PRELIMINARY DRAFT NOTICE: This Cross-cutting Roadmap, 2016 – 2019 is a preliminary draft. It has not been formally released by the U.S. Environmental Protection Agency (EPA) and should not at this stage be construed to represent Agency policy, nor the final research program.

Children's Environmental Health

Cross-cutting Roadmap

Preliminary Draft – July 2, 2014

U.S. EPA
Office of Research and Development
Washington, DC 20460

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I. Executive Summary

EPA's Office of Research and Development's (ORD's) National Research Programs (Air, Climate, and Energy; Safe and Sustainable Water Resources; Sustainable and Healthy Communities; Chemical Safety for Sustainability; Human Health Risk Assessment; and Homeland Security - http://www2.epa.gov/epa-research/strategic-research-action-plans) are aligned on the core principle of sustainability and are designed to provide the solutions the Agency and the nation need to meet today's complex environmental and human health challenges. Inevitably, significant environmental issues arise that cut across these six programs. Rather than create additional research programs for every cross-cutting issue, ORD is developing Research Roadmaps to clearly identify the science questions and associated research efforts that are ongoing in the six programs. These Roadmaps identify scientific gaps that inform the national research programs in the development of their Strategic Research Action Plans. As new, high priority, cross-cutting issues emerge, ORD expects to use this approach to integrate existing research efforts and identify needed work. Specific research products/deliverables are not included in the Roadmap as they may change as a result of ORD's planning and budgeting each year; however, ORD will use the EPA's website to provide details regarding research products/associated with implementation of this Roadmap. This Roadmap is devoted specifically to the issue of children's environmental health (CEH).

Sustainable decisions and actions are those that improve the wellbeing of individuals and communities today without compromising the health and welfare of future generations. Within this context, CEH research is conducted by the U.S. EPA to improve the scientific understanding required to support: regulatory decisions protective of children's health now and in the future; community decisions that protect and promote children's health across generations; and, ecological decisions that provide sustainable healthy environments for children. The overarching goal for EPA's CEH research program is to provide the Agency and others with the information needed to incorporate consideration of early-lifestage susceptibility and vulnerability into decision making.

This Roadmap provides a vision for EPA's CEH research specific to developmental lifestages from preconception through puberty to adulthood, recognizing that adverse consequences of exposure may not manifest until later in life. Fundamental research to provide the knowledge, infrastructure and biological understanding needed to identify and protect vulnerable and susceptible lifestages, as well as applied research to develop methods and models required to evaluate lifestage-specific risks and to support decisions protective of all early lifestages is described in this Roadmap. Translational research also is included that is required to support communities in their quest to provide sustainable, health-promoting environments for pregnant women and children. CEH research conducted and supported by EPA's ORD employs innovative, cutting-edge science that can be used to support sustainable solutions. Recognizing the broad universe of CEH and associated research, EPA has a unique mandate to focus on understanding the role of exposure to xenobiotic environmental factors during early life, in the context of important modifying factors (i.e., non-chemical stressors), on health impacts across the course of development.

EPA is currently carrying out a variety of research activities focused on understanding adverse health effects associated with environmental exposures to pregnant women and children. EPA has compiled data on children's exposures and exposure factors, and developed databases to improve access to data on exposure, human behavior, chemical use, and developmental toxicity and hazard data. Systems models are being developed for tissues and multi-organ pathways. Studies are being conducted that incorporate epidemiologic and laboratory-based approaches to provide a systems understanding of the relationship between environmental exposures in early life and the health and wellbeing throughout a person's life span (lifecourse). EPA has developed tools and models that can be used to access exposure data, forecast exposures for thousands of chemicals, and evaluate dosimetry of chemicals in the body. EPA 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.

Despite the many contributions to CEH research by ORD over the last decade, there are important gaps in scientific understanding and in tools available to support Agency strategic goals for promoting and protecting wellbeing of children. ORD leadership will be required to ensure that priority Agency needs are addressed. Significant barriers remain to effectively accessing and mining relevant information to understand and predict the role of exposures to environmental factors during early life on health impacts. Models implementing systems-based understanding of child development are required to predict potential for adverse impacts associated with economic development, chemical use, and environmental contamination. Efficient methods and tools are required to effectively address a growing range of lifestage-specific considerations and factors to assess risks where data may be limited as well as to translate information and results for use by local decisions makers.

Transforming the Agency's capacity for considering child-specific vulnerabilities requires that ORD apply advanced systems science and integrate diverse emerging data and knowledge in exposure, toxicology, and epidemiology to improve understanding of the role of exposure to environmental factors during early life on health impacts that may occur at any point over the lifecourse. The impact of integrated ORD research in CEH will be that: information and tools are available to support consideration of children's sensitivity, susceptibility, and vulnerability in risk assessments and decisions; EPA regulatory decisions consider potential impacts of environmental exposures on children's health (and do so with less uncertainty); and, local decision makers use EPA research models and decision support tools to make decisions that protect and promote children's health in community settings.

II. Introduction

Background

The mission of the EPA is to protect human health and the environment. In addressing health risks, the goal is to not only provide protection for the general population, but specifically for vulnerable individuals and groups, including children. In addition, the Agency expects that decisions and actions designed to promote and protect children's health should do so sustainably. That is, public policy for improving the health of

individuals and communities should provide effective solutions today without compromising the health and welfare of future generations.

In the Fiscal Year 2014-2018 EPA Strategic Plan, the Agency "recognizes environmental justice, children's health, and sustainable development are all at the intersection of people and place. These goals are not mutually exclusive. Throughout all our work to achieve more livable communities, EPA is committed to ensuring we focus on children's health and environmental justice." (U.S. Environmental Protection Agency, 2014h). As such, ORD has identified children's health as a cross-cutting research area.

Over the last few decades there have been a number of key legislative and policy initiatives that have been crucial for EPA's mission to protect children's health. In response to concern about the potential vulnerability of children to dietary exposure of pesticides, the U.S. Congress requested that the National Academy of Sciences (NAS) study this critical public health issue. In 1993, the NAS released a report entitled Pesticides in the Diets of Infants and Children that described significant differences in toxicity and exposure of pesticides between children and adults (National Academy of Sciences, 1993). The NAS recommended that changes be made in regulatory practice. "Most importantly, estimates of expected total exposure to pesticide residues should reflect the unique characteristics of the diets of infants and children and should account also for all non-dietary intakes of pesticides. … Determinations of safe levels of exposure should take into consideration the physiological factors that can place infants and children at greater risk of harm than adults."

The NAS study led Congress to enact the Food Quality Protection Act (FQPA) in 1996, which significantly amended the Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA) and the Federal Food Drug, and Cosmetic Act (FFDCA) and set a new risk standard of ensuring "reasonable certainty of no harm." Effective protection of children was emphasized through EPA's use of an extra ten-fold children's safety factor when establishing tolerances unless data were available to show that a different factor was protective. The NAS report also provided the impetus for a series of actions within EPA and across the federal government to address the importance of assessing children's environmental health internally within EPA and across the federal government.

Since the 1990s, EPA has enacted a number of policies and strategies to protect children's health. In 1995 (and reaffirmed in 2013), EPA adopted its **Policy on Evaluating Health Risks to Children** (U.S. Environmental Protection Agency, 1995) to consider the risks to infants and children consistently and explicitly as a part of assessments generated during the decision making process, including the setting of standards to protect public health and the environment. In 2000, ORD released its **Strategy for Research on Environmental Risks to Children** (U.S. Environmental Protection Agency, 2000) to strengthen the scientific foundation of EPA risk-based assessments and risk management decisions that support children's health and welfare. In 2006, EPA prepared its Guide to Considering Children's Health When Developing EPA Actions: Implementing Executive Order 13045 and EPA's Policy on Evaluating Health Risks to Children (U.S. Environmental Protection Agency, 2006a). This guidance outlines the key steps in developing actions where children's health should be considered.

Table 1 presents a summary of the major U.S. government (executive and legislative branches), EPA and other federal agencies, international organizations, and states' laws, policies, and guidance on the protection of children's health from environmental hazards.

Table 1. Key governmental and international actions on children's environmental health

Organization	Year	Title	Content
		U.S. Government	
Presidential Executive Order	1997	Presidential Executive Order 13045 – Protection of Children from Environmental Health Risks and Safety Risks (http://www.gpo.gov/fdsys/pkg/FR-1997-04-23/pdf/97-10695.pdf)	Requires all federal agencies to assign a high priority to addressing health and safety risks to children, coordinate research priorities on children's health, and ensure that their standards take into account the special risks to children.
106th U.S. Congress	2000	Children's Health Act (Public Law 106-310) (http://www.gpo.gov/fdsys/pkg/PLAW-106publ310/pdf/PLAW-106publ310.pdf)	Directed NIH, NIEHS, CDC, and EPA to conduct a National Children's Study.
President's Task Force (co-chaired by HHS and EPA)	2001	Presidential Task Force on Children's Environmental Health and Safety Meets. HUD Announces $67 Million in Grants to Fight Childhood Lead Poisoning (http://archive.hhs.gov/news/press/2001pres/20011024a.html)	The task force's priorities were to examine programs that combat childhood lead poisoning and the increased incidence of asthma.
110th U.S. Congress	2007	Energy Independence and Security Act of 2007	Required EPA to develop school siting guidelines and school environmental health guidelines.
President's Task Force (co-chaired by HHS and EPA)	2012	Coordinated Federal National Action Plan to Reduce Racial and Ethnic Asthma Disparities (http://www.epa.gov/childrenstaskforce)	The goal is to reduce disparities in the burden caused by asthma, particularly among children.
		EPA	
	1995	Policy on Evaluating Health Risks to Children (U.S. Environmental Protection Agency, 1995) (http://www2.epa.gov/children/epas-policy-evaluating-risk-children-0)	The risks to infants and children should be considered consistently and explicitly as part of risk assessments, including the setting of standards to protect public health and the environment.
	1996	National Agenda to Protect Children's Health from Environmental Threats (http://www2.epa.gov/children/epas-national-agenda-protect-childrens-health-environmental-threats)	All standards should be protective of heightened risks faced by children; develop a scientific research strategy regarding child-specific environmental threats; develop new policies regarding exposures faced by children.
	1996	Enactment of The Food Quality Protection Act (http://www.epa.gov/pesticides/health/children-standards.html)	Improved the safety standards that EPA uses in evaluating pesticide risks, especially risks to children.
	1997	Creation of the Office of Children's Health Protection (OCHP) (http://www2.epa.gov/children/history-childrens-environmental-health-protection-epa)	Mission is to make the health protection of children a fundamental goal of public health and environmental protection.
	1997	Creation of the Pediatric Environmental Health Specialty Units (PEHSUs) with ATSDR	PEHSUs translate research into public health and clinical practice, educate

		health providers and consult on pediatric environmental health issues.
1998	Children's Environmental Health and Disease Research Centers (CEHCs) (Jointly funded with NIEHS) (http://epa.gov/ncer/childrenscenters/)	Explores ways to reduce children's health risks from environmental contaminants.
2005 - 2008	New risk assessment guidance: Guidance on Selecting Age Groups for Monitoring and Assessing Childhood Exposures to Environmental Contaminants (U.S. Environmental Protection Agency, 2005a) (http://www.epa.gov/raf/publications/guidance-on-selecting-age-groups.htm); Supplemental Guidance for Assessing Susceptibility from Early-Life Exposure to Carcinogens (U.S. Environmental Protection Agency, 2005b)(http://www.epa.gov/raf/publications/cancer_guidelines/sup-guidance-early-life-exp-carcinogens.htm); A Framework for Assessing Health Risk of Environmental Exposures to Children (U.S. Environmental Protection Agency, 2006b) (http://cfpub.epa.gov/ncea/risk/recordisplay.cfm?deid=158363); Child-Specific Exposure Factors Handbook (U.S. Environmental Protection Agency, 2008) (http://cfpub.epa.gov/ncea/risk/recordisplay.cfm?deid=199243) (The latest information on child-specific exposure factors can be found in the 2011 Exposure Factors Handbook)	Risk assessment guidance for assessing childhood environmental health issues.
2010	Working for Environmental Justice and Children's Health (part of EPA's Strategic Plan, 2011-15) (http://www.epa.gov/planandbudget/strategicplan.html	Emphasis on development and use of the latest science on children's unique vulnerabilities.
2013	Protections for Subjects in Human Subjects Research with Pesticides (http://www.epa.gov/oppfead1/guidance/human-test.htm)	Provides for additional protection of susceptible subpopulations and prohibits EPA-sponsored research involving intentional exposures of pregnant women or children to any environmental substance. Implementation of this guidance has broad implications for children's environmental health research.
2013	ORD establishes six integrated, transdisciplinary National Research Programs: Air, Climate and Energy (ACE); Safe and Sustainable Water Resources (SSWR); Sustainable and Health Communities (SHC); Chemical Safety for Sustainability (CSS); Human Health Risk Assessment (HHRA); Homeland Security (HS) (http://www2.epa.gov/aboutepa/about-office-research-and-development-ord)	Provides the scientific foundation, methods, and tools that EPA needs to fulfill its mission of protecting human health and the environment.
2013	EPA's 1995 Policy on Evaluating Health Risks to Children is reaffirmed by EPA's current Administrator ((http://www2.epa.gov/sites/production/files/2013-11/documents/childrens_enviromental_health_risk_2013_reaffirmation_memorandum.pdf)	"This reaffirmation strengthens EPA's commitment to leadership in children's environmental health as well as the leadership of the Office of Children's Health Protection … and continues to encourage much needed research…"

Other Federal Agencies, Countries, and International Organizations			
FDA	2010	Advancing Regulatory Science for Public Health (http://www.fda.gov/downloads/scienceresearch/specialtopics/regulatoryscience/ucm228444.pdf)	Identifies improving child health as one of the major areas in which advancement in the field can improve public health.
HUD	2009	The Healthy Homes Strategic Plan (http://portal.hud.gov/hudportal/HUD?src=/program_offices/healthy_homes)	Roadmap in the protection of the health of children and other sensitive populations in a comprehensive and cost-effective manner.
Canada	2010	National Strategic Framework on Children's Environmental Health (http://www.hc-sc.gc.ca/ewh-semt/pubs/contaminants/framework_children-cadre_enfants/index-eng.php#a0)	Guides the development of action plans for the protection of children living in Canada from exposure to environmental hazards.
European Union	2013	The Helix Project (http://www.projecthelix.eu/)	A collaborative project using novel tools and methods to characterize early life exposure to a wide range of environmental hazards and which will be integrated and linked with data on major child health outcomes.
World Health Organization (WHO)	2004	Children's Environment and Action Plan for Europe (http://www.euro.who.int/__data/assets/pdf_file/0006/78639/E83338.pdf)	Developed four regional priority goals and committed the member states to develop and implement national children's environment and health action plans.
	2012	State of the Science of Endocrine Disrupting Chemicals (http://www.who.int/ceh/publications/endocrine/en/)	Presents scientific knowledge on exposure to and effects of endocrine disrupting chemicals.
	2013	Guidance on identifying important lifestages for monitoring and assessing risks from exposures to environmental contaminants (http://www.who.int/ceh/publications/exposures_environmental_contaminants/en/)	Presents a harmonized set of age bins for monitoring and assessing risks from exposures to chemicals for global use that focuses on preconception through adolescence.
States			
California	2001	Prioritization of Toxic Air Contaminants - Children's Environmental Health Protection Act (http://oehha.ca.gov/air/toxic_contaminants/SB25finalreport.html)	Presents information on chemicals that are identified as toxic air contaminants that may cause infants and children to be particularly susceptible to illness.
Washington	2008	Chemicals of High Concern to Children - Children's Safe Product Act (http://www.ecy.wa.gov/programs/swfa/cspa/)	Presents information on chemicals that are toxic and have either been found in children's products or have been documented to be present in human tissues.
Minnesota	2014	Chemicals of Special Concern to Children's Health (http://www.health.state.mn.us/divs/eh/children/chemicals.html)	Presents information on chemicals that may adversely affect children's health.

Current Drivers for CEH Research

There are three key drivers that define the need for, and focus of, EPA-led CEH research: 1) EPA's 2014-2018 Strategic Plan, 2) EPA program office mandates, and 3) Recent scientific research findings related to CEH issues.

EPA's 2014-2018 Strategic Plan - The EPA Strategic Plan released in early 2014 calls specifically for applied research in CEH under two of the five strategic goals: Goal 3, Cleaning-Up Communities and Advancing Sustainable Development; and Goal 4, Ensuring Safety of Chemicals and Preventing Pollution.

In the area of cleaning up communities, research to enhance the ability to adequately consider children's unique susceptibilities and vulnerabilities will provide the Agency, State, Tribal, and local decision makers with the knowledge needed to make smart, systems-based decisions that will inform a balanced approach to their cleanup and development needs. EPA's chemical safety research will provide the scientific foundation to support safe and sustainable use of chemicals, including the systems understanding needed to adequately protect the health of children and other vulnerable groups.

In addition, the EPA Strategic Plan emphasizes the importance of leveraging and building on existing partnerships to achieve strategic objectives. This includes partnering "with research organizations and academic institutions to focus and advance basic research and create models and measures to expand the conversation on environmental and human health concerns to address priority-focused, locally based problems, specifically including … children's environmental health issues." (U.S. Environmental Protection Agency, 2014h).

EPA's Program Office Drivers - Each EPA program office has different mandates to protect children from environmental health risks, depending on the environmental laws and guidance specific to the program office. EPA has also established the Office of Children's Health Protection, a cross-cutting office that establishes links across the EPA program offices and with other Agencies on CEH issues.

> Office of Children's Health Protection (OCHP): EPA established OCHP in May 1997 to make the protection of children's health a fundamental goal of public health and environmental protection in the U.S. OCHP supports and facilitates Agency efforts to protect children's health from environmental threats through participation in: regulation and standards development; research planning; risk assessment guidance and policy development; and outreach and partnerships with health care professionals, youth groups, and community groups. Important OCHP projects have included: EPA's Clean, Green, and Healthy Schools Initiative (http://www.epa.gov/schools/); increasing environmental health literacy of students and educators; support of Pediatric Environmental Health Specialty Units (http://aoec.org/pehsu/index.html) which serves as a resource about CEH for health care providers, communities, and the public; and publication (in partnership with

the Office of Policy) of "America's Children and the Environment" (http://www.epa.gov/ace/), which evaluates and communicates trends in environmental contaminants that may contribute to childhood disease.

OCHP also provides children's health expertise in Agency rulemakings and other actions, including the Integrated Risk Information System (IRIS) and many other programs across the Agency. Data and analytical tools from ORD are valuable to OCHP's cross-cutting involvement in these priority actions for children's health.

Office of Chemical Safety and Pollution Prevention (OCSPP): The Toxic Substances Control Act (TSCA) provides EPA with the authority to require reporting, record-keeping and testing requirements, and restrictions related to chemical substances and/or mixtures. OCSPP carries out these requirements by reviewing new and existing chemicals, evaluating chemical hazard, including hazard relevant to developmental and reproductive toxicological endpoints, and exposure, including exposures of children to environmental chemicals. EPA is currently working with Congress, and members of the public, the environmental community, and industry to reauthorize TSCA. EPA is working with these groups to modernize and strengthen the tools available under TSCA to prevent harmful chemicals from entering the marketplace and to increase confidence that those chemicals that remain are safe and do not endanger the environment or human health, especially for consumers, workers, and children.

Recently, as part of EPA's approach to enhance the Agency's existing chemicals management program, OCSPP identified 83 chemicals (TSCA Workplan Chemicals) for further assessment under TSCA (http://www.epa.gov/oppt/existingchemicals/pubs/workplans.html). These chemicals were selected based on five criteria: hazard, exposure, persistence, bioaccumulation, and use, including use in children's products.

OCSPP developed the Endocrine Disruptor Screening Program (EDSP) in response to statutory language in the Federal Food, Drug, and Cosmetic Act (FFDCA) and in the Safe Drinking Water Act (SDWA) that requires EPA to screen pesticides for their potential to produce effects similar to those produced by the female hormone, estrogen, and gives EPA the authority to screen certain other chemicals and to include other endocrine effects. In 2005, OCSPP selected 67 chemicals for the initial round of endocrine screening based on their relatively high potential for human exposure. These chemicals consisted of pesticide active ingredients and high production volume chemicals used as inert ingredients in pesticide formulation. In 2010, OCSPP selected 109 chemicals for the second round of endocrine screening, consisting of drinking water contaminants, such as halogenated organic chemicals, dioxins, flame retardants, plastics, pharmaceuticals and personal care products (http://www.epa.gov/endo/pubs/prioritysetting/index.htm).

In 2010, OCSPP announced plans to make better use of computational toxicology tools in the EDSP and developed the EDSP21 workplan. This workplan outlines an approach for using computational or *in silico* models and molecular-based high-throughput assays to prioritize and screen chemicals to determine their potential to interact with the estrogen, androgen, or thyroid hormonal systems.

(http://www.epa.gov/endo/pubs/edsp21_work_plan_summary%20_overview_final.pdf).

EPA's current pesticide review processes focus on ensuring that pesticide registrations comply with the Endangered Species Act and achieve broader Agency objectives for water quality protection. The review processes will continue to place emphasis on the protection of potentially sensitive populations, such as children, by reducing exposures from pesticides used in and around homes, schools, and other public areas.

Office of Water (OW): In the standard setting process for chemicals in drinking water, OW is required, under Section 103 of the 1996 Amendments to the Safe Drinking Water Act, to determine "the effects of the contaminant on the general population and on groups within the general population such as infants, children, pregnant women, the elderly, individuals with a history of serious illness, or other subpopulations that are identified as likely to be at greater risk of adverse health effects due to exposure to contaminants in drinking water than the general population."

While the 1996 SDWA amendments uses the term "subpopulation" to describe groups with unique attributes, including those defined by age or lifestage, since 2005 EPA has recognized the importance of distinguishing between population groups that form a relatively fixed portion of the population (e.g., groups based on ethnicity) and lifestages or age groups that are inclusive of the entire population. The term "lifestage" refers to a distinguishable time frame in an individual's life characterized by unique and relatively stable behavioral and/or physiological characteristics that are associated with development and growth. Thus, childhood should be viewed as a sequence of lifestages, from birth, through infancy and adolescence.

OW considers the effect of contaminants upon children's health in the standard setting process by following EPA's guidance on children's health issues: "Supplemental Guidance for Assessing Susceptibility from Early Life Exposure to Carcinogens" (http://www.epa.gov/raf/publications/cancer_guidelines/sup-guidance-early-life-exp-carcinogens.htm) and "A Framework for Assessing Health Risks of Environmental Exposures to Children" (http://cfpub.epa.gov/ncea/risk/recordisplay.cfm?deid=158363). OW uses these guidances in its qualitative assessment of the adverse health effects of contaminants, and for carcinogens, OW factors in age-dependent susceptibility in its dose-response assessment.

Office of Air and Radiation (OAR): In conducting risk assessments for air toxics, OAR routinely seeks to identify the highest risks to those population subgroups—such as children—that may be more vulnerable to certain environmental contaminants than are adults. Such assessments are conducted for all air toxics rulemakings, including

National Emissions Standards for Hazardous Air Pollutants (NESHAPS, otherwise known as Maximum Achievable Control Technology or MACT standards) and Residual Risk rules. During these assessments, OAR specifically estimates risks to children and/or determines if children are disproportionately affected by their exposures and/or behavioral patterns. OAR uses dose-response values which specifically account for the differential sensitivity of children as compared to adults and has developed exposure estimates for mutagenic carcinogens (e.g., vinyl chloride and polycyclic aromatic hydrocarbons) which specifically account for the greater vulnerability of children to these compounds during their developmental years, based on EPA's "Supplemental Guidance for Assessing Susceptibility from Early Life Exposure to Carcinogens" (http://www.epa.gov/raf/publications/cancer_guidelines/sup-guidance-early-life-exp-carcinogens.htm).

OAR also carefully considers impacts on children's health as part of the periodic reviews of the national ambient air quality standard (NAAQS), in which the Agency must consider whether the standards are requisite to protect public health, including the health of at-risk subgroups, with an adequate margin of safety. Evaluating the effects of criteria air pollutants in children has been a central focus in several recent NAAQS reviews, including reviews of the lead, ozone, and particulate matter standards, which resulted in revised standards to strengthen public health protection.

Office of Solid Waste and Emergency Response (OSWER): OSWER provides policy, guidance and direction for the Agency's waste and clean-up programs, emergency response, the management of hazardous substances and waste, and the redevelopment of contaminated sites. OSWER implements its mission under a variety of mandates, including the Comprehensive Environmental Response, Compensation and Liability Act (CERCLA), the Resource Conservation and Recovery Act (RCRA), and Brownfields Revitalization Act. In addressing this mission, OSWER works to understand and protect the health of populations, taking into account unique susceptibilities and vulnerabilities of children.

OSWER directly considers potential impacts to sensitive subpopulations, including children in it risk assessment and risk management actions. Consistent with the National Contingency Plan [40 CFR 430(e)(2)(i)(A)(10], OSWER's cleanup under Superfund actions ensure that exposures to the human population, including sensitive subgroups, are without adverse effect during a lifetime or part of a lifetime, incorporating an adequate margin of safety. The Risk Assessment Guidance for Superfund (RAGS) documents provide specific guidance on the incorporation of child specific factors, including body weight, timing of exposure, and unique exposure pathway considerations, such as dust and soil intake rates.

Regional Offices: Each Regional Office has a Children's Environmental Health coordinator that is responsible for leading the Children's Environmental Health Program in their region, and to engage with the other regional coordinators, including Regional School Coordinators and risk assessors. These programs are

based on national and regional strategies to protect children's environmental health through a number of regulations and voluntary programs. While exposures can occur in any number or variety of locations, the regions work with decision-makers to understand and reduce exposures in home, learning and play environments.

Scientific Drivers Related to Adverse Health Outcomes

Recent research findings on the relationship of environmental contributions to children's health outcomes are important drivers for EPA's CEH research. The following is a summary of some of the key recent research findings concerning environmental contaminants and their relationship to four adverse health outcomes of high interest to the Agency and for which ORD has active CEH research: birth outcomes, neurodevelopmental disorders, asthma, and metabolic disease.

Birth outcomes: A variety of environmental contaminants have been associated with birth outcomes including birth defects, low birth weight, and premature birth, which in turn may presage abnormal development and lead to chronic diseases later in life.

- Air pollution, particularly exposure to fine particles ($PM_{2.5}$), has been associated with preterm birth and low birth weight in a number of epidemiological studies (Dadvand et al., 2013; Stieb, Chen, Eshoul, & Judek, 2012).
- Recent findings from both epidemiology and animal studies indicate that *in utero* exposures to chemicals such as arsenic that are associated with low birth weight may also be associated with later health outcomes in the offspring (Boekelheide et al., 2012).
- Environmental chemicals, including organochlorine pesticides, organic solvents, and air pollutants are being investigated for their potential association with congenital heart disease (Gorini, Chiappa, Gargani, & Picano, 2014).

Neurodevelopmental Disorders: Neurodevelopmental effects of chemicals, including lower IQ, learning deficits and other indicators of poor cognitive function, and adverse effects on behavior, have been shown in animal models and from *in utero* exposure to pregnant women and children in epidemiological studies.

- Neurotoxicants that have been associated with developmental effects include lead, methylmercury, PCBs, arsenic, toluene, manganese, fluoride, chlorpyrifos, dichlorodiphenyltrichlorethane, and tetrachloroethylene (Grandjean & Landrigan, 2014).
- There is limited to suggestive evidence for an association between exposure to air pollutants, organophosphate pesticides, brominated flame retardants, phthalates, bisphenol A, and perfluorinated compounds and adverse neurodevelopmental effects (Bellinger, 2013; Choi, Sun, Zhang, & Grandjean, 2012; Rodriguez-Barranco et al., 2013; Yim, Harden, Toms, & Norman, 2014).
- Recent children's cohort studies implicate prenatal exposure to polycyclic aromatic hydrocarbons (PAHs) from air pollution and bisphenol A with attention problems, anxiety and aggressive behavior in boys (F. Perera et al., 2012; F. P. Perera et al., 2011).

- The possible link between environmental contaminants and increasing prevalence of attention deficit hyperactivity disorder and autism is an area of active investigation. One hypothesis being evaluated considers the sensitivity of the embryo and fetus to thyroid disturbance and evidence of human in utero exposure to contaminants associated with thyroid pathways. In addition, potential for gene-environment interactions are being studied. (Citations)

Asthma: The incidence and severity of childhood asthma continues to rise in the U.S. More is known about environmental factors that exacerbate asthma severity than those that cause asthma, but recent evidence implicates air pollution as a causative factor.

- Asthma disproportionately impacts minority children, especially in urban communities typified by low income and high levels of air pollution, poor indoor air quality, and other social factors (Akinbami et al., 2012).
- Substantial evidence has associated *in utero* or early life exposures to environmental tobacco smoke, ambient and indoor air pollutants, and inhaled allergens (dust mites, pets and pollens) with asthma incidence and/or severity in children (Dick, Doust, Cowie, Ayres, & Turner, 2014; Selgrade, Blain, Fedak, & Cawley, 2013).
- Genetic factors and gene-environment interactions also play a role in asthma causation (Rigoli et al., 2011). Environmental exposures may also impact asthma risk through epigenetic mechanisms, an emerging area of study (Kabesch, 2014; Salam, Zhang, & Begum, 2012).

Metabolic Disease: Metabolic disease, including childhood obesity, is increasing in the U.S. and many other countries across the world. The rise in metabolic disease is of particular concern because the risk of life-threatening diseases, such as diabetes, cardiovascular disease, and cancer is increased in persons with metabolic disease.

- The possibility that environmental chemicals can influence childhood obesity is currently under investigation, with the following chemicals being studied: dioxins, PCBs, DDT, DDE, perfluoroalkyls, PBDEs, phthalates, bisphenol A, organotins, lead, air pollution, diethylstilbestrol, anti-psychotic drugs, and thiazolidinediones. Some of these chemicals have been shown to increase obesity in laboratory animals and *in vitro* studies have shown cell differentiation that may indicate an association between certain chemicals and obesity (Karoutsou & Polymeris, 2012; La Merrill & Birnbaum, 2011).
- Epigenetic reprogramming may be a contributing factor in childhood obesity and other metabolic diseases, and is an area of intense study (Janesick & Blumberg, 2011).

Purpose

Protecting children's health from environmental risks remains a critical and enduring part of EPA's mission. EPA conducts and supports CEH research to inform regulatory decisions and to support community decision-making to promote sustainable healthy environments for children. Given recent advances in the science of risk assessment, it has now become an opportune time to re-examine and update EPA's path forward for critical CEH research.

The purpose of this CEH Roadmap is to describe EPA's strategic vision for CEH research, building upon and extending the problems and needs identified in EPA's 2000 research strategy. This new vision aims to use all science, particularly 21st Century science and systems approaches to: improve our understanding of how environmental factors affect children's health and contribute to the most prevalent diseases and disorders; incorporate basic human health research into the development of innovative new approaches for assessing risks associated with early lifestage exposures, including prenatal and lactational exposures; and translate basic and applied research findings to inform new ways by which the Agency and others can take action to prevent or reduce adverse children's environmental health outcomes and promote sustainably healthy environments in communities where children live, play and learn.

The ORD cross-cutting Research Roadmaps are not intended to be new research strategies for Strategic Research Action Plans (StRAPs). Rather, they take a cross-cutting look at existing and imminent ORD research portfolios and emerging StRAPs for each National Research Program (NRP) and describe the focus of ongoing research and the direction of the planned research. They also inform future research planning in relevant NRPs. As such, this cross-cutting Research Roadmap has two important attributes: 1) the research needs described are "owned" by an NRP and articulated as either existing or planned (definitively or aspirationally) in a near-term timeframe; and 2) research needs described are those for which EPA/ORD needs to play a transformative leadership role.

This Roadmap is focused specifically on CEH research. There is a separate Roadmap for research on environmental justice which will articulate research and needs specific to all lifestages, and highlight research that addresses both CEH and environmental justice (health disparity) concerns.

The lifestage scope of the research described in this Roadmap specifically considers impacts associated with exposure during or across developmentally sensitive windows. EPA has official guidance defining early lifestage specific age bins. **Error! Reference source not found.** outlines these lifestages which are the specific focus for Roadmap research. Note that while exposures from preconception through adolescence are of primary interest, impacts may extend throughout the lifecourse into adult lifestages and across generations. Here the lifecourse is depicted as a circle to convey the concept of intergenerational impacts from environmental exposures.

In this Roadmap we identify CEH research being conducted in ORD, evaluate within the context of the vision for future research, and identify major knowledge gaps to inform ORD research planning.

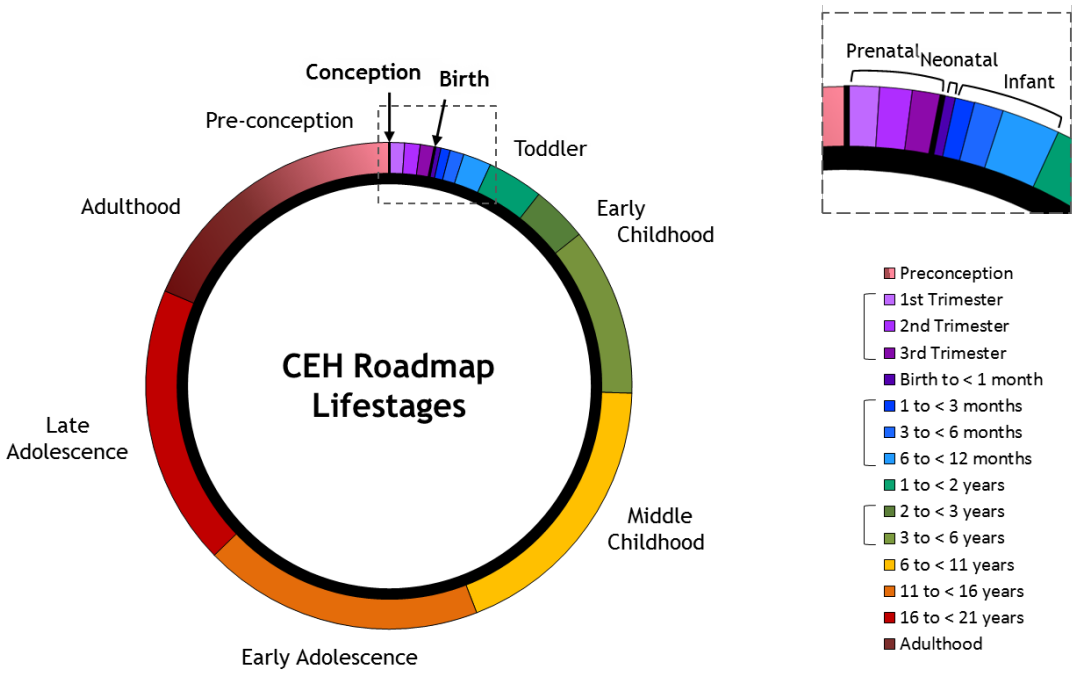


Figure 1. Depiction of lifestages specific to CEH Roadmap research. The lifecourse is depicted as a circle to convey the concept of intergenerational impacts associated with environmental exposures.

III. Research Scope

Expanded Problem Statement

Within the broad sphere of children's environmental health, the overarching goal for EPA's CEH research is to provide the Agency and others with the information needed to incorporate consideration of early lifestage sensitivity, susceptibility and vulnerability into decision making, including community decisions related to sustainability.

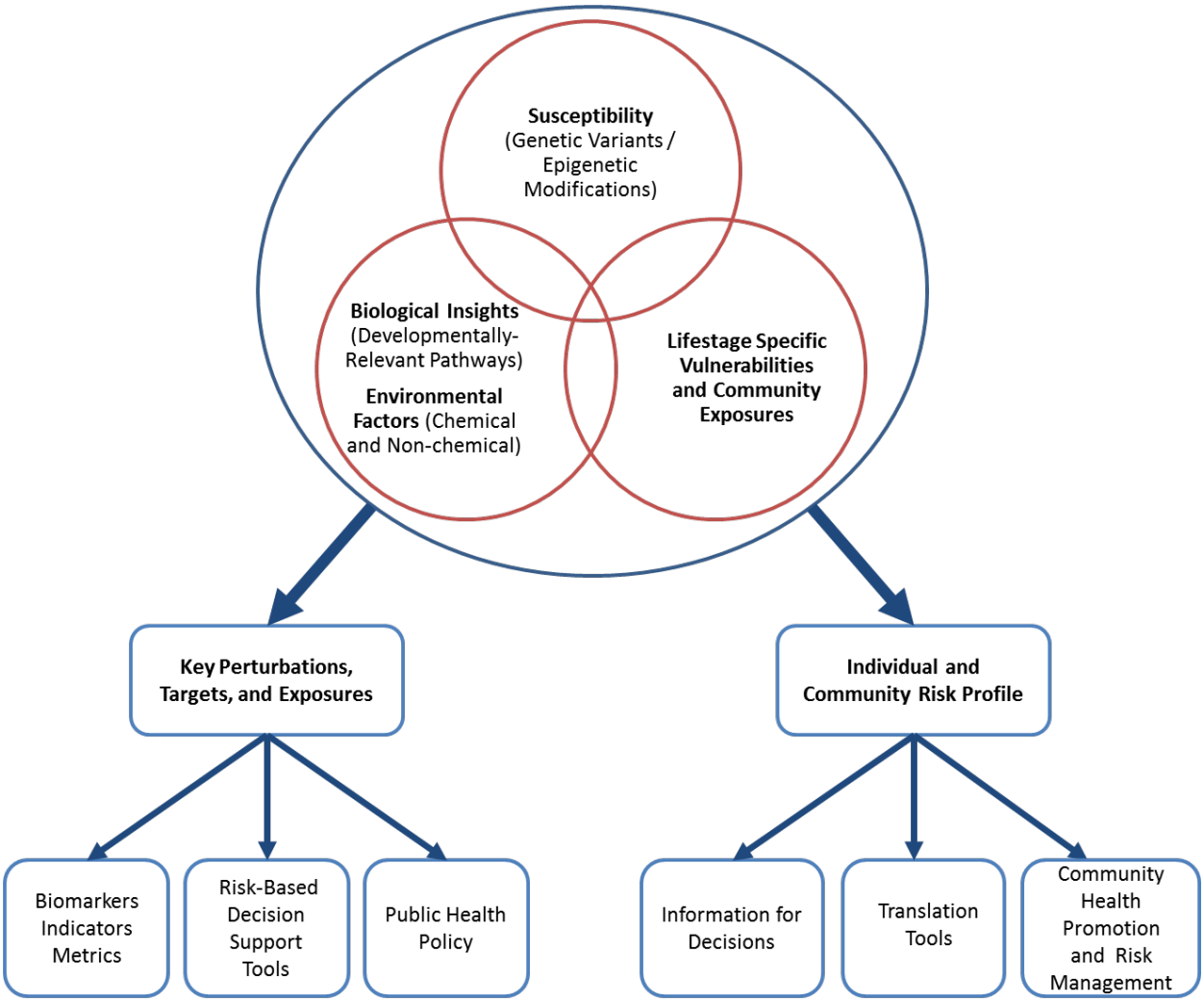
EPA has a unique mandate to focus on understanding the role of exposure to xenobiotic environmental factors during early life, in the context of important modifying factors (i.e., non-chemical stressors), on health impacts over the course of a lifetime.

Importantly, the Agency and stakeholders require translation of cutting edge science to incorporate consideration of early lifestage sensitivity, susceptibility and vulnerability into decision making. The translation framework presented in Figure 2 (adapted from (McCarthy et al., 2008)) considers two routes by which ORD research will provide required information and tools. In the first, identification of toxicity pathways coupled to identification of important environmental factors (exposures) provides new opportunities to inform decision making and public health protection at the population level. Decision support tools developed along this route may include: (1) biomarkers,

metrics, and indicators for measuring and monitoring environmental exposures as well as providing early indication of toxicological impacts; (2) models for risk-based decision making, informed by detailed understanding of relevant environmental stressors and associated perturbations to toxicity pathways; and (3) public policy to prevent or mitigate adverse exposures to protect and promote human health and welfare. The second translational route lies through using knowledge of individual patterns of exposure and disease predisposition to develop community-based approaches to health promotion and risk management. Here, environmental health research and public policy can only fully empower communities to manage risks by providing a clear understanding of important exposures and where these can be locally controlled.

Considerations of individual variation based on genetic susceptibility, lifestage, timing of exposures, and interaction of non-chemical stressors is required context for both routes and for holistic assessment of risk factors associated with complex environmental disease. By requiring characterization of biologically relevant exposure, the framework presented in Fig. 2 facilitates translation of advances and findings in computational toxicology to information that can be directly used to support risk assessment for decision making and improved public health. In addition, application of this framework will inform design of future exposure and epidemiology studies such that data gaps along all levels of biological organization (i.e., from molecular through population levels) are targeted in a systems-based fashion. Such a strategic implementation of toxicology, exposure and epidemiology research is required to ensure efficient use of resources committed to children's health studies. Further, over time and with the generation of requisite information, this framework will facilitate elucidation of gene–environment interactions and important environmental contributions to complex disease.

Figure 2. Children's Environmental Health Research Translation Framework (adapted from (Cohen Hubal et al., 2010))



Science Challenges

To provide the science, information and decision support tools required to promote and protect children's health and wellbeing, EPA's CEH research is designed to address the following four priority research areas:

- Knowledge infrastructure to provide early lifestage-specific data and information;
- Systems (biological) understanding of the relationship between environmental exposures and health outcomes across development;
- Methods and models fit for purpose to evaluate early lifestage-specific risks and to support decisions protective of all early lifestages;
- Translational research to incorporate CEH into tools fit for purpose to inform community actions and decisions.

For each of these research areas, this Roadmap provides the general scope of the area, key research questions, and specific research needed to provide the answers.

Research Area 1: Knowledge infrastructure to provide lifestage-specific data and information

While much of these data may come from outside the Agency, key data required to support risk-based decisions requires targeted Agency support and the knowledge systems to facilitate integration and analysis to identify and protect susceptible lifestages.

Key research questions: What data and information are most critical for:

- Characterizing early lifestage vulnerabilities and susceptibility in the areas of exposure. toxicokinetics, toxicodynamics, and disease etiology;
- Evaluating linkages between early life environmental exposures and health outcomes, including those that may appear later in life.
- Reducing early lifestage-related uncertainties in exposure and risk characterization to provide the basis for EPA's policy decisions?

Integrated impact: Information on early lifestage exposure and hazard is incorporated into ORD integrated applications to provide accessible data and tools to support Agency program- and decision-specific needs for chemical and pathogen evaluation, multiple stressor characterization, and risk assessment.

Research Area 2: Systems understanding of the relationship between environmental exposures and health outcomes across development

A holistic understanding of the factors that impact children's health, specific to each stage of development, is needed in order to attribute, reduce and eliminate risks specific to the environmental exposures over which EPA has regulatory authority. Systems level understanding of key biological pathways and emergent behaviors may be applied to support decisions that protect susceptible lifestages. EPA CEH research is designed to develop this understanding by considering exposures to chemicals and chemical classes of concern as well as the influence of non-chemical stressors and the built environment on children's health outcomes. Toxicological and epidemiological studies on exposure to chemical and non-chemical stressors are included in this research area.

Children encounter a number of chemicals in the natural and/or built environment. Key chemicals/classes of current and emerging focus include chemicals that EPA regulates including: manufactured chemicals (pesticides, solvents, industrial chemicals) across their lifecycles; other materials such as nanomaterials; hazardous chemicals released to the environment through improper waste disposal or accidental releases to the environment; environmental contaminants resulting from human activities such as energy generation (air pollutants); and water disinfection.

A biological and systems understanding is needed to understand the extent to which environmental stressors contribute to the childhood diseases and disorders prevalent today, including: abnormal birth outcomes (neonatal mortality, premature birth, morbidity, birth defects), metabolic and endocrine imbalance (associated with obesity), cognitive disorders related to neurodevelopmental dysfunction (learning problems, attention deficit hyperactivity disorder (ADHD), autism), respiratory dysfunction such as asthma.

Key research questions:

- By what biological adverse outcome pathways (AOPs) do environmental contaminants contribute to important childhood health outcomes, such as adverse birth outcomes, obesity, cognitive disorders, and asthma?
- What are the systems-level influences of the chemical and natural and built environments on these health outcomes?
- How can we evaluate risks associated with exposures to chemical mixtures including the contribution of non-chemical stressors across the course of development?

Integrated impact: Systems information across all levels of organization associated with development and childhood disease and wellbeing is incorporated into predictive modeling to inform Agency risk assessments and environmental programs.

Specific research to provide biological systems understanding of the relationship between environmental exposures and health outcomes across development:

- Identification of AOPS for chemicals that disrupt specific developmental processes.
- Linkage of environmental exposures to health outcomes via AOPs including outcomes apparent at birth and those which contribute to later onset of disease in childhood or adulthood.
- Development and evaluation of systems models to understand and predict developmental toxicity.
- Systems level understanding of the complex interactions between multiple chemical stressors and how these interact with non-chemical stressors (other environmental and socioeconomic factors), and genetics, including informing how those interactions may affect children's health.

Research Area 3: Methods and models fit for purpose to evaluate early lifestage-specific risks and to support decisions protective of all susceptible and vulnerable early lifestages

Risk assessors and risk managers need access to available data and information pertinent to children's unique susceptibilities and vulnerabilities, as well as methods for analyzing and integrating the information, in order to adequately consider these factors in decision making.

Key research questions: What methods, models and decision support tools are needed to:

- Provide the Agency access to the available data needed for risk-based decisions.
- Evaluate how and to what extent pregnant women and children are exposed to environmental stressors.
- Evaluate how associated health outcomes vary by specific early lifestages and exposure patterns.
- Support analysis of potential risks associated with exposures to multiple chemicals in the context of other important environmental stressors across development.

Integrated impact: Evaluated, accessible risk assessment tools are developed to provide and enhance agency capacity for advanced analysis to support program-specific children's environmental health evaluations and sustainable decisions.

Specific models and methods to evaluate early lifestage specific risks and support regulatory decisions including:

- Efficient, cost effective methods for monitoring children's exposures.
- Tools for assessing exposure (timing and duration)-dose-response relationships in children including physiologically-based pharmacokinetic (PBPK) models that incorporate early life-stage specific parameters.
- Novel computational tools to incorporate estimates of developmental toxicity into risk assessments.
- Risk assessment tools for incorporating multiple exposures across multiple vulnerable stages to estimate risks that may accrue over time.
- Web-based tools that incorporate early lifestage-specific factors for predicting source-to-effects.
- Extend models and methods to estimate children's exposures at spatial and temporal scales relevant to the pollutant and health endpoint of concern.

Research Area 4: Translational research and tools fit for purpose to support community actions and decisions

Federal, State, Tribal and local governments make decisions at multiple scales (national to local) that impact children's health and wellbeing. Decision support tools that incorporate multiple factors about the built and natural environments that contribute to children's health, along with child-specific exposure and risk factors (including non-chemical stressors), can support informed decisions that protect and promote children's health in the communities where they live, learn, and play. Ideally, these tools should be developed through partnerships and active engagement with affected communities and suitable for use across geographic scales.

Key research questions:

- What are the real-world environmental exposures to children in their homes, schools and communities and how do they contribute to children's health risks?
- How do social and economic factors, including those specific to place, influence lifestage- specific exposure and risk?

- What tools can provide communities with the lifestage-specific information needed to support local decisions and actions?
- How can information regarding real-world environmental exposures to children inform community-based decisions in key sectors (land use; buildings and infrastructure; transportation; waste and materials management) to meet community needs?
- What are the most effective measures to prevent adverse environmental exposures, how effective have these been, and how can these be best communicated to communities and parents?

Integrated impact: Tools are developed for incorporating CEH factors when evaluating impacts of community-level decisions on sustainable, health-promoting environments for children.

Specific research and tools to inform community decisions designed to protect and promote CEH:

- Methods and models for measuring or estimating exposures in pregnant women and children to environmental contaminants and potentially harmful substances in air, water, house dust, soil, and products encountered in their day to day lives.
- Models for estimating cumulative exposures and how they may vary in indoor vs. outdoor environments.
- Methods for measuring the sustainable benefits and costs of community decisions designed to promote CEH such as increasing green space or access to healthy foods.
- Community assessment tools (e.g., geographic information system (GIS) models) that identify sources of exposures as well as health-promoting factors with respect to specific places where children live, recreate, or attend school.
- Approaches for incorporating CEH into Health Impact Assessments.
- Approaches and guidance for optimizing the built environment to sustainably protect and foster CEH.

Research Alignment and Coordination

The four Research Areas involve cross-cutting issues that are not specific to individual NRPs. Each of the following NRPs: Air, Climate, and Energy (ACE); Chemical Safety for Sustainability (CSS); Human Health Risk Assessment (HHRA); Sustainable and Healthy Communities (SHC); and Safe and Sustainable Water Resources (SSW) conducts research in one or more of the four Research Areas and several of the NRPs conduct research in all four areas (see Table 2).

ORD's research partner organizations, including the Association of Toxic Substances and Disease Registry (ATSDR), the Centers for Disease Control (CDC), the Department of Health and Human Services (DHHS), the Food and Drug Administration (FDA), the Department of Housing and Urban Development (HUD), the National Institute of Environmental Health Sciences (NIEHS), the National Institutes of Health (NIH), and the National Toxicology Program (NTP) are also involved in several of the four Research Areas. Specifically, these organizations have carried out a great deal of work in Research

Area 4 on evaluating the impacts of real-world exposures to children and how these exposures contribute to children's health risks.

Table 2. CEH Research efforts as distributed across the four research areas.

Research Area	ACE	CSS	HHRA	SHC	SSWR
1		X	X	X	
2	X	X		X	X
3		X	X	X	
4	X	X	X	X	

IV. Cross-cutting ORD Research

Current and Planned ORD Research

This section summarizes ORD's current and recently completed research activities (2012-15) as they are aligned with the four CEH research themes described in Section III. These research activities are implemented by ORD's NRPs according to their respective StRAPs (http://www.epa.gov/research/research-programs.htm). Each activity addresses NRP-specific outputs and at the same time contributes to achieving the CEH Roadmap outcomes. The NRP with key responsibility for each of the activities is provided in parentheses after the project name in this section, as follows:

- ACE = Air, Climate, and Energy Research
- CSS = Chemical Safety for Sustainability Research
- HHRA = Human Health Risk Assessment Research
- SHC = Sustainable and Healthy Communities Research
- SSWR = Safe and Sustainable Water Resources Research

See Appendix A for further details on the research activities outlined below, as well as information on additional ORD research activities; Appendix B for a summary of ORD published research on CEH outcomes from 2008 – 2014; and Appendix C for databases and tools that ORD has developed that include CEH information.

Current ORD activities in Research Area 1 (knowledge infrastructure to provide early lifestage-specific data and information) include the compilation of data on exposure factors, human behavior, chemical usage, and childhood physiological parameters, and the development of databases that provide the results of high throughput *in vitro* assays and *in vivo* studies. Under Research Area 2 (systems understanding of the relationship between environmental exposures and health outcomes across development), ORD is developing bioinformatics-based, adverse outcome pathway, and simulation models to evaluate the toxicity of environmental chemicals. In addition, Children's Research Centers and place-based studies are evaluating the relationship between exposure and a variety of health outcomes in children and adolescents, leading to an increased understanding of how interactions among complex stressors may increase the sensitivity of children. Research Area 3 (methods and models fit for purpose to

evaluate early lifestage-specific risks and to support decisions protective of all early lifestages) includes the development of exposure assessment tools and human exposure models for environmental chemicals. ORD is developing dosimetry models and using new approaches to categorize lifestages and to evaluate chemical mixtures. Under Research Area 4 (translational research to incorporate CEH into tools fit for purpose to inform community actions and decisions), ORD is developing decision support tools to enable communities to reach informed decision on community development and healthful environments. ORD is also translating research findings on children's health into findings that are useful to communities and other local groups as they develop strategies to work on local environmental health issues.

Research Area 1: Knowledge infrastructure to provide early lifestage-specific data and information

Currently, knowledge resources are being developed under Research Area 1 in the following three areas: A) exposure information, B) early lifestage pharmacokinetic parameters, and C) developmentally relevant hazard data. ORD's relevant research in each of these areas is summarized as follows:

1.1 Exposure Information

Exposure data are critical for characterizing children's environments and for evaluating interactions of children with the environment across development.

1.1.1 Exposure Factors Handbook (HHRA)

Data about children's exposures and exposure factors, such as lifestage specific modeled estimates of soil and dust ingestion is incorporated into EPA's Exposure Factors Handbook (U.S. Environmental Protection Agency, 2011); available at http://cfpub.epa.gov/ncea/risk/recordisplay.cfm?deid=236252. The exposure factors include: drinking water consumption, soil and dust ingestion, inhalation rates, dermal factors including skin area and soil adherence factors, consumption of fruits and vegetables, fish, meats, dairy products, and homegrown foods, human milk intake, human activity factors, consumer product use, and building characteristics.

1.1.2 Consolidated Human Activity Database (CHAD)

ORD's Consolidated Human Activity Database (CHAD) is a compilation of data on human behavior from 24 individual studies (U.S. Environmental Protection Agency, 2014d); available at: http://www.epa.gov/heasd/chad.html. This resource includes more than 50,000 individual data days of detailed location and activity data and corresponding demographic data including age, sex, employment, and education level. Data are included for all ages, including infants and children.

1.1.3 ExpoCast Database (CSS)

ExpoCast Database (ExpoCastDB) was developed to improve access to human exposure data from observational studies, including those funded by ORD. ExpoCastDB consolidates measurements of chemicals of interest in environmental and biological media collected from homes and child care centers. ExpoCastDB is

available as a searchable database (U.S. Environmental Protection Agency, 2014g); available at: http://actor.epa.gov/actor/faces/ExpoCastDB/Home.jsp on EPA's Aggregated Computational Resource (ACToR) system, an online data warehouse that collects data on over 500,000 chemicals from over 1000 public sources (U.S. Environmental Protection Agency, 2014a); available at: http://actor.epa.gov/actor/faces/ACToRHome.jsp.

1.1.4 Chemical and Product Categories (CSS)
Chemical and Product Categories (CPCat) is a database of information on how chemicals are used (U.S. Environmental Protection Agency, 2014b); available at: http://actor.epa.gov/actor/faces/CPCatLaunch.jsp. CPCat contains information on the uses of chemicals (including use by children); products that contain chemicals; manufacturers of the products; and a hierarchy of consumer product "use" categories. It also contains information on any regulations or studies in which the chemical has been considered hazardous to children.

1.2 Early Lifestage Pharmacokinetic Parameters

Pharmacokinetic and pharmacodynamic parameters for all lifestages are required to predict the potential for health effects from exposures to environmental chemicals. Child-specific parameters are used to characterize dose to the developing child *in utero,* after birth through lactational exposure, and during early infancy through prepubertal ages.

1.2.1 Enzyme Ontogeny Databaes (CSS)
Chemicals are often biotransformed in the body by activating and/or detoxifying enzymes whose expression changes over time from the developing embryo to adulthood. Thus, metabolic capacity based on the spectrum and relative quantity of critical enzymes at different lifestages can play an important role in determining childhood susceptibility to environmental chemicals. ORD has developed an enzyme ontogeny database that is useful for the development of PBPK models to explore metabolism-based variability during early lifestages.

1.3 Developmentally Relevant Hazard Data

Data from *in vivo* animal studies, screening assays, and other study types are needed in order to carry out risk and hazard assessments on environmental chemicals. ORD has developed databases that allow for easy access to developmental hazard data that is being used to link environmental exposures at early lifestages with health outcomes in children and later in life.

1.3.1 ToxCast Database (CSS)
ToxCastDB provides results of high throughput *in vitro* assays. Biology covered in the large set of assays include endpoints related to endocrine, reproductive, and developmental toxicity and a major proportion of the assays are human-based cells or proteins. ToxCastDB is available as a searchable database through the ACToR system (U.S. Environmental Protection Agency, 2014i); available at: http://actor.epa.gov/actor/faces/ToxCastDB/Home.jsp.

1.3.2 Toxicity Reference Database (CSS)
Toxicity Reference Database (ToxRefDB) contains data from thousands of *in vivo* animal studies and is available as a searchable database through the ACToR system (U.S. Environmental Protection Agency, 2014j); available at: http://actor.epa.gov/toxrefdb/faces/Home.jsp. Developmental toxicity data includes results from studies on more than 380 chemicals with 18 endpoints for both the rat and rabbit, while the reproductive toxicity information is based on the results from multigenerational reproductive studies on 316 chemicals, with 19 parental, reproductive, and offspring endpoints.

1.3.3 Adverse Outcome Pathway Wiki (CSS)
An Adverse Outcome Pathway (AOP) is a conceptual framework that portrays existing knowledge concerning the linkage between a direct molecular initiating event and an adverse outcome. The goal of an AOP is to provide the framework to connect the two events. AOP Wiki is a wiki-based tool that provides an interface for collaborative sharing of established AOPs and building new AOPs (Anonymous, 2014); available at: http://aopkb.org/aopwiki/index.php/Main_Page. AOP Wiki uses templates to make it easier for users to include the information needed for proper evaluation of an AOP.

Research Area 2: Systems understanding of the relationship between environmental exposures and health outcomes across development

Research Area 2 has been divided into the following two subgroups: A) systems biology to predict developmentally relevant outcomes and B) systems understanding of complex stressors. ORD's relevant research in each of these areas is summarized as follows:

2.1 Systems Biology to Predict Developmentally Relevant Outcomes

Systems models for tissues and multi-organ pathways specific to embryo-fetal and neonatal development are being developed. These models increase our understanding of the biologic mechanisms of chemical stressors that contribute to childhood health outcomes.

2.1.1 Bioinformatics-Based Models (CSS)
As discussed in section **Error! Reference source not found.**, ToxCastDB uses high throughput biochemical and cellular *in vitro* assays to evaluate the toxicity of environmental chemicals. The development of predictive models is being carried out in phases, with the development and publication of first-generation (Phase I) ToxCast predictive models for reproductive toxicity (M. T. Martin et al., 2011) and developmental toxicity (Sipes et al., 2011) . Pathways for endocrine disruption (Reif et al., 2010), embryonic stem cell differentiation (Chandler et al., 2011) and disruption of blood vessel development (Kleinstreuer et al., 2011) have been linked to the Phase I ToxCast *in vitro* data. For the next ~700 compounds in Phase II, where animal toxicology is less well-characterized, ORD is developing plausible model structures that deal with the possibility of additional relevant interactions

and components beyond those represented in the first-generation predictive models.

2.1.2 AOP Models (CSS)
ORD is developing AOP models, such as the vascular AOP model, with the aim of establishing the predictive value of chemical disruption of blood vessel development (vasculogenesis) during critical windows of embryonic and fetal development. A vasculogenesis model is being tested in Zebra fish embryos and in embryonic stem cells and as additional individual AOPs are developed, they can be assembled into AOP networks that may aid the prediction of more complex interactions and outcomes resulting from exposure to complex mixtures and/or chemicals with multiple modes of actions.

2.13 Simulation Models (CSS)
Simulation models predict chemical toxicity using relevant biologic information, such as the influence of subcellular pathways and networks on the development of tissues and organs. ORD is developing the Virtual Embryo model, a simulation model of predictive toxicology of children's health and development, which can be applied to prenatal or postnatal (including lactational) exposures.

2.2 Systems Understanding of Complex Stressors
Epidemiologic, animal studies, and *in vitro* assays are being used to develop a systems understanding of the relationship between environmental exposures as stressors and lifestage-specific susceptibility and vulnerability.

2.2.1 Laboratory Based Studies (CSS and SHC)
Intramural ORD research has used a variety of *in vitro* models to evaluate the effects of chemical exposure in developmentally relevant systems. Cell (e.g., human multipotent neuroprogenitors, rodent embryonic stem cells, specific pathway-responsive modified hepatocytes), organ (e.g., human and rodent palatal shelves), and whole rodent embryo cultures, as well as whole organisms (developing zebrafish) have been used to address issues of toxic response. Many of these models have been developed, characterized and refined to answer specific research questions. Several model systems have been used to evaluate the effects of chemicals to aid in the translation of high throughput data in the ToxCast assays. *In vitro* approaches using adipocyte stem cells are also being developed as potential predictors of obesity and to explore cellular mechanisms of action of specific chemicals.

Experimental research is also addressing causality in lifecourse (longitudinal) rodent studies where effects of early life exposures on postnatal development and multiple health outcomes can be evaluated under controlled laboratory conditions. These studies are also being used to examine the extent to which modifying factors such as diet, exercise and stress may alter sensitivity to chemical stressors, a question relevant to diverse community settings and conditions.

2.2.2 Epidemiologic Studies (SHC and ACE)

EPA-NIEHS Children's Environmental Health and Disease Prevention Research Centers (CEHC) - The EPA-National Institute of Environmental Health Sciences (NIEHS) jointly funded Children's Environmental Health and Disease Prevention Research Centers (CEHCs, or "Children's Centers") Program, ongoing since 1998, continues to generate exposure and biomarker data in pregnant women and children, along with mechanistic data in experimental models, in order to show relationships between exposure to chemical contaminants and a variety of children's health outcomes, and to identify critical windows of susceptibility (U.S. Environmental Protection Agency, 2014e); available at: www.epa.gov/ncer/childrenscenters; http://cfpub.epa.gov/ncer_abstracts/index.cfm/fuseaction/recipients.display/rfa_id/560/records_per_page/ALL. The long-range goals of this STAR Program include understanding how environmental factors affect children's health, and promoting translation of basic research findings into intervention and prevention methods to prevent adverse health outcomes (*Table 3*).

Table 3. Current EPA/NIEHS Children's Environmental Health and Disease Prevention Research Centers Exploring Associations Between Exposures and Health Outcomes in Children.

Institution – P.I.	Chemical Exposures and Other Stressors	Outcomes	Underlying Mechanisms (molecular, genetic, social factors)
Brown University – Boekelheide	Arsenic, EDCs (estradiol, BPA, genistein), dietary restriction	Fetal liver, lung and prostate development; prostate cancer in later life	Endocrine disruption; Epigenetic changes in organ development
Columbia University – Perera	Endocrine Disrupting Compounds (BPA), PAHs,	Neurodevelopmental disorders such as problems with learning and behavior; obesity and metabolic disorders	Endocrine disruption; Epigenetic reprogramming and metabolic syndrome
Dartmouth College – Karagas	Arsenic in drinking water and food	Growth and development; immune response	Epigenetic changes and influence of gut microbiome
Duke University/ University of Michigan – Miranda	Environmental, social and individual susceptibility factors, PM, Ozone	Disparities in birth outcomes; respiratory health in infants	Social determinants of childhood disease
Duke University – Murphy	Environmental tobacco smoke	ADHD; neurobehavioral dysfunction	Epigenetic modulation in fetal and child development
Johns Hopkins University – Diette	Airborne pollutants (particulate matter, nitrogen dioxide), allergens, urban diets	Asthma	Dietary contributions to asthma ,based on anti-oxidant and anti-inflammatory impacts on immune function and inflammation
National Jewish Health – Schwartz, Szefler	Air pollution (ozone, PM, NO_2), ambient bacterial endotoxin	Asthma; immune system function; determinants of host defense	Host-immune responses and TL4 receptor function; interactions between ozone and endotoxin
University of California at Berkeley - Buffler, Metayer	Pesticides, tobacco-related contaminants, chemicals in housedust (PCBs, PBDEs)	Childhood leukemia	Epigenetic and genetic influences
University of	Pesticides (DDT,	Neurodevelopment; growth	Epigenetic reprogramming; altered

California at Berkeley – Eskenazi	manganese), flame retardants	and timing of puberty; obesity	endocrine status
University of California at Berkeley – Hammond, Balmes, Shaw	Ambient air pollutants (airborne PAHs), in utero exposure to traffic-related pollutants, endotoxin	Birth defects/preterm birth, immune system dysfunction (asthma/allergies), obesity/glucose dysregulation	Gene variants in biotransformation enzymes; molecular mechanisms e.g., altered T-cell function; neighborhood factors
University of California at Davis – Van de Water	BPDEs, pyrethroid insecticides, perfluorinated compounds, POPs	Autism spectrum disorder (ASD)	Immune dysfunction and autoimmunity; genetic/epigenetic contributions
University of California, San Francisco – Woodruff	EDCs, PBDEs (BDE-47), PFCs (PFOA), psychosocial stress	Placental and fetal development, adverse birth outcomes	Gene expression changes via epigenetic mechanism; contribution of psychosocial stress
University of Illinois at Urbana-Champaign – Schantz	EDCs (phthalates, BPB); high fat diet	Neurological and reproductive development	Endocrine disruption; oxidative stress
University of Michigan – Peterson, Padmanabhan	BPA, phthalates, lead, cadmium	Birth outcomes; child weight gain; body composition; activity patterns; hormonal levels; sexual maturation; metabolomics and risk of metabolic syndrome	Dietary influences; epigenetics and gene expression changes; oxidative stress
University of Southern California – McConnell	Near-roadway air pollution including elemental carbon, PM 2.5	Obesity; fat distribution; metabolic phenotypes; systemic inflammation	Expression of genes in metabolic pathways; beta cell function; oxidative stress;
University of Washington – Faustman	Agricultural pesticides	Altered neurodevelopment	Genetic susceptibility; neurotoxicity ; oxidative stress; cellular pathways underlying neurodevelopment

Clean Air Research Centers (ACE) **-** ORD's Clean Air Research Centers Program (STAR) includes a number of epidemiologic projects directly relevant to children's environmental health. Two currently active Centers are producing new data and knowledge on the relationship between air pollution and children's health, with final reports expected in 2015. The Center at Emory University is generating "Novel estimates of pollutant mixtures and pediatric health in two birth cohorts," and the Center at Harvard University is evaluating "Longitudinal effects of multiple pollutants on child growth, blood pressure and cognition." (U.S. Environmental Protection Agency, 2012); available at: http://www.epa.gov/ncer/quickfinder/airquality.html

Place-Based Studies (ACE and SHC) - ORD recognizes that combinations of stressors are often unique to a particular community setting and that interventions to improve children's health must take this complexity into account. For example, a STAR grant and ORD in-house project, "The Near-Road Exposures and Effects of Urban Air Pollutants Study (NEXUS)" (ACE) examined the influence of traffic related

air-pollutants on respiratory outcomes in a cohort of 139 asthmatic children (ages 6-14) who lived close to major roadways in Detroit, Michigan. Another place-based study, "The Mechanistic Indicators of Childhood Asthma (MICA)" (SHC) study was designed to pilot an integrative approach in children's health research. MICA incorporates exposure metrics, internal dose measures, and clinical indicators to decipher the biological complexity inherent in diseases such as asthma and cardiovascular disease with etiology related to gene-environment interactions. Additionally, grantees are conducting place-based research such as exploring: interactions among stress and air pollution in community settings; how school conditions influence academic performance (SHC); and how to predict exposures for children living near a Superfund site (ACE).

Research Area 3: Methods and models fit for purpose to evaluate early lifestage-specific risks and to support decisions protective of all susceptible and vulnerable early lifestages

Research Area 3 has been divided into the following two subgroups: A) exposure, and B) dosimetry models. ORD's relevant research in each of these areas is summarized as follows:

3.1 Exposure

ORD has developed tools to increase the usability and access to exposure data, models to predict exposure by a variety of pathways and routes, and approaches for categorizing lifestage changes and prioritizing chemical mixtures.

3.1.1 EPA ExpoBox (HHRA)

EPA ExpoBox is a web-based compendium of over 800 exposure assessment tools that provides links to exposure assessment databases, models, and references (U.S. Environmental Protection Agency, 2013c); available at: http://www.epa.gov/risk/expobox/docs/Expobox_Fact-Sheet_Nov13.pdf. It includes approaches for exposure assessments, tiers and types of exposure assessments, chemical classes, routes of exposure to chemicals, lifestages and populations, and exposure media. It also includes, in a searchable and downloadable format, the full list of exposure factors from the Exposure Factors Handbook (see section **Error! Reference source not found.**).

3.1.2 SHEDS-HT Model (CSS)

The Stochastic Human Exposure and Dose Simulation–HT (SHEDS-HT) model is a screening-level human exposure model for chemicals. Exposure results can also be estimated for individual age-gender cohorts. Exposure-relevant information specific to children included in SHEDS-HT includes age-specific behaviors (such as hand-to-mouth contact and use of consumer products), time spent in microenvironments, and food intakes.

3.1.3 ExpoCast (CSS)

ExpoCast is a rapid, high-throughput model using off the shelf technology that predicts exposures for thousands of chemicals (U.S. Environmental Protection

Agency, 2014f); available at: http://epa.gov/ncct/expocast/. ORD research is generating and incorporating new information about age-dependent exposures (e.g., product use) into ExpoCast so that this model can be more specifically applied to capture children's unique vulnerabilities to support risk-based decisions.

3.2 Dosimetry Models

ORD has developed a number of dosimetry models that assess exposure, predict dose, and describe the kinetics of environmental chemicals as related to children's health.

3.2.1 Empirical Models (CSS)

Persistent Bioaccumulative Toxicants - A statistical model was developed for predicting levels of polybrominated diphenyl ethers (PBDEs) in breast milk, based on serum data from the National Health and Nutrition Examination Survey (NHANES) (Marchitti, LaKind, Naiman, Berlin, & Kenneke, 2013). In this research, congener-specific linear regression partitioning models were developed and applied to 2003-2004 NHANES serum data for U.S. women. These models provide a sustainable method for estimating population-level concentrations of PBDEs in U.S. breast milk and should improve exposure estimates in breastfeeding infants.

ORD is now applying this approach to other environmental chemicals (dioxins, perfluorinated compounds (PFCs), polychlorinated biphenyls (PCBs), and organochlorine pesticides). ORD is also working on developing a comprehensive quantitative structure-activity relationship (QSAR)-based model for predicting milk:serum partitioning ratios for classes of chemicals where serum and milk data are not available to construct regression models.

In vitro to In vivo Extrapolation - ORD has proposed an approach to link results from *in vitro* high throughput studies with population group-specific dosimetry for neonates, children, and adults, and exposure estimates (Wetmore et al., 2014). For nine ToxCast chemicals, pharmacokinetic models for multiple population groups were constructed that predicted chemical concentrations in the blood at steady state. These models have potential application to estimate chemical-specific pharmacokinetic uncertainty factors and to estimate population group-specific oral equivalent dose values to aid in chemical prioritization and identifying population groups with greater susceptibility to potential pathway perturbations.

3.2.2 PBPK Models

Virtual Embryo Project (CSS) - ORD has developed a life-stage PBPK model which has been incorporated into the Virtual Embryo project. This model was developed to computationally investigate the relationship between chemical exposure, tissue dosimetry and *in vitro* markers of critical events related to AOPs. The model includes time-changing physiological and biochemical descriptors related to a pregnant mother, fetal growth, and child exposure through lactation.

Ethanol (ACE) - To supplement and complete PBPK models in the literature, ORD developed PBPK models to describe the kinetics of ethanol in adult, pregnant, and

neonatal rats for the inhalation, oral, and intravenous routes of exposure (S. A. Martin et al., 2012).

Research Area 4: Translational research and tools fit for purpose to support community actions and decisions

Research Area 4 has been divided into the following four subgroups: A) decision support tools, B) problem driven research, C) translational research, and D) social determinants of health. ORD's relevant research in each of these areas is summarized as follows:

4.1 Decision Support Tools

ORD is developing decision support tools for State, Tribal and local governments and other organizations in order to make sound decisions about both community development and healthful environments, and to avoid unintended consequences.

4.1.1 Community-Focused Exposure and Risk Screening Tool (SHC)
ORD has developed the Community Focused Exposure and Risk Screening Tool (C-FERST) (U.S. Environmental Protection Agency, 2013a); available at: http://www.epa.gov/heasd/c-ferst/, which has been developed as a "toolkit" for step-by-step community assessment guidance (e.g., Community Action for Renewed Environment (CARE) roadmap), GIS maps, reports, fact sheets, best practices, and potential solutions. Children's health issues in C-FERST currently include childhood lead exposure, childhood asthma, and schools. Recently, C-FERST was used, along with other tools, to inform a Health Impact Assessment (HIA) related to school renovation decisions in Springfield, Massachusetts.

4.1.2 EnviroAtlas (SHC)
EnviroAtlas, scheduled for public release in 2014 will include, at least for selected urban areas, such indicators as the locations of schools, recreational areas and factors relevant to health outcomes (demographics, income) and access to transportation routes and indicators of ecosystem services such as tree cover (related to heat, recreation, green-space accessibility). This tool also includes an Eco-Health Relationship Browser (U.S. Environmental Protection Agency, 2013b); available at: http://www.epa.gov/research/healthscience/browser/introduction.html. Health outcomes currently searchable in the browser of direct relevance to CEH include low birth weight and preterm birth, asthma, ADHD, and obesity.

4.2 Problem-Driven Research

Studies are being conducted to further the understanding of linkages between human health and environmental exposures. Communities are using results of these analyses to make decisions concerning renovation of schools, location of recreational areas, and future development.

4.2.1 EPA Pilot Study Add-on to the Third Study Site of the Green Housing Study (SHC)

The Green Housing Study is a collaborative effort between the U.S. Department of Housing and Urban Development (HUD) and the Centers for Disease Control and Prevention (CDC). In partnership with HUD and CDC, ORD will collect additional multimedia measurements and questionnaire data from the index children actively participating in the Green Housing Study and a sibling(s) in order to characterize personal, housing, and community factors influencing children's potential exposures to indoor contaminants at various lifestages.

4.2.2 Dust and soil ingestion (SHC)
ORD is using models to estimate different exposure parameters, such soil and dust ingestion rates, in children. For example, ORD used the SHEDS-Soil/dust model to estimate soil and dust ingestion rates for young children at two Taiwanese locations, and for simulations pertinent to U.S. children in specific age categories (Glen, Smith, & Van Der Wiele, 2013).

4.2.3 Chemical and Non-chemical Stressors and Childhood Obesity (SHC)
ORD is currently completing a state-of-the-science literature review to identify chemical and non-chemical stressors related to childhood obesity. Numerous chemical and non-chemical stressors were identified and grouped into the following domains: individual, family, community, and chemical. Data shows that there is not always a positive association with a stressor and childhood obesity, and that there can be inconsistent correlations between the same stressors and obesity. However, there is sufficient evidence to suggest the interactions of multiple stressors may contribute to the childhood obesity epidemic.

4.2.4 Chemical and Non-chemical Stressors and Neurocognitive Health (SHC)
ORD is conducting research to examine stressors related to neurocognitive health in children, ages 3-6 years. Key exposure factors were identified for each developmental lifestage from pregnancy to 3-6 years old. These elements were incorporated into a model and the results suggest that some childhood exposures (e.g., socioeconomic status, parent-child interaction, diet, built environment) not only present as key factors, but act as effect modifiers of stressors experienced during pregnancy and infancy (e.g., lead, pesticides, prenatal stress).

4.2.5 Community Multi-scale Air Quality Model (ACE)
The EPA's Community Multi-scale Air Quality (CMAQ) Model is a powerful computational tool used by EPA and states for air quality management that gives detailed information about the concentrations of air pollutants in a given area. Comparison of data from the CMAQ model with birth outcomes or childhood hospital admissions for asthma has generated data on associations between pollutant exposure (i.e., particulate matter (PM) or ozone) and health outcomes (U.S. Environmental Protection Agency, 2014c), available at: http://www.epa.gov/AMD/Research/RIA/cmaq.html.

See Appendix A for examples of problem-driven research on PCBs in Schools (HHRA) and Child-Specific Exposure Scenarios examples (HHRA).

4.3 Translational Research

Translational research involves translating the results from research on children's health into findings that are useful to communities, neighborhoods, health care providers, or other groups as they develop strategies to work on local environmental health issues.

4.3.1 EPA/NIEHS Children's Center Program (SHC)

As discussed in section **Error! Reference source not found.**, the EPA-NIEHS co-funded Children's Centers (CEHCs) Program is generating exposure and biomarker data in pregnant women and children, showing relationships between exposure and a variety of children's health outcomes, and identifying critical windows of susceptibility (U.S. Environmental Protection Agency, 2014e); available at: www.epa.gov/ncer/childrenscenters. A critical and unique component of the Children's Centers Program is the inclusion of Community Outreach and Translation Cores. These cores use a variety of innovative approaches to translate research findings and intervention strategies to community stakeholders (see *Table 4*).

Table 4. EPA/NIEHS Children's Centers Community Outreach and Translation – Community Partners.

Institution – P.I.	Study Site Location(s)	Community Outreach and Translation – with Community Partners
Brown University – Boekelheide	Providence, Rhode Island	Silent Spring Institute, Environmental Justice League of Rhode Island
Columbia University – Perera	New York City (Northern Manhattan and South Bronx), Poland, China	Bronx Borough Presidents Office, Bronx Health Link, Columbia Community Partnership for Health, Columbia University Head Start, Community Health Worker Network of NYC, Dominican Medical Association, New York, Harlem Children's Zone Asthma Initiative, Harlem Health Promotion, Northern Manhattan Perinatal Partnership, Nos Quedamos, WE ACT for Environmental Justice
Dartmouth College – Karagas	Hanover, New Hampshire	Dartmouth-Hitchcock Concord Clinic, Concord Hospital Family Clinic, Concord Obstetrics and Gynecology Professional Associates, Concord Women's Care, Family Tree Health Care (Warner, NH), Dartmouth Hitchcock Lebanon Clinic, Concord Hospital, The Family Place, Dartmouth-Hitchcock Medical Center, New Hampshire Department of Environmental Health Services, New Hampshire Birth Conditions Program, University of New Hampshire Department of Molecular, Cellular and Biomedical Sciences
Duke University/ University of Michigan – Miranda	Durham, North Carolina and Ann Arbor, Michigan	Durham Congregations, Associations, and Neighborhoods (CAN), Triangle Residential Options for Substance Abusers (TROSA), Durham Affordable Housing Coalition, Partnership Effort for the Advancement of Childrens Health/Clear Corps (PEACH), Durham People's Alliance, Durham County Health Department, Lincoln Community Health Center, Duke University Nursing School Watts School of Nursing, City of Durham Department of Neighborhood Improvement Services, City of Durham Department of Community Development, Children's Environmental Health Branch of NC Department of Environment and Natural Resources, North Carolina Asthma Alliance, East Coast Migrant Head Start, North Carolina Community Health Center Association, North Carolina Rural Communities Assistance Project
Duke University – Murphy	Durham, North Carolina	DukeEngage Program, El Centro Hispano (local Latino community), Partnership for a Healthy Durham

Johns Hopkins University – Diette	Baltimore, Maryland	Baltimore City Head Start Program, Baltimore City Health Department Healthy Homes Program, Baltimore School Food Services Program, Healthy Stores Program, Maryland Asthma Control Program, Women Infants and Children (WIC) nutrition programs
National Jewish Health – Schwartz, Szefler	Denver, Colorado	Colorado Asthma Coalition, Colorado Clinical Guidelines Collaborative, Colorado Department of Public Health and Environment, Denver Public School System, Lung Association of Colorado, Rocky Mountain Prevention Research Center, EPA Region 8, Alamosa Public School, Denver Health, Colorado Public Health, Practice Based Research Network, Regional Air Quality Council, Colorado Air Quality Commission, Grand Junction Housing Authority, Western Colorado Math & Science Center, Region 8 Pediatric Environmental Health Specialty Unit (PEHSU)
University of California at Berkeley – Buffler, Metayer	Berkeley, California	Network of 8 clinical institutions in northern and central California participating in the Northern California Childhood Leukemia Study (NCCLS), national community of pediatric health care professionals with an interest in environmental health issues; national community of persons interested in leukemia; California community of persons interested in childhood leukemia; Region 9 Pediatric Environmental Health Specialty Unit (PEHSU)
University of California at Berkeley – Eskenazi	Berkeley and Salinas, California	Clinica de Salud del Valle de Salinas, Natividad Medical Center, South County Outreach Effort (SCORE), Monterey County Health Department, California Rural Legal Assistance (CRLA) Program, Grower/Shipper
University of California at Berkeley/ Stanford University – Hammond, Balmes, Shaw	Berkeley, Palo Alto, Bakersfield and San Joaquin Valley, California	Medical Advocates for Healthy Air, Fresno Metro Ministry, Center on Race, Poverty, and the Environment, San Joaquin Valley Latino Environmental Advancement Project (LEAP), El Comite para el Bienestar de Earlimart, Coalition for Clean Air, San Joaquin Valley Cumulative Health Impact Project (SJV-CHIP), Central California Environmental Justice Network, Central Valley Air Quality Coalition, Californians for Pesticide Reform
University of California at Davis – Van de Water	Davis, California	Families for Early Autism Treatment, Learning Disabilities Association, Parents Helping Parents, San Francisco Bay Chapter of the Autism Society of America, Alameda County Developmental Disabilities Council, Cure Autism Now, State of California health/developmental service providers, California Departments of Developmental Services and Health Services, California Regional Centers and Office of Environmental Health Hazard Assessment
University of California, San Francisco – Woodruff	San Francisco, California	American College of Obstetricians and Gynecologists (ACOG District IX), Association of Reproductive Health Professionals, Physicians for Social Responsibility (PSR) San Francisco Bay Area Chapter, WORKSAFE (California Coalition for Worker Occupational Safety & Health Protection), California Department of Health Occupational Health Branch
University of Illinois at Urbana-Champaign – Schantz	Urbana-Champaign, Illinois and New Bedford, Massachusetts	Illinois Action for Children (IAFC), American Academy of Pediatrics (AAP), Just-In-Time Parenting, Champaign-Urbana Public Health Department, Great Lakes Center for Environmental Health, Cambridge Health Alliance, Carle Foundation Hospital, Provena Covenant Medical Center
University of Michigan – Peterson, Padmanabhan	Ann Arbor, Michigan and Mexico City, Mexico	Early Life Exposures in Mexico to Environmental Toxicants (ELEMENT), National Institute of Public Health, Mexico City, Detroit Hispanic Development Corporation
University of Southern	Los Angeles, California	The Children's Clinic (Long Beach and South Bay), Asian and Pacific Islander Obesity Prevention Alliance, East Yard Communities for Environmental

California – McConnell		Justice, Digital Rain Factory, Los Angeles Parks Foundation, The Trust for Public Land Center for Park Excellence, Policies for Livable, Active Communities and Environments (PLACE) of Los Angeles, Trade, Health and Environment Impact Project, Center for Community Action & Environmental Justice (Riverside and San Bernardino), Coalition for a Safe Environment (Wilmington), East Yard Communities for Environmental Justice (Commerce and East L.A.), Long Beach Alliance for Children with Asthma, Outreach Program of Southern California Environmental Health Sciences Center Los Angeles (USC/UCLA), Urban & Environmental Policy Institute, Occidental College
University of Washington – Faustman	Yakima Valley, Washington State	Community members in the Yakima Valley, Farm Workers Union, Growers' Association, Washington State Department of Health and Department of Agriculture, Farm Workers' Union, Yakima Valley Farm Workers Clinics, Radio KDNA (Spanish language), Washington State Department of Labor and Industries, Columbia Legal Services, Washington State Migrant Council, EPA Region 10

4.4 Social Determinants of Health (Place-Based Studies)

ORD is carrying out research on the biological, environmental, and social conditions that may contribute to disparities in health outcomes in children.

4.4.1 NIMHD Centers of Excellence on Environment and Health Disparities (SHC)
Social determinants of health are a focus of research in the *EPA- NIMHD Centers of Excellence on Environment and Health Disparities* (http://www.epa.gov/ncer/ehs/disparities/health-disparities.html). ORD, through an interagency agreement with the National Institute of Minority Health and Health Disparities (NIMHD) (http://www.nih.gov/about/almanac/organization/NIMHD.htm) is supporting the establishment of transdisciplinary networks of excellence in health disparities research to achieve a better understanding of the complex interactions of biological, social and environmental determinants of population health.

One of these Center projects, "Analysis and Action on the Environmental Determinants of Health and Health Disparities" (University of South Carolina) is exploring six areas of health disparities that contribute disproportionately to premature death and morbidity found among poor and racial/ethnic minorities (e.g., infant mortality). Another project, "Environmental Health Disparities Research" (University of Texas) is exploring the individual- and neighborhood-level contributions to disparities in children's pulmonary health.

4.4.2 Environmental and Community Factors Influence Effectiveness of Medical Treatment for Asthma (SHC)
An ORD study, in collaboration with the University of North Carolina, "Observational Assessment of Baseline Asthma Control as a Susceptibility Factor for Air Pollution Health Effects in African-American Children with Persistent Asthma", is examining factors that contribute to asthma disparities in adolescents. The study is following a cohort of African American youth with moderate-to-severe asthma and examining a variety of factors including air pollution, home

environment, and community issues that may contribute to the high rate of asthma in this population and the relative effectiveness of medical treatments.

4.4.3 Integrated Approaches to Sustain the Built and Natural Environment and the Communities they Support (SHC)
In this study, researchers are using GIS tools and multi-layered mapping to examine relationships between access to green space and birth outcomes. Analyses focus on associations between birth measures across the greater Durham-Chapel Hill, North Carolina area and various measures of green space around the home, including tree cover along busy roadways.

Summary of ORD CEH Research Partnerships

ORD has partnered with a number of other Federal agencies and independent organizations to further CEH research. *Table 5* lists some of ORD's partner organizations and the CEH programs that are currently underway through these partnerships.

Table 5. ORD Partner Organizations

Partners	Research	Description
NTP/NIEHS	Children's Environmental Health and Disease Research Centers (http://epa.gov/ncer/childrenscenters/)	Research to increase understanding how environmental factors affect children's health and promote translation of basic research findings into intervention and prevention methods to prevent adverse health outcomes.
NTP/NIEHS	Systematic review of progestin use during pregnancy (http://dx.doi.org/10.1289/ehp.1306711)	Systematic review of progestin use during pregnancy with interest on the effects in the mother and offspring after exposure during pregnancy/gestation.
NTP/NIEHS & NICHD; CDC	National Children's Study (http://www.nationalchildrensstudy.gov/Pages/default.aspx)	Multi-year research study examining the effects of environmental influences on the health and development of children.
ATSDR; Association of Occupational and Environmental Clinics	Pediatric Environmental Specialty Units (http://aoec.org/pehsu/aboutus.html)	Ten specialty units across the U.S. that are a source of medical information and advice on environmental conditions that influence children's health.
HUD; CDC	EPA Pilot Study Add-On to the Green Housing Study	Study that is collecting additional multimedia measurements and questionnaire data from the index children in the Green Housing Study and a sibling(s) in order to characterize personal, housing, and community factors influencing children's potential exposures to indoor contaminants at various lifestages.
CDC	National Birth Defects Prevention Study (http://www.nbdps.org/)	Population-based, case-control study examining the causes of birth defects.
NIH/National Institute of Minority Health and Health Disparities	STAR Centers of Excellence of Environment and Health Disparities (http://www.epa.gov/ncer/ehs/disparities/h	Networks of excellence in health disparities research to achieve a better understanding of the complex interactions

	ealth-disparities.html)	of biological, social and environmental determinants of population health.
DHHS, FDA, Health Resources and Services Administration, NIH, Office of the Assistant Secretary for Health, HUD, DOJ, and DOT	Interagency Asthma Disparities Workgroup (part of the President's Task Force on Environmental Health Risks and Safety Risks to Children) (www.epa.gov/childrenstaskforce)	Workgroup with the goal of reducing the burden caused by asthma, particularly among minority children and children with family incomes below the poverty level.

Examples of ORD Integration

ORD research is a collaborative effort spread across all of its research programs. Table 6 demonstrates EPA's research programs that are involved in research on four children's health outcomes: adverse birth outcomes, childhood obesity, cognitive function, and asthma and airway function. See Appendix A for more details about this research.

Table 6. CEH Research efforts as distributed across EPA's National Research Programs.

	CHILDREN'S HEALTH OUTCOMES			
RESEARCH AREA	**Adverse Birth Outcomes**	**Childhood Obesity**	**Cognitive Function**	**Asthma & Airway Function**
Knowledge Infrastructure	CSS	CSS, HHRA	CSS, HHRA	HHRA
Systems Understanding	CSS, SHC, SSWR, ACE	CSS, SHC	CSS, SHC, ACE	SHC, ACE
Methods & Models	CSS, HHRA	CSS, HHRA	CSS, HHRA	ACE, HHRA
Community Decision Support	SHC, ACE	SHC	SHC	SHC, ACE

Opportunities for Further Integration

TO BE COMPLETED IN FINAL CROSS-CUTTING ROADMAP

V. Research Gaps & Priority Research Needs

Synthesis of Existing Gaps

TO BE COMPLETED IN FINAL CROSS-CUTTING ROADMAP

Prioritized Research Needs for ORD

This section highlights priority research needs identified for each of the four CEH Roadmap research areas. The bullet points present the strategic research gaps and the discussion provides examples of research needs and potential approaches to begin to

address these needs. Gaps in science and tools required to address the roadmap research questions and to support Agency needs for CEH protection and promotion were identified by the roadmap working group based on: reviewing the current ORD portfolio and planned research in evolving StRPAPs; understanding of research activities in other federal agencies; and emerging scientific understanding of important factors associated with CEH. Priorities for ORD CEH research were identified based on two key criteria: (1) Research is within the scientific scope of the programmatic StRAPs and one or more of the NRPs and their program partners have identified the research as high priority and have made a commitment to enabling and supporting the research to address the priority; and (2) EPA can play a pivotal leadership role. These are not intended to be incremental contributions.

Research Area 1: Knowledge infrastructure to provide early lifestage-specific data and information

Early lifestage-specific data that could support Agency decisions are being generated at an increasing pace both within EPA and across the wider children's health research community. However, significant barriers remain to effectively access and mine relevant information to understand and predict the role of exposures to environmental factors during early life on health impacts. Priority Agency needs in this research area are for:

- Accessible data on critical lifestage-specific factors that influence children's vulnerability and resilience to environmental insults, including efficient links to access/collate knowledge and data about such factors from research conducted across the wider CEH research community,
- Accessible information on lifestage-specific determinants of activities, behaviors, physiology and exposure,
- Accessible information on susceptibility to chemicals and other contaminants based on lifestage (absorption, distribution, metabolism, excretion (ADME), toxicity, and PBPK considerations),
- Associated data on genetic susceptibility and increased susceptibility due to health and nutritional status, including pre-existing diseases and disorders,
- Accessible lifestage-specific data for non-chemical stressors linked to the built and natural environments, and to social and economic factors,
- Accessible data and information that shows the inter-relationships between chemical exposures and factors modifying those exposures.

ORD can begin to address these gaps by leveraging current activities within the NRPs to apply advanced approaches for curating and providing access to data through high interest use-cases (i.e., research focused on addressing a gap in one or more of the other three research areas described in this Roadmap). For example, ORD has multiple activities focused on providing web-based information resources and associated web services to efficiently access these data (e.g., dashboards) as inputs to design workflows and analysis tools and reports from the EPA/NIEHS Children's Centers are posted on EPA's National Center for Environmental Research (NCER) website.

ORD has also developed a novel semi-automated approach using bioinformatics and computational techniques to mine the literature and facilitate systematic review. Using MeSH terms, ORD can find articles of interest and search in a systematic way. First, articles of interest are captured into a set database using specific MeSH annotations. The MeSH terms for this first pass are generally related to chemicals, proteins, or adverse outcomes of interest, but may include any MeSH terms. Second, this set of publications are queried using additional terms (e.g., proteins, cell-processes, species) to find articles where these terms are co-annotated. The co-annotation of terms gives plausible hypotheses about their associations, as well as the publication reference, without having to manually search the literature. Once these relationships and articles are identified, the article can be manually evaluated for evidence of this association. This database and mining approach is useful for identifying global hypotheses about associations of interest such as chemical-protein, chemical-cell process, or chemical-adverse outcome at all levels of biological complexity. These relationships can then be used to build AOPs, understand unappreciated connections, and identify current data gaps.

These approaches can be applied in the context of NRP- specific and cross-cutting ORD CEH research to amplify the impact of investments in studies, models, and decision support tools.

Research Area 2: Systems understanding of the relationship between environmental exposures and health outcomes across development

The NIH (including NIEHS and NICHD) is currently investing significant resources in research to increase our understanding of the fundamental shared mechanisms of complex disease, susceptibility across the life span to diseases resulting from environmental factors, and links between the totality of environmental exposures and biological pathways (National Institute of Environmental Health Sciences, 2012). EPA's Strategic Plan translates this fundamental knowledge to provide a systems understanding that is necessary to adequately protect the health of children. As such, ORD can provide leadership in addressing priority gaps associated with using systems-based understanding of biology (from the molecular, tissue, and organ level out to the individual and population) to predict the potential for adverse impacts associated with development, chemical use, and environmental contamination. To effectively provide this leadership will require strategic implementation of ORD's STAR extramural grants program and leveraging of partnerships such as the National Children's Study. Priority gaps in this area are broad and include the need for:

- Improved understanding of critical environmental factors, and interactions, that impact children's growth and development at EPA-defined early lifestages (U.S. Environmental Protection Agency, 2005a) and across the lifecourse,
- Understanding of the extent to which environmental stressors contribute to the childhood diseases and disorders prevalent today, including: abnormal birth outcomes (neonatal mortality, premature birth, morbidity, birth defects), metabolic and endocrine imbalance (associated with obesity and neurological

outcomes), cognitive disorders related to neurodevelopmental dysfunction (learning problems, attention deficit hyperactivity disorder (ADHD), autism), and respiratory dysfunction such as asthma.

- Complex systems models that integrate key determinants to predict potential outcomes and impacts.

The Adverse Outcome Pathway (AOP) framework currently gaining traction in the toxicology and risk assessment communities provides an opportunity to integrate ORD CEH research across NRPs to begin to address these key gaps in the context of high priority assessment needs specific to early lifestages. An AOP portrays existing knowledge of linkage between a direct molecular initiating event and an adverse outcome at a biological level of organization relevant to risk assessment (i.e., actionable) (Ankley et al., 2010). These AOPs provide a framework for organizing and communicating existing knowledge concerning the linkage between molecular initiating events, intermediate key events along a toxicity pathway, and apical adverse outcomes traditionally considered relevant to risk assessment and/or regulatory decision-making. When developed and evaluated in a rigorous manner, AOPs provide a scientifically-defensible foundation for extrapolating from mechanistic data to predicted apical outcomes. Additionally, as individual AOPs are developed, they can be assembled into AOP networks that may aid the prediction of more complex interactions and outcomes resulting from exposure to complex mixtures and/or chemicals with multiple modes of action. These AOP networks then afford the opportunity to integrate and evaluate the potential for impacts associated with nonchemical stressors, in addition to chemical stressors. By considering AOPs and AOP networks associated with important developmental processes, as well as those associated with disease endpoints of concern, mechanistic toxicology information and epidemiology insights can be brought together for model development and analysis of critical knowledge gaps.

A major challenge is to translate AOP frameworks across scales of biological organization (molecules, cells, tissues, populations) and function, while incorporating critical windows of exposure, dose, pharmacodynamics, and pharmacokinetics. Multiscale modeling and simulation is a powerful approach for capturing and analyzing biological information that is inaccessible or unrealizable from traditional modeling and experimental techniques. For example, virtual tissue models (VTMs) afford the opportunity to develop science without conducting studies in children. By simulating a range of predicted effects, the earliest signs of adversity can be identified, and new testable hypotheses aimed at improving the accuracy of inferences from *in vitro* data. These same modeling approaches can be applied to capture the complexity of children's interactions with the environment in their home, school and community as well as to postulate key environmental determinants of health.

ORD will continue to identify effective strategies for fostering emerging scientific understanding and encouraging application of the latest science to inform Agency decisions. For example, the importance of epigenetic changes, i.e., the alteration of birth outcomes and/or the reprogramming of cells to promote disease susceptibility and metabolic dysfunctions that could occur later in life, is just beginning to be understood. Some of the EPA/NIEHS Children's Centers are currently doing work in this area and

further research is needed, using both experimental and epidemiological approaches, to help increase the understanding of the extent to which environmentally-induced epigenetic changes can contribute both to future disease status and to future resilience.

Research Area 3: Methods and models fit for purpose to evaluate early lifestage-specific risks and to support decisions protective of all susceptible and vulnerable early lifestages

As guidance for incorporating consideration of lifestage specific risks into Agency decisions are implemented, the need to incorporate a wide range of lifestage specific information into workflows and analytical tools to support assessments has increased. Methods and tools are needed to effectively address a growing range of considerations and factors where data may be limited. Priority needs are for:

- Rapid, efficient methods to characterize children's total environments, including the built and natural environments, where pregnant women and children live, learn, and play,
- Rapid, efficient methods for evaluating potential for developmental toxicity Science-based tools to support consideration of critical child-specific vulnerabilities for environmental and health policy decisions that promote and protect children's health.

For example, there is currently only limited information on exposures and exposure factors for infants and children less than 6 years of age. In addition, even when there is information on exposure levels from biomonitoring or other sources, there is little knowledge on the pathways of exposure, i.e., whether the exposure is predominantly from air, food, water, or other sources. Such information remains a critical gap in EPA's Exposure Factors Handbook (U.S. Environmental Protection Agency, 2011), a resource that is widely used across the Agency and by other organizations to conduct chemical risk assessments. Novel, ultra-low burden approaches are required to develop the exposure factor information and data required to support these Agency assessments of risks in early life. There are also important gaps in methods and approaches for characterizing potential exposures associated with the home, school, and community environment required to assess risks associated with real-world exposures to mixtures as well as to characterize potential modifying factors for more holistic decisions and solutions.

Another high priority Agency research need is for continued development and evaluation of assays and testing schemes to identify the potential for developmental toxicity and human-relevance across the full range of critical endpoints. Assays that can be implemented in rapid, cost effective schemes are of particular priority to facilitate development of data for thousands of chemicals in commerce that have not been evaluated for potential impacts to developmental pathways.

Research Area 4: Translational research and tools fit for purpose to support community actions and decisions

A lifecourse approach to health considers how an individual's current and future health may be affected by the dynamic interaction among social, biological, and environmental

influences over time. It underscores the importance of multiple risk and protective influences and considers how the presence or absence of these influences during critical and sensitive stages of development may affect the health of individuals or selected populations (National Research Council, 2011). There is expected to be significant investment by NIH, as part of the National Children's Study, and through NIEHS research to support public health in vulnerable populations and groups, including children. EPA leadership will be required to enable research that meets targeted needs for translational tools incorporating lifestage- specific considerations to provide local decision makers with the knowledge needed to inform a balanced approach to community cleanup and development. Priority needs are for:

- Translational tools that can be used by community decision makers to access and use quality data sources specific to promote children's healthy development,
- Research related to child-specific impacts of exposure to non-chemical and chemical stressors at the community level.

State, Tribal and local governments make decisions that impact children's health and wellbeing in communities and settings (e.g., schools, daycare facilities, homes) where they live, work and play. In order to optimize child (lifestage)-specific settings, community decision makers need access to information on the health impacts of multiple factors in the built and natural environment that contribute, in positive or negative ways, to children's health, and their importance relative to each other. A lifecourse approach is needed to identify the types of decisions that focus on child- (or lifestage-) specific environments. By taking a lifecourse approach and building such information into decision support tools, community decision makers can optimize features of the built and natural environments so as to reduce (eliminate, prevent) risk and actively promote healthy development and wellbeing.

Informing 2016 – 2019 ORD Research Planning

Objective: Apply advanced and emerging science to understand and predict the role of exposure to xenobiotic environmental factors during early life, in the context of important non-chemical stressors, on health impacts across the course of development. Develop tools to address the complexity of CEH and support decisions that promote health and wellbeing of children.

Conceptual Framework

Systems theory provides the required framework for linking exposure science, toxicology, and epidemiology to study, characterize, and make predictions about the complex interactions between children and environmental stressors (both chemical and nonchemical) across the course of development (**Error! Reference source not found.**). Multifactorial exposures to individuals, communities, and populations are captured horizontally from left to right (source-to-dose response with feedback), while outcome hierarchy is captured vertically from bottom to top (adverse outcome pathway). Kinetics and dynamics of these complex systems processes are not depicted, but are

critical to meet the objective of moving toward development of predictive tools for supporting risk-based decisions.

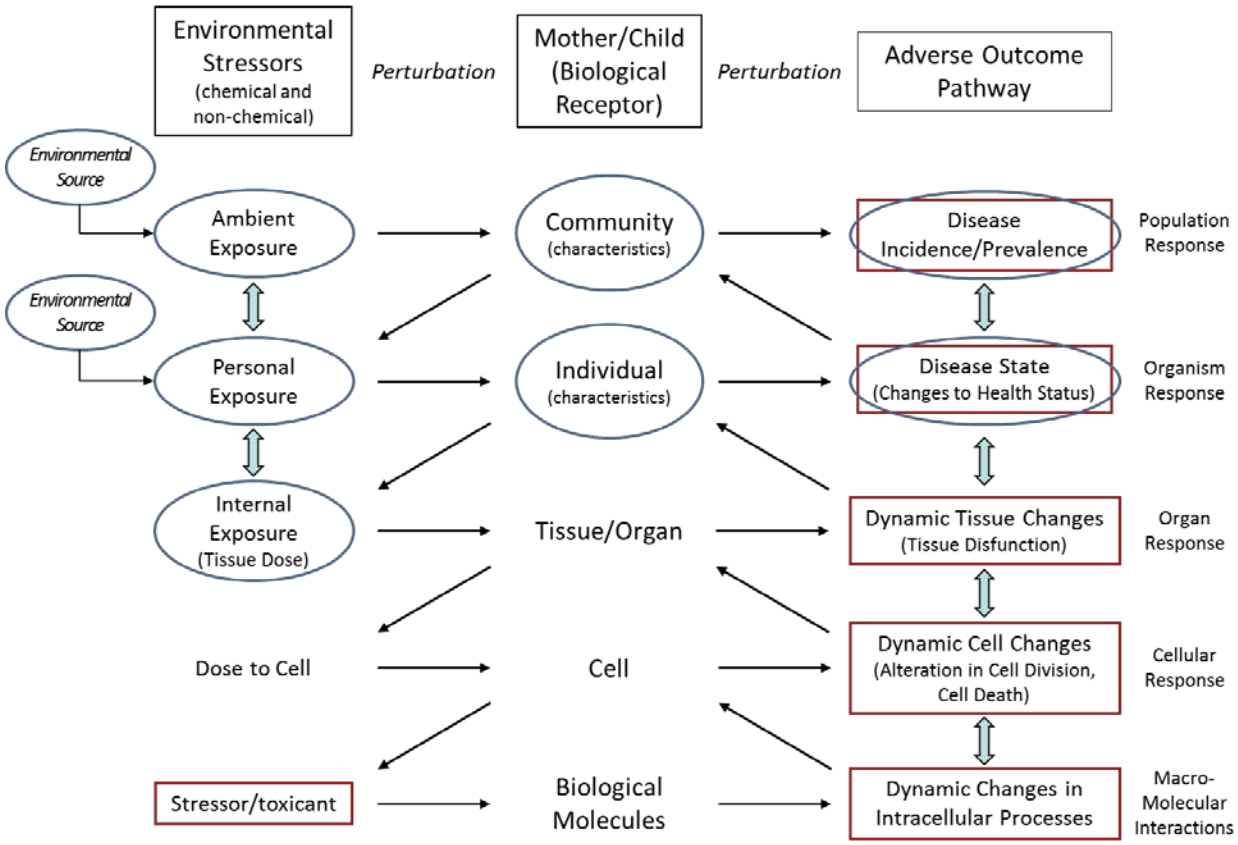


Figure 3. Concept for integrated CEH research in ORD.

The science developed will support consideration of multiple vulnerability and susceptibility factors for risk based decisions. Exposure assessment and risk assessment require population and community-specific information or exposure factors that may vary significantly based on geography and cultural practices. These factors have been reviewed and a framework has been described to facilitate systematic consideration of these contextual factors for exposure and risk assessment (see *Table 7*) (DeFur et al., 2007).

Table 7. Examples of specific vulnerability factors (DeFur et al., 2007)

Environmental Conditions (habitat quality)		Receptor Characteristics (individual or group quality)	
Location	Noise	Biological factors	Adaptability
Geographic area	Social environment	Genetics	Intensity
Urban	Segregation	Gender	Mood
Rural	Crime	Genetic diversity	Persistence/attention span
Proximity to industrial sites	Chaos	Genetic flux	Distractibility
Proximity to roads and traffic	Conflict	Susceptibility	Sensitivity
Time indoors, time outdoors	Social support	Developmental or lifestage	Activities/behaviors
Quality of setting	Immigration/ emigration	Age	Physical activity
Natural environment	Family or group stability	Population structure	Hygiene
Air quality	Violence	Physical health status	Diet
Water quality	Racism	Low birth weight	Product use
Climate, habitat	Resources	Chronic disease-obesity	Smoking
Built environment	Social capital	Compromised immune function	Substance abuse
Land use	Wealth	Asthma	Religious practice
Housing quality	Employment opportunities	Acute disease-exposure	Social factors
Housing density	Schools	Infection	Race/ethnicity
Occupant density	Medical care	Nutrition	SES
Sanitation	Food availability	Injury	Population size
Traffic density	System complexity and redundancy	Psychologic factors	Diversity
		Mental/emotional health	Number of species
		Depression	Marital status
		Hostility	Educational status
		Poor coping skills	Other
		Temperament	

Conceptual Approach

EPA CEH Research will apply complex systems science to integrate the rapidly expanding body of information on children's environments with advancing insights on developmental processes to inform the understanding of key factors contributing toward health outcomes. This understanding will be translated and tools provided to support Agency decisions that promote and protect children's health and wellbeing.

Studies will be model-driven to direct resources toward filling priority scientific gaps and to facilitate advancement of Agency capacity to be predictive of potential risks. This approach iteratively measures, mines, models, and manipulates (4M's) to extract maximum understanding from extant data and to provide tools that support holistic evaluation of the complex interactions that determine health impacts of early life exposures. To ensure short term impact in support of Agency needs, the scope of the research will be targeted by implementing studies through case examples focused on priority health outcomes and exposures as identified by ORD Program Office Partners through the NRPs.

Measurement includes obtaining multi-dimensional information of the system through a variety of methods including high-throughput data capture. This involves much of the same data capture approaches that have been traditionally performed, but broadens the space through increasing system complexity (e.g., cellular processes, metabolism, protein location, receptor binding, enzyme activation/inhibition, biomarkers of exposure, environmental concentrations) and efficiency (e.g., rapid screening methods requiring fewer materials and increasing output).

Mining includes the organized compilation of the multi-dimensional data into usable databases, and bioinformatics approaches which mine the database to develop plausible relationships providing systems-based hypotheses, including for example, putative AOPs.

Modeling includes developing statistically-based signatures (i.e., metrics) and computational-mechanistic models from the relevant information. These models are complex, nonlinear, and interconnected integrating the data beyond a linear process.

Manipulation includes functional studies to predict system-level behaviors *in silico* and to evaluate model performance. An iterative process of prediction-validation is necessary to refine models in order to adequately represent the human-environment system at important levels of organization, whether the consequences result in normal development and wellbeing or adverse consequences to development and health.

This approach calls for knowledgebase-driven methods to incorporate information from past and current research, compilation of plausible pathways and mechanism of exposure and toxicity, models that can predict whether or not a chemical will elicit an adverse outcome, simulations that can incorporate these models, validation models for checks and balances, and acceptance and integration into current risk assessment paradigms, as well as integrating these data in new ways to evaluate risk.

Application of this common approach to identify the most important environmental factors driving early-life exposures and associated health outcome over the lifecourse will address key scientific gaps required to support the Agency's mission and strategic goals for protecting and promoting children's wellbeing.

Example 1: Birth Outcomes (Vascular VTMs)

The Virtual Tissue Modeling (VTM) project focuses on biologically-driven assembly to enable (*in vitro*) and simulate (*in silico*) key events in an AOP framework with respect to spatio-temporal dynamics in human development. The overall goal is to advance the mechanistic understanding of how chemical disruption of cell lineage, fate and behavior propagates to higher levels of biological organization and adverse developmental outcomes. Genomic and environmental signals act cohesively during successive windows of development. When disrupted, these changes can impact aspects of maternal or filial development leading to an array of adverse birth outcomes (e.g., malformations, low birth weight).

Embryonic vascular network assembly is a complex process characterized by the formation of geometric tubular networks (vasculogenesis). The early pattern is based on differential cell growth, migration and survival along a growth factor (VEGF-A) gradient as well as differential cell adhesion and cell folding that connect the endothelial cell network and create a patent luminal channel, respectively. Subsequent growth and remodeling of the primitive capillary network (angiogenesis) is mediated by invasive angiogenic sprouting induced by local growth factors linked to oxygen tension as well as shear-stress signals following establishment of blood flow (Perfahl et al., 2011; Shirinifard et al., 2009). To understand and predict impacts of chemical exposures on this system, computational systems models have been built that incorporate all of the systems biology framework components (measurement, mining, modeling, manipulation). This provides a good example for how the systems biology approach can be applied to a particular developmental system.

Measurement: Data of chemical-biology perturbations came from the EPA's ToxCast program, as well as from text mining the public literature. A number of ToxCast assays specifically related to the vascular system were selected for incorporation into AOPs and computational simulation models. These assays and targets came from a human primary co-culture cell system with eight cell lineages (e.g., endothelial, peripheral blood, coronary artery smooth muscle, fibroblasts) evaluating protein secretion readouts (e.g., tissue factor, VCAM-1, MCP-1, uPAR, MMPs, TGFb, collagen), cell-free assays evaluating protein binding (e.g., VEGF, endothelin) and enzyme activity (e.g., caspase, ephrin, MMPs, Tie2), and cell-based assays evaluating transcriptional regulation (e.g., RAR, VDR, TGFb). A litany of MeSH terms was developed based on annotated genes, canonical pathways and cellular processes that could be linked to normal and abnormal vasculogenesis and angiogenesis to identify relevant vasculature-related articles and co-annotated concepts and principles.

Mining: Mining techniques combined literature mining integration tools (eLibrary) and bioinformatics approaches for making predictions about putative Vascular Disrupting Compounds (pVDCs). Using the MeSH terms indicated above on the public literature domain limited the articles to 100,000. These articles were organized in a way to assist in finding relevant relationships described in the articles and annotated in the MeSH terms. In the case of angiogenesis, for instance, the relationship between angiogenesis and proteins are captured by extracting co-annotations for neovascularization and proteins. Similarly, chemicals co-annotated with neovascularization are extracted into another sheet and organized by whether the chemical appears from the MeSH annotations to have an adverse effect on neovascularization or to have a therapeutic effect on neovascularization. The protein annotations are further processed to look at co-annotations in the literature which coarsely indicates a biological relationship. Although the exact nature of the relationship is not identifiable from the annotations, the knowledge that two proteins are co-annotated is a helpful starting point for more in depth exploration and further research. These associations are helpful in elucidating AOPs within the modeling section.

Chemicals were identified to be potential vascular disruptors, pVDCs, through identifying and prioritizing the ToxCast HTS assays relevant to vascular development. Six broad classes of assay targets (24 in total) were identified from the HTS assays, including receptor tyrosine kinases (VEGFR2, TIE2), GPCR-based chemokine signals (CXCL10, CCL2) and the GPI-anchored signals from matrix remodeling (PAI1, uPAR) among others. Next, the chemical-assay target activities for each chemical were used to rank the chemicals as least to most likely to affect the developing vasculature system. This provided a list of potential chemicals to pursue in follow-up modeling and confirmation steps across 1060 chemicals in the ToxCast library.

Modeling: AOPs delineate the documented, plausible, and testable processes by which a chemical induces molecular perturbations and the associated biological responses that describe how the molecular perturbations cause effects at the subcellular, cellular, tissue, organ, whole animal, and population levels of observation. This concept identifies the pathway linking a molecular initiating event (MIE) to an adverse outcome. To identify potential MIEs, the gene ontology (GO) and mammalian phenotype (MP) browsers of the Mouse Genome Informatics database (http://www.informatics.jax.org/) were searched for terms affiliated with the disruption of vascular development. Terms for abnormal vasculogenesis [MP:0001622; 72 genotypes, 73 annotations] and abnormal angiogenesis [MP:0000260; 610 genotypes, 894 annotations] were captured into a table as well as the gene and protein and then both were linked to ToxCast assays. This list had 65 target genes with bona fide roles in vasculogenesis or angiogenesis, 50 of which had evidence of abnormal embryonic vascular development based on genetic mouse models (Knudsen & Kleinstreuer, 2011). The proposed AOP for embryonic vascular disruption is shown in Figure 4.

An integrated understanding of the mechanisms and key events underlying embryonic vascular disruption requires a modeling framework to link relevant information about molecular pathways and cellular processes with the kinetics and dynamics of the system that describe the interactions and functioning of those elements. A systems biology approach is required to extend traditional conceptual linear models into computational models that are ideally quantitative or predictive. In building a simulation model of this process, each simulated cell in the model, like a biological cell, has an inherent capacity to process local information from the microenvironment and respond according to its own genetic blueprint or history. The key molecular players and cellular behaviors of concern were identified via the eLibrary, AOP framework, and ToxCast assay data. By incorporating these data and critical pathways and processes (e.g., extracellular matrix remodeling, chemokine pathways, growth factor signaling), the model can test certain hypotheses on cell signaling interactions and emergent vessel network topologies following chemical disturbance of specified growth factors, cell-surface receptors, and breakdown of the extracellular matrix. Discrete cellular behaviors (growth, adhesion, proliferation, apoptosis, chemotaxis) and parameters (growth factor diffusion, decay, secretion and uptake rates and cell size, motility, growth rate) were programmed into the simulation. Model outputs (cell number, angiogenic index, average vessel

length/diameter, number of branching points) were compared to histological data for accurate representation.

Manipulation: Confirmation studies for the AOP and simulation model on vascular development included several anti-angiogenic reference compounds: 5HPP-33 (thalidomide analogue), TNP-470 (Wnt inhibitor), PTK787 (VEGFR2 inhibitor), and AG1478 (EGFR inhibitor). The 5HPP-33 reference compound was confirmed active in ToxCast Phase II assays across the AOP signature. In collaboration with scientists at the DOW Chemical company, 5HPP-33 and TNP-470 were shown to interfere with microvessel outgrowth in aortic explant assay and caused lethality (5HPP-33 ≥ 15µM) and malformations (TNP-470 ≥ 0.25 µM) in rat whole embryo culture. Computer simulation with 5HPP-33 predicted similar exposure-related morphological effects. RNA-Seq analyses were proposed to aid in understanding the specificity of the vasculogenesis-disruption mechanisms and allow identification of novel gene targets perturbed following chemical exposure. RNA-Seq analysis conducted on rat embryos (GD10) exposed to 5HPP-33 and TNP-470 in vitro revealed concentration-dependent effects on vasculogenesis genes (i.e., VCAM1, TNF, CASP8, HIF1A, AHR). These studies provide evidence that the science is correctly understood within the context of this research and that the predictions are plausible.

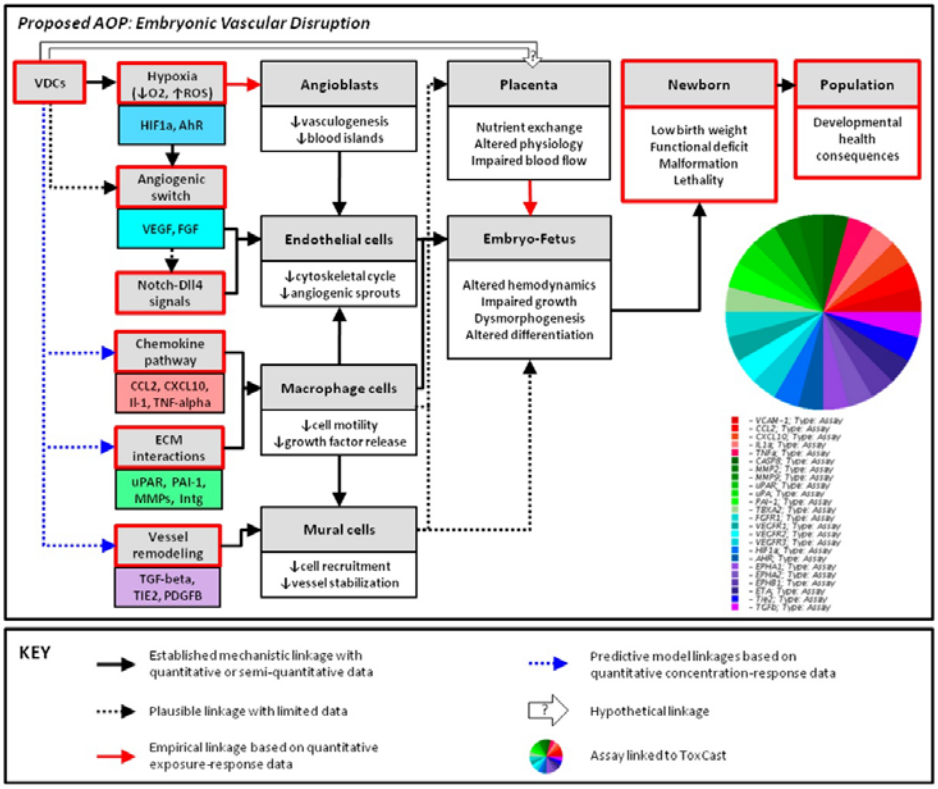


Figure 4. Proposed AOP for embryonic vascular disruption.

Example 2: Asthma (MICA Study)

Despite recent evidence suggesting that the very large increase in asthma incidence and prevalence observed in recent years may be slowing (Akinbami, Mooreman, & Liu, 2011), the global burden of this complex disease remains at an all-time high. More than 20 million Americans have asthma, including approximately 7 million children under the age of 18. The cost of treating asthma in children under 18 in the U.S. is estimated at $3.2 billion per year. Prevalence of asthma in low income and minority children in the United States is disproportionately higher (Akinbami et al., 2011; von Mutius & Hartert, 2013).

The Mechanistic Indicators of Asthma (MICA) study was designed to investigate whether genomic data (blood gene expression), viewed together with a spectrum of exposure, effects, and clinical and susceptibility markers can increase the sensitivity required to define exposure-response-effects relationships and provide mechanistic insight for further hypothesis generation and testing. As such, this study provides an example of how a systems biology approach can support a more holistic understanding of the multifactorial etiology of environmental disease (Gallagher et al., 2011).

***Measurement**:* A nested case-control cohort of 205 non-asthmatic and asthmatic children, (9-12 years of age), from Detroit, Michigan were recruited. The integrated study design and framework for MICA is shown in Figure 5. The MICA design focuses on environmental exposures, susceptibility, asthma and other health measures, including risk factors associated with obesity and cardiovascular disease. Information on a wide range of risk factors relevant to asthma and asthma exacerbations were characterized through collection of exposure metrics, lung function tests and biological and clinical indicators measured in blood, urine, and fingernails. The study includes environmental measures (indoor and outdoor air, vacuum dust), biomarkers of exposure (cotinine, metals, total and allergen specific Immunoglobulin E, polycyclic aromatic hydrocarbons, volatile organic carbon metabolites) and clinical indicators of health outcome (immunological, cardiovascular and respiratory). In addition, blood gene expression and candidate SNP analyses were conducted. Selected measurements are highlighted in Figure 5.

***Mining**:* Traditional analysis of complex disease considers one domain of data at a time to identify associations between biomarkers or bioindicators and disease outcomes. The commonly employed methodologies used require a clearly defined phenotype representative of multiple underlying disease processes for traditional supervised methods or a disease clearly identifiable by genomic or clinical data for traditional unsupervised methods, neither of which is true of complex disease. The large data sets that are now widely available can be mined to define novel, mechanistically distinct disease subtypes (endotypes) in a completely data-driven manner. Approaches for maximizing the discovery potential of these data sets are still an area of significant research. Alternative approaches for mining the MICA data were evaluated (e.g., Student's t-test, single data domain clustering and the Modk-prototypes algorithm). To best exploit strengths and limitations of the MICA data, a novel multi-step decision tree-

based method was developed to define endotypes. This new method gave the best segregation of asthmatics and non-asthmatics, and it provided easy access to all genes and clinical covariates that distinguish the groups (Williams-DeVane et al., 2013).

Modeling: As noted above, gene expression data were combined with hematologic, immunologic, and cardiopulmonary covariates to define mechanistically distinct subtypes (or endotypes). A novel method was used to integrate the clinical covariate data with gene expression resulting in a recursive partitioning tree that segregated individuals according to their asthma status. The resulting tree model assembled asthmatic subjects into purely data driven endotypes. These endotypes were consistent with previous classifications, though the data suggest multiple mechanistically distinct neutrophilic subtypes. Functional characterization of the genes and associated covariates revealed a complex interaction among Th2 mediated lung inflammation, heightened systemic innate immune response, and potentially metabolic syndrome in discriminating asthma endotypes. These findings support a prominent role for systemic inflammation due to heightened innate immune responsiveness across the asthma syndrome and suggest that new biomarkers are needed to better classify mechanistically distinct neutrophilic endotypes.

Manipulation: Characteristics of the data-driven derived endotypes from this study are consistent with previously published endotypes based solely on clinical diagnostic criteria, but this data-driven method provides mechanistic understanding that is not possible when using established clinical markers alone. One theme that emerges from this analysis is the interplay between innate and adaptive immune responses across endotypes. Results also suggest a role for broad systemic inflammation in addition to the localized hyperreactivity in the lung as a major driver for asthma. The findings of this data-driven mining and modeling approach are consistent with studies demonstrating that weight loss improves asthma symptoms without significant changes in markers of airway inflammation. Of note, body mass index (BMI) alone is not a predictor of asthma in the MICA study, in contrast with other recent studies; this may be because MICA looks at asthma prevalence in children rather than correlates of asthma onset. The MICA study, among others, putatively identifies underlying mechanisms linking obesity and asthma through systemic inflammation related to metabolic syndrome and increases the relevance and understanding of clinical findings.

The result of applying this holistic approach to the study of asthma in children is a better understanding of the various asthma endotypes and a scientifically defensible foundation for the evaluation of the many environmental factors influencing each mechanistically distinct endotype. Non-eosinophilic asthmatics likely fall into multiple mechanistically distinct subgroups or endotypes**.** Exacerbation of asthma by obesity and metabolic syndrome likely occurs through enhanced systemic inflammation, which will not be detected by biomarkers reliant on airway inflammation.
Asthma biomarkers reliant on airway inflammation may miss endotypes driven by systemic inflammation. The increasing incidence of asthma due to the rise in obesity will expand the proportion of these endotypes.

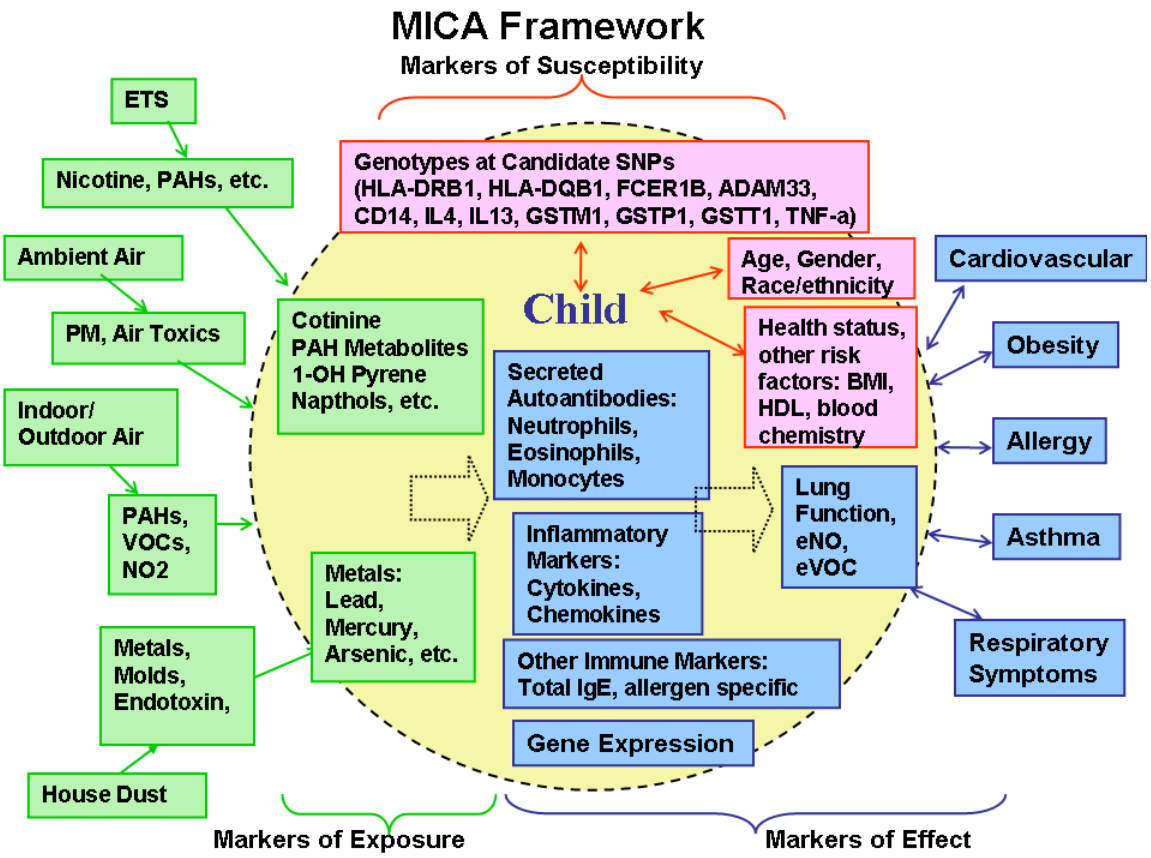


Figure 5. The overall MICA study design includes exposure, biomarkers of exposure, clinical indicators, genomic data (blood gene expression and SNP) and health status indicators.

Example 3: The Future of Cross-Cutting CEH Research

The traditional risk-based assessment paradigm supports decisions to minimize adverse impacts associated with environmental exposures. Clearly, removing chemical/pollution stressors is a necessary and essential component of children's health protection. Community planning and development decisions are designed from the holistic perspective of both minimizing risks while at the same time providing an environment that supports and promotes healthy (optimal) child development. Such a goal is an inherent property of sustainability. To support this goal, novel methods are required to incorporate and consider the complexity associated with these decisions and to compare alternatives and evaluate outcomes.

For example, the same agent-based modeling tools used by the ORD Virtual Tissues Modeling project to simulate how chemical perturbations at the cellular level propagate to higher levels of biological organization can potentially be applied to simulate population level interactions of children in a community. It has been suggested that health behavior research is a candidate for application of complex systems modeling

approaches to address empirical questions that cannot be addressed using the regression approaches common to the field of social epidemiology (Galea, Hall, & Kaplan, 2009). Similarly, these approaches could provide the capacity to integrate the vast array of information required to computationally test and evaluate community-level interventions and public-policy decisions designed to improve CEH. By designing cross-cutting ORD research to extend these approaches across all levels of organization, important gaps in data and understanding can be efficiently identified for targeted study and data collection. The conceptual research framework and approach described in these three examples, implemented through case examples of high priority to ORD program office and regional partners, will facilitate integrated research required to support holistic and sustainable decisions in support of CEH.

VI. Summary

CEH research is conducted by the EPA to improve the scientific understanding required to support: regulatory decisions protective of children's health now and in the future; community decisions that protect and promote children's health across generations; and, ecological decisions that provide sustainable healthy environments for children. The overarching goal for EPA's CEH research program is to provide the Agency and others with the information needed to incorporate consideration of early lifestage susceptibility and vulnerability into decision making.

EPA's CEH research is designed to address four priority research areas: 1) knowledge infrastructure to provide early lifestage-specific data and information; 2) systems (biological) understanding of the relationship between environmental exposures and health outcomes across development; 3) methods and models fit for purpose to evaluate early lifestage-specific risks and to support decisions protective of all susceptible and vulnerable early lifestages; 4) translational research and tools fit for purpose to support community actions and decisions.

EPA is currently carrying out research in each of these four areas and plans to build on this research as it plans for the future. EPA will continue to partner with other Federal agencies and independent organizations to further CEH research. 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 that will support Agency decisions that promote and protect children's health and wellbeing. Model-driven studies will be used to direct resources toward filling priority scientific research gaps and to advance the Agency goals of protecting human health and the environment.

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Appendix B. ORD's Current Research Activities

This Appendix presents more information on the research activities that are presented in Section IV of the document as well as information on additional research activities. The NRP with key responsibility for each of the activities is provided in parentheses after the project name in this section.

- ACE = Air, Climate, and Energy Research
- CSS = Chemical Safety for Sustainability Research
- HHRA = Human Health Risk Assessment Research
- SHC = Sustainable and Healthy Communities Research
- SSWR = Safe and Sustainable Water Resources Research

Research Area 1. Knowledge infrastructure to provide early lifestage-specific data and information

Currently knowledge resources are being developed under Research Area 1 in the following three areas: 1) Exposure Information, 2) Early Lifestage Pharmacokinetic Parameters, and 3) Developmentally Relevant Hazard Data. ORD's relevant research in each of these areas is summarized as follows:

1.1 Exposure Information

Exposure data are critical for characterizing children's environments and for evaluating interactions of the child with that environment across development.

1.1.1 Exposure Factors Handbook (HHRA)

Data about children's exposures and exposure factors, such as lifestage specific modeled estimates of soil and dust ingestion is incorporated into EPA's Exposure Factors Handbook {U.S. Environmental Protection Agency, 2011 #59}; available at http://cfpub.epa.gov/ncea/risk/recordisplay.cfm?deid=236252. This important resource is used by exposure assessors both inside and outside the Agency to obtain data on lifestage specific exposure factors to calculate human exposure to environmental agents. These factors include: drinking water consumption, soil and dust ingestion, inhalation rates, dermal factors including skin area and soil adherence factors, consumption of fruits and vegetables, fish, meats, dairy products, homegrown foods, human milk intake, human activity factors, consumer product use, and building characteristics.

1.1.2 Consolidated Human Activity Database (CHAD)

ORD's Consolidated Human Activity Database (CHAD) is a compilation of data on human behavior from 24 individual studies {U.S. Environmental Protection Agency, 2014 #66}; available at: http://www.epa.gov/heasd/chad.html. This resource includes more than 50,000 individual data days of detailed location and activity data and corresponding demographic data including age, sex, employment, and education level. These data are used in human exposure and health studies and models used for exposure and risk assessment. Data are included for all ages, including children as young as infants. Recent information added to CHAD for children includes data from the 2008 phase of the Child Development Supplement of the University of Michigan's Panel Study for Income Dynamics (PSID).

1.1.3 ExpoCast Database (CSS)

ExpoCast Database (ExpoCastDB) was developed to improve access to human exposure data from observational studies, including those funded by ORD. ExpoCastDB consolidates measurements of chemicals of interest in environmental and biological media collected from homes and child care centers. Data currently include the amounts of these chemicals found in food, drinking water, air, dust, indoor surfaces and urine. The current publicly released version of ExpoCastDB includes data for 99 unique chemicals primarily consisting of active ingredients in pesticide products. Chemical concentrations measured in samples collected for three observational studies are included: the American Healthy Homes Survey (AHHS), the First National Environmental Health Survey of Child Care Centers (CCC), and the Children's Total Exposure to Persistent Pesticides and Other Persistent Organic Pollutants (both CTEPP NC and CTEPP OH) studies.

ExpoCastDB is available as a searchable database {U.S. Environmental Protection Agency, 2014 #67}; available at: http://actor.epa.gov/actor/faces/ExpoCastDB/Home.jsp) on EPA's Aggregated Computational Resource (ACToR) system, an online data warehouse that collects data on over 500,000 chemicals from over 1000 public sources {U.S. Environmental Protection Agency, 2014 #68}; available at: http://actor.epa.gov/actor/faces/ACToRHome.jsp). Controlled vocabularies are used to facilitate searching and analyses across datasets and to encourage standardized reporting of observational exposure information. ExpoCastDB provides a separate interface within ACToR to facilitate linkage of exposure measurement data with data on toxicity, environmental fate, and chemical manufacturing and usage information.

1.1.4 Chemical and Product Categories (CSS)

Chemical and Product Categories (CPCat) is a database of information on how chemicals are used {U.S. Environmental Protection Agency, 2014 #69}; available at: http://actor.epa.gov/actor/faces/CPCatLaunch.jsp. As with ExpoCast, CPCat is available as a searchable database within ACToR. CPCat contains information on the uses of chemicals; products that contain chemicals; manufacturers of the products; and a hierarchy of consumer product "use" categories. Examples of the types of uses in this database include uses in: consumer products; automotive products; agricultural chemicals; and pesticides. It also contains information on use by children and lists any regulations or studies in which the chemical has been considered hazardous to children.

1.2 Early Lifestage Pharmacokinetic Parameters

Pharmacokinetic and pharmacodynamic parameters for all lifestages are required to predict the potential for health effects from exposures to environmental chemicals. Child-specific parameters are used to characterize dose to the developing child *in utero,* after birth through lactational exposure, and during early infancy through prepubertal ages.

1.2.1 Enzyme Ontogeny Database (CSS)

Chemicals are typically metabolized in the body sequentially by activating and detoxifying enzymes that change over time from the developing embryo to adulthood. Therefore, the availability of certain enzymes at different lifestages could play an important role in determining the susceptibility of children, compared to adults, to environmental chemicals. ORD has developed an enzyme ontogeny database

that can be used as a screening tool to explore metabolism-based variability, based on enzyme differences, during early lifestages.

1.3 Developmentally Relevant Hazard Data

Data from *in vivo* animal studies, screening assays, and other study types are needed in order to carry out risk and hazard assessments on environmental chemicals. ORD has developed databases that allow for easy access to developmental hazard data that is being used to link environmental exposures at early lifestages with health outcomes in children and later in life.

1.3.1 ToxCast Database (CSS)

ToxCastDB provides results of high throughput *in vitro* assays. Biology covered in the large set of assays include endpoints related to endocrine, reproductive, and developmental toxicity and a major proportion of the assays are human-based cells or proteins. Information about the assay design, chemical dose, and experimental set-up are also provided in the database. ToxCastDB is available as a searchable database through the ACToR system {U.S. Environmental Protection Agency, 2014 #70}; available at: http://actor.epa.gov/actor/faces/ToxCastDB/Home.jsp.

1.3.2 Toxicity Reference Database (CSS)

Toxicity Reference Database (ToxRefDB) contains data from thousands of *in vivo* animal studies and is available as a searchable database through the ACToR system {U.S. Environmental Protection Agency, 2014 #71}; available at: http://actor.epa.gov/toxrefdb/faces/Home.jsp. Information on study design, dosing, and treatment-related effects from subchronic, chronic, cancer, developmental, and reproductive studies are included in the database. The developmental toxicity information includes results from studies on more than 380 chemicals with 18 endpoints for both the rat and rabbit, while the reproductive toxicity information is based on the results from multigenerational reproductive studies on 316 chemicals, with 19 parental, reproductive, and offspring endpoints.

1.3.3 Adverse Outcome Pathway Wiki (CSS)

An Adverse Outcome Pathway (AOP) is a conceptual framework that portrays existing knowledge concerning the linkage between a direct molecular initiating event and an adverse outcome. The goal of an AOP is to provide the framework to connect the two events. In developing information on early lifestage toxicity, ToxCast provides the infrastructure to predict pathways of toxicity by probing the fundamental nature of chemical interaction(s) with their potential molecular targets and cellular consequences. However, since toxicity is an expression of lesion propagation to higher levels of biological organization, AOP models are needed to provide weight-of-evidence for biological plausibility across the developmental linkages leading to observable endpoints in the newborn or child. Multi-cellular interactions, such as between immune cells and endothelial cells during angiogenesis for example, play important roles in utero-placental development, embryogenesis, and other AOPs linked to childhood development. These AOPs can be used to integrate multi-dimensional data with vast biological knowledge.

AOP Wiki is a wiki-based tool that provides an interface for collaborative sharing of established AOPs and building new AOPs {Anonymous, 2014 #45}; available at:

http://aopkb.org/aopwiki/index.php/Main_Page. AOP Wiki uses templates to make it easier for users to include the information needed for proper evaluation of an AOP.

Research Area 2. Systems understanding of the relationship between environmental exposures and health outcomes across development

Research Area 2 has been divided into the following two subgroups: A) Systems Biology to Predict Developmentally Relevant Outcomes and B) Systems Understanding of Complex Stressors. ORD's relevant research in each of these areas is summarized as follows:

2.1 Systems Biology to Predict Developmentally Relevant Outcomes

Systems models for tissues and multi-organ pathways specific to embryo-fetal and neonatal development are being developed. These models increase our understanding of the biologic mechanisms of chemical stressors that contribute to childhood health outcomes.

2.1.1 Bioinformatics-Based Models (CSS)

As discussed in section 1.3.1, ToxCastDB uses high throughput biochemical and cellular *in vitro* assays to evaluate the toxicity of environmental chemicals. ORD has developed bioinformatics-based models using ToxCastDB in a two-step process: 1) examining which assays were associated with chemicals having certain toxicity profiles, such as developmental or reproductive toxicity, and 2) developing predictive models using these assay associations to predict the likelihood of reproductive, developmental, or other types of toxicity of chemicals that had not been tested *in vivo*. The development of predictive models is being carried out in phases, with the development and publication of first-generation (Phase I) ToxCast predictive models for reproductive toxicity {Martin, 2011 #29} and developmental toxicity {Sipes, 2011 #39}. These models anchored *in vitro* data to *in vivo* endpoints for a set of ~300 data-rich chemicals. Pathways for endocrine disruption {Reif, 2010 #34}, embryonic stem cell differentiation {Chandler, 2011 #10} and disruption of blood vessel development {Kleinstreuer, 2011 #26} have been linked to the Phase I ToxCast *in vitro* data. For the next ~700 compounds in Phase II, where animal toxicology is less well-characterized, ORD is developing plausible model structures that deal with the possibility of additional relevant interactions and components beyond those represented in the first-generation predictive models.

2.1.2 AOP Models (CSS)

ORD is developing AOP models, such as the vascular AOP model, with the aim of establishing the predictive value of chemical disruption of blood vessel development (vasculogenesis) during critical windows of embryonic and fetal development. Using computer-based simulation tools, vasculogenesis and its disruption can be visualized in the virtual absence and presence of specific chemicals across a given dose range. This model is being tested in Zebra fish embryos and in embryonic stem cells and provides information for individual chemicals and chemical families on potential reproductive and developmental toxicity and susceptibility by developmental stage. As additional individual AOPs are developed, they can be assembled into AOP networks that may aid the prediction of more complex interactions and outcomes resulting from exposure to complex mixtures and/or chemicals with multiple modes of actions.

2.1.3 Simulation Models (CSS)

Simulation models predict chemical toxicity using relevant biologic information, such as the influence of subcellular pathways and networks on the development of tissues and organs. ORD is developing the Virtual Embryo model, a simulation model of predictive toxicology of children's health and development, which can be applied to prenatal or postnatal (including lactational) exposures. This model uses cell-based systems and knowledge databases to generate and integrate chemical, biological and toxicological information at all levels of biologic organization (molecular, cell, tissue, organ, and organism) in order to enhance the predictive power to evaluate potential chemical toxicity. The virtual model uses AOP models, such as the model for vasculogenesis (section 2.1.2) and endocrine system models, as modules in the model. Additional models for palate formation (predicting cleft palate), limb formation (predicting limb defects), eye development (predicting retinal disease) and phallus development (predicting hypospadias) are under active development.

2.2 Systems Understanding of Complex Stressors

Epidemiologic, animal studies, and *in vitro* assays are being used to develop a systems understanding of the relationship between environmental exposures as stressors and lifestage-specific susceptibility and vulnerability. A critical component of a systems approach is determining how interactions among complex stressors – chemical and non-chemical (social, physical) – may increase the sensitivity of children.

2.2.1 Laboratory Based Studies (CSS, SHC, and SSWR)

Intramural ORD research has used a variety of *in vitro* models to evaluate the effects of chemical exposure in developmentally relevant systems (CSS). Cell (e.g., human multipotent neuroprogenitors, rodent embryonic stem cells, specific pathway-responsive modified hepatocytes), organ (e.g. human and rodent palatal shelves), and whole rodent embryo cultures, as well as whole organisms (developing zebrafish) have been used to address issues of toxic response. Many of these models have been developed, characterized and refined to answer specific research questions. Several model systems have been used to evaluate the effects of chemicals to aid in the translation of high throughput data in the ToxCast assays.

Intramural ORD research is also using *in vivo*, longitudinal study designs with rodents to explore causation and characterize how *in utero* and neonatal environmental stressors may alter development and thereby contribute to adverse health outcomes in adulthood (SHC). For example, ongoing work is examining how alterations in endocrine function during fetal and early childhood may impair adrenal and reproductive function during and after puberty. Researchers are also exploring lifelong changes in physiology that may result from fetal and neonatal exposures and predispose an individual to metabolic syndrome (obesity, hypertension, diabetes), impaired neurological function, and altered immune responses. Molecular and epigenetic mechanisms are being explored in these studies and companion *in vitro* models designed to identify toxicity pathways. Intramural researchers are designing studies to address hypotheses generated by epidemiologic studies, such as those being conducted by the Children's Centers (see section 2.B.3 below), in order to elucidate mechanisms and characterize modifying factors such as prenatal stress.

Laboratory based studies are also examining the cumulative risk of mixtures of chemicals. For example, ongoing studies are examining dose- and effect- additivity models for considering combined impacts of endocrine disruptors that perturb reproductive tract development after *in utero* exposures (SHC). Similarly, the combined impact of disinfection byproducts in drinking water on developmental processes and children is being examined (SSWR). *In vitro* and *in vivo* studies are investigating the effects of cumulative exposure to disinfection byproducts in drinking water, comparing two common disinfection methods (chlorination and chloramination). These mixtures are also being evaluated in mouse embryonic stem cells.

2.2.2 Epidemiologic Studies (SHC and ACE)

EPA-NIEHS Children's Environmental Health and Disease Prevention Research Centers (SHC)

The EPA-National Institute of Environmental Health Sciences (NIEHS) co-funded Children's Environmental Health and Disease Prevention Research Centers (CEHCs, or "Children's Centers") Program, ongoing since 1998, continues to generate exposure and biomarker data in pregnant women and children in order to show relationships between exposure and a variety of children's health outcomes, and to identify critical windows of susceptibility {U.S. Environmental Protection Agency, 2014 #72}; available at: www.epa.gov/ncer/childrenscenters; http://cfpub.epa.gov/ncer_abstracts/index.cfm/fuseaction/recipients.display/rfa_id/560/records_per_page/ALL). Jointly funded by EPA and NIEHS through the STAR grant program, the long-range goals include understanding how environmental factors affect children's health, and promoting translation of basic research findings into intervention and prevention methods to prevent adverse health outcomes. To achieve these goals, the program fosters research collaborations among basic, clinical, and behavioral scientists with participation from local communities. The Children's Centers Program celebrated its 15th anniversary in 2013 with a meeting in Washington, D.C., including comments from EPA Administrator Gina McCarthy.

The Children's Centers are currently collecting exposure data on pesticides, bisphenol A (BPA), phthalates, brominated flame retardants, metals such as arsenic, lead and manganese, and air pollutants including polyaromatic hydrocarbons (PAHs) and environmental tobacco smoke. Collectively, they are examining a wide range of health outcomes in cohorts of children including adverse birth outcomes, asthma and respiratory dysfunction, autism and other neurobehavioral problems including ADHD, obesity and metabolic syndrome, altered immune function and childhood cancer (Table 1). Increasingly, they are focused on potential epigenetic mechanisms by which exposures during gestation and early life may reprogram gene expression and set the stage for a variety of health conditions later in life. Furthermore, several Centers maintain or have access to longitudinal birth cohorts whose members are now entering puberty, making it possible to address multifactorial environmental public health questions relevant to adolescents.

Several Centers focus on childhood asthma as a common health outcome for which racial and ethnic disparities exist. These studies approach asthma from multiple fronts including air pollution from near-road exposures (as both causative and exacerbating), and the effectiveness of medical and dietary interventions. These studies and other STAR and ORD in-house studies on asthma causation and intervention described later address place-based community scenarios and are contributing to meeting

EPA commitments in the *Coordinated Federal Action Plan to Reduce Racial and Ethnic Asthma Disparities* {President's Taskforce on Environmental Health Risks and Safety Risks to Children, 2012 #54}.

Table 8. Current Children's Environmental Health and Disease Prevention Research Centers Exploring Associations Between Exposures and Health Outcomes in Children.

Institution – P.I.	Chemical Exposures and Other Stressors	Outcomes	Underlying Mechanisms (molecular, genetic, social factors)
Brown University – Boekelheide	Arsenic, EDCs (estradiol, BPA, genistein), dietary restriction	Fetal liver, lung and prostate development; prostate cancer in later life	Endocrine disruption; Epigenetic changes in organ development
Columbia University – Perera	Endocrine Disrupting Compounds (BPA), PAHs,	Neurodevelopmental disorders such as problems with learning and behavior; obesity and metabolic disorders	Endocrine disruption; Epigenetic reprogramming and metabolic syndrome
Dartmouth College – Karagas	Arsenic in drinking water and food	Growth and development; immune response	Epigenetic changes and influence of gut microbiome
Duke University/ University of Michigan – Miranda	Environmental, social and individual susceptibility factors, PM, Ozone	Disparities in birth outcomes; respiratory health in infants	Social determinants of childhood disease
Duke University – Murphy	Environmental tobacco smoke	ADHD; neurobehavioral dysfunction	Epigenetic modulation in fetal and child development
Johns Hopkins University – Diette	Airborne pollutants (particulate matter, nitrogen dioxide), allergens, urban diets	Asthma	Dietary contributions to asthma ,based on anti-oxidant and anti-inflammatory impacts on immune function and inflammation
National Jewish Health – Schwartz, Szefler	Air pollution (ozone, PM, NO_2), ambient bacterial endotoxin	Asthma; immune system function; determinants of host defense	Host-immune responses and TL4 receptor function; interactions between ozone and endotoxin
University of California at Berkeley - Buffler, Metayer	Pesticides, tobacco-related contaminants, chemicals in housedust (PCBs, PBDEs)	Childhood leukemia	Epigenetic and genetic influences
University of California at Berkeley – Eskenazi	Pesticides (DDT, manganese), flame retardants	Neurodevelopment; growth and timing of puberty; obesity	Epigenetic reprogramming; altered endocrine status
University of California at Berkeley – Hammond, Balmes, Shaw	Ambient air pollutants (airborne PAHs), in utero exposure to traffic-related pollutants, endotoxin	Birth defects/preterm birth, immune system dysfunction (asthma/allergies), obesity/glucose dysregulation	Gene variants in biotransformation enzymes; molecular mechanisms e.g., altered T-cell function; neighborhood factors
University of California at Davis – Van de Water	BPDEs, pyrethroid insecticides, perfluorinated compounds, POPs	Autism spectrum disorder (ASD)	Immune dysfunction and autoimmunity; genetic/epigenetic contributions

Institution – P.I.	Chemical Exposures and Other Stressors	Outcomes	Underlying Mechanisms (molecular, genetic, social factors)
University of California, San Francisco – Woodruff	EDCs, PBDEs (BDE-47), PFCs (PFOA), psychosocial stress	Placental and fetal development, adverse birth outcomes	Gene expression changes via epigenetic mechanism; contribution of psychosocial stress
University of Illinois at Urbana-Champaign – Schantz	EDCs (phthalates, BPB); high fat diet	Neurological and reproductive development	Endocrine disruption; oxidative stress
University of Michigan – Peterson, Padmanabhan	BPA, phthalates, lead, cadmium	Birth outcomes; child weight gain; body composition; activity patterns; hormonal levels; sexual maturation; metabolomics and risk of metabolic syndrome	Dietary influences; epigenetics and gene expression changes; oxidative stress
University of Southern California – McConnell	Near-roadway air pollution including elemental carbon, PM 2.5	Obesity; fat distribution; metabolic phenotypes; systemic inflammation	Expression of genes in metabolic pathways; beta cell function; oxidative stress;
University of Washington – Faustman	Agricultural pesticides	Altered neurodevelopment	Genetic susceptibility; neurotoxicity ; oxidative stress; cellular pathways underlying neurodevelopment

Clean Air Research Centers (ACE)

ORD's Clean Air Research Centers Program (STAR) includes a number of epidemiologic projects directly relevant to children's environmental health. Two currently active Centers are producing new data and knowledge on the relationship between air pollution and children's health, with final reports expected in 2015. The Center at Emory University is generating "Novel estimates of pollutant mixtures and pediatric health in two birth cohorts," and the Center at Harvard University is evaluating "Longitudinal effects of multiple pollutants on child growth, blood pressure and cognition." {U.S. Environmental Protection Agency, 2012 #60}; available at: http://www.epa.gov/ncer/quickfinder/airquality.html.

Place-Based Studies (ACE, SHC and SSWR)

ORD recognizes that combinations of stressors are often unique to a particular community setting and that interventions to improve children's health must take this complexity into account. For example, ongoing place-based studies are examining the contributions of housing quality and mold to the severity of childhood asthma in children exposed to near-road air pollution (ACE). Other studies are showing that the social-economic status of a community can significantly alter the response of resident asthmatics to wood smoke from nearby wildfires (SHC). These studies are designed to inform community intervention decisions and benefit community sustainability.

A STAR grant and ORD in-house project, "The Near-Road Exposures and Effects of Urban Air Pollutants Study (NEXUS)" examined the influence of traffic related air-pollutants on respiratory outcomes in a cohort of 139 asthmatic children (ages 6-14) who lived close to major roadways in Detroit, Michigan (ACE). An integrated measurement and modeling approach was used to quantitatively determine the

contribution of traffic sources to near-roadway air pollution and predictive models were used to estimate air quality and exposures for the children {Vette, 2013 #44}.

A STAR grant project, "Effects of Stress and Traffic Pollutants on Childhood Asthma in an Urban Community," (SHC)(University of Medicine and Dentistry of New Jersey) is assessing young study participants (9-14 years old) with persistent asthma to correlate changes in asthma status with changes in air pollution measures and incorporate the influence of stress (evaluated with behavioral and biological indicators). In another STAR project, "Community Stressors and Susceptibility to Air Pollution in Urban Asthma" (SHC) (University of Pittsburgh), researchers are exploring the interdependent and synergistic effects of community stressors and traffic-related air pollution on asthma exacerbation among children aged 5-17 years. They are applying variants of spatial poisson regression and multi-level time-series modeling using syndromic surveillance and hospitalization databases by accessing emergency department visits and hospitalization records to examine the association between exposure to air pollution and increases in asthma in children.

Geospatial tools are also being developed and deployed in place-based children's health research to improve characterization of complex built and natural environments at various scales. For example, STAR grantees from Texas State University, Texas A&M, Texas Dept of State Health Services, and University of North Carolina-Charlotte are collaborating on a project called "Air Pollution-Exposure-Health Effect Indicators: Mining Massive Geographically-Referenced Environmental Health Data to Identify Risk Factors for Birth Defects" (SHC). Using air pollution exposure assessment methods, visual data mining tools, and epidemiological analysis procedures, they are defining new environmental public health indicators linking exposure metrics and birth defects.

Additional new knowledge about how the built environment, especially learning environments, influence children's health and performance, potentially in both positive and negative ways, is also being generated by STAR grantees. Currently, grantees from the New York Department of Health are exploring linkages between school-related environments, children's school performance, and environmental policies (report due in 2015) (SHC). More recently, a 2013 RFA solicited research on "Healthy Schools: Environmental Factors, Children's Health and Performance, and Sustainable Building Practices" (SHC) {U.S. Environmental Protection Agency, 2013 #62}; available at: http://epa.gov/ncer/rfa/2013/2013_star_healthy_schools.html. This research will investigate the impact of indoor pollutants, as well as outdoor pollutants being drawn indoors in schools, on children's health and ability to learn. These grants will be announced in 2014.

An ORD and EPA Region 6 study (SSWR) is examining water-related exposures and birth defects, in a five county area surrounding Corpus Christi, Texas. Previous studies noted an elevated rate of birth defects in and around the Corpus Christi area. In this study, ORD is conducting analyses to determine the extent and locations of clusters of birth defects and is examining the relationship between these clusters to water and other environmental exposures.

Evaluating Impact of Co-Exposure to Multiple Stressors

Research is ongoing on new methods for modeling and assessing cumulative exposure and risk. For example, "Estimation of Childhood Lead Exposure at the Census Tract Level Based on Aggregate Sources" (SHC) was a multi-factor analysis of cumulative lead exposure that increased the knowledge base concerning lead exposure in children.

A STAR grant project called "Effects-Based Cumulative Risk Assessment in a Low-Income Urban Community near a Superfund Site" (ACE) (Harvard School of Public Health) is leveraging data from an ongoing birth cohort study and public databases to predict exposures as a function of all chemical stressors of interest. The resulting health risk characterization will include geospatial and demographic variability and trends over time.

MICA Study (CSS and SHC)

The Mechanistic Indicators of Childhood Asthma (MICA) study was designed to pilot an integrative approach in children's health research. MICA incorporates exposure metrics, internal dose measures, and clinical indicators to decipher the biological complexity inherent in diseases such as asthma and cardiovascular disease with etiology related to gene-environment interactions. A cohort of 205 non-asthmatic and asthmatic children, (9-12 years of age) from Detroit, Michigan, was recruited. The study includes environmental measures (indoor and outdoor air, vacuum dust), biomarkers of exposure (cotinine, metals, allergen specific IgE, PAH and volatile organic carbon (VOC) metabolites) and clinical indicators of health outcome (immunological, cardiovascular and respiratory). In addition, blood gene expression and candidate single nucleotide polymorphism (SNP) analyses were conducted. Based on an integrative design, the MICA study provides an opportunity to evaluate complex relationships between environmental factors, physiological biomarkers, genetic susceptibility and health outcomes {Gallagher, 2011 #1}.

Research Area 3. Methods and models fit for purpose to evaluate early lifestage-specific risks and to support decisions protective of all susceptible and vulnerable early lifestages

Research Area 3 has been divided into the following two subgroups: A) Exposure, and B) Dosimetry Models. ORD's relevant research in each of these areas is summarized as follows:

3.1 Exposure

Exposure factors and exposure data (section 1.1) need to be easily accessible to risk assessors in order to assess the effects of environmental chemicals on children. ORD has developed tools to increase the usability and access to exposure data, models to predict exposure by a variety of pathways and routes, and approaches for categorizing lifestage changes and prioritizing chemical mixtures.

3.1.1 EPA ExpoBox (HHRA)

EPA ExpoBox is a web-based compendium of over 800 exposure assessment tools that provides links to exposure assessment databases, models, and references {U.S. Environmental Protection Agency, 2013 #63}; available at: http://www.epa.gov/risk/expobox/docs/Expobox_Fact-Sheet_Nov13.pdf. It includes approaches for exposure assessments, tiers and types of exposure assessments, chemical classes, routes of exposure to chemicals, lifestages and populations, and exposure media. It also includes, in a searchable and downloadable format, the full list of exposure factors from the Exposure Factors Handbook (see section 1.1.1).

3.1.2 SHEDS-HT Model (CSS)

The Stochastic Human Exposure and Dose Simulations–HT (SHEDS-HT) model is a screening-level human exposure model for chemicals. Pathways included in the model include near-field direct and indirect use of chemicals in the home (e.g., use of personal care products, cleaning products, and pesticides), emission of chemicals from building materials, and dietary consumption of contaminated foods. SHEDS-HT is a probabilistic model that produces population-level distributions of exposures by the dermal, inhalation, and ingestion routes. Exposure results can also be estimated for individual age-gender cohorts. Exposure-relevant information specific to children included in SHEDS-HT includes age-specific behaviors (such as hand-to-mouth contact and use of consumer products), times spent in microenvironments, and food intakes.

3.1.3 ExpoCast (CSS)

ExpoCast is a rapid, high-throughput model using off the shelf technology that predicts exposures for thousands of chemicals {U.S. Environmental Protection Agency, 2014 #73}; available at: http://epa.gov/ncct/expocast/. ExpoCast evaluated 1,763 chemicals for estimating exposure due to industrial releases and a simple indicator of consumer product use. ORD research is generating and incorporating new information about age-dependent exposures (e.g., product use) into ExpoCast so that this model can be more specifically applied to capture children's unique vulnerabilities to support risk-based decisions.

3.1.4 Lifestage Categories for Monitoring and Assessing Exposures to Children (SHC)

ORD has developed a consistent set of childhood lifestage categories for researchers to use when assessing childhood exposure and potential dose to environmental contaminants {Firestone, 2007 #3}. The standard lifestage categories are: birth to <1 month; 1 to <3 months; 3 to <6 months; 6 to <11 years; 11 to <16 years; and 16 to <21 years. These categories consider developmental changes in various behavioral, anatomical, and physiological characteristics that impact exposure and potential dose. These lifestage categories were recommended by EPA to be used as standard age groups in exposure and risk assessments in the report entitled "Guidance on Selecting Age Groups for Monitoring and Assessing Childhood Exposures to Environmental Contaminants" {U.S. Environmental Protection Agency, 2005 #57}; available at: http://www.epa.gov/raf/publications/pdfs/AGEGROUPS.PDF.

In order to harmonize lifestage categories for monitoring and assessing risks from exposures to chemicals for global use, the World Health Organization (WHO) recommended adapting ORD's lifestage categories, as presented above {Cohen Hubal, 2013 #7}.

3.1.5 Biogeographical Approach for Prioritizing Chemical Mixtures (CSS)

In a study of the co-occurrence pattern of pesticides in child care centers {Tornero-Velez, 2012 #42}. ORD used methods from the field of biogeography to investigate co-occurrence patterns in chemicals. The results showed that the co-occurrence of pesticides in the child care centers was not random but was highly structured, leading to the co-occurrence of specific combinations of pesticides. ORD concluded that chemical mixtures arise, in part through nonrandom processes such as economic factors, engineered formulations, and differential degradation such that the observed number of combinations tends to be less than the theoretical random number of combinations. The biogeographical approach

will be highly useful for prioritizing chemical mixtures in risk assessment and to calculate co-occurrence probabilities of mixtures of chemicals.

3.2 Dosimetry Models

ORD has developed a number of dosimetry models that assess exposure, predict dose, and describe the kinetics of environmental chemicals as related to children's health.

3.2.1 Empirical Models

Persistent Bioaccumulative Toxicants (CSS)

A statistical model was developed for predicting levels of polybrominated diphenyl ethers (PBDEs) in breast milk, based on serum data from the National Health and Nutrition Examination Survey (NHANES) {Marchitti, 2013 #28}. In this research, congener-specific linear regression partitioning models were developed and applied to 2003-2004 NHANES serum data for U.S. women. The predictions of PBDE levels in breast milk were consistent with reported concentrations in 11 U.S. studies.

ORD is now applying this approach to other environmental chemicals (dioxins, perfluorinated compounds (PFCs), polychlorinated biphenyls (PCBs), and organochlorine pesticides); it is expected that these models will facilitate the use of available biomonitoring serum data (e.g., NHANES) to better characterize infant exposures. ORD is also working on developing a comprehensive quantitative structure-activity relationship (QSAR)-based model for predicting milk:serum partitioning ratios for classes of chemicals where serum and milk data are not available to construct regression models. This QSAR model will predict the potential of an environmental chemical to partition into breast milk and can be used to improve exposure and risk estimates for breastfeeding infants.

In vitro to In vivo Extrapolation (CSS)

ORD has proposed an approach to link results from *in vitro* high throughput studies with population group specific-dosimetry for neonates, children, and adults, and exposure estimates. For nine ToxCast chemicals, pharmacokinetic models for multiple subpopulations were constructed that predicted chemical concentrations in the blood at steady state. These models have potential application to estimate chemical-specific pharmacokinetic uncertainty factors and to estimate subpopulation-specific oral equivalent dose values to aid in chemical prioritization and indentifying subpopulations with greater susceptibility to potential pathway perturbations {Wetmore, 2014 #86}.

Community Multi-scale Air Quality Model (CMAQ)

The EPA's Community Multi-scale Air Quality (CMAQ) Model is a powerful computational tool used by EPA and states for air quality management that gives detailed information about the concentrations of air pollutants in a given area. Comparison of data from the CMAQ model with birth outcomes or childhood hospital admissions for asthma has generated data on associations between pollutant exposure (i.e., particulate matter (PM) or ozone) and health outcomes {U.S. Environmental Protection Agency, 2014 #84}, available at: http://www.epa.gov/AMD/Research/RIA/cmaq.html.

Pesticide Biomarker Measurements in Children (CSS)

ORD is investigating the utility of various biomarkers for determining exposure to environmental chemicals in children. In a study consolidating the results from several large- and small-scale observational studies on children's exposure to pesticides, ORD compared measurements of urinary metabolites of select pesticides with the kinetic parameters of the pesticides {Egeghy, 2011 #4}. The temporal variability of the metabolites detected, based on time of pesticide application, as well as the relative importance of dietary exposure compared to the indirect ingestion, dermal and inhalation routes were examined. The results showed that urinary biomarker levels provided only limited evidence of pesticide application and appeared to be affected by differences in the contribution of each exposure route to total intake.

3.2.2 PBPK Models (CSS)

Virtual Embryo Project

ORD has developed a life-stage PBPK model, as part of the Virtual Embryo project in the predictive toxicology of children's health and development following prenatal or lactational exposure to environmental chemicals. This model was developed to computationally investigate the relationship between chemical exposure, tissue dosimetry and *in vitro* markers of critical events related to AOPs. The model includes time-changing physiological and biochemical descriptors related to a pregnant mother, fetal growth, and child exposure through lactation.

Ethanol

To supplement and complete PBPK models in the literature, ORD developed PBPK models to describe the kinetics of ethanol in adult, pregnant, and neonatal rats for the inhalation, oral, and intravenous routes of exposure. The three models accurately predicted the kinetics of ethanol, including the absorption, peak concentration, and clearance across multiple datasets. This work provides comprehensive life-stage models of ethanol pharmacokinetics and represents the first step in developing models for use with blends of ethanol and gasoline that are commonly used in the U.S. {Martin, 2012 #5}.

Research Area 4. Translational research and tools fit for purpose to support community actions and decisions

Research Area 4 has been divided into the following four subgroups: A) Decision Support Tools, B) Problem Driven Research, C) Translational Research, and D) Social Determinants of Health. ORD's relevant research in each of these areas is summarized as follows:

4.1 Decision Support Tools

ORD is developing decision support tools for State, Tribal and local governments in order to make sound decisions about both community development and healthful environments, and to avoid unintended consequences.

4.1.1 Community-Focused Exposure and Risk Screening Tool (SHC)

ORD has developed the Community Focused Exposure and Risk Screening Tool (C-FERST) {U.S. Environmental Protection Agency, 2013 #64}; available at: http://www.epa.gov/heasd/c-ferst/ to enhance access to information for environmental health decision-making. Developed in collaboration with several pilot communities, and scheduled for public release in 2014 following external peer review, this web-based tool provides a repository of information for >40 environmental issues. Children's health issues in C-FERST currently include childhood lead exposure, childhood asthma, and schools. By providing a public venue for communicating ORD science and EPA guidance and solutions, C-FERST can empower communities with information for prioritizing and addressing environmental issues. C-FERST will soon provide data and maps of modeled childhood lead exposures for local impact estimates and targeting enforcement activities. Future versions of C-FERST will incorporate additional research results and features to help address children's environmental and cumulative risk issues.

Health Impact Assessment

Recently, C-FERST was used, along with other tools, to inform a Health Impact Assessment (HIA) related to school renovation decisions in an environmental justice community. The HIA for the Gerena Elementary School in Springfield, Massachusetts—one of EPA's first HIAs, and the first school building focused HIA in the field—is a collaboration between EPA and stakeholders including the Massachusetts Departments of Public Health and Environmental Protection, city, school, and community groups. The purpose of this HIA is to provide and help process information to help the City of Springfield narrow down options for renovation and improvement at the Gerena School to those that will best address environmental problems, reduce potential negative health impacts such as asthma exacerbations, and enhance well-being of the school community. The school is directly under a highway and adjacent to roadways and a railway, so the project is considering transportation-related indoor air exposures as well as those from flooding, moisture, mold and other indoor environmental issues in the school.

In the process, EPA is learning how its science can be used in the HIA process and incorporating HIA into its decision-support tools. A new HIA roadmap is being incorporated into C-FERST to facilitate broad access to information, guidance, and best practices in conducting future HIAs. ORD led the assessment phase of the HIA for this elementary school, including indoor and outdoor air monitoring, building systems evaluation, and data analysis.

4.1.2 EnviroAtlas (SHC)

EnviroAtlas, scheduled for public release in 2014 will include, at least for selected urban areas, such indicators as the locations of schools, recreational areas and factors relevant to health outcomes (demographics, income) and access to transportation routes and indicators of ecosystem services such as tree cover (related to heat, recreation, green-space accessibility). This tool also includes an Eco-Health Relationship Browser {U.S. Environmental Protection Agency, 2013 #65}; available at: http://www.epa.gov/research/healthscience/browser/introduction.html (launched in 2012), a user-friendly web-based browser which illustrates linkages between human health and ecosystem services, i.e., the benefits supplied by nature. Health outcomes currently searchable in the browser of direct relevance to CEH include low birth weight and preterm birth, asthma, ADHD, and obesity. Expansion of the browser to more completely address children's health is being considered.

4.2 Problem-Driven Research

Studies have been conducted to further the understanding of linkages between human health and environmental exposures. Communities are using results of these analyses to make decisions concerning renovation of schools, location of recreational areas, and future development.

4.2.1 EPA Pilot Study Add-On to the Third Study Site of the Green Housing Study (SHC)

The Green Housing Study is a collaborative effort between the U.S. Department of Housing and Urban Development (HUD) and the Centers for Disease Control and Prevention (CDC). Three main goals of the Green Housing Study are to: 1) compare levels of certain chemical and biological agents and non-chemical stressors in green versus traditional, multi-family, low-income housing; 2) ascertain differences in the health of the residents in these homes; and 3) assess the economic impacts of the "greening" of housing—particularly those related to health. These goals will be accomplished in ongoing building renovation programs sponsored by HUD. Green housing includes strategies to reduce exposure to environmental contaminants, including but not limited to the use of integrated pest management practices, the use of low/no volatile organic compound (VOC) materials (e.g., paints, carpets), and improved insulation and ventilation practices. Briefly, both the green-renovated and comparison (no renovation) homes will be from the same housing development or neighborhood to ensure homogeneity with regard to housing type and other socioeconomic factors. Changes in environmental measurements (pesticides, VOCs, particulate matter [i.e., PM2.5 and 1.0], indoor allergens, and fungi) over a 1-year post-renovation period will be compared to pre-renovation measurements, such that each home's measurements will be compared with its own baseline measurements. This study design enables both a pre- and post-renovation comparison as well as a comparison between green-renovated and control homes in order to detect differences in exposure levels and asthma outcomes. Residents will participate for 1 month prior to renovation, the time required for renovation of their home, and 12 months after completion of the renovation. The duration of participation for residents of comparison homes is the same.

In partnership with HUD and CDC, ORD will leverage this opportunity to collect additional multimedia measurements and questionnaire data from the index children actively participating in the Green Housing Study and a sibling(s) in order to characterize personal, housing, and community factors influencing children's potential exposures to indoor contaminants at various lifestages. Additionally, by recruiting siblings of the index children, ORD will begin to examine how lifestage affects children's exposures when children have the potential to be exposed to the same chemicals in consumer products found in their environment.

4.2.2 Dust and soil ingestion (CSS and SHC)

ORD is using models to estimate different exposure parameters, such as soil and dust ingestion rates, in children. These parameters are used in exposure and risk assessments to evaluate the health outcomes of environmental chemicals in children. For example, ORD used the SHEDS-Soil/dust model to estimate soil and dust ingestion rates for young children at two Taiwanese locations. One site was designated as the control, since the village in which the homes were located was thought to be less likely impacted by the pollutants under investigation. The other site was designated as a near road exposure site. Inputs were developed for both types of sites. In addition, similar SHEDS-Soil/dust simulations were conducted for U.S. children. The ages of the children simulated ranged from 6 months up to (but less than) 36

months. The children were divided into three age categories: 6 months to <12 months; 12 months to <24 months; 24 months to <36 months and soil and dust ingestion rates were estimated through model simulation {Glen, 2013 #55}.

4.2.3 Chemical and Non-Chemical Stressors and Childhood Obesity (SHC)

Childhood obesity has tripled in the last three decades and now affects 17% of children in the U.S. In 2010, the percentage of obese children in the U.S. was nearly 18% for both 6-11 and 12-19 years of age. Recent evidence in the literature suggests that exposure to selected environmental chemicals may impact obesity. Socioeconomic status, ethnicity, and the built environment may also impact obesity. Recent studies have also shown that poor quality food outlets in close proximity to neighborhoods or schools increased the likelihood of poor quality food purchases. While much research has focused on individual stressors impacting obesity, little research has emphasized the complex interactions of numerous chemical and non-chemical stressors affecting a child's health and well-being.

ORD is conducting research in this area to (1) identify and characterize chemical and non-chemical stressors that impact childhood obesity; (2) identify key stressors across a range of stressor domains; and (3) characterize the interactions of these key stressors on children's health.

ORD is currently completing a state-of-the-science literature review to identify chemical and non-chemical stressors related to childhood obesity. Using this information, a searchable database was created and analyzed to identify key stressors. Numerous chemical and non-chemical stressors were identified and grouped into the following domains: individual, family, community, and chemical. Stressors were related to the child and their everyday environments (home and community) and used to characterize child health and well-being. Data shows that there is not always a positive association with a stressor and childhood obesity, and that there can be inconsistent correlations between the same stressors and obesity. However, there is sufficient evidence to suggest the interactions of multiple stressors may be the cause of the childhood obesity epidemic.

4.2.4 Chemical and Non-Chemical Stressors and Neurocognitive Health (SHC)

Early childhood (0-6 years old) is a time of significant brain growth and foundational skills development essential for school readiness and academic achievement. Maximizing a child's learning potential can be achieved only with complete knowledge of stressors that impact learning. Many studies attempt to identify associations between individual exposure factors and neurocognitive development. However, extending from pregnancy to a child's first day of school, numerous stressors (e.g., chemicals, prenatal stress, behaviors, family violence) may influence children's neurocognitive development and health and well-being. Additionally, community-level decisions related to land use, transportation, buildings and infrastructure, and waste and materials management may also influence a child's health and well-being by impacting their home and learning environments.

ORD is conducting research to examine stressors related to neurocognitive health in children ages 3-6 years to (1) identify and characterize individual stressors associated with neurocognitive development and (2) develop a conceptual model that identifies key stressors and their possible interactions.

ORD completed a literature review across multiple databases (e.g., PubMed, Web of Science, PsychInfo) utilizing the search strings: neurodevelopment or cognition and children. Assessment of the quality of the study and its applicability to the general population was conducted to identify key stressors

associated with neurocognitive health and to develop a conceptual model using a multi-level systems approach.

Key exposure factors were identified for each developmental lifestage from pregnancy to 3-6 years old. These factors were grouped three different ways according to (1) the type of occurrence (e.g., individual, home, school, community), (2) characterization as an individual health, social, environmental or economic determinant, and (3) how decisions regarding land use, buildings and infrastructure, waste and materials management, and transportation have impacted them. These elements were incorporated into the model and the results suggest that some childhood exposures (e.g., SES, parent-child interaction, diet, built environment) not only present as key factors, but act as effect modifiers of stressors experienced during pregnancy and infancy (e.g., lead, pesticides, prenatal stress).

4.2.5 Community Multi-scale Air Quality Model (ACE)

The EPA's Community Multi-scale Air Quality (CMAQ) Model is a powerful computational tool used by EPA and states for air quality management that gives detailed information about the concentrations of air pollutants in a given area. Comparison of data from the CMAQ model with birth outcomes or childhood hospital admissions for asthma has generated data on associations between pollutant exposure (i.e., particulate matter (PM) or ozone) and health outcomes (U.S. Environmental Protection Agency, 2014c), available at: http://www.epa.gov/AMD/Research/RIA/cmaq.html.

4.2.6 PCBs in Schools (HHRA)

ORD research characterized sources of exposure to PCBs in school environments, showing that both window caulking and light ballasts have contributed to exposures in older schools . Findings from this research showed that caulk put in place between 1950 and 1979 can contain as much as 30% PCBs and can contaminate adjacent material such as masonry or wood. Fluorescent light fixtures that still contain their original PCB-containing light ballasts may rupture and emit PCBs. Encapsulation, a PCB containment method, was shown to be effective only when the PCB content in the source was low. EPA used the results of this research to update its guidance to building owners and school administrators on how to reduce exposures to PCBs that may be found in schools (U.S. Environmental Protection Agency, 2013e); available at: http://www.epa.gov/pcbsincaulk/caulkresearch.htm.

4.2.7 Child-Specific Exposure Scenarios Examples (HHRA)

The "Child-Specific Exposure Scenarios Examples" is a companion document to the "Exposure Factors Handbook: 2011 Edition" (EFH) (see section 1.1.1). The purpose of the "Child-Specific Exposure Scenarios Examples" is to present childhood exposure scenarios using data from the "Child-Specific Exposure Factors Handbook" (U.S. Environmental Protection Agency, 2008); available at: http://cfpub.epa.gov/ncea/risk/recordisplay.cfm?deid=199243 and updated children's data from the EFH (U.S. Environmental Protection Agency, 2011); available at: http://cfpub.epa.gov/ncea/risk/recordisplay.cfm?deid=236252. These scenarios are not meant to be inclusive of every possible scenario, but they are intended to provide a range of scenarios that show how to apply exposure factors data to characterize childhood exposures. The example scenarios were compiled from questions and inquiries received from users of the earlier versions of the EFH on how to select data from the Handbook. The scenarios presented in the report promote the use of the standard set of age groups recommended by EPA in the report entitled "Guidance on Selecting Age Groups for

Monitoring and Assessing Childhood Exposures to Environmental Contaminants" (U.S. Environmental Protection Agency, 2005); available at http://www.epa.gov/raf/publications/pdfs/AGEGROUPS.PDF (see section 3.1.7).

4.3 Translational Research

Translational research involves translating the results from research on children's health into findings that are useful to communities, neighborhoods, or other groups as they develop strategies to work on local environmental health issues. Many of the studies discussed above in section 2.2.2 above include translational components, involving environmental health communication, community outreach, and collaboration with local community groups.

4.3.1 CEHC Program (SHC)

As discussed in section 2.2.2, the EPA-NIEHS co-funded CEHC Program is generating exposure and biomarker data in pregnant women and children, showing relationships between exposure and a variety of children's health outcomes, and identifying critical windows of susceptibility {U.S. Environmental Protection Agency, 2014 #72}; available at: www.epa.gov/ncer/childrenscenters. Collectively they are examining a wide range of health outcomes in cohorts of children including adverse birth outcomes, asthma and respiratory dysfunction, and other diseases.

A critical and unique component of the Children's Centers Program is the inclusion of a Community Outreach and Translation Core. These cores use a variety of innovative approaches to translate research findings and intervention strategies to the community. As summarized in Table 2, outreach and translation involves a wide variety of community partners including community advocacy and environmental justice organizations, state and city health departments, state and city environmental protection and natural resources departments, city governments, health care providers, schools and educational advocacy groups, and various programs in universities. Thus, research translation benefits environmental health broadly by influencing decisions at all levels, from health policy to personal choices.

Table 9. EPA/NIEHS Children's Centers Community Outreach and Translation – Community Partners

Institution – P.I.	Study Site Location(s)	Community Outreach and Translation – with Community Partners

Institution – P.I.	Study Site Location(s)	Community Outreach and Translation – with Community Partners
Brown University – Boekelheide	Providence, Rhode Island	Silent Spring Institute, Environmental Justice League of Rhode Island
Columbia University – Perera	New York City (Northern Manhattan and South Bronx), Poland, China	Bronx Borough Presidents Office, Bronx Health Link, Columbia Community Partnership for Health, Columbia University Head Start, Community Health Worker Network of NYC, Dominican Medical Association, New York, Harlem Children's Zone Asthma Initiative, Harlem Health Promotion, Northern Manhattan Perinatal Partnership, Nos Quedamos, WE ACT for Environmental Justice
Dartmouth College – Karagas	Hanover, New Hampshire	Dartmouth-Hitchcock Concord Clinic, Concord Hospital Family Clinic, Concord Obstetrics and Gynecology Professional Associates, Concord Women's Care, Family Tree Health Care (Warner, NH), Dartmouth Hitchcock Lebanon Clinic, Concord Hospital, The Family Place, Dartmouth-Hitchcock Medical Center, New Hampshire Department of Environmental Health Services, New Hampshire Birth Conditions Program, University of New Hampshire Department of Molecular, Cellular and Biomedical Sciences
Duke University/ University of Michigan – Miranda	Durham, North Carolina and Ann Arbor, Michigan	Durham Congregations, Associations, and Neighborhoods (CAN), Triangle Residential Options for Substance Abusers (TROSA), Durham Affordable Housing Coalition, Partnership Effort for the Advancement of Childrens Health/Clear Corps (PEACH), Durham People's Alliance, Durham County Health Department, Lincoln Community Health Center, Duke University Nursing School Watts School of Nursing, City of Durham Department of Neighborhood Improvement Services, City of Durham Department of Community Development, Children's Environmental Health Branch of NC Department of Environment and Natural Resources, North Carolina Asthma Alliance, East Coast Migrant Head Start, North Carolina Community Health Center Association, North Carolina Rural Communities Assistance Project
Duke University – Murphy	Durham, North Carolina	DukeEngage Program, El Centro Hispano (local Latino community), Partnership for a Healthy Durham
Johns Hopkins University – Diette	Baltimore, Maryland	Baltimore City Head Start Program, Baltimore City Health Department Healthy Homes Program, Baltimore School Food Services Program, Healthy Stores Program, Maryland Asthma Control Program, Women Infants and Children (WIC) nutrition programs
National Jewish Health – Schwartz, Szefler	Denver, Colorado	Colorado Asthma Coalition, Colorado Clinical Guidelines Collaborative, Colorado Department of Public Health and Environment, Denver Public School System, Lung Association of Colorado, Rocky Mountain Prevention Research Center, EPA Region 8, Alamosa Public School, Denver Health, Colorado Public Health, Practice Based Research Network, Regional Air Quality Council, Colorado Air Quality Commission, Grand Junction Housing Authority, Western Colorado Math & Science Center, Region 8 Pediatric Environmental Health Specialty Unit (PEHSU)
University of California at Berkeley – Buffler, Metayer	Berkeley, California	Network of 8 clinical institutions in northern and central California participating in the Northern California Childhood Leukemia Study (NCCLS), national community of pediatric health care professionals with an interest in environmental health issues; national community of persons interested in leukemia; California community of persons interested in childhood leukemia; Region 9 Pediatric Environmental Health Specialty Unit (PEHSU)
University of California at Berkeley – Eskenazi	Berkeley and Salinas, California	Clinica de Salud del Valle de Salinas, Natividad Medical Center, South County Outreach Effort (SCORE), Monterey County Health Department, California Rural Legal Assistance (CRLA) Program, Grower/Shipper

Institution – P.I.	Study Site Location(s)	Community Outreach and Translation – with Community Partners
University of California at Berkeley/ Stanford University – Hammond, Balmes, Shaw	Berkeley, Palo Alto, Bakersfield and San Joaquin Valley, California	Medical Advocates for Healthy Air, Fresno Metro Ministry, Center on Race, Poverty, and the Environment, San Joaquin Valley Latino Environmental Advancement Project (LEAP), El Comite para el Bienestar de Earlimart, Coalition for Clean Air, San Joaquin Valley Cumulative Health Impact Project (SJV-CHIP), Central California Environmental Justice Network, Central Valley Air Quality Coalition, Californians for Pesticide Reform
University of California at Davis – Van de Water	Davis, California	Families for Early Autism Treatment, Learning Disabilities Association, Parents Helping Parents, San Francisco Bay Chapter of the Autism Society of America, Alameda County Developmental Disabilities Council, Cure Autism Now, State of California health/developmental service providers, California Departments of Developmental Services and Health Services, California Regional Centers and Office of Environmental Health Hazard Assessment
University of California, San Francisco – Woodruff	San Francisco, California	American College of Obstetricians and Gynecologists (ACOG District IX), Association of Reproductive Health Professionals, Physicians for Social Responsibility (PSR) San Francisco Bay Area Chapter, WORKSAFE (California Coalition for Worker Occupational Safety & Health Protection), California Department of Health Occupational Health Branch
University of Illinois at Urbana-Champaign – Schantz	Urbana-Champaign, Illinois and New Bedford, Massachusetts	Illinois Action for Children (IAFC), American Academy of Pediatrics (AAP), Just-In-Time Parenting, Champaign-Urbana Public Health Department, Great Lakes Center for Environmental Health, Cambridge Health Alliance, Carle Foundation Hospital, Provena Covenant Medical Center
University of Michigan – Peterson, Padmanabhan	Ann Arbor, Michigan and Mexico City, Mexico	Early Life Exposures in Mexico to Environmental Toxicants (ELEMENT), National Institute of Public Health, Mexico City, Detroit Hispanic Development Corporation
University of Southern California – McConnell	Los Angeles, California	The Children's Clinic (Long Beach and South Bay), Asian and Pacific Islander Obesity Prevention Alliance, East Yard Communities for Environmental Justice, Digital Rain Factory, Los Angeles Parks Foundation, The Trust for Public Land Center for Park Excellence, Policies for Livable, Active Communities and Environments (PLACE) of Los Angeles, Trade, Health and Environment Impact Project, Center for Community Action & Environmental Justice (Riverside and San Bernardino), Coalition for a Safe Environment (Wilmington), East Yard Communities for Environmental Justice (Commerce and East L.A.), Long Beach Alliance for Children with Asthma, Outreach Program of Southern California Environmental Health Sciences Center Los Angeles (USC/UCLA), Urban & Environmental Policy Institute, Occidental College
University of Washington – Faustman	Yakima Valley, Washington State	Community members in the Yakima Valley, Farm Workers Union, Growers' Association, Washington State Department of Health and Department of Agriculture, Farm Workers' Union, Yakima Valley Farm Workers Clinics, Radio KDNA (Spanish language), Washington State Department of Labor and Industries, Columbia Legal Services, Washington State Migrant Council, EPA Region 10

4.4 Social Determinants of Health

ORD is carrying out research on the biological, environmental, and social conditions that may contribute to disparities in health outcomes in children. Although the scope of this research extends well beyond a lifestage-specific focus, some specific activities are targeting children's environmental health.

4.4.1 STAR Centers of Excellence on Environment and Health Disparities (SHC)

Social determinants of health are a focus of research in the *STAR Centers of Excellence on Environment and Health Disparities* (http://www.epa.gov/ncer/ehs/disparities/health-disparities.html). ORD, in collaboration with the National Institute of Minority Health and Health Disparities (NIMHD) (http://www.nih.gov/about/almanac/organization/NIMHD.htm), through an Interagency Agreement, is supporting the establishment of transdisciplinary networks of excellence in health disparities research to achieve a better understanding of the complex interactions of biological, social and environmental determinants of population health. The collaboration promotes coordination efforts within the NIMHD Centers for Excellence in health disparities research, addressing racial and socioeconomic disparities in environmentally mediated health outcomes and access to healthy community environments.

One of these Center projects, "Analysis and Action on the Environmental Determinants of Health and Health Disparities" (University of South Carolina) will explore six areas of health disparities that contribute disproportionately to premature death and morbidity found among poor and racial/ethnic minorities (e.g., infant mortality). This project is developing a relational database and web portal for integration of data on health outcomes, natural and built environment and social environment. Another, "Environmental Health Disparities Research" (University of Texas) will explore the individual- and neighborhood-level contributions to disparities in children's lung health.

4.4.2 Environmental and Community Factors Influence Effectiveness of Medical Treatments for Asthma (SHC)

An ORD study, in collaboration with the University of North Carolina, "Observational Assessment of Baseline Asthma Control as a Susceptibility Factor for Air Pollution Health Effects in African-American Children with Persistent Asthma", is examining factors that contribute to asthma disparities in adolescents. The study is following a cohort of African American youth with moderate-to-severe asthma and examining a variety of factors including air pollution, home environment, and community issues that may contribute to the high rate of asthma in this population and the relative effectiveness of medical treatments.

4.4.3 Integrated Approaches to Sustain the Built and Natural Environment and the Communities They Support: Children's Health Example (SHC)

In this study, researchers are using GIS tools and multi-layered mapping to examine relationships between access to green space and birth outcomes. Analyses focus on associations between birth measures across the greater Durham-Chapel Hill, North Carolina area and various measures of green space around the home, including tree cover along busy roadways

Climate change (ACE)

Young children may be disproportionately affected by climate change and would require specific adaptations to respond to climate-related stressors. Research is using a multidisciplinary assessment approach to identify those aspects of climate change to which vulnerable populations are most

sensitive, most likely to be exposed, and most able to adapt, and determine how vulnerability to climate change may interact with non-climate environmental stressors.

Current research is evaluating health effects associated with events expected to increase in frequency during climate change, incorporating age-category-specific effect estimates. Where possible, child-specific effects will be reported. Related research on climate change, relevant although not necessarily specific to children's health, includes impacts of increased ground level ozone and weather events influencing allergic, chronic, waterborne and infectious disease risks.

Appendix C. Literature Search of ORD CEH Activities

A literature search of EPA-ORD children's environmental health activities was performed in EPA Science Inventory using the following search conditions. The table lists individual hyperlinks to the Science Inventory, where more information on each of the manuscripts may be found.

Search Boundaries Peer Reviewed Journals; Jan. 1, 2008 – April 1, 2014

Search Terms adolescence, adolescent, child, childhood, children, developmental, daycare, early life, epigenetic, fetal, in utero, infant, maternal, paternal, perinatal, postnatal, pregnancy, pregnant, prenatal, school, young adult

Total Results 309

Year	Publication
2014	Assessing the bioavailability and risk from metal-contaminated soils and dusts
2013	A Computational Model Predicting Disruption of Blood Vessel Development
2013	Comprehensive assessment of a chlorinated drinking water concentrate in a rat multigenerational reproductive toxicity study
2013	Controlled Exposures Of Human Volunteers To Diesel Engine Exhaust: Biomarkers Of Exposure And Health Outcomes
2013	Decreased Pulmonary Function Measured in Children Exposed to High Environmental Relative Moldiness Index Homes
2013	Effect of Treatment Media on the Agglomeration of Titanium Dioxide Nanoparticles: Impact on Genotoxicity, Cellular Interaction, and Cell Cycle
2013	Evaluation of iodide deficiency in the lactating rat and pup using a biologically based dose-response model
2013	Family and home characteristics correlate with mold in homes
2013	Harnessing genomics to identify environmental determinants of heritable disease
2013	Higher Environmental Relative Moldiness Index (ERMI) Values Measured in Homes of Asthmatic Children in Boston, Kansas City and San Diego
2013	Higher environmental relative moldiness index values measured in homes of adults with asthma, rhinitis, or both conditions
2013	Human Exposures to PAHs: an Eastern United States Pilot Study
2013	Improving Infant Exposure and Health Risk Estimates: Using Serum Data to Predict Polybrominated Diphenyl Ether Concentrations in Breast Milk
2013	Lasting Effects on Body Weight and Mammary Gland Gene Expression in Female Mice upon Early Life Exposure to n-3 but Not n-6 High-Fat Diets
2013	Lead, Allergen, and Pesticide Levels in Licensed Child Care Centers in the United States
2013	Meta-analysis of toxicity and teratogenicity of 133 chemicals from zebrafish developmental toxicity studies
2013	Microbial content of household dust associated with exhaled NO in asthmatic children
2013	Release of silver from nanotechnology-based consumer products for children
2013	Stenotrophomonas, Mycobacterium, and Streptomyces in home dust and air: associations with moldiness and other home/family characteristics
2013	The Incredible Shrinking Cup Lab: An Investigation of the Effect of Depth and Water Pressure on Polystyrene
2013	Thermoregulatory deficits in adult long evans rat offspring exposed perinatally to the antithyroidal drug, propylthiouracil
2013	Use Of High Content Image Analyses To Detect Chemical-Mediated Effects On Neurite Sub-Populations

	In Primary Rat Cortical Neurons
2012	Activation of mouse and human Peroxisome Proliferator-Activated Receptor-alpha (PPARa) by Perfluoroalkyl Acids(PFAAs): Further investigation of C4-C12 compounds
2012	An In Vitro Assessment of Bioaccessibility of Arsenicals in Rice and the Use of this Estimate within a Probabilistic Exposure Model
2012	Assessment of Circulating Hormones in and Nonclinical Toxicity Studies: General Concepts and Considerations
2012	Biogeographical Analysis of Chemical Co-Occurrence Data to Identify Priorities for Mixtures Research
2012	Carbaryl Effects On Oxidative Stress In Brain Regions Of Adolescent And Senescent Brown Norway Rats
2012	Children's Exposure to Pyrethroid Insecticides at Home: A Review of Data Collected in Published Exposure Measurement Studies Conducted in the United States
2012	Combining continuous near-road monitoring and inverse modeling to isolate the effect of highway expansion on a school in Las Vegas
2012	Community duplicate diet methodology: A new tool for estimating dietary exposure to pesticides
2012	Comparison of Chemical-induced Changes in Proliferation and Apoptosis in Human and Mouse Neuroprogenitor Cells
2012	Comparison of Four Probabilistic Models (CARES, Calendex, ConsEspo, SHEDS) to Estimate Aggregate Residential Exposures to Pesticides
2012	Comparison of Work-related Symptoms and Visual Contrast Sensitivity between Employees at a Severely Water-damaged School and a School without Significant Water Damage
2012	Conference Report: Advancing the Science of Developmental Neurotoxicity (DNT) Testing for Better Safety Evaluation
2012	Development and Preparation of Lead-Containing Paint Films and Diagnostic Test Materials
2012	Development of Multi-Route Physiologically-based Pharmacokinetic Models for Ethanol in the Adult, Pregnant, and Neonatal Rat
2012	Developmental Exposure to Valproate or Ethanol Alters Locomotor Activity and Retino-Tectal Projection Area in Zebrafish Embryos
2012	Developmental Neurotoxicity Testing: A Path Forward
2012	Developmental Thyroid Hormone Disruption: Prevalence, Environmental Contaminants and Neurodevelopmental Consequences
2012	Developmental Toxicity Evaluations of Whole Mixtures of Disinfection By-products using Concentrated Drinking Water in Rats: Gestational and Lactational Effects of Sulfate and Sodium
2012	Developmental Toxicity Evaluations of Whole Mixtures of Disinfection By-products using Concentrated Drinking Water in Rats: Gestational and Lactational Effects of Sulfate and Sodium*
2012	Developmental Triclosan Exposure Decreases Maternal,Fetal, and Early Neonatal Thyroxine: Dynamic and Kinetic Data Support for a Mode-of-Action
2012	Economic benefits of using adaptive predictive models of reproductive toxicity in the context of a tiered testing program
2012	Effects of a Glucocorticoid Receptor Agonist, Dexamethasone, on Fathead Minnow Reproduction, Growth, and Development
2012	Effects of perfluorooctanoic acid (PFOA) on expression of peroxisome proliferator-activated receptors (PPAR) and nuclear receptor-regulated genes in fetal and postnatal mouse tissues
2012	Environmentally-Relevant Mixtures in Cumulative Assessments: An Acute Study of Toxicokinetics and Effects on Motor Activity in Rats Exposed to a Mixture of Pyrethroids
2012	Fetal programming and environmental exposures: Implications for prenatal care and preterm birth
2012	Genomic biomarkers of phthalate-induced male reproductive developmental toxicity: A targeted rtPCR array approach for defining relative potency
2012	GIS-modeled indicators of traffic-related air pollutants and adverse pulmonary health among children in El Paso, Texas, USA

2012	Infant Origin of Childhood Asthma Associated with Specific Molds
2012	Iron accumulates in the lavage and explanted lungs of cystic fibrosis patients
2012	Magnetic Resonance Imaging and Volumetric Analysis: Novel Tools to Study Thyroid Hormone Disruption and Its Effect on White Matter Development
2012	Maternal air pollution exposure induces fetal neuroinflammation and predisposes offspring to obesity in aduthood in a sex-specific manner
2012	Maternal Diesel Inhalation Increases Airway Hyperreactivity in Ozone Exposed Offspring
2012	Metabolomic Response of Human Embryonic Stem Cell Derived Germ-like Cells after Exposure to Steroid Hormones
2012	Nitric Oxide and Superoxide Mediate Diesel Particle Effects in Cytokine-Treated Mice and Murine Lung Epithelial Cells – Implications for Susceptibility to Traffic-Related Air Pollution
2012	Perfluorooctanoic acid effects on ovaries mediate its inhibition of peripubertal mammary gland development in Balb/c and C57Bl/6 mice
2012	Perflurooctanoic Acid Induces Developmental Cardiotoxicity in Chicken Embryos and Hatchlings
2012	Peroxisome Proliferator-Activated Receptorα (Pparα) Agonists Differentially Regulate Inhibitor Of Dna Binding (Id2) Expression In Rodents And Human Cells
2012	PPAR involvement in PFAA developmental toxicity
2012	Predicting Later-Life Outcomes of Early-Life Exposures
2012	Quantifying Children's Aggregate (Dietary and Residential) Exposure and Dose to Permethin: Application and Evaluation of EPA's Probabilistic SHED-Multimedia Model
2012	Rearing Conditions Differentially Affect the Locomotor Behavior of Larval Zebrafish, but not Their Response to Valproate-Induced Developmental Neurotoxicity*
2012	Research Opportunities for Cancer Associated with Indoor Air Pollution from Solid-Fuel Combustion
2012	Seasonality Of Rotavirus In South Asia: A Meta-Analysis Approach Assessing Associations With Temperature, Preciptation, And Vegetation Index
2012	Some Chronic Rhinosinusitis Patients Have Significantly Elevated Populations of Seven Fungi in their Sinuses
2012	Strategies for Evaluating the Environment-Public Health Interaction of Long-Term Latency Disease: The Quandary of the Inconclusive Case-Control Study
2012	The Developmental Neurotoxicity Guideline Study: Issues with Methodology, Evaluation and Regulation
2012	Toluene Effects on Gene Expression in the Hippocampus of Young-Adult, Middle-Age and Senescent Brown Norway Rats
2012	Toluene effects on the motor activity of adolescent, young-adult, middle-age and senescent male Brown Norway rats
2012	Transcriptional Ontogeny of the Developing Liver
2012	Tumors and Proliferative Lesions in Adult Offspring After Maternal Exposure to Methylarsonous Acid During Gestation in CD1 Mice
2012	Zebrafish Developmental Screening of the ToxCast™ Phase I Chemical Library
2011	Adverse Outcome Pathways During Early Fish Development: A Framework for Identifying and Implementing Alternative Chemical Prioritization Strategies
2011	Age-related behavioral effects of methomyl in Brown Norway rats
2011	Age-related differences in acute neurotoxicity produced by mevinphos, monocrotophos, dicrotophos, and phosphamidon
2011	Aging and the Environment: Importance of Variability Issues in Understanding Risk
2011	Air Pollution and Health: Emerging Information on Susceptible Populations
2011	Akt1 protects against germ cell apoptosis in the post natal mouse testis following lactational exposure to 6-N-propylthiouracil

2011	Allergens in household dust and serological indicators of atopy and sensitization in Detroit children with history--based eivdence of asthma
2011	Altered cardiovascular reactivity and osmoregulation during hyperosmotic stress in adult rats developmentally exposed to polybrominated diphenyl ethers (PBDEs)
2011	An Assessment of the Exposure of Americans to Perflourooctane Sulfonate: A Comparison of Estimated Intake with Values Inferred from NHANES Data
2011	Aroclor-1254, a developmental neurotoxicant, alters energy metabolism-and intracellular signaling-associated protein networks in rat cerebellum and hippocampus
2011	Assessing Locomotor Activity in Larval Zebrafish: Influence of Extrinsic and Intrinsic Variables
2011	Assessing the Quantitative Relationships between Preschool Children's Exposures to Bisphenol A by Route and Urinary Biomonitoring
2011	Association between Perchlorate and indirect indicators of thyroid dysfunction in NHANES 2001-2002, a Cross-Sectional, Hypothesis-Generating Study
2011	Booming Markets for Moroccan Argan Oil Appear to Benefit Some Rural Households While Threatening the Endemic Argan Forest
2011	Combined retrospective analysis of 498 rat multi-generation reproductive toxicity studies: on the impact of parameters related to F1 mating and F2 offspring
2011	Comparative pharmacokinetics of perfluorononanoic acid in rat and mouse
2011	Comparative sensitivity of human and rat neural cultures to chemical-induced inhibition of neurite outgrowth
2011	Comparison of Wipe Materials and Wetting Agents for Pesticide Residue Collection from Hard Surfaces
2011	Current Practices and Future Trends in Neuropathology Assessment for Developmental Neurotoxicity Testing
2011	Development of a multiplex microsphere immunoassay for the quantitation of salivary antibody responses to selected waterborne pathogens
2011	Developmental Thyroid Hormone Insufficiency Reduces Expression of Brain-Derived Neurotrophic Factor (BDNF) in Adults But Not in Neonates
2011	Developmental toxicity testing for safety assessment: new approaches and technologies
2011	Di-pentyl phthalate dosing during sexual differentiation disrupts fetal testis function and postnatal development of the male Sprague dawley rat with greater relative potency than other phthalates
2011	Disruption of Embryonic Vascular Development in Predictive Toxicology
2011	Dose-response assessment of fetal testosterone production and gene expression levels in rat testes following in utero exposure to diethylhexyl phthalate, diisobutyl phthalate, diisoheptyl phthalate and diisononyl phthalate
2011	Effect of maternal exposure to ozone on reproductive outcome and immune, inflammatory, and allergic responses in the offspring
2011	Environmental Impact on Vascular Development Predicted by High Throughput Screening
2011	Evaluation of 309 environmental chemicals using a mouse embryonic stem cell adherent cell differentiation and cytotoxicity assay
2011	Evaluation of Genetic Susceptibility to Childhood Allergy and Asthma in an African American Urban Population
2011	Feasibility of assessing the public health impacts of air pollution reduction programs on a local scale: New Haven accountability case study
2011	Fetal Programming of Adult Disease: Implications for Prenatal Care
2011	Generation and Characterization of Neurogeninl-GFP Transgenic Medaka for High Throughput Developmental Neurotoxicity Screening
2011	Geographic Distribution of Environmental Relative Moldiness Index (ERMI) in U.S. Homes
2011	Gestational Atrazine Exposure: Effects on Male Reproductive Development and Metabolite Distribution

	in the Dam, Fetus, and Neonate
2011	Hepatic Xenobiotic Metabolizing Enzyme Gene Expression Through the Life Stages of the Mouse
2011	High environmental relative moldiness index during infancy as a predictor of asthma at 7 years of age
2011	Identifying developmental toxicity pathways for a subset of ToxCast chemicals using human embryonic stem cells and metabolomics
2011	ILSI/HESI Maternal Toxicity Workshop Summary: Maternal Toxicity and its Impact on Study Design and Data Interpretation
2011	Impact of Low-Level Thyroid Hormone Disruption Induced by Propylthiouracil on Brain Development and Function
2011	In Vitro And In Vivo Approaches For The Measurement Of Oral Bioavailability Of Lead (Pb) In Contaminated Soils: A Review
2011	In Vitro Assessment of Developmental Neurotoxicity: Use of Microelectrode Arrays to Measure Functional Changes in Neuronal Network Ontogeny*
2011	Influence on Transfer of selected synthetic pyrethroids from treated Formica® to Foods
2011	Investigating the American Time Use Survey from an Exposure Modeling Perspective
2011	Marginal Iodide Deficiency and Thyroid Function: Dose-response analysis for quantitative pharmacokinetic modeling
2011	Maternal Influences on Epigenetic Programming of the Developing Hypothalamic-Pituitary-Adrenal Axis
2011	Mechanistic Indicators of Childhood Asthma (MICA): piloting an integrative design for evaluating environmental health
2011	Methodologies for Estimating Cumulative Human Exposures to Current-Use Pyrethroid Pesticides
2011	microRNAs: Implications for Air Pollution Research
2011	Modeled Estimates of Soil and Dust Ingestion Rates for Children
2011	Monoclonal Antibodies to Hyphal Exoantigens Derived from the Opportunistic Pathogen Aspergillus terreus
2011	Mortality in the Agricultural Health Study: 1993 - 2007
2011	Mysid Population Responses to Resource Limitation Differ from those Predicted by Cohort Studies
2011	Neurochemical Changes Following a Single Dose Polybrominated Diphenyl Ether 47 in Mice
2011	On the Use of a PM2.5 Exposure Simulator to Explain Birthweight
2011	Pesticides on Household Surfaces May Influence Dietary Intake of Children
2011	PPARs and Xenobiotic-Induced Adverse Effects:Relevance to Human Health
2011	Predictive models of prenatal developmental toxicity from ToxCast high-throughput screening data
2011	Pregnancy loss and eye malformations in offspring of F344 rats following gestational exposure to mixtures of regulated trihalomethanes and haloacetic acids
2011	Recommendations for Developing Alternative Test Methods for Screening and Prioritization of Chemicals for Developmental Neurotoxicity
2011	Review of Pesticide Urinary Biomarker Measurements from Selected US EPA Children's Observational Exposure Studies
2011	Silver Nanopartilces After Zebrafish Development and Larval Behavior: Distinct Roles for Particle Size, Coating and Composition
2011	Spore trap analysis and MSQPCR in evaluating mold burden: a flooded gymnasium case study
2011	Streptomycetes in house dust: associations with housing characteristics and endotoxin
2011	Temporal Evaluation of Effects of a Model 3B-Hydroxysteroid Dehydrogenase Inhibitor on Endocrine Function in the Fathead Minnow
2011	The effects of prenatal exposure to atrazine on pubertal and postnatal reproductive indices in the female rat

2011	The Promise of Exposure Science
2011	The Reliability of Using Urinary Biomarkers to Estimate Human Exposures to Chlorpyrifos and Diazinon
2011	Thyroid-stimulating Hormone (TSH): Measurement of Intracellular, Secreted, and Circulating Hormone in Xenopus laevis and Xenopus tropicalis
2011	Tobacco Smoke Exposure and Altered Nasal Responses to Live Attenuated Influenza Virus
2011	Toluene effects on Oxidative Stress in Brain regions of Young-adult, Middleage,and Senescent Brown Norway Rats
2011	Toxicity and recovery in the pregnant mouse after gestational exposure to the cyanobacterial toxin, cylindrospermopsin
2011	Traditional Mold Analysis Compared to a DNA-based Method of Mold Analysis with Applications in Asthmatics' Homes
2011	Use of Genomic Data in Risk Assessment Case Study: II. Evaluation of the Dibutyl Phthalate Toxicogenomic Dataset
2011	Use of high content image analysis to detect chemical-induced changes in synaptogenesis in vitro
2011	Windsor, Ontario Exposure Assessment Study: Design and Methods Validation of Personal, Indoor and Outdoor Air Pollution Monitoring
2011	Zebrafish – As an Integrative Model for Twenty-first Century Toxicity Testing
2010	A Different Approach to Validating Screening Assays for Developmental Toxicity
2010	A Meta-Analysis of Children's Object-to-Mouth Frequency Data for Estimating Non-Dietary Ingestion Exposure
2010	Acute Neuroactive Drug Exposures alter Locomotor Activity in Larval Zebrafish
2010	Age, Dose, and Time-Dependency of Plasma and Tissue Distribution of Deltamethrine in Immature Rats
2010	Aging And Susceptibility To Toluene In Rats: A Pharmacokinetic, Biomarker, And Physiological Approach
2010	Aging-Related Carbaryl Effects In Brown Norway Rats
2010	Altered Health Outcomes in Adult Offspring of Sprague Dawley and Wistar Rats Undernourished During Early or Late Pregnancy
2010	An Evaluation of the Mode of Action Framework for MutagenicCarcinogens Case Study II: Chromium (VI)
2010	Are Developmentally-Exposed C57BL/6 Mice Insensitive to Suppression of TDAR by PFOA?
2010	Biomarkers of acute respiratory allergen exposure: Screening for sensitization potential
2010	Changes in mitogen-activated protein kinase in cerebeller granule neurons by polybrominated diphenyl ethers and polychlorinated biphenyls
2010	Characterization of Thyroid Hormone Transporter Protein Expression during Tissue-specific Metamorphic Events in Xenopus tropicalis
2010	Concentration, Chlorination, and Chemical Analysis of Drinking Water for Disinfection Byproduct Mixtures Health Effects Research: U.S. EPA's Four Lab Study
2010	Developmental Effects of Perfluorononanoic acid in the Mouse Are Dependent on Peroxisome Proliferator-Activated Receptor-alpha
2010	Developmental Exposure to a Commercial PBDE mixture, DE·71: Neurobehavioral, Hormonal, and Reproductive Effects
2010	Developmental Triclosan Exposure Decreases Maternal and Offspring Thyroxine in Rats*
2010	Early Temporal Effects of Three Thyroid Hormone Synthesis Inhibitors in Xenopus laevis
2010	Effects of prenatal diesel exhaust inhalation on pulmonary inflammation and development of specific immune responses
2010	Effects of Prenatal Exposure to a Low Dose Atrazine Metabolite Mixture on pubertal timing and prostrate Development of Male Long Evans Rats
2010	Evaluation of Deltamethrin Kinetics and Dosimetry in the Maturing Rat using a PBPK Model

2010	Feasibility of Community Food Item Collection for the National Children's Study
2010	Fetal malformations and early embryonic gene expression response in cynomolgus monkeys maternally exposed to thalidomide
2010	Field Turbidity Methods for the Determination of Lead in Acid Extracts of Dried Paint
2010	Gene Expression Changes in Developing Zebrafish as Potential Markers for Rapid Developmental Neurotoxicity Screening
2010	Gene Expression Profiling In Wild-Type And Ppara-Null Mice Exposed To Perfluorooctane Sulfonate Reveals Ppara-Independent Effects
2010	Hypoxia and the Edema Syndrome: Elucidation of a Mechanism of Teratogenesis
2010	In utero and lactational exposure to bisphenol A, in contrast to ethinyl estradiol, does not alter sexually dimorphic behavior, puberty, fertility, and anatomy of female LE rats
2010	In Utero Exposure To An AR Antagonist Plus An Inhibitor Of Fetal Testosterone Synthesis Inducescumulative Effects On F1 Male Rats
2010	Investigation of Reagent Gases for the Positive Chemical Ionization of Select Polybrominated Diphenyl Ethers
2010	Markers of murine embryonic and neural stem cells, neurons and astrocytes: reference points for developmental neurotoxicity testing
2010	Modeling the interaction of binary and ternary mixtures of estradiol with bisphenol A and bisphenol A F in an in vitro estrogen mediated transcriptional activation assay (T47D-KBluc)
2010	Moderate Developmental undernutrition: Impact on growth and cognitive function in youth and old age
2010	Neural Progenitor Cells as Models for High-Throughput Screens of Developmental Neurotoxicity: State of the Science
2010	Neuroendocrine Actions of Organohalogens: Thyroid Hormones, Arginine Vasopressin, and Neuroplasticity
2010	Neuronal models for evaluation of proliferation in vitro using high content screening
2010	Organophosphorus and Pyrethroid Insecticide Urinary Metabolite Concentrations in Young Children Living in a Southeastern United States City
2010	Participant-Based Monitoring of Indoor and Outdoor Nitrogen Dioxide, Volatile Organic Compounds, and Polycyclic Aromatic Hydrocarbons among MICA-Air Households
2010	Peroxisome Proliferator Activated Receptors Alpha, Beta, and Gamma mRNA and protein expression in human fetal tissues
2010	Phenotypic and physiologic variability in nasal epithelium cultured from smokers and non-smokers exposed to secondhand tobacco smoke
2010	Quantitative assessment of neurite outgrowth in human embryonic stem cell derived hN2 cells using automated high-content image analysis
2010	The CAESAR models for developmental toxicity
2010	The Effects of Simazine, a Chlorotriazine Herbicide, on Female Pubertal Development*
2010	The Etiology of Cleft Palate: a 50 year search for mechanistic and molecular understanding
2010	The Hemimelic extra toes mouse mutant: Historical perspective on unraveling mechanisms of dysmorphogenesis
2010	Visually Observed Mold And Moldy Odor Versus Quantitatively Measured Microbial Exposure In Homes
2010	What do we need to know prior to thinking about incorporating an epigenetic evaluation into safety assessments
2009	A high sensitivity of children to swimming associated gastrointestinal illness (response to letter by Linn)
2009	A participant-based approach to indoor/outdoor air monitoring in Community Health Studies
2009	Age, strain, and gender as factors for increased sensitivity of the mouse lung to inhaled ozone
2009	Analyses of School Commuting Data for Exposure Modeling Purposes

2009	Analysis of PFOA in Dosed CD1 Mice Part 1: Methods Development for the Analysis of Tissues and Fluids from Pregnant and Lactating Mice and Their Pups
2009	Analysis of PFOA in Dosed CD-1 Mice Part 2: Disposition of PFOA in Tissues and fluids from pregnant and lactating mice and their pups
2009	Characterization of Ontogenetic Changes in Gene Expression in the Fathead Minnow Pimephales promelas
2009	Childhood Asthma and Environmental Exposures at Swimming Pools: State of the Science and Research Recommendations
2009	Concentration and persistence of tin in rat brain and blood following dibutyltin exposure during development
2009	Contact with beach sand among beach-goers and risk of illness
2009	Correlation between ERMI values and other moisture and mold assessments of homes in the American Healthy Home Survey
2009	Cummulative and antagonistic effects of a mixture of the antiandrogrens vinclozolin and iprodione in the pubertal male rat:
2009	Cumulative Effects of in Uetro Administration of Mixtures of "Antiandrogens" on Male Rat Reproductive Development
2009	Current Development in Reproductive Toxicity Testing of Pesticides
2009	Developmental exposure to polychlorinated biphenyls (PCBs) interferes with experience-dependent dendritic plasticity and ryanodine receptor expression in weanling rats
2009	Developmental Profile and effects of perinatal PBDE exposure in Hepatic Phase I, II, III and deiodinase I gene expression involved in thyroid hormone metabolism in male rat pups
2009	Devopmental toxicity of perfluorooctane Sulfonate (PFOS) is not dependent on expression on peroxisome proliferator activated receptor-alpha (PPAR-alpha)in the mouse
2009	Effects of maternal and pre-weaning undernutrition in rat offspring: Age at reproductive senescence and intergenerational pup growth and viability
2009	Effects of Perfluorooctanoic Acid on Mouse Mammary Gland Development and Differentiation Resulting from Cross-Foster and Restricted Gestational Exposures
2009	Gene Expression Profiling in the Liver and Lung of Perfluorooctane Sulfonate-Exposed Mouse Fetuses: Comparison to Changes Induced by Exposure to Perfluorooctanoic Acid
2009	Impact of lifestage and duration of exposure on arsenic-induced proliferative lesions and neoplasia in C3H mice
2009	Locomotion in Larval Zebrafish: Influence of Time of Day, Lighting and Ethanol
2009	Longitudinal Mercury Monitoring Within the Japanese and Korean Communities (United States): Implications for Exposure Determination and Public Health Protection
2009	Maternal drinking water arsenic exposure and perinatal outcomes in Inner Mongolia, China, Journal
2009	Methodological issues in studies of air pollution and reproductive health
2009	Mode of Action for Reproductive and Hepatic Toxicity Inferred from a Genomic Study of Triazole Antifungals
2009	Neighborhood deprivation and small-for-gestaional-age term births among non-Hispanic whites and non-Hispanic blacks in the United States
2009	Peroxisome proliferator-activated receptor alpha (PPARalpha) agonists down-regulate alpha2-macroglobulin expression by a PPARalpha-dependent mechanism
2009	Pharmacokinetic Modeling of Perfluorooctanoic Acid During Gestation and Lactation in the Mouse
2009	Phenotypic Dichotomy Following Developmental Exposure to Perfluorooctanic Acid (PFOA) Exposure in CD-1 Mice: Low Doses Induce Elevated Serum, Leptin, Insulin, and Overweight in Mid-Life
2009	Polyfluoroalkyl Chemicals in the Serum and Milk of Breastfeeding Women
2009	Predicting Residential Exposure to Phthalate Plasticizer Emitted from Vinyl Flooring - A Mechanistic Analysis

2009	Predicting Virulence of Aeromonas Isolates Based-on Changes in Transcription of c-jun and c-fos in Human Tissue Culture Cells
2009	Predictive Models for Carcinogenicity and Mutagenicity: Frameworks, State-of-the-Art, and Perspectives
2009	Profiling the activity of environmental chemicals in prenatal developmental toxicity studies using the U.S. EPA's ToxRefDB
2009	Protein Nutrition of Southern Plains Small Mammals: Immune Response to Variation in Maternal and Offspring Dietary Nitrogen
2009	Retrospective performance assessment of the draft test guideline 426 on developmental neurotoxicity
2009	Review of the expression of Peroxisome Proliferator Activated Receptors alpha (PPARα), beta (PPAR β), and gamma (PPAR() in rodent and human development
2009	Screening Tools to Estimate Mold Burdens in Homes
2009	Selenium and mercury interactions wtih emphasis on fish tissue
2009	Spatial Analysis and Land Use Regression of VOCs and NO2 from School-Based Urban Air Monitoring in Detroit-Dearborn, USA
2009	Speciation And Distribution Of Arsenic And Localization Of Nutrients In Rice Grains
2009	The Developmental Effects Of A Municipal Wastewater Effluent On The Northern Leopard Frog, Rana pipiens
2009	The Effects of In Vivo Acute Exposure to Polychlorinatedbiphenyls on Free and Total Thyroxine in Rats
2009	The herbicide linuron reduces testosterone production from the fetal rat testis both in utero and in vitro
2009	Tobacco and Pregnancy
2009	Toxicogenomic Effects Common to Triazole Antifungals and Conserved Between Rats and Humans
2009	Transgenerational Effects of Di(2-ethylhexyl) Phthalate in the SD Male Rat
2009	Use of Single Fiber Electromyographic Jitter to Detect Acute Changes in Neuromuscular Function in Young and Adult Rats
2008	A Genomic Analysis of Subclinical Hypothyroidism in Hippocampus and Neocortex of the Developing Brain -- JN
2008	A mixture of five phthalate esters inhibits fetal testicular testosterone production in a cummulative manner consistent with their predicted reproductive toxicity in the Sprague Dawley rat
2008	A mixture of seven antiandrogens induces reproductive malformations in rats
2008	Acute Postnatal Exposure To Brominated Diphenylether 47 Delays Neuromotor Ontogeny And Alters Motor Activity In Mice
2008	Acute Respiratory Health Effects Of Air Pollution On Asthmatic Children In Us Inner Cities
2008	Adult And Children's Exposure To 2,4-D From Multiple Sources And Pathways
2008	Air pollution, airway inflammation and lung function in Mexico City school children
2008	AJE invited commentary: Measuring social disparities in health - what was the question again?
2008	Assessment of chemical effects on neurite outgrowth in PC12 cells using high content screening
2008	Black-white preterm birth disparity: a marker of inequality
2008	Building a scientific framework for studying hormonal effects on behavior and on the development of the sexually dimorphic nervous system
2008	Chronic particulate exposure, mortality and cardiovascular outcomes in the nurses health study
2008	Comparative Absorption and Bioaccumulation of Polybrominated Diphenyl Ethers following Ingestion via Dust and Oil in Male Rats
2008	Comparative hepatic effects of perfluorooctanoic acid and WY 14,643 in PPARa-knocked out and wild-type mice
2008	Comparison Of Gestational Age At Birth Based On Last Menstrual Period And Ultrasound During The First Trimester

2008	Coordinated Changes in Xenobiotic Metabolizing Enzyme Gene Expression in Aging Male Rats
2008	Cytotoxic effects of propiconazole and its metabolites in mouse and human hepatoma cells and primary mouse hepatocytes
2008	Development of a high-throughput screening assay for chemical effects on proliferation and viability of immortalized human neural progenitor cells
2008	Development of glucocorticoid receptor regulation in the rat forebrain: Implications for adverse effects of glucocorticoids in preterm infants
2008	Developmental exposure to perchlorate alters synaptic transmission in hippocampus of the adult rat: in vivo studies
2008	Developmental neurotoxicity testing in vitro: Models for assessing chemical effects on neurite outgrowth
2008	Diverse mechanisms of anti-androgen action: impact on male rat reproductive tract development
2008	Environmental factors and puberty timing: Expert panel research needs
2008	Examination Of U.S. Puberty Timing Data From 1940 To 1994 For Secular Trends: Panel Findings
2008	Exhaled breath malondialdehyde as a matter of effect of exposure to airpollution in children with asthma
2008	Fetal alcohol syndrome (FAS) in C57BL/6 mice detected through proteomics screening of the amniotic fluid
2008	Fifteen years after "Wingspread"- Environmental Endocrine Disrupters and human and wildlife health: Where we are today and where we need to go
2008	Focusing On Children'S Inhalation Dosimetry And Health Effects For Risk Assessment: An Introduction
2008	Gene expression profiles following exposure to a developmental neurotoxicant, Aroclor 1254: Pathway analysis for possible mode(s) of action
2008	Gene expression profiles in the cerebellum and hippocampus following exposure to a neurotoxicant, Aroclor 1254: Developmental effects
2008	Gestational and Lactational Exposure to Ethinyl Estradiol, but not Bisphenol A, Decreases Androgen-Dependent Reproductive Organ Weights and Epididymal Sperm Abundance in the Male Long Evans Hooded Rat
2008	Higher Environmental Relative Moldiness Index (Ermism) Values Measured In Detroit Homes Of Severely Asthmatic Children
2008	Identification And Interpretation Of Developmental Neurotoxicity Effects: A Report From The Ilsi Research Foundation/Risk Science Institute Expert Working Group On Neurodevelopmental Endpoints
2008	In Vitro Effects Of Environmentally Relevant Polybrominated Diphenyl Ether (Pbde) Congeners On Calcium Buffering Mechanisms In Rat Brain
2008	Integrated Disinfection Byproducts Mixtures Research: Comprehensive Characterization Of Water Concentrates Prepared From Chlorinated And Ozonated/Postchlorinated Drinking Water
2008	Integrated Disinfection By-Products Research: Assessing Reproductive and Developmental Risks Posed by Complex Disinfection By-Product Mixtures
2008	Lack Of Alterations In Thyroid Hormones Following Exposure To Polybrominated Diphenyl Ether 47 During A Period Of Rapid Brain Development In Mice
2008	Maternal exposure to water disinfection by-products during gestation and risk of hypospadias
2008	Mercury Exposure From Fish Consumption Within The Japanese And Korean Communities
2008	Modeling Approaches For Estimating The Dosimetry Of Inhaled Toxicants In Children
2008	Mold Species in Dust from the International Space Station Identified and Quantified by Mold Specific Quantitative PCR
2008	Mold Species in Dust from the International Space Station Identified and Quantified by Mold Specific Quantitative PCR - MCEARD
2008	Nasal Contribution to Breathing and Fine Particle Deposition in Children Versus Adults

2008	Neighborhood deprivation and preterm birth among non-Hispanic black and white women in eight geographic areas in the United States
2008	Neonatal Exposure To Decabrominated Diphenyl Ether (Pbde 209) Results In Changes In Biochemical Substrates Of Neuronal Survival, Growth, And Synaptogenesis
2008	Of mice and men (and mosquitofish): Antiandrogens and androgens in the environment
2008	Perfluoroctane sulfonate-induced changes in fetal rat liver gene expression
2008	Pharmacokinetics and dosimetry of the anti-androgen vinclozolin after oral administration inthe rat
2008	Predicting Maternal Rat and Pup Exposures: How Different Are They?
2008	Protein Biomarkers Associated With Growth And Synaptogenesis In a cell culture model of neuronal development
2008	Pyrethroid Pesticides and Their Metabolites in Vacuum Cleaner Dust Collected from Homes and Day-Care Centers
2008	Quantifying Fungal Viability in Air and Water Samples using Quantitative PCR after Treatment with Propidium Monoazide (PMA)
2008	Rapid New Methods for Paint Collection and Lead Extraction
2008	Research Issues Underlying the Four-Lab Study: Integrated Disinfection Byproducts Mixtures Research
2008	The balance between oligodendrocyte and astrocyte production in major white matter tracts is linearly related to serum total thyroxine
2008	The Effect of Environmental Chemicals on Human Health -- CJA
2008	The Effects of Triclosan on Puberty and Thyroid Hormones in Male Winstar Rats
2008	The Induction Of Hepatocellular Neoplasia By Trichloroacetic Acid Administered In The Drinking Water Of The Male B6C3F1 Mouse
2008	The relationship of maternal and fetal toxicity in developmental toxicology bioassays with notes on the biological significance of the "no observed adverse effect level"
2008	Thyroid hormone status and pituitary function in adult rats given oral doses of perfluorooctanesulfonate (PFOS)
2008	Tobacco and Pregnancy: Overview of exposures and effects
2008	Traffic And Meteorological Impacts On Near-Road Air Quality: Summary Of Methods And Trends From The Raleigh Near-Road Study
2008	Undertaking Positive Control Studies As Part Of Developmental Neurotoxicity Testing: A Report From The Ilsi Research Foundation/Risk Science Institute Expert Working Group On Neurodevelopmental Endpoints
2008	Use of (1-3)-β-D-glucan Concentrations in Dust as a Surrogate Method for Estimating Specific Mold Exposures
2008	Use of electrostatic dust cloth for self-administered home allergen collection

Appendix D. CEH Tools and Databases

Name & Type	Acronym	Brief Description
Databases		
Consolidated Human Activity Database	CHAD	Compiled, detailed data on human behavior from 19 separate studies
Exposure Forecaster	ExpoCast	Automated model to predict exposures for thousands of chemicals

Database		
Aggregated Computational Toxicology Resource	ACToR	Data warehouse of all publicly available chemical toxicity data, including chemical structure, physico-chemical values, *in vitro* assay data and *in vivo* toxicology data.
Physiological Parameters Database for PBPK Modeling	-	Includes physiological parameters such as alveolar ventilation, blood flow, tissue volumes, and glomerular filtration rate used for Physiologically-Based Pharmacokinetic (PBPK) modeling
Chemical and Product Categories Database	CPCat	Database containing information on the uses of chemicals, products that contain chemicals and manufacturers of the products
Ontogeny Database on Enzymes	-	Database that can be used as a screening tool to explore metabolism-based variability, based on enzyme differences, during early lifestages
Toxicity Forecaster Database	ToxCast	Builds computational models from HTS data to forecast the potential human toxicity of chemicals
Toxicity Reference Database	ToxRef	Captures thousands of in vivo animal toxicity studies on hundreds of chemicals
Adverse Outcome Pathway Wiki	AOP Wiki	Provides an open-source interface for rapid and collaborative sharing of established AOPs and building new AOPs
Virtual Tissues Knowledgebase	VT-KB	A human and machine readable knowledgebase developed by extracting and organizing relevant facts from the scientific literature and other sources of information in to central database
Exposure Toolbox	ExpoBox	Web-based compendium of over 800 exposure assessment tools that provides links to exposure assessment databases, models, and references
Handbooks		
Exposure Factors Handbook	EFH	Summary of the available statistical data on various factors used in assessing human exposure
Models		
Stochastic Human Exposure and Dose Simulations–HT Model	SHEDS-HT	A probabilistic human exposure model that produces population-level distributions of exposures by the dermal, inhalation, and ingestion routes
Stochastic Human Exposure and Dose Simulation Model for Multimedia	SHEDS-Multimedia	A physically-based, probabilistic model, that can simulate multiple- or single-chemical exposures over time for a population via residential and dietary exposure routes for a variety of multimedia, multipathway environmental chemicals
Tools		
Community-Focused Exposure and Risk Screening Tool	C-FERST	A community mapping, information access, and assessment tool designed to help assess risk and assist in decision making with communities
EnviroAtlas	-	Collection of tools and resources that provides geospatial data, maps, research, and analysis on the relationships between nature, people, health, and the economy
Eco-Health Relationship Browser	-	Interactive tool that illustrates scientific evidence for linkages between human health and ecosystem services
Environmental Quality Index	EQI	Estimates environmental quality at the county level used to assess effects on health outcomes

Appendix E. References

Akinbami, L. J., Mooreman, J. E., Bailey, C., Zahran, H., King, M., Johnson, C., & Liu, X. (2012). *Trends in asthma prevalence, health care use, and mortality in the United States. 2001-2010*. Retrieved from http://cdc.gov/nchs/data/databriefs/db94.pdf

Akinbami, L. J., Mooreman, J. E., & Liu, X. (2011). Asthma prevalence, health care use, and mortality: United States, 2005-2009. *National Health Statistics Report, 32*, 1-16.

Ankley, G. T., Bennett, R. S., Erickson, R. J., Hoff, D. J., Hornung, M. W., Johnson, R. D., . . . Villeneuve, D. L. (2010). Adverse outcome pathways: a conceptual framework to support ecotoxicology research and risk assessment. *Environ Toxicol Chem, 29*(3), 730-741. doi: 10.1002/etc.34

Anonymous. (2014). Adverse Outcome Wiki (AOP). from http://aopkb.org/aopwiki/index.php/Main_Page

Bellinger, D. C. (2013). Prenatal exposures to environmental chemicals and children's neurodevelopment: an update. *Saf Health Work, 4*(1), 1-11. doi: 10.5491/shaw.2013.4.1.1

Boekelheide, K., Blumberg, B., Chapin, R. E., Cote, I., Graziano, J. H., Janesick, A., . . . Rogers, J. M. (2012). Predicting later-life outcomes of early-life exposures. *Environ Health Perspect, 120*(10), 1353-1361. doi: 10.1289/ehp.1204934

Chandler, K. J., Barrier, M., Jeffay, S., Nichols, H. P., Kleinstreuer, N. C., Singh, A. V., . . . Knudsen, T. B. (2011). Evaluation of 309 environmental chemicals using a mouse embryonic stem cell adherent cell differentiation and cytotoxicity assay. *PLoS One, 6*(6), e18540. doi: 10.1371/journal.pone.0018540

Choi, A. L., Sun, G., Zhang, Y., & Grandjean, P. (2012). Developmental fluoride neurotoxicity: a systematic review and meta-analysis. *Environ Health Perspect, 120*(10), 1362-1368. doi: 10.1289/ehp.1104912

Cohen Hubal, E. A., de Wet, T., Du Toit, L., Firestone, M. P., Ruchirawat, M., van Engelen, J., & Vickers, C. (2013). Identifying important life stages for monitoring and assessing risks from exposures to environmental contaminants: Results of a World Health Organization review. *Regul Toxicol Pharmacol*. doi: 10.1016/j.yrtph.2013.09.008

Cohen Hubal, E. A., Richard, A., Aylward, L., Edwards, S., Gallagher, J., Goldsmith, M. R., . . . Kavlock, R. (2010). Advancing exposure characterization for chemical evaluation and risk assessment. *J Toxicol Environ Health B Crit Rev, 13*(2-4), 299-313. doi: 10.1080/10937404.2010.483947

Dadvand, P., Parker, J., Bell, M. L., Bonzini, M., Brauer, M., Darrow, L. A., . . . Woodruff, T. J. (2013). Maternal exposure to particulate air pollution and term birth weight: a multi-country evaluation of effect and heterogeneity. *Environ Health Perspect, 121*(3), 267-373. doi: 10.1289/ehp.1205575

DeFur, P. L., Evans, G. W., Cohen Hubal, E. A., Kyle, A. D., Morello-Frosch, R. A., & Williams, D. R. (2007). Vulnerability as a function of individual and group resources in cumulative risk assessment. *Environ Health Perspect, 115*(5), 817-824. doi: 10.1289/ehp.9332

Dick, S., Doust, E., Cowie, H., Ayres, J. G., & Turner, S. (2014). Associations between environmental exposures and asthma control and exacerbations in young children: a systematic review. *BMJ Open, 4*(2), e003827. doi: 10.1136/bmjopen-2013-003827

Egeghy, P. P., Cohen Hubal, E. A., Tulve, N. S., Melnyk, L. J., Morgan, M. K., Fortmann, R. C., & Sheldon, L. S. (2011). Review of pesticide urinary biomarker measurements from selected US EPA children's observational exposure studies. *Int J Environ Res Public Health, 8*(5), 1727-1754. doi: 10.3390/ijerph8051727

Firestone, M., Moya, J., Cohen-Hubal, E., Zartarian, V., & Xue, J. (2007). Identifying childhood age groups for exposure assessments and monitoring. *Risk Anal, 27*(3), 701-714. doi: 10.1111/j.1539-6924.2007.00918.x

Galea, S., Hall, C., & Kaplan, G. A. (2009). Social epidemiology and complex system dynamic modelling as appied to health behaviour and drug use research. *Int J Drug Policy, 20*(3), 209-216.

Gallagher, J., Hudgens, E., Williams, A., Inmon, J., Rhoney, S., Andrews, G., . . . Hubal, E. C. (2011). Mechanistic indicators of childhood asthma (MICA) study: piloting an integrative design for evaluating environmental health. *BMC Public Health, 11*, 344. doi: 10.1186/1471-2458-11-344

Glen, G., Smith, L., & Van Der Wiele, C. (2013). Report on the estimation of Taiwanese soil and dust ingestion from SHEDS-soil/dust and comparison to United States results for young children (p. o. W.-a. c. n. E.-D.-.-. Prepared for Heidi Ozkaynak, Trans.).

Gorini, F., Chiappa, E., Gargani, L., & Picano, E. (2014). Potential effects of environmental chemical contamination in congenital heart disease. *Pediatr Cardiol, 35*(4), 559-568. doi: 10.1007/s00246-014-0870-1

Grandjean, P., & Landrigan, P. J. (2014). Neurobehavioural effects of developmental toxicity. *Lancet Neurol, 13*(3), 330-338. doi: 10.1016/s1474-4422(13)70278-3

Janesick, A., & Blumberg, B. (2011). Endocrine disrupting chemicals and the developmental programming of adipogenesis and obesity. *Birth Defects Res C Embryo Today, 93*(1), 34-50. doi: 10.1002/bdrc.20197

Kabesch, M. (2014). Epigenetics in asthma and allergy. *Curr Opin Allergy Clin Immunol, 14*(1), 62-68. doi: 10.1097/aci.0000000000000025

Karoutsou, E., & Polymeris, A. (2012). Environmental endocrine disruptors and obesity. *Endocr Regul, 46*(1), 37-46.

Kleinstreuer, N. C., Smith, A. M., West, P. R., Conard, K. R., Fontaine, B. R., Weir-Hauptman, A. M., . . . Cezar, G. G. (2011). Identifying developmental toxicity pathways for a subset of ToxCast chemicals using human embryonic stem cells and metabolomics. *Toxicol Appl Pharmacol, 257*(1), 111-121. doi: 10.1016/j.taap.2011.08.025

Knudsen, T. B., & Kleinstreuer, N. C. (2011). Disruption of embryonic vascular development in predictive toxicology. *Birth Defects Res C Embryo Today, 93*(4), 312-323. doi: 10.1002/bdrc.20223

La Merrill, M., & Birnbaum, L. S. (2011). Childhood obesity and environmental chemicals. *Mt Sinai J Med, 78*(1), 22-48. doi: 10.1002/msj.20229

Marchitti, S. A., LaKind, J. S., Naiman, D. Q., Berlin, C. M., & Kenneke, J. F. (2013). Improving infant exposure and health risk estimates: using serum data to predict polybrominated diphenyl ether concentrations in breast milk. *Environ Sci Technol, 47*(9), 4787-4795. doi: 10.1021/es305229d

Martin, M. T., Knudsen, T. B., Reif, D. M., Houck, K. A., Judson, R. S., Kavlock, R. J., & Dix, D. J. (2011). Predictive model of rat reproductive toxicity from ToxCast high throughput screening. *Biol Reprod, 85*(2), 327-339. doi: 10.1095/biolreprod.111.090977

Martin, S. A., McLanahan, E. D., El-Masri, H., LeFew, W. R., Bushnell, P. J., Boyes, W. K., . . . Campbell, J. L., Jr. (2012). Development of multi-route physiologically-based pharmacokinetic models for ethanol in the adult, pregnant, and neonatal rat. *Inhal Toxicol, 24*(11), 698-722. doi: 10.3109/08958378.2012.712165

McCarthy, M. I., Abecasis, G. R., Cardon, L. R., Goldstein, D. B., Little, J., Ioannidis, J. P., & Hirschhorn, J. N. (2008). Genome-wide association studies for complex traits: consensus, uncertainty and challenges. *Nat Rev Genet, 9*(5), 356-369. doi: 10.1038/nrg2344

National Academy of Sciences. (1993). *Pesticides in the Diets of Infants and Children*. Washington, D.C.: National Academies Press.

National Institute of Environmental Health Sciences. (2012). *2012-2017 Strategic Plan, Advancing Science, Improving Health: A Plan for Environmental Health Research*. (NIH Publication No. 12-7935).

National Research Council. (2011). *Child and Adolescent Health and Health Care Quality: Measuring What Matters*. Washington, D.C.: The National Academies Press.

Perera, F., Vishnevetsky, J., Herbstman, J. B., Calafat, A. M., Xiong, W., Rauh, V., & Wang, S. (2012). Prenatal bisphenol a exposure and child behavior in an inner-city cohort. *Environ Health Perspect, 120*(8), 1190-1194. doi: 10.1289/ehp.1104492

Perera, F. P., Wang, S., Vishnevetsky, J., Zhang, B., Cole, K. J., Tang, D., . . . Phillips, D. H. (2011). Polycyclic aromatic hydrocarbons-aromatic DNA adducts in cord blood and behavior scores in New York city children. *Environ Health Perspect, 119*(8), 1176-1181. doi: 10.1289/ehp.1002705

Perfahl, H., Byrne, H. M., Chen, T., Estrella, V., Alarcon, T., Lapin, A., . . . Owen, M. R. (2011). Multiscale modelling of vascular tumour growth in 3D: the roles of domain size and boundary conditions. *PLoS One, 6*(4), e14790. doi: 10.1371/journal.pone.0014790

President's Taskforce on Environmental Health Risks and Safety Risks to Children. (2012). *Coordinated Federal National Action Plan to Reduce Racial and Asthma Disparities* Retrieved from http://www.epa.gov/childrenstaskforce.

Reif, D. M., Martin, M. T., Tan, S. W., Houck, K. A., Judson, R. S., Richard, A. M., . . . Kavlock, R. J. (2010). Endocrine profiling and prioritization of environmental chemicals using ToxCast data. *Environ Health Perspect, 118*(12), 1714-1720. doi: 10.1289/ehp.1002180

Rigoli, L., Briuglia, S., Caimmi, S., Ferrau, V., Gallizzi, R., Leonardi, S., . . . Salpietro, C. (2011). Gene-environment interaction in childhood asthma. *Int J Immunopathol Pharmacol, 24*(4 Suppl), 41-47.

Rodriguez-Barranco, M., Lacasana, M., Aguilar-Garduno, C., Alguacil, J., Gil, F., Gonzalez-Alzaga, B., & Rojas-Garcia, A. (2013). Association of arsenic, cadmium and manganese exposure with neurodevelopment and behavioural disorders in children: a systematic review and meta-analysis. *Sci Total Environ, 454-455*, 562-577. doi: 10.1016/j.scitotenv.2013.03.047

Salam, M. T., Zhang, Y., & Begum, K. (2012). Epigenetics and childhood asthma: current evidence and future research directions. *Epigenomics, 4*(4), 415-429. doi: 10.2217/epi.12.32

Selgrade, M. K., Blain, R. B., Fedak, K. M., & Cawley, M. A. (2013). Potential risk of asthma associated with in utero exposure to xenobiotics. *Birth Defects Res C Embryo Today, 99*(1), 1-13. doi: 10.1002/bdrc.21028

Shirinifard, A., Gens, J. S., Zaitlen, B. L., Poplawski, N. J., Swat, M., & Glazier, J. A. (2009). 3D multi-cell simulation of tumor growth and angiogenesis. *PLoS One, 4*(10), e7190. doi: 10.1371/journal.pone.0007190

Sipes, N. S., Martin, M. T., Reif, D. M., Kleinstreuer, N. C., Judson, R. S., Singh, A. V., . . . Knudsen, T. B. (2011). Predictive models of prenatal developmental toxicity from ToxCast high-throughput screening data. *Toxicol Sci, 124*(1), 109-127. doi: 10.1093/toxsci/kfr220

Stieb, D. M., Chen, L., Eshoul, M., & Judek, S. (2012). Ambient air pollution, birth weight and preterm birth: a systematic review and meta-analysis. *Environ Res, 117*, 100-111. doi: 10.1016/j.envres.2012.05.007

Tornero-Velez, R., Egeghy, P. P., & Cohen Hubal, E. A. (2012). Biogeographical analysis of chemical co-occurrence data to identify priorities for mixtures research. *Risk Anal, 32*(2), 224-236. doi: 10.1111/j.1539-6924.2011.01658.x

U.S. Environmental Protection Agency. (1995). *Policy on evaluating health risks to children*. Retrieved from http://www.epa.gov/spc/2poleval.htm.

U.S. Environmental Protection Agency. (2000). *Strategy for research on environmental risks to children*. Washington, DC: Retrieved from http://cfpub.epa.gov/ncea/cfm/recordisplay.cfm?deid=20068.

U.S. Environmental Protection Agency. (2005a). *Guidance on selecting age groups for monitoring and assessing childhood exposures to environmental contaminants*. (EPA/630/P-03/003F). Washington, D.C.: Retrieved from http://www.epa.gov/raf/publications/guidance-on-selecting-age-groups.htm.

U.S. Environmental Protection Agency. (2005b). *Supplemental guidance for assessing susceptibility from early-life exposure to carcinogens*. (EPA/630/R-03/003F). Retrieved from http://www.epa.gov/raf/publications/cancer_guidelines/sup-guidance-early-life-exp-carcinogens.htm.

U.S. Environmental Protection Agency. (2006a). *EPA's Action Development Plan: Guide to Considering Children's Health When Developing EPA Actions*
Retrieved from http://yosemite.epa.gov/ochp/ochpweb.nsf/content/ADPguide.htm/$File/EPA_ADP_Guide_508.pdf.

U.S. Environmental Protection Agency. (2006b). *A framework for assessing health risks of environmental exposures to children*. (EPA/600/R-05/093F). Washington, DC: Retrieved from http://cfpub.epa.gov/ncea/risk/recordisplay.cfm?deid=158363.

U.S. Environmental Protection Agency. (2008). *Child-specific exposure factors handbook (final report)*. (EPA/600/R-06/096F). Washington, D.C.: Retrieved from http://cfpub.epa.gov/ncea/risk/recordisplay.cfm?deid=199243.

U.S. Environmental Protection Agency. (2011). *Exposure Factors Handbook: 2011 Edition*. Washington, D.C.: Retrieved from http://cfpub.epa.gov/ncea/cfm/recordisplay.cfm?deid=20563.

U.S. Environmental Protection Agency. (2012). Air Quality and Air Toxics. from http://www.epa.gov/ncer/quickfinder/airquality.html

U.S. Environmental Protection Agency. (2013a). Community-Focused Exposure and Risk Screening Tool (C-FERST). from http://www.epa.gov/heasd/c-ferst/

U.S. Environmental Protection Agency. (2013b). Eco-Health Relationship Browser Introduction. from http://www.epa.gov/research/healthscience/browser/introduction.html

U.S. Environmental Protection Agency. (2013c). EPA-Expo-Box: A Toolbox for Exposure and Risk Assessors. from http://www.epa.gov/risk/expobox/docs/Expobox_Fact-Sheet_Nov13.pdf

U.S. Environmental Protection Agency. (2013d). Healthy Schools: Environmental Factors, Children's Health and Performance, and Sustainable Building Practices from http://epa.gov/ncer/rfa/2013/2013_star_healthy_schools.html

U.S. Environmental Protection Agency. (2014a). Aggregated Computational Resource (ACToR). from http://actor.epa.gov/actor/faces/ACToRHome.jsp

U.S. Environmental Protection Agency. (2014b). Chemical and Product Categories (CPCat). from http://actor.epa.gov/actor/faces/CPCatLaunch.jsp

U.S. Environmental Protection Agency. (2014c). Community multi-scale air quality model (CMAQ). from http://www.epa.gov/AMD/Research/RIA/cmaq.html

U.S. Environmental Protection Agency. (2014d). Consolidated Human Activity Database - CHAD. from http://www.epa.gov/heasd/chad.html

U.S. Environmental Protection Agency. (2014e). EPA/NIEHS Children's Environmental Health and Disease Prevention Research Centers,. from

http://cfpub.epa.gov/ncer_abstracts/index.cfm/fuseaction/recipients.display/rfa_id/560/records_per_page/ALL

U.S. Environmental Protection Agency. (2014f). ExpoCast. from http://epa.gov/ncct/expocast/

U.S. Environmental Protection Agency. (2014g). ExpoCast Database (ExpoCast DB). from http://actor.epa.gov/actor/faces/ExpoCastDB/Home.jsp

U.S. Environmental Protection Agency. (2014h). *Fiscal Year 2014-2018 EPA Strategic Plan*. Washington, DC: Retrieved from http://www2.epa.gov/sites/production/files/2014-04/documents/epa_strategic_plan_fy14-18.pdf.

U.S. Environmental Protection Agency. (2014i). ToxCast Database (ToxCast DB). from http://actor.epa.gov/actor/faces/ToxCastDB/Home.jsp

U.S. Environmental Protection Agency. (2014j). Toxicity Reference Database (ToxRef DB). from http://actor.epa.gov/toxrefdb/faces/Home.jsp

Vette, A., Burke, J., Norris, G., Landis, M., Batterman, S., Breen, M., . . . Croghan, C. (2013). The Near-Road Exposures and Effects of Urban Air Pollutants Study (NEXUS): study design and methods. *Sci Total Environ, 448*, 38-47. doi: 10.1016/j.scitotenv.2012.10.072

von Mutius, E., & Hartert, T. (2013). Update in asthma 2012. *Am J Respir Crit Care Med, 188*, 150-156.

Wetmore, B. A., Allen, B., Clewell, H. J., 3rd, Parker, T., Wambaugh, J. F., Almond, L. M., . . . Thomas, R. S. (2014). Incorporating population variability and susceptible subpopulations into dosimetry for high-throughput toxicity testing. *Unpublished*.

Williams-DeVane, C. R., Reif, D. M., Cohen Hubal, E. A., Bushel, P. R., Hudgens, E. E., Gallagher, J. E., & Edwards, S. W. (2013). Decision tree-based method for integrating gene expression, demographic, and clinical data to determine disease endotypes. *BMC Systems Biology, 7*(119).

Yim, Y. R., Harden, F. A., Toms, L. M., & Norman, R. E. (2014). Health consequences of exposure to brominated flame retardants: A systematic review.