organophosphate pesticides to lung health for children. Persistent reduced lung function during childhood increases the risk for chronic obstructive pulmonary disease in adulthood. http://thorax.bmj.com/content/71/2/148.

Community members at a meeting of the University of Washington Children's Center to learn about dimethylthiophosphate levels detected in their urine during a study. They also obtained more information on pesticides and how to reduce pesticide exposure at home and in the workplace. Selected quotes from the meeting:

- "I know the importance of sometimes getting that information of what the pesticides contain and what they can do to people….These findings are important."
- "Why do we do research? Well, to learn how to prevent illness and all of that."

Infants Who Ate Rice, Rice Products Had Higher Urinary Concentrations of Arsenic

Epidemiology evidence suggests that arsenic exposure in utero and in early life is associated with adverse effects on fetal growth, as well as on infant and child immune and neurodevelopment outcomes. Arsenic has been found in rice and rice products, which are typical first foods for infants. To investigate the potential exposure from dietary sources of arsenic, a new study by the NIEHS/EPA Children's Center at Dartmouth College found that infants who ate rice products had higher urinary arsenic concentrations than those who consumed no rice. The study concludes that consumption of rice and rice products increases infants' exposure to arsenic and that efforts should be made to reduce arsenic exposure during critical periods of development. http://archpedi.jamanetwork.com/article.aspx?articleid=2514074.

Prenatal Exposure to BPA Linked to Measures of Body Fat during Childhood

Researchers from the NIEHS/EPA Children's Center at Columbia University have shown that prenatal exposure to BPA, a chemical widely used in plastic water bottles and metal cans lined with BPA-containing resin, might contribute to obesity development in young children. This study is the first to show a possible link between prenatal exposures to BPA and measures of body fat in school-aged children. Children exposed to higher concentrations of prenatal BPA had higher levels of adiposity. http://ehp.niehs.nih.gov/EHP205/.

Early Exposures to Phthalates and BPA Interfere with Metabolism

Endocrine-disrupting chemicals such as phthalates, polychlorinated biphenyls, and BPA might produce adverse developmental, reproductive, neurological, and immune effects. Researchers from the NIEHS/EPA Children's Center at the University of Michigan explored associations between in utero BPA concentrations and markers of peripubertal metabolic homeostasis. The results show phthalates and BPA were associated with metabolism biomarkers at ages 8–14 years in patterns that varied by sex and pubertal status. http://press.endocrine.org/doi/full/10.1210/jc.2015-2706.

Conferences and Meetings

2015 NIEHS/EPA Children's Centers Annual Meeting. Washington D.C., October 29 and 30, 2015. More than 260 participants registered for this annual event including researchers from the NIEHS/EPA Children's Centers and the PEHSUs, scientists from Federal agencies, and others. The agenda was developed to explore connections between research findings, clinical practice, and community outreach and translation. Speakers also discussed approaches for communicating research findings and technical information with parents and the public.

2015 Congressional Briefing. "A Healthy Start for Every Child: How the Environment Influences Health & Development" was held at the Rayburn House Office Building, on October 28, 2015. Accomplishments from the NIEHS/EPA Children's Centers were presented.

NIEHS/EPA Children's Centers Webinar Series. Monthly, in collaboration with the EPA Office of Children's Health Protection. The webinar series focused on topics related to children's environmental health, including childhood obesity, epigenetics, childcare, neurodevelopment, and prenatal exposures. The webinars featured researchers from the NIEHS/EPA Children's Centers, PEHSUs, EPA, and the National Institutes of Health (NIH). Participation ranged between 150 and 300 people from a wide variety of backgrounds, including researchers, clinicians, scientists, representatives of professional organizations, and the public.

Research Impact

FDA-proposed limit for inorganic arsenic in infant rice cereal cites research from the NIEHS/EPA Children's Centers

In April 2016, the Food and Drug Administration (FDA) proposed a limit for inorganic arsenic in infant rice cereal, citing the work of the NIEHS/EPA Children's Center at Dartmouth College. This Center has been funded by the two agencies under two separate grants since 2010.

The new limits on arsenic in infant rice cereal have received coverage by close to 500 news outlets including the New York Times and NBC News.

Link to FDA press release: http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm493740.htm

Other STAR Grants Addressing CEH Research

Table 4 highlights active STAR grants, funded by the ACE, CSS, and SHC research programs that focus on children's environmental health. These grants represent a significant investment in complementary areas of CEH research and are in addition to the NIEHS/EPA Children's Centers summarized in Table 2 and Table 3. For example, the seven Healthy Schools STAR research grants listed in Table 4 have initiated efforts investigating important linkages between building characteristics and indoor air quality, and their

subsequent relationships to children's learning performance. In FY16, these grantees worked toward developing informational tools, databases, and models to help design construction and operation practices to foster safe and healthy school environments and maximize student achievement and teacher and staff effectiveness in K–12 schools.

Table 4. Other National Center for Environmental Research/EPA STAR Grants Addressing CEH Research

Institution Name	Year Funded	Research Focus; Research Program	Topic Area
Colorado State University	2015	Healthy Schools Research Grant; SHC	Sustainable Places, Health, and Educational Research in Schools
Johns Hopkins Bloomberg School of Public Health; Baltimore City Schools; Baltimore Education Research Consortium	2015	Healthy Schools Research; SHC	Baltimore Healthy Schools: Impact of Indoor Air Quality on Health and Performance
University of Texas, Austin	2015	Healthy Schools Research; SHC	Healthy High School Partnership in Research on Indoor Environments
Health Research Inc.; NYS Department of Health	2014	Healthy Schools Research; SHC	Assessment of School Environmental Effects on Children's Health and Performance and Strengthening of State/Community Capacity to Create a Healthy and Safe Learning Environment
University of Michigan; Wayne State University	2014	Healthy Schools Research; SHC	Environmental Quality, Health, and Learning in Conventional and High Performance School Buildings
University of Nebraska, Lincoln	2014	Healthy Schools Research; SHC	Evidence-Based Interactions between Indoor Environmental Factors and their Effects on Kindergarten–12 Student Achievement
University of Oklahoma; Colorado State University; University of Oklahoma Health Sciences Center	2014	Healthy Schools Research; SHC	Balancing Sustainability, Clean Air, Healthy Learning Interiors, and Structural Safety when Designing and Building Schools
Boston University; Duke University	2014	New Methods in 21st Century Exposure Science; CSS	Residential Exposure of Young Children to Semivolatile Organic Compounds
University of California, San Francisco	2014	New Methods in 21st Century Exposure Science; CSS	Non-targeted Method for Measuring Multiple Chemical Exposures among a Demographically Diverse Population of Pregnant Women in Northern California

Table 4. Other National Center for Environmental Research/EPA STAR Grants Addressing CEH Research			
Institution Name	**Year Funded**	**Research Focus; Research Program**	**Topic Area**
University of Washington	2014	Organotypic Culture Models for Predictive Toxicology; CSS	Predictive Toxicology Center for Organotypic Cultures and Assessment of AOPs for Engineered Nanomaterials
University of Wisconsin, Madison	2014	Organotypic Culture Models for Predictive Toxicology; CSS	Human Models for Analysis of Pathways Center
Vanderbilt University; University of Pittsburgh	2014	Organotypic Culture Models for Predictive Toxicology; CSS	Vanderbilt–Pittsburgh Resource for Organotypic Models for Predictive Toxicology
Little Big Horn College; Montana State University	2014	Tribal Environmental Health; SHC	Water, Our Voice to the Future: Climate Change Adaptation and Waterborne Disease Prevention on the Crow Reservation
University of Massachusetts – Amherst; Ryerson University; University of Toronto	2014	Tribal Environmental Health; SHC	Subsistence Hunting and Associated Activities of Native North Americans in Remote Communities: Measurement of Indoor Air Quality in Tents as Related to Wood-Smoke Exposures, and the Identification of Potential Health Risks
University of Tulsa; Cherokee Nation Environmental Program and Health Services; Institute for Tribal Environmental Professionals; Navajo Nation – EPA and Department of Diné Education; Nimiipuu Health; University of Oklahoma	2014	Tribal Environmental Health; SHC	From Home to School: Tribal Indoor Air Quality Intervention Study
Harvard University	2011	Clean Air Research Center; ACE	Air Pollution Mixtures: Health Effects Across Life Stages
Emory University; Georgia Institute of Technology; University of Nevada, Reno	2010	Clean Air Research Center; ACE	Southeastern Center for Air Pollution and Epidemiology: Multi-Scale Assessment of Health Effects of Air Pollution Mixtures Using Novel Measurements and Models

E. Challenges & Opportunities

Changes in the Broader Scientific and Policy Landscape with Impact on CEH Research

FY16 presented a historic opportunity for EPA with the enactment of Frank R. Lautenberg Chemical Safety for the 21st Century Act (H.R. 2576). This Act modernizes the Toxic Substances Control Act (TSCA), and introduces several new provisions relevant to CEH:

- **Protection of potentially exposed or susceptible subpopulations:** The term "potentially exposed or susceptible subpopulation" means a group of individuals within the general population identified by the EPA Administrator who—due to either greater susceptibility or greater exposure—might be at greater risk than the general population for adverse health effects from exposure to a chemical substance or mixture, such as infants, children, or pregnant women. Moving forward, CEH research will need to be translated for application to chemical evaluations or risk assessments of new or existing substances for potential or differential harm to this subpopulation. For EPA, effective translation will require advancing the science to integrate diverse data streams—including conventional and molecular epidemiology, animal and computational toxicology, and exposure science—for practical application to regulatory risk assessments.
- **Chemical inventory reset:** The new law requires EPA to reevaluate the chemical inventory for existing and new chemicals or mixtures and prioritize those for potential to cause harm.
- **Focus on exposure characterization:** Rather than focusing on toxicity alone, this prioritization requires considering exposures up front and as components of chemical evaluations.
- **Predictive capacity:** The new law emphasizes the need to predict chemical impacts to human health and the environment before commercialization. This focus on predictive capacity is well aligned with the systems approach outlined in the CEH Research Roadmap.
- **Reduction in vertebrate testing:** Although section 4 of the new law allows EPA to require additional testing, it also requires EPA to reduce and replace, to the extent practicable and scientifically justified, the use of vertebrate animals in testing chemical substances and mixtures.

EPA's research in the Chemical Safety for Sustainability National Research Program is well positioned to support EPA's implementation of the new law:

- CSS researchers have developed methods for "nontargeted" and "suspect screening" analyses, to demonstrate novel applications of these methods for analyses of household dust for human exposures and analyses of natural waters for perfluorinated compounds. These approaches provide a platform for future research designed to identify and quantify emerging unstudied contaminants rapidly in media that are relevant to children's environmental health.
- In a continued commitment to improve the public's access to data, CSS scientists released a new interactive Chemistry Dashboard with chemistry information for over 700,000 chemicals. The publicly available dashboard is a gateway to an array of related public domain databases, provides improved access to data and models associated with chemicals of interest, and is a hub

that links many EPA research databases. The user-friendly interface, which provides access to chemical structure information and tens of thousands of physicochemical properties, is used to develop machine-learning models. The Chemistry Dashboard brings EPA a step closer to a "one-stop-shop" for data needs regarding environmental chemistry data that inform exposure and risk assessments.

- Under the new law, risk assessors will face increasing demands to assess more chemicals, with greater speed and accuracy, and to do so using fewer resources and experimental animals. New approaches in biological and computational sciences provide mechanistic information that could help in meeting these challenges. AOP provides a conceptual platform that organizes existing knowledge about the linkage between a direct molecular initiating event and an adverse outcome at a biological level of organization relevant to risk assessment. A series of CSS publications in FY16 (for example, organizing information for improved decision-making and using AOPs to link exposures to high-throughput screening data), demonstrates how applications of AOPs will improve chemical safety decisions.

Across all of ORD's National Research Programs, full consideration of at-risk populations in public health decision-making is a significant focus. Due to cumulative assault from ubiquitous environmental contaminants resulting from crumbling infrastructures, residual and ongoing pollutant exposures to lead and other metals, polychlorinated biphenyls (PCBs, especially in schools), perfluorinated compounds (PFCs), coal combustion waste, and other sources, children suffer from myriad impacts. Impacts include adverse developmental health, neurological impacts, obesity, asthma, hormone disruption (such as early onset of puberty), and cancers. Research to improve our understanding of factors affecting exposure and health outcomes will provide a scientific basis for cumulative assessment and help identify risk management options. These factors include key lifestages and subpopulations along with complex influences on health of cumulative exposures to chemical and nonchemical pollution (e.g., noise) and nonpollutant stressors (e.g., access to healthcare, healthy foods, violence, poverty, loss of social connection).

Improving Integration of Research Projects across ORD

The CEH Research Roadmap created a common research agenda and shared platform for ORD. ORD's National Research Programs have each developed cross-disciplinary research projects, but integration across the National Research Programs remains challenging. To begin addressing integration challenges, ORD formed the CEH IWG in FY16. ORD researchers, ORD National Research Program leadership, and EPA Program Office and Regional partners comprise the CEH IWG. Meeting on a monthly basis, the CEH IWG strives to stimulate dialogue vital for cross-program collaboration, to identify and prioritize CEH issues, and to serve as a resource on CEH science across EPA. This cross-program representation will continue to facilitate integration across ORD's research projects and leverage ongoing efforts to implement the strategic vision of the CEH Research Roadmap with efficiency. A focus for FY17 is identifying additional opportunities to integrate across National Research Programs and with the other cross-ORD Research Roadmaps on Nitrogen and Co-Pollutants, Climate Change, and Environmental Justice.

II. The Year Ahead

A. Near-term Research Efforts

With the establishment of the CEH IWG and the funding of several extramural grants and Centers, the year ahead holds great promise. ORD intramural CEH research efforts are in full swing, with approximately 40 publications anticipated for release in the first half of FY17. EPA will continue to partner with other Federal agencies, academia, and independent organizations to further CEH research. FY17 research will continue to apply complex systems science to integrate the rapidly expanding body of information on children's health. This information will be translated into tools and databases to support Agency decisions that promote and protect children's health and well-being. As was done in FY16 for lead, perchlorate, tire crumbs, Zika, and other topics, Agency priority to protect children's health will inform research focus and resource prioritization, allocation, and redistribution. Emerging areas, such as the role of human and environmental microbiomes in influencing children's health and the environmental determinants of cancer and critical lifestage exposures, will be incorporated into existing research plans of the National Research Programs. The focus on thyroid research will continue to be integrated into the broader understanding of neurodevelopmental health. Most importantly, the CEH IWG will increase its efforts to translate the science and facilitate the dissemination of emerging science, both across EPA and with its stakeholders.

B. Proposed Meetings and Workshops

The Children's Centers will present at the Environmental Health Science Facilities, Engagement, Scientific Advancement, and Training meeting, on December 5–8, 2016 in Durham, North Carolina. The NIEHS Division of Extramural Research will host the multiday event, which grantees, community partners, and EPA-NIEHS scientists will attend. The meeting is aimed at stimulating innovation in research approaches, communication, translational research, tools, sensors, and more; highlighting scientific accomplishments around crosscutting themes; and sharing best practices among the scientific community.

OCM Centers are planning a meeting in conjunction with the Society of Toxicology Annual Meeting in 2017. This meeting will feature research by early-career scientists, encourage additional collaboration among the Centers and other related research in ORD, and help evaluate the opportunity to integrate the OCM models in EPA's predictive toxicology research.

In addition, ORD staff, Regions, and many EPA partners will continue to present their research findings at conferences and professional meetings relevant to children's environmental health throughout FY17.

Appendix A. Completed Peer-Reviewed ORD Publications in FY16

This appendix presents ORD's FY16 manuscripts related to children's environmental health that have been accepted by peer-reviewed journals for publication. This table presents products of intramural research only. Numerous publications from extramural grants, including STAR Grants, Children's Centers, and others are tracked by the STAR program and reported publicly as required by that program. To facilitate review of the list, the articles are loosely organized by research area, such as exposure evaluation, or health outcome, such as asthma, that were identified as high priority in the CEH Research Roadmap. As much of the CEH research is crosscutting and transdisciplinary, these publications could be assigned to multiple categories. In addition, articles that are also relevant to an emerging research area —early-life determinants of cancer, the microbiome, thyroid disruption—are indicated.

Appendix A. Completed Peer-Reviewed ORD Publications in FY16				
Citation	National Research Program	Cancer	Microbi	Thyroid
Adverse Birth Outcomes				
Beggs KM, McGreal SR, McCarthy A, Gunewardena S, Lampe JN, Lau C, Apte U. The role of hepatocyte nuclear factor 4-alpha in perfluorooctanoic and perfluorooctanesulfonic acid-induced hepatocellular dysfunction. *Toxicol Appl Pharmacol,* Aug 1; 304:18-29, (2016).	CSS	•		
Douglas G, Thirkill T, Kumar P, Loi M, Hilborn E. Effect of Microcystin-LR on human placental villous trophoblast differentiation in vitro. *Environmental Toxicology,* John Wiley & Sons, Ltd., Indianapolis, IN, USA, 31(4): 427-39, (2016).	SSWR		•	
El-Masri H, Kleinstreuer N, Hines RN, Adams L, Tal T, Isaacs K, Wetmore BA, Tan YM. Life-stage physiologically based pharmacokinetic (PBPK) model application to screen environmental hazards using adverse outcome pathways (AOPs) and environmental exposure models. *Toxicol Sci,* Jul; 152(1):230-43, (2016).	CSS			
Jarema K, Hunter D, Shaffer R, Behl M, Padilla S. Acute and developmental behavioral effects of flame retardants and related chemicals in zebrafish. *Neurotoxicology and Teratology*, Elsevier Science Ltd, New York, NY, USA, 52: 194-209, (2015).	CSS			
Leung MCK, Hutson S, Seifert A, Spencer R, Knudsen T. Computational modeling and simulation of genital tubercle development. *Reproductive Toxicology,* Elsevier Science Ltd, New York, NY, USA, 1-11, (2016a).	CSS			

Appendix A. Completed Peer-Reviewed ORD Publications in FY16				
Citation	**National Research Program**	**Cancer**	**Microbi**	**Thyroid**
Adverse Birth Outcomes				
Leung M, Phuong J, Baker N, Sipes N, Klinefelter G, Martin M, McLaurin K, Setzer W, Darney S, Judson R, Knudsen T. Systems toxicology of male reproductive development: Profiling 774 chemicals for molecular targets and adverse outcomes. *Environmental Health Perspectives,* 124(7), (2016b).	CSS			
Makris, SL, Scott CS, Fox J, Knudsen, TB, Hotchkiss AK, Arzuaga X, Euling SY, Powers CM, Jinot J, Hogan KA, Abbott BD, Hunter SE, Michael G, Narotsky MG. A systematic evaluation of the potential effects of trichloroethylene exposure on cardiac development. *Reproductive Toxicology, in press* (2016).	CSS			
Poet, T., Schlosser, P., Rodriguez, C., Parod, R., Rodwell, D., Kirman, C. Using physiologically based pharmacokinetic modeling and benchmark dose methods to derive an occupational exposure limit for N-methylpyrrolidone. Regulatory Toxicology and Pharmacology, Volume 76, April 2016, Pages 102-112, ISSN 0273-2300, http://dx.doi.org/10.1016/j.yrtph.2015.12.020.	CSS			
Rappazzo K, Daniels J, Messer L, Poole C, Lobdell D. Exposure to the elemental carbon, organic carbon, nitrate and sulfate fractions of fine particulate matter and risk of preterm birth in New Jersey, Ohio, and Pennsylvania (2000-2005). *Environmental Health Perspectives,* National Institute of Environmental Health Sciences (NIEHS), Research Triangle Park, NC, USA, 123(10): 1059-65, (2015).	ACE; SHC			
Rappazzo K, Warren J, Meyer R, Herring A, Sanders A, Brownstein N, Luben T. Maternal residential exposure to agricultural pesticides and birth defects in a 2003 to 2005 North Carolina birth cohort. Birth defects research part a: clinical and molecular teratology. John Wiley & Sons, Ltd., Indianapolis, IN, USA, 1-10, (2016).	HHRA			
Rogers, J. Search for the missing lncs: gene regulatory networks in neural crest development and long non-coding RNA biomarkers of Hirschsprung's disease. *Neurogastroenterology & Motility,* John Wiley & Sons, Inc., Hoboken, NJ, USA, 28(2): 161-166, (2016).	CSS			
Tal T, Kilty C, Smith A, LaLone C, Kennedy B, Tennant A, McCollum C, Bondesson M, Knudsen T, Padilla S, Kleinstreuer N. Screening for chemical vascular disruptors in zebrafish to evaluate a predictive model for developmental vascular toxicity. *in review* (2016).	CSS			

Appendix A. Completed Peer-Reviewed ORD Publications in FY16				
Citation	**National Research Program**	**Cancer**	**Microbi**	**Thyroid**
Adverse Birth Outcomes				
Theunissen PT. Comparing rat and rabbit embryo-fetal developmental toxicity studies for 379 pharmaceuticals: On systemic dose and developmental effects. *Crit Rev Toxicol, in press* (2016).	CSS			
Asthma				
Chen C, Chao HJ, Shen W, Chen B, Lin, K, Guo YL, Vesper, S. Pilot study of mold in homes of asthmatic children in Taipei, Taiwan, using the Environmental Relative Moldiness Index. *Aerobiologia,* Springer, New York, NY, USA, 31(2): 213-218, (2015).	N/A		•	
Ghio, AJ. Asthma as a disruption in iron homeostasis. *Biometals*, Springer Netherlands, 29: 751, (2016).	SHC			
Snow S, Gordon C, Bass V, Schladweiler M, Ledbetter A, Jarema K, Phillips P, Johnstone A, Kodavanti, U. Age-related differences in pulmonary effects of acute and subchronic episodic ozone exposures in brown Norway rats. *Inhalation Toxicology,* Informa Healthcare USA, New York, NY, USA, 28(7): 313-23, (2016).	SHC			
Vesper S, Prill R, Wymer L, Adkins L, Williams R, Fulk, F. Mold contamination in schools with either high or low prevalence of asthma. *Pediatric Allergy and Immunology,* John Wiley & Sons, Inc., Hoboken, NJ, USA, 26(1): 49-53, (2015).	SHC		•	
Vesper S, H Choi, M Perzanowski, L Acosta, A Divjan, B Bolanos-Rosero, F Rivera-Mariani, G Chew. Mold populations and dust mite allergen concentrations in house dust samples from across Puerto Rico. *International Journal of Environmental Health Research,* Carfax Publishing Limited, Basingstoke, UK, 26(2): 198-207, (2016a).	SHC		•	
Vesper S, Wymer L. The relationship between environmental relative moldiness index values and asthma. *International Journal Of Hygiene And Environmental Health,* Urban & Fischer Verlag Jena, Jena, Germany, 219(1): 233-238, (2016).	SHC		•	
Vesper S, Robins T, Lewis T, Dombkowski K, Wymer L, Villegas R, Batterman Use of Medicaid and housing data may help target areas of high asthma prevalence. *J Asthma,* Jul 19:0, (2016b).	SHC		•	

Appendix A. Completed Peer-Reviewed ORD Publications in FY16				
Citation	**National Research Program**	**Cancer**	**Microbi**	**Thyroid**
Endocrine Disruption				
Armstrong B, J Lazorchak, K Jensen, H Haring, ME Smith, R Flick, D Bencic, A Biales. Reproductive effects in fathead minnows (*Pimephales promelas*) following a 21-d exposure to 17 alpha-ethinylestradiol. *Chemosphere,* Elsevier Science Ltd, New York, NY, USA, 144(1): 366-373, (2015).	N/A			
Cavallin J, A Schroeder, K Jensen, D Villeneuve, B Blackwell, K Carlson, M Kahl, C LaLone, E Randolph, G Ankley. Evaluation of whole-mount in situ hybridization as a tool for pathway-based toxicological research with early-life stage fathead minnows. *Aquatic Toxicology,* Elsevier Science Ltd, New York, NY, USA, 169: 19-26, (2015).	CSS			
Gray, E, J Furr, K Tatum-Gibbs, C Lambright, H Sampson, B Hannas, V Wilson, A Hotchkiss, P Foster. Establishing the biological relevance of dipentyl phthalate reductions in fetal rat testosterone production and plasma and testis testosterone levels. *Toxicological Sciences*. Society of Toxicology, 149(1): 178-91, (2016).	SHC			
Howdeshell, K, C Rider, V Wilson, J Furr, C Lambright, E Gray. Dose addition models based on biologically relevant reductions in fetal testosterone accurately predict postnatal reproductive tract alterations by a phthalate mixture in rats. *Toxicological Sciences.* Society of Toxicology, 148(2): 488-502, (2015).	CSS			
Karmaus, A, C Toole, D Filer, K Lewis, M Martin. High-throughput screening of chemical effects on steroidogenesis using H295R human adrenocortical carcinoma cells. *Toxicological Sciences*. Society of Toxicology, 150(2): 323-332, (2016).	CSS			
Leonard, J, Tan, Y, Gilbert, M, Isaacs, K, El-Masri, H. Estimating margin of exposure to thyroid peroxidase inhibitors using high-throughput in vitro data, high-throughput exposure modeling, and physiologically based pharmacokinetic/pharmacodynamic modeling. *Toxicological Sciences*. May 15, 2016 (1): 57-70. Epub 2016 Feb 10.	CSS			

Appendix A. Completed Peer-Reviewed ORD Publications in FY16				
Citation	**National Research Program**	**Cancer**	**Microbi**	**Thyroid**
Endocrine Disruption				
Mansouri, K, A Abdelaziz, A Rybacka, A Roncaglioni, A Tropsha, A Varnek, A Zakharov, A Worth, A Richard, C Grulke, D Trisciuzzi, D Fourches, D Horvath, E Benfenati, E Muratov, EB Wedebye, F Grisoni, GF Mangiatordi, GM Incisivo, H Hong, HW Ng, IV Tetko, I Balabin, J Kancherla, J Shen, J Burton, M Nicklaus, M Cassotti, NG Nikolov, O Nicolotti, PL Andersson, Q Zang, R Politi, RD Beger, R Todeschini, R Huang, S Farag, SA Rosenberg, S Slavov, X Hu, R Judson. CERAPP: Collaborative Estrogen Receptor Activity Prediction Project. *Environmental Health Perspectives,* National Institute of Environmental Health Sciences (NIEHS), Research Triangle Park, NC, USA, 1-49, (2016).	CSS			
Paul Friedman, K, ED Watt, MW Hornung, JM Hedge, RS Judson, KM Crofton, KA Houck, SO Simmons. Tiered high-throughput screening approach to identify thyroperoxidase inhibitors within the ToxCast Phase I and II Chemical Libraries. *Toxicological Sciences.* Society of Toxicology, May 15 (1):160-80, (2016).	CSS			•
Ryan, N, Chorley, B, Tice, RR, Judson, R, Corton, JC. Moving toward integrating gene expression profiling into high-throughput testing: A gene expression biomarker accurately predicts estrogen receptor's modulation in a microarray compendium. *Toxicological Sciences,* May; 151(1):88-103, (2016).	CSS			
Suen, AA, Jefferson, WN, Wood, CE, Padilla-Banks, E, Bae-Jump, VL, Williams, CJ SIX1 oncoprotein as a biomarker in a model of hormonal carcinogenesis and in human endometrial cancer. *Mol Cancer Res,* (2016).	CSS	•		
Epigenetics				
King, K, JB Kane, P Scarbrough, C Hoyo, S Murphy. Neighborhood and family environment of expectant mothers may influence prenatal programming of adult cancer risk: discussion and an illustrative DNA methylation example. *Biodemography and Social Biology,* Taylor and Francis, Philadelphia, PA, USA, 62(1): 87-104, (2016).	SHC	•		
Harrill, A.H., McCullough, S.D., Wood, C.E., Kahle, J.J., Chorley ,B.N. MicroRNA biomarkers of toxicity in biological matrices. *Toxicological Science*. 152 (2): 264-272, (2016).	CSS			
McCullough, SD, EC Bowers, DM On, DS Morgan, LA Dailey, RN Hines, RB Devlin, D Diaz-Sanchez. Baseline chromatin modification levels may predict interindividual variability in ozone-induced gene expression. *Toxicological Sciences.* Society of Toxicology, 150(1): 216-224, (2016).	ACE			

Appendix A. Completed Peer-Reviewed ORD Publications in FY16				
Citation	**National Research Program**	**Cancer**	**Microbi**	**Thyroid**
Epigenetics				
Perumal-Kuppusamy, S, P Kaiser, S Wesselkamper. Epigenetic regulation in environmental chemical carcinogenesis and its applicability in human health risk assessment. *International Journal of Toxicology*, Taylor & Francis, Inc., Philadelphia, PA, USA, 5(34): 384-392, (2015).	HHRA	•		
Vidal, A, V Semenova, T Darrah, A Vengosh, Z Huang, K King, M Nye, R Fry, D Skaar, R Mcguire, A Murtha, J Schildkraut, S Murphy, C Hoyo. Maternal cadmium, iron and zinc levels, DNA methylation and birth weight. *BMC Pharmacology and Toxicology*, BioMed Central Ltd, London, UK, 15: 16-20, (2015).	SHC			
Exposure Evaluation				
Arnold, B, T Wade, J Benjamin-Chung, K Schiff, J Griffith, A Dufour, S Weisberg, J Colford. Acute gastroenteritis and recreational water: highest burden among young us children. *American Journal of Public Health*, American Public Health Association, Washington, DC, USA, 106(9): 1690-97, (2016).	SSWR; SHC			
Bennett, DH, RE Moran, X Wu, N Tulve, M Clifton, M Colon, W Weathers, A Sjodin, R Jones, I Hertz-Picciotto. Polybrominated diphenyl ether (PBDE) concentrations and resulting exposure in homes in California: relationships among passive air, surface wipe and dust concentrations, and temporal variability. *Indoor Air*, Blackwell Publishing, Malden, MA, USA, 25(2): 220-229, (2015).	SHC			
Betancourt, D, T Dean, J Kim, J Levy. Genome sequence of *Stachybotrys chartarum* Strain 51-11. Genome Announcements. *American Society for Microbiology,* Washington, DC, USA, 3(6): 1114-1115, (2015).	N/A			
Bost, C., Strynar, M., Reiner, J., Zweigenbaum, J., Secoura, P., Lindstrom, A., Dye, J. U.S. domestic cats as sentinels for perfluoroalkyl substances: Possible linkages with housing, obesity, and disease. *Environmental Research*, Volume 151, November 2016, Pages 145-153	CSS			
Chien, L, M Tsou, H Hsi, P Beamer, K Bradham, Z Hseu, S Jien, C Jiang, W Dang, H Oumlzkaynak. Soil ingestion rates for children under 3 years old in Taiwan. *Journal of Exposure Science and Environmental Epidemiology*, Nature Publishing Group, London, UK, online, (2015).	SHC			

Appendix A. Completed Peer-Reviewed ORD Publications in FY16				
Citation	**National Research Program**	**Cancer**	**Microbi**	**Thyroid**
Exposure Evaluation				
Fulk, F, E Haynes, T Hilbert, D Brown, D Petersen, T Reponen. Comparison of stationary and personal air sampling with an air dispersion model for children's ambient exposure to manganese. *Journal of Exposure Science and Environmental Epidemiology*, Nature Publishing Group, London, UK, online, (2016).	SHC			
Funk, W, J Pleil, DJ Sauter, TW McDade, JL Holl. Use of dried blood spots for estimating children's exposures to heavy metals in epidemiological research. *Journal of Environmental & Analytical Toxicology*, OMICS Publishing Group, Los Angeles, CA, USA, 7: 002, (2015).	ACE			
Kaminski, M, S Lee, M Magnuson. Wide-area decontamination in an urban environment after radiological dispersion: A review and perspectives. *Environmental Science & Technology*, American Chemical Society, Washington, DC, USA, 305: 67-86, (2015).	HSRP			
Marchitti, SA, Fenton, SE, Mendola, P, Kenneke, JF, Hines, EP. Polybrominated diphenyl ethers in human milk and serum from the US EPA MAMA study: Modeled predictions of infant exposure and considerations for risk assessment. *Environmental Health Perspectives*, Jul 12. (2016).	CSS			
McEwen, A, H Hsu-Kim, N Robins, N Hagan, S Halabi, O Barras, D Richter, J Vandenberg. Residential metal contamination and potential health risks of exposure in adobe brick houses in Potosiacute, Bolivia. *Science of the Total Environment,* Elsevier BV, Amsterdam, Netherlands, 562: 237-246, (2016).	HHRA			
Melnyk, L., Wang, Z., Li, Z., Xue, J. Prioritization of pesticides based on daily dietary exposure potential as determined from the SHEDS model. *Food and Chemical Toxicology*, 96: 167-173, ISSN 0278-6915, (2016).	CSS			
Morgan, M, P Jones, J Sobus, J Chuang, NK Wilson. Using urinary biomarkers to evaluate polycyclic hydrocarbon exposures in 126 preschool children in Ohio. *International Journal of Environmental Health Research*, Carfax Publishing Limited, Basingstoke, UK, 25(6): 628-639, (2015).	SHC			
Obrycki, J, N Basta, K Scheckel, B Stevens, K Minca. Phosphorus amendment efficacy for in situ remediation of soil lead depends on the bioaccessible method. Elizabeth Guertal, David Myroid, C. Wayne Smith. *Journal of Environmental Quality*, American Society of Agronomy, Madison, WI, USA, 45(1): 37-44, (2016).	SHC			

Appendix A. Completed Peer-Reviewed ORD Publications in FY16				
Citation	**National Research Program**	**Cancer**	**Microbi**	**Thyroid**
Exposure Evaluation				
Pawlak, E, TL Noah, H Zhou, C Chehrazi, C Robinette, D Diaz-Sanchez, L Muller, I Jaspers. Diesel exposure suppresses natural killer cell function and resolution of eosinophil inflammation: A randomized controlled trial of exposure in allergic rhinitics. *Particle and Fibre Toxicology*, BioMed Central Ltd, London, UK, 13(1): 24, (2016).	ACE			
Platten, W, N Sylvest, C Warren, M Arambewela, S Harmon, K Bradham, K Rogers, T Thomas, T Luxton. Estimating dermal exposure to copper nanoparticles from the surfaces of pressure-treated lumber and implications for toxicity. D. Barcelo Culleres, J. Gan. *Science of the Total Environment*, Elsevier BV, Amsterdam, Netherlands, 548: 441-449, (2016).	CSS			
Schonfeld, T. Ethical considerations in development of future therapies for women and children. Chapter 12, Hughes, Claude L., Waters, Michael D. (ed.), *Translational Toxicology,* Springer International Publishing AG, Cham (ZG), Switzerland, 1(1): 339-371, (2016).	N/A			
Taubel, M, A Karvonen, T Reponen, A Hyvarinen, S Vesper, J Pekkanen. Application of the environmental relative moldiness index in Finland. *Applied and Environmental Microbiology*. American Society for Microbiology, Washington, DC, USA, 82(2): 578-584, (2016).	SHC		•	
Starr J.M., Li, W., Graham, S.E., Bradham, K.D., Stout Ii, D.M., Williams, A., Sylva, J. Using paired soil and house dust samples in an in vitro assay to assess the post ingestion bioaccessibility of sorbed fipronil. *J Hazard Mater*. Jul 15; 312:141-9, (2016).	SHC			
Taubel, M., A. Karvonen, T. Reponen, A. Hyvarinen, S. Vesper, and J. Pekkanen. Application of the Environmental Relative Moldiness Index in Finland. *Applied and Environmental Microbiology*. American Society for Microbiology, Washington, DC, USA, 82(2): 578-584, (2016).	SHC		•	
Winston, J. J., Emch, M., Meyer, R. E., Langlois, P., Weyer, P., Mosley, B., Luben, T. (2016). Hypospadias and maternal exposure to atrazine via drinking water in the National Birth Defects Prevention study. *Environmental Health: A Global Access Science Source*, 15(1), [76].	CSS			

Appendix A. Completed Peer-Reviewed ORD Publications in FY16				
Citation	**National Research Program**	**Cancer**	**Microbi**	**Thyroid**
Exposure Evaluation				
Tulve, N, AB Stefaniak, ME Vance, K Rogers, S Mwilu, RF LeBouf, D Schwegler-Berry, R Willis, TA Thomas, LC Marr. Characterization of silver nanoparticles in selected consumer products and its relevance for predicting children's potential exposures. *International Journal of Hygiene and Environmental Health*, Urban & Fischer Verlag Jena, Jena, Germany, 218(3): 345-357, (2015).	CSS; SHC			
Wu, J, L Jackson. Association of land use and its change with beach closure in the United States, 2004-2013. *Science of the Total Environment*, Elsevier BV, Amsterdam, Netherlands, 571: 67-76, (2016).	SHC			
Wu, X, DH Bennett, AM Calafat, K Kato, M Strynar, E Andersen, RE Moran, DJ Tancredi, N Tulve, I Hertz-Picciotto. Serum concentrations of perfluorinated compounds (PFC) among selected populations of children and adults in California. *Environmental Research*, Academic Press Incorporated, Orlando, FL, USA, 136: 264-273, (2015a).	CSS			
Wu, X, DH Bennett, RE Moran, A Sjodin, R Jones, D Tancredi, N Tulve, M Clifton, M Colon, W Weathers, I Hertz-Picciotto. Polybrominated diphenyl ether serum concentrations in a Californian population of children, their parents, and older adults: An exposure evaluation study. *Environmental Health*, Academic Press Incorporated, Orlando, FL, USA, 14(23): 1-11, (2015b).	SHC			
Neurodevelopmental Disorders				
Behl, M, Hsieh, J, Shafer, T, Mundy, W, Rice, J, Boyd, W, Freedman, J, Hunter, E, Jarema, K., Padilla, S. and Tice, R. Use of alternative assays to identify and prioritize organophosphorous flame retardants for potential developmental neurotoxicity. *Neurotoxicology and Teratology*, 52: 181-93 (2015).	CSS			
Belair, D, M Schwartz, T Knudsen, W Murphy. Human iPSC-derived endothelial cell sprouting assay in synthetic hydrogel arrays. *Acta Biomaterialia (Biomaterials)*, Elsevier B.V., Amsterdam, NETHERLANDS, 1-28, (2016).	CSS			
Gilbert, M, K Sanchez-Huerta, C Wood. Mild thyroid hormone insufficiency during development compromises activity-dependent neuroplasticity in the hippocampus of adult male rats. *Endocrinology,* 157(2): 774-87, (2016).	CSS			•

Appendix A. Completed Peer-Reviewed ORD Publications in FY16				
Citation	**National Research Program**	**Cancer**	**Microbi**	**Thyroid**
Neurodevelopmental Disorders				
Herr, D, Freeborn, D, Degn, L, Martin, SA, Ortenzio, J, Pantlin, L, Hamm, C, Boyes, W. neurophysiological assessment of auditory, peripheral nerve, somatosensory, and visual system function after developmental exposure to gasoline, e15 and e85 vapors. *Neurotoxicology and Teratology*, Elsevier Science Ltd, New York, NY, USA, 54: 78-88, (2016).	ACE			
Brown, J, Hall, D, Frank, C, Wallace, K, Mundy, W, Shafer, T. Evaluation of a microelectrode array-based assay for neural network ontogeny using training set chemicals. *Toxicol. Sci*. In Press Aug 4, 2016.	CSS			
Cotterill, E, Hall, D, Wallace, K, Mundy, W, Eglen, S, Shafer, T. characterization of early cortical neural network development in multiwell microelectrode array plates. *J. Biomolec Screen*. 21: 510-19, (2016).	CSS			
Druwe, I, T Freudenrich, K Wallace, T Shafer, W Mundy. Comparison of human induced pluripotent stem cell-derived neurons and rat primary cortical neurons as in vitro models of neurite outgrowth. *Applied In vitro Toxicology*. Mary Ann Liebert, Inc., Larchmont, NY, USA, 2(1): 26-36, (2016).	CSS			
Gilbert, M, K Sanchez-Huerta, C Wood. Mild thyroid hormone insufficiency during development compromises activity-dependent neuroplasticity in the hippocampus of adult male rats. *Endocrinology*. Endocrine Society, 157(2): 774-87, (2016).	CSS			
Herr, D, Freeborn, D, Degn, L, Martin, SA, Ortenzio, J, Pantlin, L, Hamm, C, Boyes, W. Neurophysiological assessment of auditory, peripheral nerve, somatosensory, and visual system function after developmental exposure to gasoline, E15 and E85 Vapors. *Neurotoxicology and Teratology*. Elsevier Science Ltd, New York, NY, USA, 54: 78-88, (2016).	ACE			
Kraft, A, M Aschner, DA Cory-Slechta, SD Bilbo, W Michael Caudle, S Makris. Unmasking silent neurotoxicity following developmental exposure to environmental toxicants. *Neurotoxicology and Teratology*, Elsevier Science Ltd, New York, NY, USA, 55: 38-44, (2016).	N/A			
Moser, VC, P Phillip, J Hedge, K McDaniel. Neurotoxicological and thyroid evaluations of rats developmentally exposed to tris(1,3-dichloro-2-propyl)phosphate (TDICPP) and tris(2-chloro-2-ethyl)phosphate(TCEP). *Neurotoxicology and Teratology*, Elsevier Science Ltd, New York, NY, USA, 52: 236-247, (2015).	CSS			•

Appendix A. Completed Peer-Reviewed ORD Publications in FY16				
Citation	**National Research Program**	**Cancer**	**Microbi**	**Thyroid**
Neurodevelopmental Disorders				
Mundy, W, Padilla, S, Breier, J, Crofton, K, Gilbert, M, Herr, D, Jensen, K, Radio, N, Raffaele, K, Schumacher, K, Shafer, T, Cowden, J. Expanding the test set: Chemicals with potential to disrupt mammalian brain development. *Neurotoxicology and Teratology*, Elsevier Science Ltd, New York, NY, USA, 52: 25-35, (2015).	CSS			
Ramos, RL, Van Dine, SE, Gilbert, M, Leheste, JR, Torres, G. Neurodevelopmental malformations of the cerebellar vermis in genetically engineered rats. *The Cerebellum,* Springer International Publishing AG, Cham (ZG), Switzerland, 14(5): 624-31, (2015).	CSS			
Ruiz, JD, Quackenboss, J, Tulve, N. Contributions of a child's built, natural, and social environments to their general cognitive ability: A systematic scoping review. *PLoS ONE,* Public Library of Science, San Francisco, CA, USA, 2: e0147741, (2016).	SHC			
Spring, SR, Bastian TW, Wang, Y, Kosian, P, Anderson, GW, Gilbert, ME. Thyroid hormone-dependent formation of a subcortical band heterotopia (SBH) in the neonatal brain is not exacerbated under conditions of low dietary iron (FeD). *Neurotoxicology Teratology,* Jul-Aug; 56:41-6, (2016).	CSS			•
Metabolic Syndrome				
Angrish, M, Kaiser, J McQueen, C, Chorley, B. Tipping the balance: Hepatotoxicity and the four apical key events of hepatic steatosis. *Toxicological Sciences*. April, 2016: 150(2): 261-8.	CSS			
Auerbach, S, D Filer, D Reif, V Walker, AC Holloway, J Schlezinger, S Srinivasan, D Svoboda, R Judson, JR Bucher, KA Thayer. Prioritizing environmental chemicals for obesity and diabetes outcomes research: A screening approach using ToxCast high throughput data. *Environmental Health Perspectives,* National Institute of Environmental Health Sciences (NIEHS), Research Triangle Park, NC, USA, 1-50, (2016).	CSS			
Gordon, C, K Jarema, A Johnstone, P Phillips. Effect of genetic strain and gender on age-related changes in body composition of the laboratory rat. *Physiology & Behavior*, Elsevier B.V., Amsterdam, Netherlands, 153(1): 56-63, (2016).	SHC			