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Children's Environmental Health

RESEARCH ROADMAP

Office of Research and Development
Research Roadmap: Children's Environmental Health

EPA
United States
Environmental Protection
Agency

EPA 601/R-15/001

Children's Environmental Health (CEH) Research Roadmap

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

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Executive Summary

EPA's Office of Research and Development's (ORD) 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, important scientific issues will arise that cut across these six programs. Rather than create additional research programs for every cross-cutting issue, ORD is developing Research Roadmaps for clearly identifying 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 to identify needed work. Specific research products/deliverables are not included in the Roadmap: These may change because of ORD's planning and budgeting each year. ORD will use EPA's website, however, 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 well-being of individuals and communities today without compromising the health and welfare of future generations. The current EPA Administrator has committed *"to engaging closely with states, tribes, local partners, federal agencies and business and industry leaders in the most pragmatic, collaborative and flexible way possible to achieve environmental benefits for our children and future generations"* (EPA Strategy). To meet this commitment, the Agency and stakeholders require information and tools to incorporate consideration of early lifestage sensitivity, susceptibility, and vulnerability to support sustainable decisions and actions.

Today, public awareness and concern is increasing around the prevalence of children's health outcomes in the United States, as is the desire to understand the potential role of environmental factors on those outcomes. Recent high-visibility research publications have identified associations between environmental factors and risk of diseases, including asthma, autism spectrum disorder, and childhood obesity. To date, research in this area has been limited and the complexity of exposures, disease etiology, and health outcomes makes it difficult to evaluate and interpret associations with exposures to environmental factors. Due to high-profile reports of links between increased prevalence of CEH effects and environmental factors, including air pollution and chemicals in consumer products, however, the public is looking to the Agency to address or mitigate these environmental factors. Although evidence is building of important links between CEH and environmental factors, the science in many cases is still far from actionable. More efficient and effective approaches are needed to develop an understanding of the biological basis of complex environmental disease to support intervention and prevent effects.

The challenge is to evaluate emerging scientific evidence and fill gaps required to identify key environmental factors related to CEH where the Agency can take action. Specifically, modifiable environmental factors that are practically amenable to change using available technologies, policies, and preventive and public health measures. Within this context, EPA's Office of Research and

Development (ORD) conducts CEH research to inform, support, and evaluate: 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 goal is to enable and extend the Agency's ability to take actions that minimize early life exposures for optimal well-being across all developmental lifestages, from preconception through puberty and into adulthood, recognizing that adverse consequences of exposure may not manifest until later in life.

ORD is investing heavily in CEH research—intramural, extramural, and through strategic partnerships. Through its National Research Programs, (Air, Climate, and Energy; Chemical Safety for Sustainability; Homeland Security; Human Health Risk Assessment; Safe and Sustainable Water Resources; and Sustainable and Healthy Communities), ORD is collecting and compiling data on children's exposures and providing access to information on exposure factors, human behavior, chemical use, and developmental toxicity. Complex systems models of tissues and multi-organ development are being constructed, as well as studies that combine epidemiological and laboratory-based approaches to provide a holistic understanding of the relationship between early life environmental exposures and well-being across the lifespan. ORD is developing tools and models that can be used to access data, forecast exposures for thousands of chemicals, and evaluate dosimetry of chemicals in the developing organism. ORD is also developing decision-support tools to help states, local governments, and community organizations consider potential impacts of environmental exposures in the context of decisions designed to protect and promote children's health.

Despite the many contributions to CEH research by ORD over the past decade, important gaps remain in actionable science and information required to understand, prevent, and mitigate impacts to children from real-world exposures to potentially harmful air, water, and chemicals. ORD leadership is required to bring together the science generated outside the Agency with targeted information EPA generates to build predictive capacity for evaluating alternative actions and to anticipate outcomes.

Working in conjunction with its partners in the EPA regulatory program and other EPA stakeholders, we identified four cross-cutting research areas required to address the critical science challenges in CEH facing the Agency:

(1) Knowledge infrastructure to collate information and data that are currently distributed and difficult to access;

(2) Systems understanding of the relationship between environmental exposures and health outcomes across development;

(3) Methods and models to evaluate early lifestage-specific risks and to support decisions protective of all lifestages; and

(4) Translational research and tools to support community actions and decisions.

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 environmental exposure during early life on health impacts that may occur at any point over the lifecourse.

This Children's Environmental Health Research Roadmap helps connect the dots among the research activities being implemented across the National Research Programs. Additionally, the vision articulated in this roadmap serves to focus ORD investment in CEH research on areas where EPA can play a significant leadership role and ensure this cross-cutting research is integrated and the results are impactful.

The impact of integrated ORD research in CEH will be that the:

- Agency has the necessary data to evaluate risks;
  Information on early lifestage exposure and hazard is collated and organized to provide accessible data that can be used to estimate important CEH factors and to support evaluation of risks.

- Agency has scientific basis for action;
  Systems understanding of early life exposures and associated health outcomes is used to build predictive models that enable effective Agency actions to protect the health of children.

- Agency has tools to evaluate benefits of alternatives and to support decisions;
  Evaluated, accessible tools enhance Agency capacity to consider children's unique susceptibilities and vulnerabilities adequately in Agency risk-based evaluations and sustainable public health decisions.

- Agency can enable communities to take action;
  Information and translation tools are developed to support Agency, state, tribal, and local decision makers with the knowledge needed to manage risks and to protect and promote CEH.

EPA has a unique mandate to understand the role of exposure to modifiable exogenous environmental factors during early life in the context of important modifying factors (i.e., non-chemical stressors) on health impacts during the course of development. This roadmap presents ORD's vision for providing integrated, cutting-edge science on CEH to inform Agency decisions. This roadmap will build stronger bridges to EPA partners and stakeholders who care about CEH issues. Resulting research will provide the science required for EPA actions to promote children's environmental health and well-being.

Introduction

Background

The mission of EPA is to protect human health and the environment. In addressing health risks, the goal is to provide protection not only for the general population, but also 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, today's public policy for improving the health of individuals and communities should provide effective solutions without compromising the health and welfare of future generations.

In the Fiscal Year 2014–2018 EPA Strategic Plan, the Agency "recognizes [that] 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 past few decades, several key legislative and policy initiatives have been crucial to 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, *Pesticides in the Diets of Infants and Children*, which described significant differences in toxicity and exposure of pesticides between children and adults (National Academy of Sciences, 1993). The NAS report 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 report led Congress to enact the Food Quality Protection Act in 1996, which significantly amended the Federal Insecticide, Fungicide, and Rodenticide Act and the Federal Food, Drug, and Cosmetic Act 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 10-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 to address the importance of assessing CEH within EPA and across the federal government.

Since the 1990s, EPA has enacted several policies and strategies to protect children's health. In 1995 (and reaffirmed in 2013), EPA released 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, 2006). This guidance outlines the key steps to be considered when developing actions concerning children's health.

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

Table 1. Key Governmental and International Actions on Children's Environmental Health

Organization	Year	Title	Content
		U.S. Government	
Presidential Task Force (co-chaired by HHS and EPA)	1997	Presidential Executive Order 13045 – Protection of Children from Environmental Health Risks and Safety Risks and establishment of the Presidential Task Force on Environmental Health and Safety Risks to Children (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.
	2001	HUD Announces $67 Million in Grants to Fight Childhood Lead Poisoning (http://archive.hhs.gov/news/press/2001pres/20011024a.html)	The task force's priority is to examine programs that combat childhood lead poisoning.
	2012	Released the *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.
	2013	Established a Federal Healthy Homes Workgroup and released *Advanced Healthy Housing – A Strategy for Action* (http://www2.epa.gov/children/presidential-task-force-environmental-health-and-safety-risks-children)	The goal is to support research that informs and advances healthy housing cost-effectively.
	2014	Established a Subcommittee on Climate Change, co-chaired by NIEHS, EPA, and DHS (http://www2.epa.gov/children/presidential-task-force-environmental-health-and-safety-risks-children)	In July 2014, the Subcommittee hosted an Expert Consultation on the Effects of Climate Change on Children's Health to explore these issues and to help inform the ongoing U.S. Global Change Research Program.
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.
110th U.S. Congress	2007	Energy Independence and Security Act of 2007 (http://www2.epa.gov/laws-regulations/summary-energy-independence-and-security-act)	Required EPA to develop school siting guidelines and environmental health guidelines.

Table 1. (continued) Key Governmental and International Actions on Children's Environmental Health

Organization	Year	Title	Content
		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 CEH issues.

Table 1. (continued) Key Governmental and International Actions on Children's Environmental Health

Organization	Year	Title	Content
		EPA	
	2010	"Working for Environmental Justice and Children's Health" (part of EPA's Strategic Plan, 2011–2015) (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 CEH research.
	2013	ORD establishes six integrated, transdisciplinary National Research Programs: Air, Climate, and Energy (ACE); Safe and Sustainable Water Resources (SSWR); Sustainable and Healthy Communities (SHC); Chemical Safety for Sustainability (CSS); Human Health Risk Assessment (HHRA); and Homeland Security (HSRP) (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."
	2014	*EPA's Report on the Environment* (http://www.epa.gov/roe/)	Provides the best available indicators of national trends in the environment and human health and includes CEH metrics.
		Other Federal Agencies, Countries, and International Organizations	
NIH	2014	NIH announces a notice of intent to fund the Children's Health Exposure Analysis Resource (CHEAR): a National Exposure Assessment Laboratory Network (http://grants2.nih.gov/grants/guide/notice-files/NOT-ES-15-007.html)	Laboratories will provide a comprehensive suite of laboratory-based analytical services for samples from children's health studies.
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 for the protection of the health of children and other sensitive populations comprehensively and cost-effectively.

Table 1. (continued) Key Governmental and International Actions on Children's Environmental Health

Organization	Year	Title	Content
Other Federal Agencies, Countries, and International Organizations			
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 been found in children's products or 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

Three key drivers 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 and emerging scientific findings related to CEH issues.

(1) EPA's 2014–2018 Strategic Plan

The EPA Strategic Plan released in early 2014 calls specifically for applied research in CEH in 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 consider children's unique susceptibilities and vulnerabilities adequately 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 protect the health of children and other vulnerable groups adequately.

Although neither Goal 1 (Addressing Climate Change and Improving Air Quality) nor Goal 2 (Protecting America's Waters) of the CEH research directly calls for applied research, Agency decisions and actions to meet these strategic goals require the information and tools to consider child-specific vulnerabilities.

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).

(2) EPA Program Office Drivers

EPA program offices have a variety of mandates to protect children from environmental health risks. These mandates are based on the authority established under the environmental statutes and on guidance specific to each program office.

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 United States. OCHP supports and facilitates Agency efforts to protect children's health from environmental threats through participation in regulation and standards development, risk assessment guidance and policy development, research planning, 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); 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 mixtures. OCSPP carries out these requirements by reviewing new and existing chemicals; evaluating chemical hazards, including hazards relevant to developmental and reproductive toxicological endpoints; and exposure, including exposures of children to environmental chemicals. EPA is currently working with Congress, 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 remaining chemicals 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 Work Plan Chemicals) for further assessment under TSCA (http://www.epa.gov/oppt/existingchemicals/pubs/workplans.html). The chemicals were selected based on five criteria: hazard, exposure, persistence, bioaccumulation, and use, including use in children's products.

OCSPP also regulates all use of pesticides in the United States based on legislative authority provided under the Federal Insecticide, Fungicide, and Rodenticide Act. EPA's current pesticide review processes also focus on ensuring that pesticide registrations comply with the Endangered Species Act and achieve broader Agency objectives for water quality protection. The review processes emphasize the protection of potentially sensitive populations, such as children, by reducing exposures from pesticides used in and around homes, schools, and other public areas.

The 1996 Food Quality Protection Act directs EPA to develop a screening program, using appropriate validated test systems and other scientifically relevant information, to determine whether certain substances including pesticides may have hormonal effects in humans. At the same time, the 1996 amendments to the Safe Drinking Water Act authorize EPA to screen substances that may be found in sources of drinking water for endocrine disruption potential. To carry out this directive, OCSPP established the Endocrine Disruptor Screening Program (EDSP), in which EPA is using a two-tiered screening and testing process to gather information needed to identify endocrine-active substances and take appropriate action, as mandated by Congress. In 2005, EPA began screening priority chemicals under this program including pesticide active ingredients and high-production volume-chemicals used as inert ingredients in pesticide formulation; drinking water contaminants,

such as halogenated organic chemicals; persistent chemicals such as dioxins and flame retardants; and chemicals found in 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 toxicological tools in the EDSP and developed the *EDSP21 Work Plan*. This work plan 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).

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."

OW considers the effect of contaminants on 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 this guidance in its qualitative assessment of the adverse health effects of contaminants. 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 groups, such as children, whose vulnerability to certain environmental contaminants may be higher than that of adults. Such assessments are conducted for all air toxics rulemakings, including National Emissions Standards for Hazardous Air Pollutants (otherwise known as Maximum Achievable Control Technology or MACT standards) and Residual Risk rules. During these assessments, OAR specifically estimates risks to children and determines if children are disproportionately affected by their exposures, behavioral patterns, or both. OAR uses dose-response values that 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 its periodic reviews of the National Ambient Air Quality Standards, 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 standards reviews, including for lead, ozone, and particulate matter, 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, management of hazardous substances and waste, and redevelopment of contaminated sites. OSWER implements its mission under a variety of mandates, including the Comprehensive Environmental Response, Compensation, and Liability Act, the Resource Conservation and Recovery Act, and the Small Business Liability Relief and Brownfields Revitalization Act. In addressing its mission, OSWER works to understand and protect the health of populations, taking into account the unique susceptibilities and vulnerabilities of children.

OSWER directly considers potential impacts to sensitive subpopulations, including children, in its 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 ensures that exposures to the human population, including sensitive groups, are without adverse effect during a lifetime or part of a lifetime, and incorporate an adequate margin of safety. The Risk Assessment Guidance for Superfund 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 who is responsible for leading the CEH Program in their region and engaging with other regional coordinators, including Regional School Coordinators and risk assessors. These programs are based on national and regional strategies to protect CEH through several regulations and voluntary programs. Although 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.

(3) Scientific Drivers Related to Adverse Health Outcomes

Recent and emerging research findings on the relationship of environmental contributions to children's health outcomes are important drivers for EPA's CEH research. Evidence points to associations between early life exposure to environmental contaminants and a wide range of children's health outcomes, including adverse birth outcomes, asthma, neurodevelopmental disorders, metabolic disease, and childhood cancer.

Adverse birth outcomes: Adverse birth outcomes include preterm birth, low birth weight, neonatal mortality, and birth defects. Birth defects occur in approximately 3 percent of births in this country and low birth weights are observed in 11 percent of births. In 2012, black non-Hispanic women had the highest rate of preterm birth of all racial groups (16.8 percent). Adverse birth outcomes are leading causes of infant mortality and may presage long-term problems, including motor, cognitive, visual, hearing, behavioral, and social-emotional problems.

Birth outcomes have been associated with exposure to a variety of environmental contaminants *in utero* and early in life, including fine particulate matter (Dadvand et al., 2013; Fleischer et al., 2014; Stieb et al., 2012) and chemicals such as arsenic (Boekelheide et al., 2012), organochlorine pesticides, organic solvents, and other air pollutants (Gorini et al., 2014).

Asthma: The incidence and severity of childhood asthma continues to rise. In 2009, asthma affected 7.1 million (about 10 percent) children in the United States. Asthma disproportionately impacts minority children, especially in urban communities typified by low income, high levels of air pollution, and poor indoor air quality (Akinbami et al., 2012). In families below the poverty line, 12.2 percent of children were reported to have asthma, compared to 8.7 percent of children in families above the poverty line. A higher percentage of black non-Hispanic children (16 percent) and children of "all other races" (12.4 percent) were reported to have asthma, compared to white non-Hispanic children (8.2 percent).

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. 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 or severity in children (Dick et al., 2014; Selgrade et al., 2013). Genetic factors and gene-environment interactions also play a role in asthma causation (Rigoli et al., 2011). Children with specific gene variants were shown to be at increased risk of asthma associated with air pollution (Macintyre et al., 2014). Environmental exposures may also influence asthma risk through epigenetic mechanisms, an emerging area of study (Kabesch, 2014; Salam et al., 2012).

Neurodevelopmental disorders: Developmental disabilities, including lower IQ, learning deficits, other indicators of poor cognitive function, and adverse effects on behavior, are common: About 1 in 6 children in the United States are affected. Between 1997 and 2008, the prevalence of developmental disabilities increased 17.1 percent, affecting about 1.8 million more children. The prevalence of autism increased 289 percent while attention deficit hyperactivity disorder (ADHD) increased 33 percent. Again, lower income children are disproportionately affected by developmental disabilities. Children insured by Medicaid had nearly two-fold higher prevalence than those with private insurance.

Neurotoxicants that have been associated with developmental effects include lead, methylmercury, polychlorinated biphenyls (PCBs), arsenic, toluene, manganese, fluoride, chlorpyrifos, and tetrachloroethylene (Grandjean and Landrigan, 2014). Limited evidence is emerging to suggest an association between exposure to a range of environmental contaminants, including air pollutants, organophosphate pesticides, brominated flame retardants, phthalates, bisphenol A, and perfluorinated compounds and adverse neurodevelopmental effects (Bellinger, 2013; Choi et al., 2012; Rodriguez-Barranco et al., 2013; Yim et al., 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 ADHD and autism is an area of active investigation. In addition, potential for gene-environment interactions is being studied (Hu, 2012).

Metabolic syndrome: Metabolic syndrome, a cluster of adverse health effects including obesity, altered lipid levels, and other metabolic abnormalities, is increasing globally. Prevalence of childhood obesity in the United States has recently stabilized at approximately 16 percent. The percentage of Mexican-American children that are obese is 22 percent, and 20 percent of black

non-Hispanic children are obese, compared with 14 percent of white non-Hispanic children. Prevalence of obesity is greater in children with family incomes below poverty level than in those above poverty level. The rise in obesity and related 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 an area of significant study. Chemicals that are under investigation include dioxins, PCBs, DDT, DDE, perfluoroalkyls, polybrominated diphenyl ethers (PBDEs), phthalates, bisphenol A, organotins, lead, air pollutants, PAHs, naphthalene, diethylstilbestrol, 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 and Polymeris, 2012; La Merrill and Birnbaum, 2011; Scinicariello and Buser, 2014). Epigenetic reprogramming is hypothesized to be a contributing factor in childhood obesity and metabolic syndrome and is an area of intense study (Janesick and Blumberg, 2011).

Developmental origins of disease: More generally, an increasing number of studies are addressing the hypothesis that early life exposure to environmental stressors may influence development that impacts later health and disease risk. An area of great interest involves epigenetic modification resulting from exposures during critical windows of development. The support for epigenetic change in early life comes from a large number of animal studies and a small number of observational studies in humans (Saffery and Novakovic, 2014). Evidence has been published for epigenetic changes, including DNA methylation, histone modifications, and miRNAs in developmental programming, leading to an increased risk of disease (Bernal and Jirtle, 2010; Hou et al., 2012; Vaiserman, 2014). Environmental compounds studied for their ability to cause epigenetic changes include asbestos, benzene, endocrine-disrupting compounds, and metals (Kim et al., 2012; Vaiserman, 2014).

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, now is 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 on 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 CEH 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. A separate Roadmap for research on environmental justice 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. Although many references are made to children as a 'subpopulation' (e.g., 1996 Safe Drinking Water Act amendments uses the term 'subpopulation' to describe groups with unique attributes, including those defined by age or lifestage), EPA has recognized since 2005 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 include 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 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. EPA has official guidance defining early lifestage-specific age bins, which WHO has affirmed (Cohen Hubal et al., 2013; U.S. Environmental Protection Agency, 2005).

The purpose of this roadmap is to describe and facilitate integrated ORD CEH research that will provide the Agency and stakeholders with scientific understanding, information, and tools required to address early lifestage sensitivity, susceptibility, and vulnerability for sustainable decisions and actions.

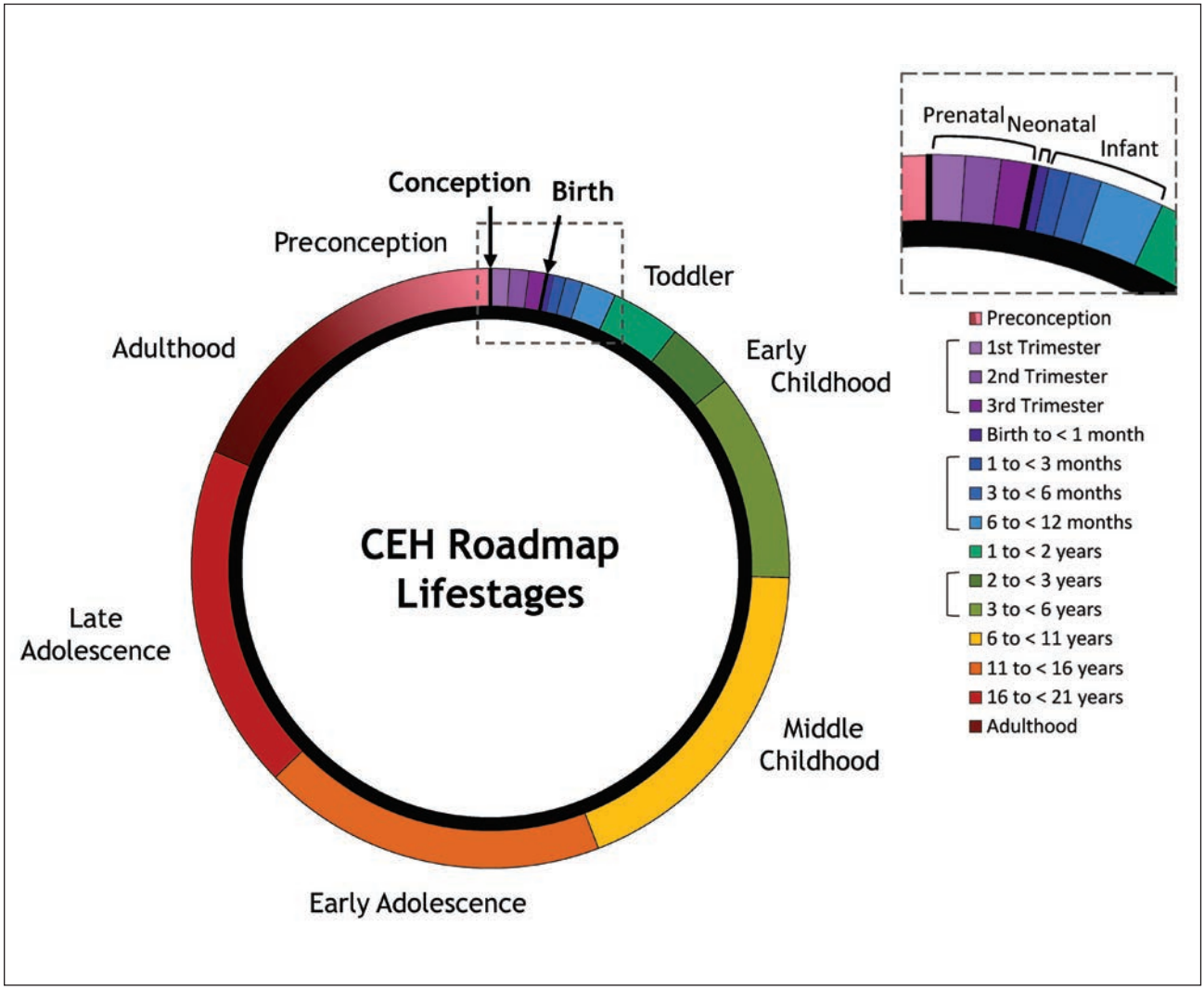

Figure 1 outlines these lifestages which are the specific focus for this Roadmap and cross-cutting CEH research. Note that although exposures from preconception through adolescence are of primary interest, impacts may extend throughout the lifecourse into adult lifestages and across generations. Here, the lifecourse is depicted as a circle to convey the concept of intergenerational impacts from environmental exposures.

Research Scope

Expanded Problem Statement

Sustainable decisions and actions are those that improve the health of individuals and communities today without compromising the health and welfare of future generations. **EPA and stakeholders require scientific understanding, information, and tools to incorporate consideration of early lifestage sensitivity, susceptibility, and vulnerability for sustainable decisions and actions.**

Within the broad sphere of CEH, EPA has a unique mandate to focus on understanding the role of exposure to modifiable 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. Specifically, applied research is required to enable and extend the Agency's ability to take action. The science challenges associated with filling this unique niche in CEH research are significant.

The Agency and stakeholders make decisions at several levels of organization—from the individual to community level all the way to the state and national levels. ORD research will provide required information and tools by considering the different types of decisions and actions required to support CEH. The CEH research translation framework presented in Figure 2 captures the important science challenges ORD CEH research addresses within this context. Two general translation routes are depicted: one focused on providing cutting-edge science for effective public health policy and efficient risk management at the national level and the second at the community level.

Understanding of developmental biology, impacts to biological pathways resulting from perturbations at critical windows of development, and genetic and environmental factors that may produce or modify these perturbations forms the scientific basis for both translation routes. In the first, identification of toxicity pathways coupled with identification of important environmental factors (exposures) provides new opportunities to anticipate impacts by considering early indicators of adversity and monitoring for emerging environmental contaminants. Information and tools along this translation route will 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 and providing early indication of toxicological impacts; and (2) models for risk-based decision making, informed by detailed understanding of relevant environmental stressors and associated perturbations to toxicity pathways. In the second translational route, knowledge of individual patterns of exposure and disease predisposition resulting from the full range of community-level determinants provides opportunities to develop community-based approaches to health promotion and risk management. Here, information and decision support tools are developed to inform and support actions by communities to manage risks and promote health by providing a clear understanding of important exposures and how 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 capturing the

science challenges of characterizing biologically relevant exposure, the framework presented in Figure 2 facilitates translation of advances and findings in computational toxicology to information that can be directly used to support risk-based decisions to improve public health. In addition, this framework captures the challenge of addressing data gaps along all levels of biological organization (i.e., from molecular through population levels) in a systems-based fashion to optimize design of future exposure and epidemiological studies. Such a strategic implementation of toxicological, exposure, and epidemiological research is required to ensure efficient use of resources committed to children's health studies.

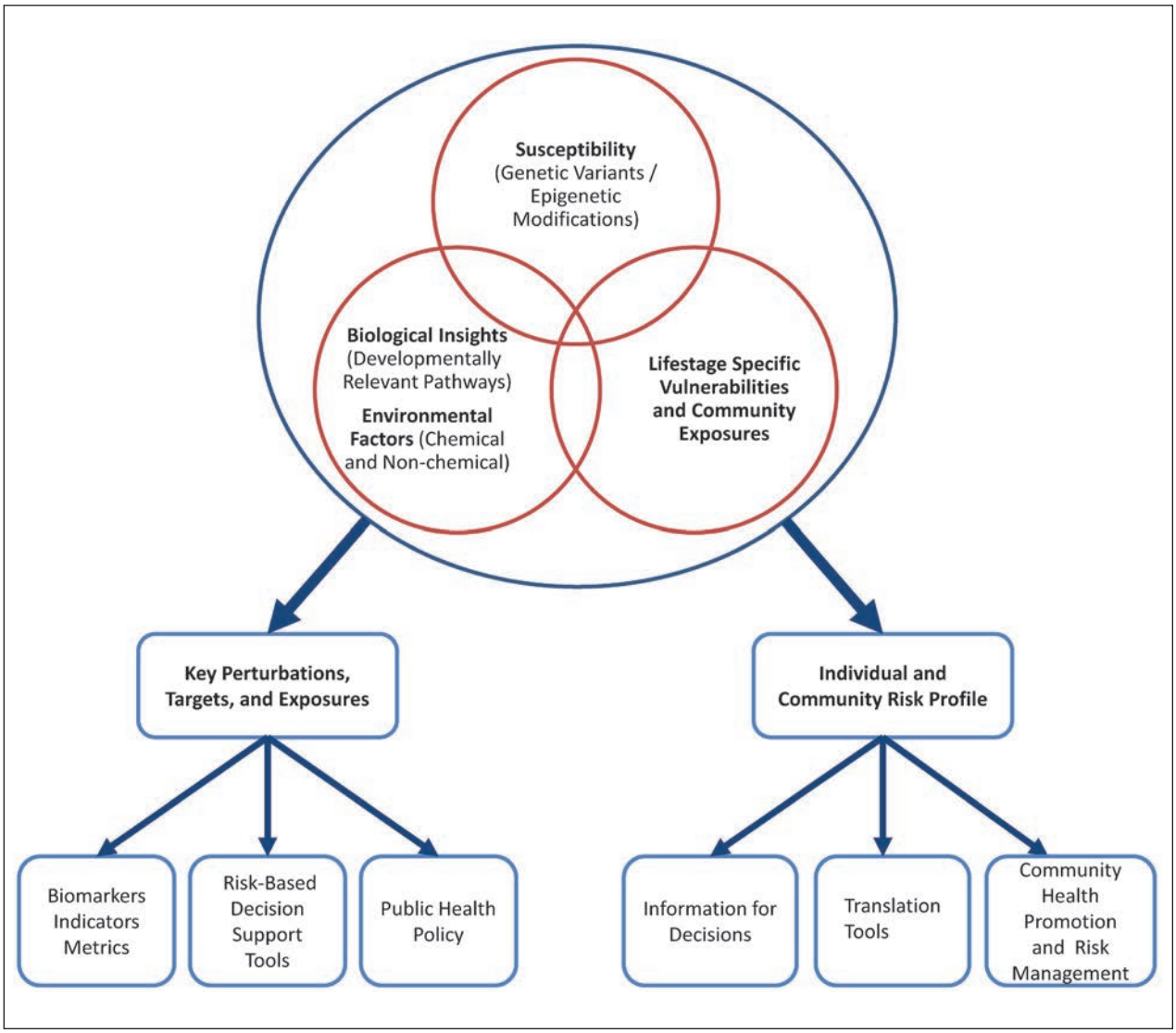

Figure 2. Children's environmental health research translation framework (Adapted from Cohen Hubal et al., 2010).

ORD research is designed and implemented through case examples that allow for demonstration and evaluation of research products. ORD works with EPA program partners and regions through its six National Research Programs to identify useful case examples, develop and demonstrate the research products fit-for-purpose, and evaluate the value added of ORD information and tools to both inform decisions and support measurement of impact resulting from those decisions.

Children's Environmental Health Research Areas

Working in conjunction with its partners in the EPA regulatory programs and other EPA stakeholders, EPA identified four cross-cutting research areas required to address the critical science challenges in CEH facing the Agency. To provide the science, information, and decision support tools required for promoting and protecting children's health and well-being, EPA's CEH research is designed to address the following four priority research areas:

(1) Knowledge infrastructure to address the problem that information and data are distributed and difficult to access.

(2) Systems understanding of the relationship between environmental exposures and health outcomes across development.

(3) Methods and models to evaluate early lifestage-specific risks and to support decisions protective of all lifestages.

(4) Translational research and tools to support 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 address the problem that information and data are distributed and difficult to access

Information and data required for supporting Agency and stakeholder decisions and actions for promoting and protecting children are distributed and may be difficult to access. Much of these data are generated outside the Agency but are critical for evaluating emerging scientific evidence for the role of key environmental factors in CEH, identifying data gaps required to reduce uncertainties in model predictions, and providing effective decision support tools. In all cases, the knowledge systems to facilitate integration and analysis of CEH data are required to identify and protect susceptible lifestages.

Key research questions addressed in this research area are:

- What data and information are most critical for characterizing early lifestage vulnerabilities and susceptibility in the areas of exposure, toxicokinetics, toxicodynamics, and disease etiology?
- What data and information are most critical for evaluating linkages between early life environmental exposures and health outcomes, including those that may appear later in life?

- What data and information are most critical for reducing early lifestage-related uncertainties in exposure and risk characterization to provide the basis for EPA's policy decisions?

Anticipated integrated impact:

Agency has data it needs to evaluate risks. Information on early lifestage exposure and hazard is collated and organized to provide accessible data that can be used to estimate important CEH factors and to support evaluation of risks.

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 to attribute, reduce, and eliminate risks specific to the environmental exposures over which EPA has regulatory authority. Systems-level understanding of the relationship between environmental exposures and health outcomes across development is required to build predictive models that enable effective Agency decisions and actions that protect susceptible lifestages. EPA CEH research is designed to develop this understanding by considering exposures to chemicals and chemical classes of concern and 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.

Key research questions addressed in this research area are:

- By what common biological pathways do environmental contaminants contribute toward early origins of disease and important childhood health outcomes, such as adverse birth outcomes, asthma, neurological disorders and metabolic syndrome?
- What key perturbations and biological targets are associated with developmentally relevant adverse outcome pathways (AOPs)?
- What are the systems-level influences of the chemical, built, and natural environments on these biological pathways and health outcomes?
- How can we evaluate the individual and community risk profiles associated with exposures to chemical mixtures, including the contribution of non-chemical stressors across the course of development?

Anticipated integrated impact:

Agency has scientific basis for action.
Systems understanding of early life exposures and associated health outcomes are used to build predictive models that enable effective Agency actions to protect the health of children.

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

- Identification of AOPs for chemicals that disrupt specific developmental processes.
- Evaluation of relevance/concordance of laboratory animal models for human health.
- Linkage of environmental exposures to health outcomes via AOPs, including outcomes apparent at birth and those that 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 among 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 to evaluate early lifestage-specific risks and to support decisions protective of all lifestages

Risk assessors and risk managers need methods to measure lifestage-specific exposure, toxicity, health endpoints, and models and tools to analyze and integrate the information to consider lifestage-specific factors adequately for sustainable decisions.

Key research questions:

- What methods, models, and decision support tools are needed to enable the Agency to use all available data to inform risk-based decisions?
- What methods, models, and decision support tools are needed to evaluate how and to what extent pregnant women and children are exposed to environmental stressors?
- What methods, models, and decision support tools are needed to evaluate how associated health outcomes vary by specific early lifestages and exposure patterns?
- What methods, models, and decision support tools are needed to support analysis of potential risks associated with exposures to multiple chemicals in the context of other important environmental stressors across development?

Anticipated integrated impact:

Agency has tools to evaluate benefits of alternatives and support decisions. Evaluated, accessible tools enhance Agency capacity to consider children's unique susceptibilities and vulnerabilities adequately for Agency risk-based evaluations and sustainable public health decisions.

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

- 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 lifestage-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.
- Models and methods extended 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 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 well-being. 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 (e.g., land use, buildings and infrastructure, transportation, and waste and materials management) to meet community needs?
- What are the most effective actions to prevent adverse environmental exposures and promote child well-being, how effective are they, and how can they best be communicated to communities and parents?

Anticipated integrated impact:

Agency can enable communities to take action. Information and translation tools are developed to support Agency, state, tribal, and local decision makers with the knowledge needed to manage risks and to protect and promote CEH.

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

- 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 vary in indoor versus 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 and health-promoting factors with respect to specific places where children live, learn, and play.
- Approaches for incorporating CEH into health impact assessments.
- Approaches and guidance for optimizing the built environment to protect and foster CEH sustainably.

Research Alignment and Coordination

The four priority CEH Research Areas are cross-cutting to ORD's six National Research Programs (NRPs). Currently, one or more of the four Research Areas is contained within each of the following NRPs: Air, Climate, and Energy (ACE); Chemical Safety for Sustainability (CSS); Human Health Risk Assessment (HHRA); Safe and Sustainable Water Resources (SSWR); and Sustainable and Healthy Communities (SHC). Several NRPs conduct research in all four areas. Details of the research are described in the individual NRP Strategic Research Action Plans.

Modifiable environmental factors addressed by ORD research include chemicals/classes of current and emerging focus in which the Agency has a role in setting policy or in developing regulatory actions. These include manufactured chemicals and materials (pesticides, solvents, industrial chemicals, 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. Across the NRPs, research is focused on providing systems understanding of the role of modifiable environmental factors in childhood diseases and disorders prevalent today, including adverse birth outcomes, asthma, neurodevelopmental disorders, and metabolic outcomes. Table 2 summarizes the individual NRP contributions to the four research areas in the context of these prevalent CEH health outcomes.

In addition, to meet the Agency's mandate for protecting children, ORD relies heavily on strategic partnerships with dozens of organizations ranging from other federal agencies, state governments, and international organizations to academia, nongovernmental organizations, and industry. All of the strategic partners have an interest in promoting and protecting children's health. Strategic partnerships are finalized through numerous types of agreements, such as STAR Grant, Cooperative Research and Development Agreement, Materials Transfer Agreement, or Memorandum of Understanding.

One of ORD's leading partners in CEH research is the National Institute of Environmental Health Sciences (NIEHS). EPA, through its STAR Grants program, and NIEHS jointly fund the Children's Environmental Health and Disease Research Centers. Currently, 16 active centers conduct research to increase the understanding of how environmental factors affect children's health, and promote translation of basic research findings into intervention and prevention methods to prevent adverse health outcomes. Other important partnerships include those of the Association of Toxic Substances and Disease Registry (ATSDR), Centers for Disease Control and Prevention (CDC), Department of Health and Human Services (DHHS), Food and Drug Administration (FDA), Department of Housing and Urban Development (HUD), and several institutes at the National Institutes of Health (NIH). These partnerships are critical for both conducting basic research on children's health and for implementing research focused on interventions that support CEH.

Table 2. CEH Research Efforts as Distributed Across the Four Research Areas

CHILDREN'S HEALTH OUTCOMES				
RESEARCH AREA	**Adverse Birth Outcomes**	**Asthma**	**Neurodevelopmental Disorders**	**Metabolic Syndrome**
Knowledge Infrastructure	CSS	HHRA	CSS, HHRA	CSS, HHRA
Systems Understanding	CSS, SHC, SSWR, ACE	SHC, ACE	CSS, SHC, ACE	CSS, SHC
Methods & Models	CSS, HHRA	ACE, HHRA	CSS, HHRA	CSS, HHRA
Community Decision Support	SHC, ACE	SHC, ACE	SHC	SHC

Cross-Cutting ORD Research

Current ORD Research

This section summarizes ORD's current and recently completed research activities (2012–2015) as they are aligned with the four CEH research areas described in the preceeding section. 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 objectives. 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
- SSWR= Safe and Sustainable Water Resources Research
- SHC = Sustainable and Healthy Communities Research

See Appendix A for further details on the research activities outlined below and for 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) 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), 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) 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), ORD is developing decision support tools to enable communities to provide healthy environments for children. ORD is also translating research findings on children's health to inform communities and other local groups as they develop environmental health-related strategies that are sustainable.

Research Area 1: Knowledge infrastructure to address the problem that information and data are distributed and difficult to access

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 below.

(1) Exposure Information

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

Exposure Factors Handbook (HHRA)

Data about children's exposures and exposure factors, such as lifestage-specific modeled estimates of soil and dust ingestion, are incorporated into EPA's *Exposure Factors Handbook* (U.S. EPA, 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.

Consolidated Human Activity Database (SHC)

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.

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 childcare centers. ExpoCastDB is 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.

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.

(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.

Enzyme Ontogeny Database (CSS)

Chemicals are often biotransformed in the body by activating or detoxifying enzymes the expression for which 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.

(3) Developmentally Relevant Hazard Data

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

ToxCast Database (CSS)

ToxCastDB provides results of high-throughput *in vitro* assays. Biological data 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 a searchable database through the ACToR system (U.S. Environmental Protection Agency, 2014i); available at: http://actor.epa.gov/actor/faces/ToxCastDB/Home.jsp.

Toxicity Reference Database (CSS)

Toxicity Reference Database (ToxRefDB) contains data from thousands of *in vivo* animal studies and is 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 include 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.

Adverse Outcome Pathway Wiki (CSS)

An 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 including the information needed for proper evaluation of an AOP easier for users. Developmentally relevant AOPs are being incorporated. Currently, endocrine pathways are well represented.

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

Research Area 2 is divided into two subgroups: (1) systems biology to predict developmentally relevant outcomes, and (2) systems understanding of complex stressors. ORD's relevant research in each of these areas is summarized below.

(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 the Agency's understanding of the biological mechanisms of chemical stressors that contribute to childhood health outcomes.

Bioinformatics-Based Models (CSS)

As discussed on page 27, 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 approximately 700 compounds in Phase II, where animal toxicology is less well characterized, ORD is developing plausible model structures that address the possibility of additional relevant interactions and components beyond those represented in the first-generation predictive models.

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 or chemicals, or both, with multiple modes of actions.

Simulation Models (CSS)

Simulation models predict chemical toxicity using relevant biological 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) Systems Understanding of Complex Stressors

Epidemiological, 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.

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), whole rodent embryo cultures, and whole organisms (e.g., 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 translating 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(longitudinal) lifecourse rodent studies in which 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.

Epidemiological Studies (SHC and ACE)

EPA/NIEHS Children's Environmental Health and Disease Prevention Research Centers (CEHC)

Since 1998, the EPA/NIEHS jointly funded Children's Environmental Health and Disease Prevention Research Centers (CEHCs, or 'Children's Centers') Program has been generating exposure and biomarker data in pregnant women and in children, along with mechanistic data in experimental models, to show relationships between exposure to chemical contaminants and various 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	EDCs (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 (PM, NO_2), allergens, urban diets	Asthma	Dietary contributions to asthma, based on antioxidant 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 house dust (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
University of California at 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

Table 3. (continued) 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)
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 includes several epidemiologicsl projects directly relevant to CEH. 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 account for this complexity. 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 years) who lived close to major roadways in Detroit, MI. Another place-based study, *The Mechanistic Indicators of Childhood Asthma (MICA) Study* (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 to evaluate early lifestage-specific risks and to support decisions protective of all lifestages

Research Area 3 is divided into two subgroups: (1) exposure, and (2) dosimetry models. ORD's relevant research in each area is summarized below.

(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.

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/expobox. 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 page 26).

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 be estimated for individual age-gender cohorts. Exposure-relevant information specific to children included in SHEDS-HT includes age-specific behaviors (e.g., hand-to-mouth contact, use of consumer products), time spent in micro-environments, and food intakes.

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 applied more specifically to capture children's unique vulnerabilities to support risk-based decisions.

(2) Dosimetry Models

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

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], PCBs, and organochlorine pesticides). ORD is also working on developing a comprehensive quantitative structure-activity relationship-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 predict 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.

PBPK Models

Virtual Embryo Project (CSS)

ORD has developed a life-stage PBPK model that has been incorporated into the Virtual Embryo project. This model was developed to investigate computationally the relationship among 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 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 to support community actions and decisions

Research Area 4 is divided into four subgroups: (1) decision support tools, (2) problem-driven research, (3) translational research, and (4) social determinants of health. ORD's relevant research in each of these areas is summarized below.

(1) Decision Support Tools

ORD is developing decision support tools for state, tribal, and local governments and other organizations to make sound decisions about community development and healthful environments, and to avoid unintended consequences.

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/.

It 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 related to school renovation decisions in Springfield, Massachusetts.

EnviroAtlas (SHC)

EnviroAtlas includes, for selected urban areas, such indicators as the locations of schools and recreational areas, factors relevant to health outcomes (demographics, income), access to transportation routes, and indicators of ecosystem services such as tree cover (related to heat, recreation, green-space accessibility). This tool 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.

(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.

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 HUD and CDC. In partnership with HUD and CDC, ORD will collect additional multimedia measurements and questionnaire data from the index of children actively participating in the Green Housing Study and a sibling(s) to characterize personal, housing, and community factors influencing children's potential exposures to indoor contaminants at various lifestages.

Dust and Soil Ingestion (SHC)

ORD is using models to estimate different exposure parameters, such as 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).

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 show that a positive association of a stressor and childhood obesity is not always present, and correlations between the same stressors and obesity can be inconsistent. Sufficient evidence, however, suggests that interactions of multiple stressors may contribute to the childhood obesity epidemic.

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 ages 3–6 years. These elements were incorporated into a model, with the results suggesting that some childhood exposures (e.g., socioeconomic status, parent-child interaction, diet, built environment) were not only present as key factors, but also act as effect modifiers of stressors experienced during pregnancy and infancy (e.g., lead, pesticides, prenatal stress).

Community Multi-scale Air Quality Model (ACE)

EPA's Community Multi-scale Air Quality (CMAQ) Model is a powerful computational tool EPA and states use 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 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 additional examples of problem-driven technical support and research on PCBs in Schools (HHRA) and Child-Specific Exposure Scenarios examples (HHRA).

(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.

EPA/NIEHS Children's Center Program (SHC)

As discussed on page 29, the EPA/NIEHS jointly 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 for 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 Office of the President; 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 Quedamo; 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 Children's Health/Clear Corps (PEACH); Durham People's Alliance; Durham County Health Department; Lincoln Community Health Center; Duke University, 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, NC	DukeEngage Program; El Centro Hispano (local Latino community); Partnership for a Healthy Durham
Johns Hopkins University – Diette	Baltimore, MD	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, CO	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; EPA Region 8 Pediatric Environmental Health Specialty Unit (PEHSU)

Table 4. (continued) 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
University of California at Berkeley – Buffler, Metayer	Berkeley, CA	Network of eight clinical institutions in northern and central California participating in the Northern California Childhood Leukemia Study (NC-CLS); 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, CA	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 Association of Central California
University of California at Berkeley/ Stanford University – Hammond, Balmes, Shaw	Berkeley, Palo Alto, Bakersfield and San Joaquin Valley, CA	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, CA	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 at San Francisco – Woodruff	San Francisco, CA	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, IL, and New Bedford, MA	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, MI, and Mexico City, Mexico	Early Life Exposures in Mexico to Environmental Toxicants (ELEMENT); National Institute of Public Health, Mexico City, Mexico; Detroit Hispanic Development Corporation

Table 4. (continued) 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
University of Southern California – McConnell	Los Angeles, CA	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, WA	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) 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.

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.

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

Integrated Approaches to Sustain the Built and Natural Environment and the Communities They Support (SHC)

In this study, researchers are using GIS tools and multilayered 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 several other federal agencies and independent organizations to further CEH research. One example where EPA reached out to leverage expertise and capacity with partner federal agencies is on the topic of endocrine disruption. Evidence is mounting that some chemicals disrupt the endocrine system. The endocrine system regulates biological processes throughout the body and is sensitive to small changes in hormone concentrations. Some of this research has identified dose-response relationships that have nonmonotonic curves. Nonmonotonic dose-response curves are of concern because they do not follow the usual assumption made in toxicology: as dose decreases, response decreases. In addition, more complex interactions and outcomes resulting from exposure to complex mixtures or chemicals, or both, with multiple modes of action are not addressed well with existing models and assessment tools. Prenatal and early life exposures are of particular concern, and additional complexity is associated with the fact that these exposures may lead to health impacts across the lifespan. As a result, there is a need to shift thinking about how potential for adverse impacts and ultimately riskis evaluated. To evaluate the evidence in this arena comprehensively, EPA has formed a working group with experts from several EPA offices, FDA, NIEHS, and National Institute of Child Health and Human Development (NICHD) to explore this issue and to write a state-of-the-science paper.

Table 5 lists some of ORD's partner organizations and the CEH programs that are currently underway through these partnerships.

Table 5. ORD Partnerships and Activities

Partners	Research	Description
NTP/NIEHS	Children's Environmental Health and Disease Research Centers (http://epa.gov/ncerchildrenscenters/)	Research to increase understanding of 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 in the effects on 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 United States 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 collecting additional multimedia measurements and questionnaire data from the index children in the Green Housing Study and a sibling(s) 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/health-disparities.html)	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.
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.
CAAT DNT workshop 2014	Center for Alternatives to Animal Testing (CAAT) workshop on developmental neurotoxicity testing (http://caat.jhsph.edu/programs/workshops/DNT4/)	Presented information on cutting-edge technologies used to develop alternative tests for developmental neurotoxicity testing.

Research Gaps and Priority Research Needs

In the context of Agency mandates for CEH information (Background, page 4), the decision context as presented in the Translation Framework (Figure 2), and a set of high-visibility child health outcomes (Appendix D) identified by ORD, and Program Partner members of the CEH roadmap working group, a gap analysis was conducted to identify and prioritize needs for ORD research in CEH.

The ORD portfolio of active and planned CEH research as described in the evolving NRP Strategic Research Action Plans was reviewed. A strong set of tools for addressing current regulatory mandates was identified. Gaps remain around specific needs for science and information to incorporate consideration of early lifestage sensitivity, susceptibility, and vulnerability into these tools. Building confidence that EPA decisions are fully considering lifestage-specific issues will require incorporating extant data and developing targeted information to reduce uncertainties in model predictions and risk-based assessments.

Emerging scientific understanding of CEH and the potential role of modifiable exogenous environmental factors was reviewed for a set of high-visibility health outcomes. Prevalence and trends were summarized, as was evidence pointing to associations between early life exposure to environmental contaminants and the following children's health outcomes: adverse birth outcomes, asthma, neurodevelopmental disorders, metabolic syndrome, and childhood cancer. In addition, maturing scientific understanding of shared mechanisms for these complex environmental diseases (e.g., endocrine disruption) was considered. Building evidence in support of the Developmental Origins of Health and Disease hypothesis, including implications of epigenetic effects (Saffery and Novakovic, 2014), was also identified as an important scientific driver for research in CEH as part of this gap analysis.

The scope of CEH research activities in other federal agencies was evaluated. NIH (including NIEHS and National Institute of Child Health and Human Development, NICHD) are investing significantly in research to increase the understanding of fundamental, shared mechanisms of complex disease, genetic susceptibility across the lifespan to environmental diseases, and a broad range of other modifying factors, including psychosocial stressors (National Institute of Environmental Health Sciences, 2012). Based on this gap analysis, rather than duplicate these investments, ORD clearly will need to leverage these efforts and identify pivotal leadership roles for EPA.

Obvious gaps remain in actionable science and information required to understand, prevent, and mitigate impacts to children from **real-world** exposures to air, water, and chemicals. ORD leadership is required to bring together the science generated outside the Agency with targeted information EPA generates to build predictive capacity to evaluate alternative actions and to anticipate outcomes. 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.

Research Area 1: Knowledge infrastructure to address the problem that information and data are distributed and difficult to access

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 access and mine relevant information effectively 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:

- 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 interrelationships 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 access these data efficiently (e.g., dashboards) as inputs to design workflows and analysis tools.

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 systematically. 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 is 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, and the publication reference, without having to search the literature manually. 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 the Agency's 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 necessary for adequately protecting 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 levels to the individual and population levels) to predict the potential for adverse impacts associated with development, chemical use, and environmental contamination. To provide this leadership effectively requires strategic implementation of ORD's STAR extramural grants program and leveraging of other cross-Agency partnerships. Priority gaps in this area are broad and include the need for:

- Improved understanding of critical environmental factors and interactions that affect children's growth and development at EPA-defined early lifestages (U.S. Environmental Protection Agency, 2005) 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, ADHD, autism); and respiratory dysfunction such as asthma.
- Models of complex systems 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 addressing the key gaps in 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 about the links between molecular initiating events, intermediate key events along a toxicity pathway, and apical adverse outcomes traditionally considered relevant to risk assessment and regulatory decision making. When rigorously developed and evaluated, 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 or chemicals, or both, 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 and with disease endpoints of concern, mechanistic toxicological information and epidemiological 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 can be developed. These same modeling approaches can be applied to capture the complexity of children's interactions with the environment in their home, school, and community and 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—the alteration of birth outcomes 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 working 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 to both future disease status and future resilience.

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

As guidance for incorporating the consideration of lifestage-specific risks into Agency decisions has been 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 for effectively addressing a growing range of considerations and factors for which data may be limited. Priority needs exist 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 to evaluate the potential for developmental toxicity.
- Science-based tools to support the consideration of critical child-specific vulnerabilities to inform environmental and health policy decisions that promote and protect children's health.

For example, only limited information on exposures and exposure factors for infants and children less than 6 years of age is currently available. In addition, even when information on exposure levels from biomonitoring or other sources is available, knowledge of the predominant pathways of exposure—air, food, water, or other sources—is minimal. Such information remains a critical gap in EPA's Exposure Factors Handbook (U.S. Environmental Protection Agency, 2011), a resource 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. Important gaps also occur in methods and approaches for characterizing potential exposures associated with the home, school, and community environments required to assess risks associated with real-world exposures to mixtures and 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 potential applications for developmental toxicity and human-relevance across the full range of critical endpoints. Assays that can be implemented in rapid, cost-effective schemes are particularly key to facilitate development of data for thousands of chemicals in commerce that have not been evaluated for potential impacts on developmental pathways.

Research Area 4: Translational research and tools 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). NIH is expected to invest significantly in supporting public health in vulnerable populations and groups, including children. EPA leadership will be required to enable research meeting the targeted needs for translational tools that incorporate lifestage-specific considerations so that local decision makers are provided with the knowledge they need to inform a balanced approach to community cleanup and development. Priority needs exist for:

- Translational tools that community decision makers can use to access 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 influence children's health and well-being in communities and settings (e.g., schools, daycare facilities, homes) where they live, learn, and play. To optimize child- or lifestage-specific settings, community decision makers need access to information on the health impacts of multiple factors in the built and natural environments that contribute positively or negatively to children's health, and the relative importance of these factors. 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 to reduce (eliminate, prevent) risk and actively promote healthy development and well-being.

Informing 2016–2019 ORD Research Planning

EPA ORD National Research Programs (Air, Climate, and Energy; Chemical Safety for Sustainability; Homeland Security; Human Health Risk Assessment; Safe and Sustainable Water Resources; and Sustainable and Healthy Communities at http://www2.epa.gov/epa-research/strategic-research-action-plans) are aligned on the core principle of sustainability and designed to provide the solutions the Agency and the Nation need to meet today's complex environmental and human health challenges. Inevitably, important scientific 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 identify the science questions clearly and articulate the associated ongoing research efforts 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: These may change as a result of ORD's planning and budgeting each year. ORD will provide details regarding research products associated with implementation of this Roadmap, however, on the EPA website. In this section, EPA elaborates on the objectives of integrated ORD research in CEH and on the approach for enabling this research throughout the National Research Programs.

> **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 well-being 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 (Figure 3). 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.

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 6) (DeFur et al., 2007).

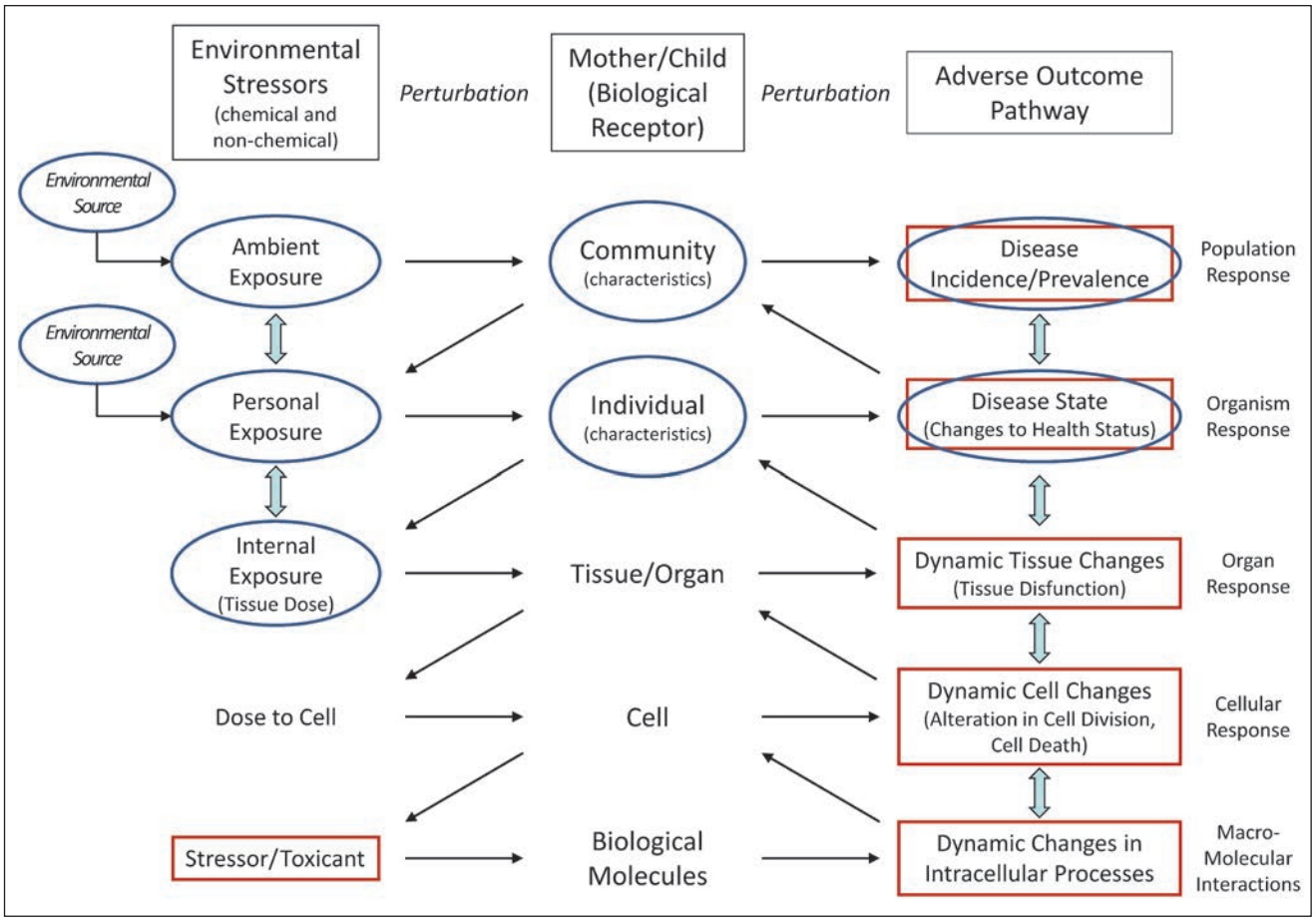

Figure 3. Concept for integrated CEH research in ORD.

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 to health outcomes. This understanding will be translated and tools provided to support Agency decisions that promote and protect children's health and well-being.

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.

Table 6. Examples of specific vulnerability factors (Defur et al., 2007)

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

Measurement includes obtaining multidimensional 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 that 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 for adequately representing the human-environment system at important levels of organization, whether the consequences result in normal development and well-being 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 mechanisms of exposure and toxicity, models that can predict whether a chemical will elicit an adverse outcome, simulations that can incorporate these models, validation models for checks and balances, acceptance and integration into current risk assessment paradigms, and integration of 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 well-being.

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 influence aspects of maternal or filial development, leading to an array of adverse birth outcomes (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 and 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 and 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 systems biology framework components (measurement, mining, modeling, manipulation). The vascular VTMs provide a good example for how the systems biology approach can be applied to a particular developmental system.

Measurement: Data of chemical-biology perturbations were taken from the EPA ToxCast program and from text mining of the public literature. Several 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 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 is 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 examine co-annotations in the literature, which coarsely indicate biological relationships. 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 process 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 along with 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 and Kleinstreuer, 2011). The proposed AOP for embryonic vascular disruption is shown in Figure 4.

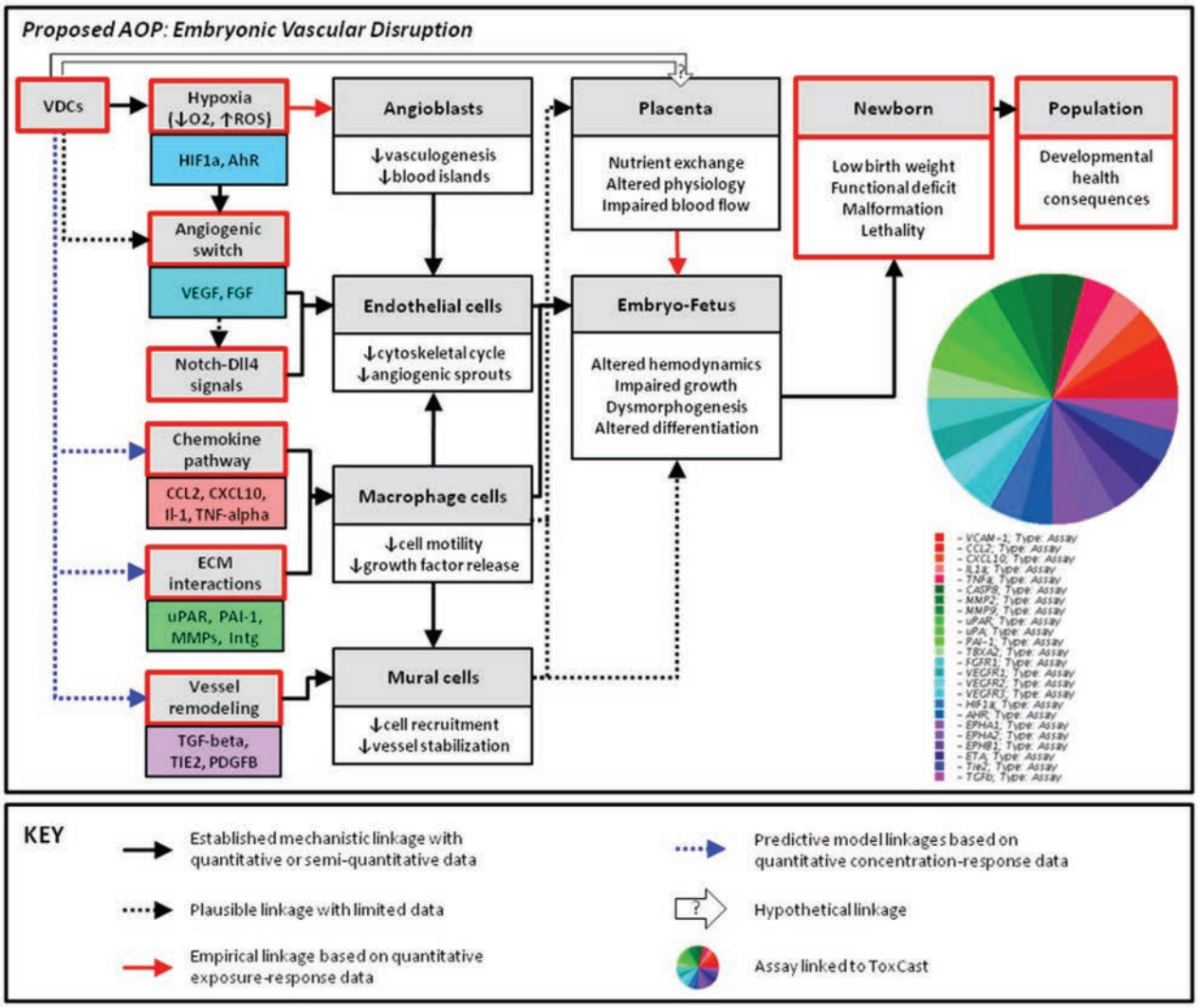

Figure 4. Proposed AOP for embryonic vascular disruption.

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, 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 enable 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.

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 et al., 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 United States 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 and 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; George et al., 2015).

Measurement: A nested case-control cohort of 205 non-asthmatic and asthmatic children (9–12 years of age), from Detroit, MI, 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, respiratory). In addition, blood gene expression and candidate SNP analyses were conducted. Selected measurements are highlighted in Figure 5.

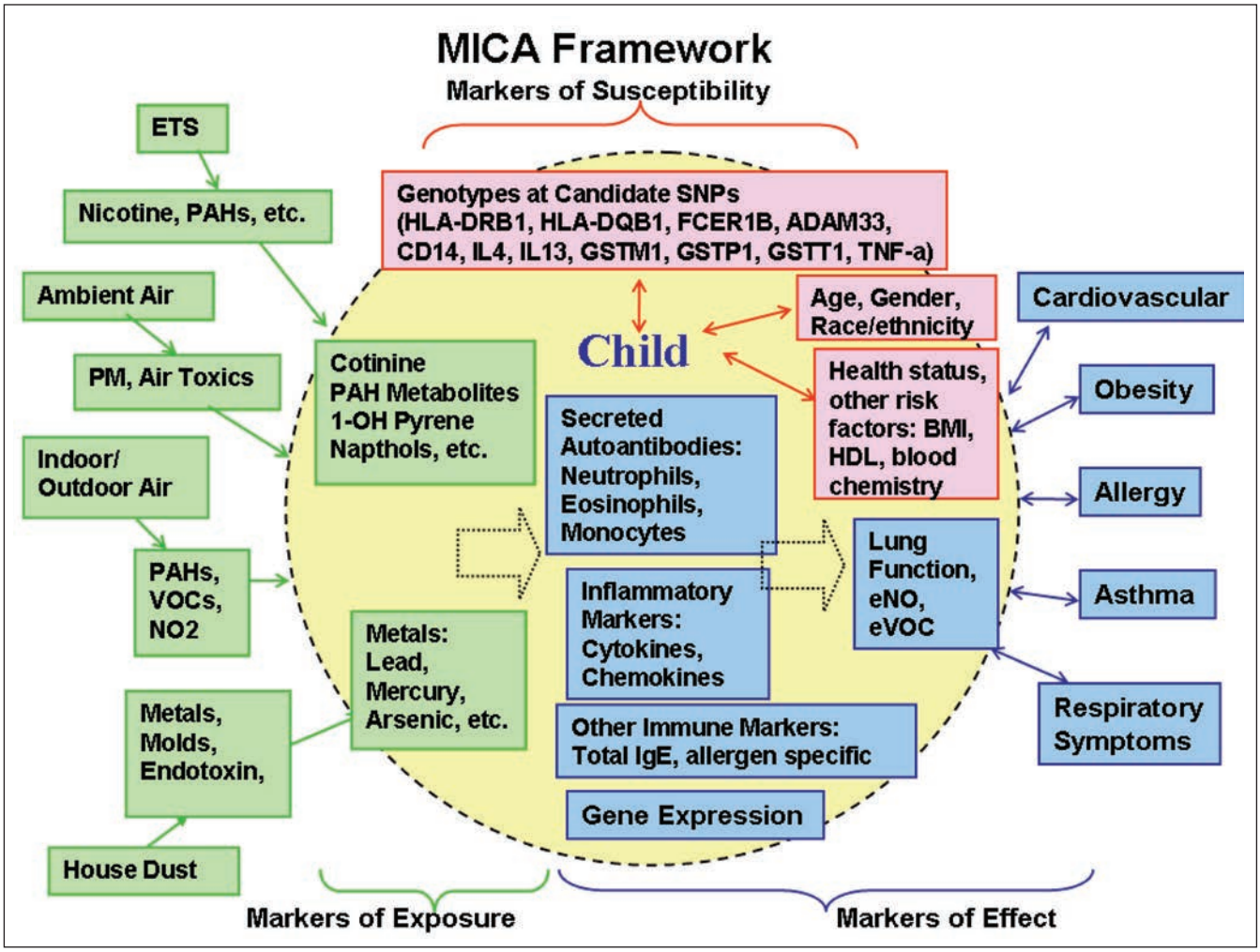

Figure 5. The overall MICA Study design includes exposure, biomarkers of exposure, clinical indicators, genomic data (blood gene expression and SNP), and health status indicators.

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, the Modk-prototypes algorithm). To exploit strengths and limitations of the MICA data fully, a novel multistep, decision tree-based method was developed to define endotypes. This new method gave the best segregation of asthmatics and non-asthmatics and 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, although 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 examines 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 evaluating the many environmental factors influencing each mechanistically distinct endotype. Non-eosin-

ophilic 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 asthma incidence due to the rise in obesity will expand the proportion of these endotypes.

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 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 the ORD Virtual Tissues Modeling project uses 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. Using health behavior research for application of complex systems modeling approaches has been suggested for addressing 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 for computationally testing and evaluating 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 identified efficiently 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.

Summary

EPA conducts CEH research 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; and (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 intends 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 well-being. 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 A: ORD's Current Research Activities

This appendix presents more information on the research activities presented in the *Cross-Cutting ORD Research* section of the document and information on additional research activities. The National Research Program (NRP) having key responsibility for each activity 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
- SSWR = Safe and Sustainable Water Resources Research
- SHC = Sustainable and Healthy Communities Research

See Table A1 for a summary of these research activities.

Table A1. ORD's current research activities

Research Area 1. Knowledge Infrastructure to Provide Early Lifestage-Specific Data and Information		
Title	**Research Program**	**Description**
Exposure Information		
Exposure Factors Handbook	HHRA	Databases and handbook with information on children's exposures and exposure factors; human behavior; amounts of chemicals currently found in food, drinking water, air, dust, indoor surfaces, and urine; and chemical usage.
Consolidated Human Activity Database	CSS	
ExpoCast Database	CSS	
Chemical and Product Categories Database	CSS	
Early Lifestage Pharmacokinetic Parameters		
Enzyme Ontogeny Database	CSS	Database that can be used as a screening tool to explore metabolism-based variability, based on enzyme differences, during early lifestages.
Developmentally Relevant Hazard Data		
ToxCast Database	CSS	Data from *in vivo* animal studies, screening assays, and other study types are included in these databases.
Toxicity Reference Database	CSS	
Adverse Outcome Pathway (AOP) Wiki	CSS	A wiki-based tool that provides an interface for collaborative sharing of established AOPS and for building new AOPs.

Table A1. (continued) ORD's current research activities

Research Area 2. Systems Understanding of the Relationship Between Environmental Exposures and Health Outcomes Across Development		
Title	**Research Program**	**Description**
Systems Biology to Predict Developmentally Relevant Outcomes		
Bioinformatics-Based Models	CSS	System models for tissues and multi-organ pathways specific to embryo-fetal and neonatal development. Examples include: first-generation ToxCast predictive models for reproductive and developmental toxicity, the Vascular AOP model, and the Virtual Embryo model.
AOP Models	CSS	
Simulation Models	CSS	
Systems Understanding of Complex Stressors		
Laboratory Based Studies	CSS, SHC, and SSWR	Includes *in vitro* models to evaluate the effects of chemical exposure in developmentally relevant systems and *in vivo* models with rodents studying issues such as alterations in endocrine function during fetal and early childhood and its effect during and after puberty.
Epidemiological Studies		
EPA/NIEHS Children's Environmental Health and Disease Research Centers (CEHC Program)	SHC and ACE	Jointly funded by EPA and NIEHS through the STAR grant program, the CEHC program explores ways to reduce children's health risks from environmental contaminants. Health outcomes under investigation include adverse birth outcomes, asthma, autism, obesity, altered immune function, and cancer.
Clean Air Research Centers	ACE	Studies investigating the relationship between air pollutants and children's health.
Place-Based Studies	ACE, SHC, and SSWR	Includes studies investigating housing quality, traffic-related air pollutants, indoor air pollutants, and water-related exposures and their effect on children's health outcomes.
Co-Exposure to Multiple Stressors	SHC and ACE	New methods for modeling and assessing cumulative exposure and risk.
MICA Study	CSS and SHC	Study incorporates exposure metrics, internal dose measures, and clinical indicators to investigate gene-environment interactions in asthma and cardiovascular disease.

Table A1. (continued) ORD's current research activities

Research Area 3. Methods and Models Fit for Purpose to Evaluate Early and Lifestage-Specific Risks and to Support Decisions Protective of all Susceptible and Vulnerable Lifestages		
Title	**Research Program**	**Description**
Exposure		
EPA ExpoBox	HHRA	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 for prioritizing chemical mixtures.
SHEDS-HT Model	CSS	
ExpoCast	CSS	
Lifestage Categories for Monitoring and Assessing Exposures to Children	SHC	
Biogeographical Approach for Prioritizing Chemical Mixtures	CSS	
Dosimetry Models		
Empirical Models		
Persistent Bioaccumulative Toxicants	CSS	Models that assess exposure and predict dose based on measurements of biomarkers and kinetic parameters.
In vitro to *in vivo* Extrapolation	CSS	
Community Multi-scale Air Quality Model	CSS	
Pesticide Biomarker Measurements in Children	CSS	
PBPK Models		
Virtual Embryo Project	CSS	PBPK models that investigate the relationships between exposure, tissue dosimetry, and kinetics of environmental chemicals.
Ethanol	CSS	

Research Area 4. Translational Research and Tools Fit for Purpose to Support Community Actions and Decisions		
Title	**Research Program**	**Description**
Decision Support Tools		
Community-Focused Exposure and Risk Screening Tool	SHC	Tools that enhance access to information for environmental health decision making.
EnviroAtlas	SHC	

Table A1. (continued) ORD's current research activities

Research Area 4. (continued) Translational Research and Tools Fit for Purpose to Support Community Actions and Decisions		
Title	**Research Program**	**Description**
Problem-Driven Research		
EPA Pilot Study Add-On to the Third Study Site of the Green Housing Study	SHC	Studies that increase the understanding of the linkages between human health and environmental exposures that will be useful for community decision making.
Dust and Soil Ingestion	CSS and SHC	
Chemical and Non-Chemical Stressors and Childhood Obesity	SHC	
Chemical and Non-Chemical Stressors and Neurocognitive Health	SHC	
Community Multi-Scale Air Quality Model	ACE	
PCBs in School	HHRA	
Child-Specific Scenarios Examples	HHRA	
Translational Research		
EPA/NIEHS Children's Environmental Health and Disease Research Centers (CEHC Program)	SHC	Includes a Community Outreach and Translation Core that uses a variety of approaches to translate research findings and intervention strategies for the community.
Social Determinants of Health		
STAR Centers of Excellence on Environment and Health Disparities	SHC	Studies investigating the complex interactions of biological, social, and environmental determinants of population health.
Environmental and Community Factors Influence Effectiveness of Medical Treatments for Asthma	SHC	
Integrated Approaches to Sustain the Built and Natural Environment and the Communities They Support: Children's Health Example	SHC	
Climate Change	ACE	Research on impacts of increased ground-level ozone and weather events influencing allergic, chronic, waterborne, and infectious disease risks.

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 area is summarized below:

(1) Exposure Information

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

Exposure Factors Handbook (HHRA)

Data about children's exposures and exposure factors, such as lifestage-specific modeled estimates of soil and dust ingestion are 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. 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 such as 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.

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. EPA, 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. These data are used in human exposure and health studies and in 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).

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 childcare 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 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. 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.

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. 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.

(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.

Enzyme Ontogeny Database (CSS)

Chemicals are typically metabolized in the body sequentially by activating and detoxifying enzymes, the expression for which 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.

(3) Developmentally Relevant Hazard Data

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

ToxCast Database (CSS)

ToxCastDB provides results of high-throughput *in vitro* assays. Biologal data covered in the large set of assays includes 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 setup is also provided in the database. ToxCastDB is a searchable database through the ACToR system (U.S. Environmental Protection Agency, 2014h); available at: http://actor.epa.gov/actor/faces/ToxCastDB/Home.jsp.

Toxicity Reference Database (CSS)

Toxicity Reference Database (ToxRefDB) contains data from thousands of *in vivo* animal studies and is a searchable database through the ACToR system (U.S. Environmental Protection Agency, 2014i); 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 is included in the database. The developmental toxicity information includes results from studies on more than 380 chemicals with 18 endpoints for 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.

Adverse Outcome Pathway Wiki (CSS)

An 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. Because toxicity is an expression of lesion propagation to higher levels of biological organization, however, 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. Multicellular 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 multidimensional data with vast biological knowledge.

AOP Wiki is a wiki-based tool that provides an interface for collaborative sharing of established AOPs and for building new AOPs (Anonymous, 2014); available at: http://aopkb.org/aopwiki/index.php/Main_Page. AOP Wiki uses templates to make including the information needed for proper evaluation of an AOP easier for users.

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

Research Area 2 is divided into two subgroups: (1) systems biology to predict developmentally relevant outcomes and (2) systems understanding of complex stressors. ORD's relevant research in each of these areas is summarized below:

(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 biological mechanisms of chemical stressors that contribute to childhood health outcomes.

Bioinformatics-Based Models (CSS)

As discussed on page 66, 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 are 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 chemical toxicity not 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 (M. T. Martin et al., 2011) and developmental toxicity (Sipes et al., 2011). These models anchored *in vitro* data to *in vivo* endpoints for a set of approximately 300 data-rich chemicals. 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 approximately 700 compounds in Phase II, for which animal toxicology is less well characterized, ORD is developing plausible model structures that address the possibility of additional relevant interactions and components beyond those represented in the first-generation predictive models.

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 zebrafish 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 or chemicals, or both, with multiple modes of actions.

Simulation Models (CSS)

Simulation models predict chemical toxicity using relevant biological 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 biological organization (molecular, cell, tissue, organ, organism) to enhance the predictive power in evaluating potential chemical toxicity. The virtual model uses AOP models, such as the model for vasculogenesis (see section above) and endocrine system models, as modules. 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) Systems Understanding of Complex Stressors

Epidemiological, 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.

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 (human multipotent neuroprogenitors, rodent embryonic stem cells, specific pathway-responsive modified hepatocytes), organ (human and rodent palatal shelves), whole rodent embryo cultures, and whole organisms (e.g., 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 translating 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 epidemiologicsl studies, such as those being conducted by the Children's Centers (see next section below), 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.

Epidemiological Studies (SHC and ACE)

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

Since 1998, the EPA NIEHS co-funded Children's Environmental Health and Disease Prevention Research Centers (CEHCs, or 'Children's Centers') Program, has been generating exposure and biomarker data in pregnant women and in children to show relationships between exposure and various 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. 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., where EPA Administrator Gina McCarthy delivered comments.

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, which include 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 A2). Increasingly, the Centers 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 possible the examination of 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 help EPA meet its 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).

Table A2. 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	EDCs (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

Table A2. (continued) 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)
Johns Hopkins University – Diette	Airborne pollutants (PM, NO_2), 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, Berkeley - Buffler, Metayer	Pesticides, tobacco-related contaminants, chemicals in house dust (PCBs, PBDEs)	Childhood leukemia	Epigenetic and genetic influences
University of California, Berkeley – Eskenazi	Pesticides (DDT, manganese), flame retardants	Neurodevelopment; growth and timing of puberty; obesity	Epigenetic reprogramming; altered endocrine status
University of California, 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, 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 several epidemiological 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, 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 account for this complexity. 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 socio-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 years) who lived close to major roadways in Detroit, Michigan (ACE). An integrated measurement and modeling approach was used to quantify 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 et al., 2013).

A STAR Grant project, E*ffects 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 (ages 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 ages 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 University, the Texas Department of State Health Services, and University of North Carolina-Charlotte are collaborating on a project, *Air Pollution-Exposure-Health Effect Indicators: Mining Massive Geographically-Referenced Environmental Health Data to Identify Risk Factors for Birth Defects* (SHC). Using assessment methods for air pollution exposure, 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, influences children's health and performance, potentially in both positive and negative ways, is 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, 2013d); available at: http://epa.gov/ncer/rfa/2013/2013_star_healthy_schools.html. This research will investigate the impact of indoor pollutants and outdoor pollutants drawn indoors in schools on children's health and ability to learn.

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 birth defect clusters and is examining the relationship between these clusters 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) is a multifactor analysis of cumulative lead exposure that increased the knowledge base of lead exposure in children.

A STAR Grant project, E*ffects-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 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 (ages 9–12) 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 among environmental factors, physiological biomarkers, genetic susceptibility, and health outcomes (Gallagher et al., 2011).

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 is divided into the following two subgroups: (1) exposure, and (2) dosimetry models. ORD's relevant research in each area is summarized below:

(1) Exposure

Exposure factors and exposure data (Exposure Information, page 65) need to be easily accessible to risk assessors 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.

EPA Expo-Box (HHRA)

EPA-Expo-Box is a Web-based compendium of over 800 exposure assessment tools that provides links to exposure assessment databases, models, and references (U.S. EPA, 2013c); available at: http://www.epa.gov/expobox. 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 (page 65).

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 be estimated for individual age-gender cohorts. Exposure-relevant information specific to children included in SHEDS-HT includes age-specific behaviors (e.g., hand-to-mouth contact, use of consumer products), times spent in microenvironments, and food intakes.

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/. ExpoCast evaluated 1763 chemicals for estimating exposure due to industrial releases or 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 applied more specifically to capture children's unique vulnerabilities to support risk-based decisions.

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,

Moya, Cohen Hubal, Zartarian, & Xue, 2007). 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 influence 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 "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.

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 et al., 2013).

Biogeographical Approach for Prioritizing Chemical Mixtures (CSS)

In a study of the co-occurrence pattern of pesticides in childcare centers (Tornero-Velez, Egeghy, & Cohen Hubal, 2012), ORD used biogeographic methods to investigate co-occurrence patterns in chemicals. The results showed that the co-occurrence of pesticides in the childcare centers was not random but 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 andfor calculating co-occurrence probabilities of mixtures of chemicals.

(2) Dosimetry Models

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

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, 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. 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], PCBs, and organochlorine pesticides). The expectation is that these models will facilitate the use of available biomonitoring serum data (e.g., NHANES) to characterize infant exposures more fully. ORD is also working on developing a comprehensive quantitative structure-activity relationship-based model for predicting milk:serum partitioning ratios for classes of chemicals for which serum and milk data are not available to construct regression models. This QSAR model, which will predict the potential of an environmental chemical to partition into breast milk, 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 subpopulation-specific oral equivalent dose values to aid in prioritizing chemicals and identifying subpopulations with greater susceptibility to potential pathway perturbations (Wetmore et al., 2014).

Community Multi-scale Air Quality Model (CMAQ)

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 (particulate matter [PM] and ozone) and health outcomes (U.S. Environmental Protection Agency, 2014c), 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 et al., 2011). The temporal variability of the metabolites detected, based on time of pesticide application, and 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.

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 investigate computationally the relationship among 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 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. Three models accurately predicted the kinetics of ethanol, including the absorption, peak concentration, and clearance across multiple datasets. This work provides comprehensive lifestage 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 United States. (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 is divided into four subgroups: (1) decision-support tools, (2) problem-driven research, (3) translational research, and (4) social determinants of health. ORD's relevant research in each area is summarized below:

(1) Decision-Support Tools

ORD is developing decision-support tools for state, tribal and local governments to make sound decisions about community development and healthful environments and to avoid unintended consequences.

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/ The tool's purpose is to enhance access to information for environmental health decision making. Developed in collaboration with several pilot communities, this Web-based tool provides a repository of information for more than 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 and city, school, and community groups. The purpose of this HIA was to provide and help process information in an effort to assist the City of Springfield in narrowing the options for renovation and improvement at the Gerena School. The focus was options that would best address environmental problems, reduce potential negative health impacts such as asthma exacerbations, and enhance well-being of the school community. The school is located directly under a highway overpass and is adjacent to roadways and a railway, so the project is considering transportation-related indoor air exposures and exposures from flooding, moisture, mold, and other indoor environmental issues in the school.

In the process, EPA is investigating how its science could be used in the HIA process and how to incorporate 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.

EnviroAtlas (SHC)

EnviroAtlas includes, for selected urban areas, such indicators as the locations of schools and recreational areas, factors relevant to health outcomes (demographics, income), access to transportation routes, and indicators of ecosystem services such as tree cover (related to heat, recreation, green-space accessibility). This tool includes an Eco-Health Relationship Browser (U.S. Environmental Protection Agency, 2013b), available at: http://www.epa.gov/research/healthscience/browser/introduction.html (launched in 2012). This user-friendly Web-based browser illustrates linkages between human health and ecosystem services—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 address children's health more completely is being considered.

(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.

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 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. The green-renovated and comparison (no renovation) homes will be from the same housing development or neighborhood to ensure homogeneity in housing type and other socio-economic factors. Environmental measurements (pesticides, VOCs, particulate matter [i.e., PM2.5 and 1.0], indoor allergens, and fungi) over a one-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 a comparison of homes before and after renovations and a comparison of green-renovated and control homes to detect differences in exposure levels and asthma outcomes. Residents will participate for one month prior to renovation, during the time required for renovation of their home, and for 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 multi-media measurements and questionnaire data from the index children actively participating in the Green Housing Study and a sibling(s) 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.

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, because the village in which the homes were located was considered 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 to ≤ 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, Smith, & Van Der Wiele, 2013).

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

Childhood obesity has tripled in the past three decades and now affects 17 percent of children in the United States. In 2010, the percentage of obese U.S. children was nearly 18 percent for children ages 6–11 and 12–19 years. Recent evidence in the literature suggests that exposure to selected environmental chemicals may influence obesity. Socio-economic status, ethnicity, and the built environment also may influence obesity. Recent studies also have shown that poor-quality food outlets close to neighborhoods or schools increased the likelihood of poor-quality food purchases. Although 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 show that a positive association of a stressor and childhood obesity is not always present, and correlations between the same stressors and obesity can be inconsistent. Sufficient evidence, however, suggests the interactions of multiple stressors may be the cause of the childhood obesity epidemic.

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

Early childhood (ages 0–6 years) 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 affect learning. Many studies attempt to identify associations between individual exposure factors and neurocognitive development. From pregnancy to a child's first day of school, however, numerous stressors

(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) using the search strings: neurodevelopment or cognition and children. The quality of the study and its applicability to the general population was assessed 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 ages 3–6 years. These factors were grouped 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 the factors. These elements were incorporated into the model, with the results suggesting that some childhood exposures (e.g., SES, parent-child interaction, diet, built environment) were not only present as key factors, but also act as effect modifiers of stressors experienced during pregnancy and infancy (e.g., lead, pesticides, prenatal stress).

Community Multi-scale Air Quality Model (ACE)

EPA's Community Multi-scale Air Quality (CMAQ) Model is a powerful computational tool EPA and states use 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 or ozone) and health outcomes (U.S. Environmental Protection Agency, 2014c); available at: http://www.epa.gov/AMD/Research/RIA/cmaq.html.

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 applied between 1950 and 1979 can contain as much as 30 percent PCBs and can contaminate adjacent material such as masonry or wood. Fluorescent light fixtures that contain the 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.

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 page 65). Its purpose 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 *Guidance on Selecting Age Groups for Monitoring and Assessing Childhood Exposures to Environmental Contaminants* (U.S. Environmental Protection Agency, 2005) (last section, page 74); available at http://www.epa.gov/raf/publications/pdfs/AGEGROUPS.PDF.

(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 address local environmental health issues. Many of the studies discussed in the section on epidemiological studies (page 69) include translational components, involving environmental health communication, community outreach, and collaboration with local community groups.

CEHC Program (SHC)

As discussed previously (see page 69), the EPA/NIEHS jointly funded CEHC Program is generating exposure and biomarker data in pregnant women and in 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. 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 in each center. These cores use a variety of innovative approaches to translate research findings and intervention strategies to the community. As summarized in Table A3, 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 A3. 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, RI	Silent Spring Institute; Environmental Justice League of Rhode Island
Columbia University – Perera	New York City (Northern Manhattan and South Bronx), Poland, China	Bronx Borough Office of the President; 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 Quedamo; WE ACT for Environmental Justice
Dartmouth College – Karagas	Hanover, NH	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, NC and Ann Arbor, MI	Durham Congregations, Associations, and Neighborhoods (CAN); Triangle Residential Options for Substance Abusers (TROSA); Durham Affordable Housing Coalition; Partnership Effort for the Advancement of Children's Health/Clear Corps (PEACH); Durham People's Alliance; Durham County Health Department; Lincoln Community Health Center; Duke University, 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, NC	DukeEngage Program; El Centro Hispano (local Latino community); Partnership for a Healthy Durham
Johns Hopkins University – Diette	Baltimore, MD	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, CO	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; EPA Region 8 Pediatric Environmental Health Specialty Unit (PEHSU)
University of California at Berkeley – Buffler, Metayer	Berkeley, CA	Network of eight 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)

Table A3. (continued) 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
University of California at Berkeley – Eskenazi	Berkeley and Salinas, CA	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 Association of Central California
University of California at Berkeley/ Stanford University – Hammond, Balmes, Shaw	Berkeley, Palo Alto, Bakersfield and San Joaquin Valley, CA	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, CA	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, CA	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, IL and New Bedford, MA	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, MI 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, CA	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, WA	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) 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.

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, the natural and built environment and the 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.

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

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. EPA recently awarded grants to six groups and institutions to study the health effects of climate change on tribes. These grants will fund research on improving air quality and reducing environmental factors that trigger asthma; threats to food sustainability; coastal climate impacts to traditional foods, cultural sites, and tribal community health and well-being; and food security and tribal health.
(http://indiancountrytodaymedianetwork.com/2014/07/23/epa-awards-5-million-research-climate-change-and-tribal-health-156029).

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Appendix B. 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 manuscript titles from EPA Science Inventory (http://cfpub.epa.gov/si/index.cfm), where more information on each may be found.

Search Boundaries Peer Reviewed Journals; January 1, 2008–March 25, 2015

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 341

Year	Publication
2015	A Disadvantaged Advantage in Walkability: Findings from Socioeconomic and Geographic Analysis of National Built Environment Data in the United States
2015	Air toxics and epigenetic effects: ozone altered microRNAs in the sputum of human subjects
2015	Cardiomyopathy confers susceptibility to particulate matter-induced oxidative stress, vagal dominance, arrhythmia, and pulmonary inflammation in heart failure-prone rats
2015	Ferrates: Greener Oxidants with Multimodal Action in Water Treatment Technologies
2015	Short-term variability and predictors of urinary pentachlorophenol levels in Ohio preschool children
2015	The Effects of Perfluorinated Chemicals on Adipocyte Differentiation In Vitro
2014	A Short-term In vivo Screen using Fetal Testosterone Production, a Key Event in the Phthalate Adverse Outcome Pathway, to Predict Disruption of Sexual Differentiation
2014	Applicability of the Environmental Relative Moldiness Index for Quantification of Residential Mold Contamination in an Air Pollution Health Effects Study
2014	Assessing the bioavailability and risk from metal-contaminated soils and dusts
2014	Cellular Interactions and Biological Responses to Titanium Dioxide Nanoparticles in HepG2 and BEAS-2B Cells: Role of Cell Culture Media
2014	Environmental Relative Moldiness Index and Associations with Home Characteristics and Infant Wheeze
2014	Environmentally Relevant Mixing Ratios in Cumulative Assessments: A Study of the Kinetics of Pyrethroids and Their Ester Cleavage Metabolites in Blood and Brain; and the Effect of a Pyrethroid Mixture on the Motor Activity of Rats
2014	Exposures of 129 preschool children to organochlorines, organophosphates, pyrethroids, and acid herbicides at their homes and daycares in North Carolina
2014	Exposure to fine particulate matter during pregnancy and risk of preterm birth among women in New Jersey, Ohio, and Pennsylvania, 2000–2005
2014	Flame Retardant Exposures in California Early Childhood Education Environments
2014	GPS-based Microenvironment Tracker (MicroTrac) Model to Estimate Time-Location of Individuals for Air Pollution Exposure Assessments: Model Evaluation in Central North Carolina

Year	Publication
2014	High Throughput Heuristics for Prioritizing Human Exposure to Environmental Chemicals
2014	In Situ Formation of Pyromorphite Is Not Required for the Reduction of in Vivo Pb Relative Bioavailability in Contaminated Soils
2014	Immediate and long-term consequences of vascular toxicity during zebrafish development
2014	Influence of Urbanicity and County Characteristics on the Association between Ozone and Asthma Emergency Department Visits in North Carolina
2014	Modeling Spatial and Temporal Variability of Residential Air Exchange Rates for the Near-Road Exposures and Effects of Urban Air Pollutants Study (NEXUS)
2014	Neurophysiological Assessment of Auditory, Peripheral Nerve, Somatosensory, and Visual System Functions after Developmental Exposure to Ethanol Vapors
2014	Perchlorate exposure is associated with oxidative stress and indicators of serum iron homeostasis among NHANES 2005–2008 subjects
2014	Perfluorinated Compounds: Emerging POPs with Potential Immunotoxicity
2014	Phenotypic and genomic responses to titanium dioxide and cerium oxide nanoparticles in Arabidopsis germinants
2014	Relationships of Chemical Concentrations in Maternal and Cord Blood: A Review of Available Data
2014	Selective Cognitive Deficits in Adult Rats after Prenatal Exposure to Inhaled Ethanol
2014	Simvastatin and Dipentyl Phthalate Lower Ex vivo Testicular Testosterone Production and Exhibit Additive Effects on Testicular Testosterone and Gene Expression Via Distinct Mechanistic Pathways in the Fetal Rat
2014	The Citizen Science Toolbox: A One-Stop Resource for Air Sensor Technology
2014	Toward Quantitative Analysis of Water-Energy-Urban-Climate Nexus for Urban Adaptation Planning
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

Year	Publication
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

Year	Publication
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 adulthood 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

Year	Publication
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 Permethrin: 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, Precipitation, 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 evidence of asthma
2011	Altered cardiovascular reactivity and osmoregulation during hyperosmotic stress in adult rats developmentally exposed to polybrominated diphenyl ethers (PBDEs)

Year	Publication
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

Year	Publication
2011	Fetal Programming of Adult Disease: Implications for Prenatal Care
2011	Generation and Characterization of Neurogenin1-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

Year	Publication
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 Nanoparticles 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

Year	Publication
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 Mutagenic Carcinogens 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 Induces Cumulative Effects On F1 Male Rats
2010	Investigation of Reagent Gases for the Positive Chemical Ionization of Select Polybrominated Diphenyl Ethers

Year	Publication
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

Year	Publication
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	Cumulative and antagonistic effects of a mixture of the antiandrogrens vinclozolin and iprodione in the pubertal male rat
2009	Cumulative effects of in utero 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	Developmental 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-gestational-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

Year	Publication
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 (PPARγ) in rodent and human development
2009	Screening Tools to Estimate Mold Burdens in Homes
2009	Selenium and mercury interactions with emphasis on fish tissue
2009	Spatial Analysis and Land Use Regression of VOCs and NO_2 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 Polychlorinated biphenyls 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
2008	A mixture of five phthalate esters inhibits fetal testicular testosterone production in a cumulative manner consistent with their predicted reproductive toxicity in the Sprague Dawley rat
2008	A mixture of seven antiandrogens induces reproductive malformations in rats

Year	Publication
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 air pollution in children with asthma
2008	Fetal alcohol syndrome (FAS) in C57BL/6 mice detected through proteomics screening of the amniotic fluid

Year	Publication
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 (ERMI^{SM}) 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 in the rat

Year	Publication
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
2008	The Effects of Triclosan on Puberty and Thyroid Hormones in Male Wistar 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 C. 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 http://www.epa.gov/healthresearch/consolidated-human-activity-database-chad-use-human-exposure-and-health-studies-and
Exposure Forecaster Database	ExpoCast	Automated model to predict exposures for thousands of chemicals http://actor.epa.gov/actor/faces/ExpoCastDB/Home.jsp
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. http://actor.epa.gov/actor/faces/ACToRHome.jsp
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 http://cfpub.epa.gov/ncea/risk/recordisplay.cfm?deid=204443&CFID=49068267&CFTOKEN=79671437
Chemical and Product Categories Database	CPCat	Database containing information on the uses of chemicals, products that contain chemicals, and manufacturers of the products http://actor.epa.gov/cpcat/faces/home.xhtml
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 http://cfint.rtpnc.epa.gov/ncea/recordisplay.cfm?deid=260543
Toxicity Forecaster Database	ToxCast	Builds computational models from HTS data to forecast the potential human toxicity of chemicals http://www.epa.gov/chemical-research/toxicity-forecasting
Toxicity Reference Database	ToxRef	Captures thousands of *in vivo* animal toxicity studies on hundreds of chemicals http://www.epa.gov/comptox/toxrefdb/
Adverse Outcome Pathway Wiki	AOP Wiki	Provides an open-source interface for rapid and collaborative sharing of established AOPs and building new AOPs https://aopkb.org/aopwiki/index.php/Main_Page
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 http://www.epa.gov/chemical-research/virtual-tissue-models-predicting-how-chemicals-impact-development

Name & Type	Acronym	Brief Description
Exposure Toolbox	Expo-Box	Web-based compendium of over 800 exposure assessment tools that provides links to exposure assessment databases, models, and references http://www.epa.gov/expobox
Handbooks		
Exposure Factors Handbook	EFH	Summary of the available statistical data on various factors used in assessing human exposure http://cfpub.epa.gov/ncea/risk/recordisplay.cfm?deid=20563&CFID=49068519&CFTOKEN=44679105
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 http://www.epa.gov/chemical-research/stochastic-human-exposure-and-dose-simulation-sheds-estimate-human-exposure
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 http://www.epa.gov/chemical-research/stochastic-human-exposure-and-dose-simulation-sheds-estimate-human-exposure
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 http://www.epa.gov/healthresearch/community-focused-exposure-and-risk-screening-tool-c-ferst
EnviroAtlas	—	Collection of tools and resources that provides geospatial data, maps, research, and analysis on the relationships between nature, people, health, and the economy http://www.epa.gov/enviroatlas
Eco-Health Relationship Browser	—	Interactive tool that illustrates scientific evidence for linkages between human health and ecosystem services http://www.epa.gov/enviroatlas/enviroatlas-eco-health-relationship-browser
Environmental Quality Index	EQI	Estimates environmental quality at the county level used to assess effects on health outcomes https://catalog.data.gov/dataset/usepa-environmental-quality-index-eqi-air-water-land-built-and-sociodemographic-domains-transf

Appendix D
Environmental Stressors and Childhood Disorders

The following is a summary of information on five childhood disorders: childhood cancer, asthma, adverse birth outcomes, autism, and metabolic syndrome, including the current state of scientific knowledge on the contribution of environmental stressors to the causation of the disorders. Information on prevalence, trends, and research activities across the federal government on each of the five disorders is also presented.

Childhood Cancer

Definition

- Childhood cancer is not a single disease but a variety of malignancies in which abnormal cells divide in an uncontrolled manner (U.S. Environmental Protection Agency, 2013).
- The most common childhood cancers are leukemias (cancers of the white blood cells) and cancers of the brain or central nervous system (U.S. Environmental Protection Agency, 2013).
- Other less common childhood cancers include neuroblastoma, Wilms tumor, rhabdomyosarcoma, and osteosarcoma (Congressional Childhood Cancer Caucus, 2014).

Prevalence

- Childhood cancer is the leading cause of death (other than injuries) in U.S. children ages 1 to 14 (U.S. Environmental Protection Agency, 2013).
- An estimated 15,780 children (up to 19 years of age) will be diagnosed with cancer, and 1,960 will die of the disease in 2014 (National Cancer Institute, 2014).
- As of 2010, there were approximately 380,000 survivors of childhood cancer in the United States (National Cancer Institute, 2014).

Trends

- Over the past 20 years, the incidence of children diagnosed with all forms of cancer has increased from 11.5 cases per 100,000 children in 1975 to 14.8 cases per 100,000 children in 2004 (Congressional Childhood Cancer Caucus, 2014).
- Death rates from childhood cancer have declined in the past 20 years, with the 5-year survival rate increasing; for all childhood cancers combined, the survival rate increased from 58.1 percent in 1975–1977 to 79.7 percent in 1996–2003 (Congressional Childhood Cancer Caucus, 2014).
- Increased survival rates have been especially dramatic for acute lymphoblastic leukemia (ALL), which is the most common childhood cancer, from a 5-year survival rate of <10 percent in the 1960's to about 90 percent in 2003–2009 (National Cancer Institute, 2014).

Causes

- Genetic syndromes such as Down syndrome, exposure to high levels of ionizing radiation, and certain pharmaceutical agents used in chemotherapy are known risk factors for childhood cancer, but they explain only a small percentage of childhood cancer cases (National Cancer Institute, 2014).
- Critical genes and processes regulating development are studied for their association with childhood cancer, with certain genes associated with an increased risk of ALL and other types of childhood cancer (Evans et al., 2014).
- Different types of cancer affect children at different ages, and recent studies suggest that susceptibility to some cancers in adulthood may be determined by prenatal exposures (U.S. Environmental Protection Agency, 2013).
- Environmental factors are under investigation for their association with childhood cancer (U.S. Environmental Protection Agency, 2013).
- Research suggests that childhood cancer may be caused by a combination of genetic predisposition and environmental exposure (U.S. Environmental Protection Agency, 2013).

Evidence for Environmental Risk Factors

- Pesticides

- *A meta-analysis of 31 studies reported a significant association between prenatal maternal occupational pesticide exposure (but not paternal occupational pesticide exposure) and childhood leukemia (Wigle, Turner, & Krewski, 2009).*
- *In a meta-analysis of 13 case-control studies (Bailey et al., 2014a) researchers reported a significantly increased risk of acute myeloid leukemia (AML) in children with maternal exposure to pesticides during pregnancy and a slightly increased risk of ALL in children with paternal exposure around conception.*
- *Research suggests that parental, prenatal, and childhood exposure to pesticides may be associated with a higher risk of brain tumors in children (U.S. Environmental Protection Agency, 2013).*

- Hazardous air pollutants (HAPs)

- *An increased risk for childhood leukemia was found in census tracts where children were exposed to 25 potentially carcinogenic HAPs (Reynolds et al., 2003).*
- *A meta-analysis of nine studies (Boothe, Boehmer, Wendel & Yip, 2014) on residential traffic exposure and childhood leukemia reported that childhood leukemia is associated with residential exposure during the postnatal period, but not during the prenatal period.*
- *Some studies have found an association between leukemia and traffic density and vehicle density (surrogate measures of exposure to motor vehicle exhaust), while others found no association, with review studies concluding that the overall evidence is inconclusive (U.S. Environmental Protection Agency, 2013).*

- Environmental Tobacco Smoke

- *The U.S. Surgeon General concluded that there is suggestive evidence that prenatal and*

postnatal exposure to environmental tobacco smoke can lead to leukemia and brain tumors in children (U.S. Department of Health and Human Services, 2006).

- Paint
- *In a meta-analysis of 13 studies, Bailey et al., (2014) did not report an association between parental occupational exposure to paint and childhood leukemia.*
- Indoor Air Pollution
- *Gao et al. (2014) found an increased risk for ALL with indoor air pollution consisting of nitrogen dioxide and 17 types of volatile organic compounds (VOCs).*
- *Deziel et al. (2014) reported an increased risk for ALL with increasing concentrations of polycyclic aromatic hydrocarbons (PAHs) in house dust.*
- Power Lines
- *Some studies have found an association between exposure to power lines and childhood cancer and other studies have found no association (U.S. Environmental Protection Agency, 2013).*
- *A variety of national and international organizations concluded that the link between exposure to very low frequency electromagnetic fields and cancer is controversial or weak (U.S. Environmental Protection Agency, 2013).*
- Radiation and Radon
- *Some studies have reported an association between radon and childhood leukemia, while others have reported no association (U.S. Environmental Protection Agency, 2013).*
- *Kendall et al. (2012) reported an association between naturally occurring gamma radiation and childhood leukemia.*

Research Activities across the Federal Government

- EPA/NIEHS Children's Environmental Health and Disease Prevention Research Centers www.epa.gov/ncer/childrenscenters
- *A study at the University of California at Berkeley is investigating the association of pesticides, tobacco-related contaminants, and chemicals in house dust and childhood leukemia.*

Asthma

Definition

- Asthma is a disease of the lungs in which the airways become blocked and cause breathing difficulties (Asthma and Allergy Foundation of America, 2014).
- Asthma is commonly divided into two types: allergic (extrinsic) asthma and non-allergic (intrinsic) asthma (Asthma and Allergy Foundation of America, 2014).
- Asthma triggers are substances or conditions that cause asthma symptoms to appear (Asthma and Allergy Foundation of America, 2014).

Prevalence

- In the year 2009, asthma affected 7.1 million (about 10%) of children in the U.S (U.S. Environmental Protection Agency, 2013).
- 10.7% of boys, compared to 8.0% of girls, were reported to have asthma in 2009 (a statistically significant difference) (U.S. Environmental Protection Agency, 2013).
- In 2009, children living in families below the poverty line, 12.2% were reported to have asthma compared to 8.7% of children living in families above the poverty line (a statistically significant difference) (U.S. Environmental Protection Agency, 2013).
- In 2007-2010, a higher percentage of black non-Hispanic children (16%) and children of "all other races" (12.4%) were reported to have asthma, compared to white non-Hispanic children (8.2%) (U.S. Environmental Protection Agency, 2013).

Trends

- The percentage of children with asthma increased substantially from 1980 to 1996 and remains at high rates today (U.S. Environmental Protection Agency, 2013).
- The proportion of children reported to have asthma increased from 8.7% in 2001 to 9.4% in 2010 (U.S. Environmental Protection Agency, 2013).
- In 2010, 5.7% of all children were reported to have had one or more asthma attacks in the previous 12 months (U.S. Environmental Protection Agency, 2013).

Causes

- Researchers believe genetic and environmental factors may interact to cause asthma, probably early in life. These factors include: inherited factors that increase the risk of developing allergies; parents who have asthma; certain respiratory infections during childhood; and contact with airborne allergens or viruses during early childhood (National Institutes of Health, 2014).
- Known asthma triggers include: exercise; weather; secondhand smoke; dust mites; molds; cockroaches and pests; pets; nitrogen dioxide; chemical irritants; outdoor air pollution; and wood smoke (U.S. Environmental Protection Agency, 2014).
- Recent research suggests that epigenetic mechanisms may play a role in the development of asthma (Kabesch, 2014).

Evidence for Environmental Risk Factors

- Outdoor air pollutants

- *Particulate matter, ozone, nitrogen dioxide, carbon monoxide, and sulfur dioxide have been associated with increased asthma symptoms in children (U.S. EPA, 2013).*
- *Long-term ozone exposure may be a contributing factor in the development of asthma, particularly among children who frequently exercise outdoors (McConnell et al., 2012).*
- *Hazardous air pollutants being studied for their possible association with asthma include acrolein, formaldehyde, nickel, and chromium (Leikauf, 2002).*
- *Prenatal exposure to polycyclic aromatic hydrocarbons (PAHs) (hazardous air pollutants found in diesel exhaust, secondhand smoke, and wood smoke), has been associated with the*

development of asthma in children (Rosa et al., 2011).

- *Many studies have found an association between traffic-related air pollution (i.e., living close to busy roads) and the occurrence of new cases of asthma or exacerbation of existing asthma symptoms (U.S. Environmental Protection Agency, 2013).*

• Indoor air pollutants

- *McGwin et al. (2010), a meta-analysis of 7 studies, concluded that there was a significant association between exposure to formaldehyde (a chemical released from carpet and furniture) and increased asthma symptoms in children.*
- *Volatile organic compounds (VOCs) released in the home have been associated with the onset and exacerbation of asthma (Chin et al., 2014).*
- *Biological sources such as pets, mold, dust mites, cockroaches, and other pests have been shown to increase existing asthma symptoms in children (Dales et al., 2008; Apelberg et al., 2001; Breysse et al., 2010; Portnoy et al., 2008; Douwes and Pearce 2003; Fisk et al., 2007).*
- *The Institute of Medicine (2000) concluded that exposure to dust mites can cause asthma in susceptible children, and exposure to cockroaches may cause asthma in young children.*

• Environmental Tobacco Smoke

- *The U.S. Surgeon General concluded that exposure to environmental tobacco smoke results in more severe asthma symptoms in children (U.S. Department of Health and Human Services, 2006).*

• Green infrastructure

- *Urban tree cover was shown to significantly reduce ambient concentrations of particulate matter, ozone, carbon monoxide, sulfur dioxide, and nitrogen dioxide (Nowak et al., 2006).*
- *Lovasi et al. (2008) reported that asthma was negatively correlated with urban street trees in New York City; an increase in tree density of 343 trees/km^2 was associated with a 29% lower asthma prevalence in 4- and 5-year-old children.*
- *Dadvand et al. (2014) reported that proximity to forest land, percent tree cover and percent green space around the home were linked to reduced asthma, while proximity to parks was correlated with increased asthma and allergies. The authors hypothesized that trees generally buffer air pollutants that can exacerbate asthma, but there may be more exotic species planted in parkland that produce airway irritants.*
- *Dales et al. (1991) reported that the odds of asthma for children were increased 29% when dampness and/or mold were present in the home. Green infrastructure can mitigate asthma risk in low-lying neighborhoods, because trees, wetlands, and other vegetated land cover absorb stormwater, reducing the extent and duration of floods.*

Research Activities Across the Federal Government

• Coordinated Federal Action Plan to Reduce Racial and Ethnic Asthma Disparities – HHS, EPA, HUD. www.epa.gov/childrenstaskforce

- *Presents a framework across the federal government to accelerate actions to reduce disparities in asthma.*

- EPA-Funded Research

- *A study at the University of North Carolina is examining factors that contribute to asthma disparities in children.*
- *A study at the University of Medicine and Dentistry of New Jersey is correlating changes in asthma status with air pollution and stress in children with persistent asthma.*
- *A study at the University of Pittsburgh is exploring the effects of community stressors and traffic-related air pollution on asthma in children.*

- EPA/NIEHS Children's Environmental Health and Disease Prevention Research Centers
  www.epa.gov/ncer/childrenscenters

- *A study at Johns Hopkins University is investigating the association between outdoor air pollutants, including particulate matter and nitrogen dioxide, and asthma in children.*
- *A study at the National Jewish Health Center is investigating the relationship between air pollution and the development of asthma in children.*

- NIEHS Funded Research
  http://www.niehs.nih.gov/research/supported/recovery/critical/childhealth/

- *A study at Johns Hopkins University is investigating the impact of indoor air pollutants and the incidence of asthma in children.*
- *A study at Children's Hospital Medication Center, Cincinnati, OH, is studying diesel exhaust and its role in the development of asthma in children.*

- NIH - National Asthma Control Initiative
  http://www.nhlbi.nih.gov/health-pro/resources/lung/naci/

- *Multi-component, mobilizing and action-oriented effort to engage diverse stakeholders who are concerned about or involved in improving asthma control with the ultimate aim of bringing the asthma care that patients receive in line with evidence-based recommendations.*
- *NIH - National Asthma Education and Prevention Program*
  http://www.nhlbi.nih.gov/about/org/naepp/index.htm
- *Ultimate goal of the program is to enhance the quality of life for patients with asthma and decrease asthma-related morbidity and mortality.*

Adverse Birth Outcomes

Definition

- Adverse birth outcomes include preterm birth (births before 37 weeks of pregnancy), low birth weight, neonatal mortality, and birth defects (U.S. Environmental Protection Agency, 2013).
- Preterm and infants with low birth weight are at a greater risk for infant death and complications involving effects on the respiratory, gastrointestinal, immune, and central nervous systems (U.S. Environmental Protection Agency, 2013).
- Longer-term problems of preterm birth include motor, cognitive, visual, hearing, behavioral, and social-emotional problems (U.S. Environmental Protection Agency, 2013).

- Birth defects consist of a range of structural and chromosomal abnormalities that occur before birth (U.S. Environmental Protection Agency, 2013).

Prevalence

- Birth defects are the leading cause of infant death in the first year of life in the United States (U.S. Environmental Protection Agency, 2013).
- From 2004 to 2006, birth defects affected approximately 3 percent of births in the United States, with the highest number of cases reported for Down syndrome, cleft lip, and cleft palate (Centers for Disease Control, 2014).
- Effects from preterm birth and low birth weight are the second leading cause of infant death in the United States (U.S. Environmental Protection Agency, 2013).
- The preterm birth rate varies depending on the age of the mother, with women ages 20 to 39 having the lowest rate of preterm birth, compared to women under 20 years of age and women over 40 years of age (U.S. Environmental Protection Agency, 2013).
- Multiple-birth babies are five times more likely to be born preterm than are singleton babies (U.S. Environmental Protection Agency, 2013).

Trends

- The rate of preterm birth showed an increasing trend between 1993 and 2006, ranging from 11 percent in 1993 to its highest value of 12.8 percent in 2006. Since that time, the rate has declined to 11.5 percent in 2012 (U.S. Environmental Protection Agency, 2013; March of Dimes, 2014).
- In 2012, black non-Hispanic women had the highest rate of preterm birth of all racial groups (16.8 percent), although it decreased from a high of 18.5 percent in 2006 (U.S. Environmental Protection Agency, 2013).
- It is difficult to identify national trends for birth defects because there is no unified national monitoring system; available information comes from state birth defects monitoring systems and birth certificates (U.S. Environmental Protection Agency, 2013).

Causes

- Increases in maternal age, rates of multiple births, use of early Cesarean sections and labor inductions, changes in neonatal technology, assisted reproductive technologies, chronic maternal health problems, maternal smoking, use of alcohol or illicit drugs, maternal and fetal infections, placental problems, inadequate maternal weight gain, and socioeconomic factors have been associated with preterm birth and low birth weight (U.S. Environmental Protection Agency, 2013).
- Some birth defects are inherited. In addition, alcohol use, smoking, and insufficient folate in a woman's diet are known causes of birth defects (U.S. Environmental Protection Agency, 2013).
- A variety of environmental factors are under investigation for their association with adverse birth outcomes (U.S. Environmental Protection Agency, 2013).

Evidence for Environmental Risk Factors

- Outdoor Air Pollutants

- *Stieb, Chen, Eshoul, & Judek (2012), a meta-analysis of 62 studies, concluded that particulate matter, nitrogen dioxide, and carbon monoxide are associated with adverse birth outcomes, including low birth weight and preterm birth.*

- *A number of studies have reported associations between airborne polycyclic aromatic hydrocarbons (PAHs) and reduced birth weight and fetal growth restriction (U.S. Environmental Protection Agency, 2013).*

- *Several studies have reported associations between residential proximity to traffic during pregnancy and an increased risk of preterm birth; however, the Health Effects Institute (2010) reviewed the existing studies and concluded that there is inadequate and insufficient evidence to infer a causal relationship.*

- *Wigle et al. (2008), a literature review, concluded that nitrogen dioxide, sulfur dioxide, and particulate matter are associated with certain cardiac birth defects.*

- Indoor Air Pollutants

- *Smoke from traditional cookstoves, fueled by wood, coal, or dung, has been associated with an increase in low birth weight and other adverse health effects (National Institutes of Environmental Health Sciences, 2014).*

- Hazardous Waste Sites

- *Multiple studies have reported an association between residences near hazardous waste sites and an increased risk of birth defects, particularly neural tube defects and congenital heart disease (U.S. Environmental Protection Agency, 2013).*

- *Yauck, Malloy, Blair, Simpson, & McCarver (2004) and Brender, Zhan, Langlois, Suarez, & Scheuerle (2008) reported an association between hazardous waste sites that emit heavy metals or solvents and birth defects.*

- *Currie, Greenstone, & Moretti (2011) reviewed birth records of children born to mothers living near any of the 154 Superfund sites and reported an overall reduced incidence of birth defects.*

- Environmental Tobacco Smoke

- *The U.S. Surgeon General concluded that exposure of pregnant women to environmental tobacco smoke causes a small reduction in mean birth weight, and that the evidence is suggestive (but not sufficient to infer causation) of a relationship between maternal exposure to environmental tobacco smoke during pregnancy and preterm delivery (U.S. Department of Health and Human Services, 2006).*

- Pesticides

- *Many studies have reported an association between maternal and paternal exposure to pesticides and an increased risk of birth defects in children; however, Wigle et al. (2008), in a review of the literature, concluded that the data are inadequate to confirm an association between pesticide exposure and the risk of birth defects.*

- Endocrine Disrupting Chemicals

- *Several studies have reported an association between endocrine disrupting chemicals and urogenital malformations in newborn boys, such as cryptorchidism and hypospadias (U.S. Environmental Protection Agency, 2013).*

- Solvents

- *McMartin, Chu, Kopecky, Einarson, & Koren (1998), a meta-analysis of several studies of women's occupational exposure to organic solvents, reported an increased risk of birth defects and oral cleft palates in children born to women exposed to these solvents.*

- *Wigle et al. (2008), in a review of the literature, concluded that the evidence linking paternal exposure to solvents to neural tube defects was suggestive of an association, but not strong enough to make conclusions about a causal relationship.*

- Phthalates

- *Several studies have reported associations between prenatal exposure to some phthalates and preterm birth, shorter gestational length, and low birth weight; however, one study reported that longer gestational length and increased risk of Cesarean section delivery were associated with phthalate exposure (U.S. Environmental Protection Agency, 2013).*

- Disinfection By-Products

- *Several studies have reported associations between disinfection by-products and an increased risk of birth defects, particularly neural tube defects and oral clefts; however, Wigle et al., (2008), in a review of the literature, concluded that the evidence is too limited to make conclusions about an association between disinfection by-products and birth defects.*

- *Studies on disinfection by-products and preterm birth have shown conflicting results (U.S. Environmental Protection Agency, 2013).*

- Polychlorinated Biphenyls (PCBs)

- *Baibergenova, Kudyakov, Zdeb, & Carpenter (2003) reported that increased exposure to PCBs from fatty fish consumption was associated with lower birth weights, while Longnecker, Klebanoff, Brock, & Guo (2005) did not observe an association between PCB exposure and low birth weight or preterm delivery.*

- Perfluorinated Compounds

- *Some studies have reported an association between perfluorinated compounds, particularly perfluorooctane sulfonic acid (PFOS) and perfluorooctanoic acid (PFOA), and adverse birth outcomes including low birth weight, decreased head circumference, reduced birth weight, and smaller abdominal circumference (U.S. Environmental Protection Agency, 2013).*

- Health Promotion: Engagement with Nature

- *Increasing tree cover near a mother's home by 10 percent can have a marginal decrease on incidence of low-birth weight, lowering these by 1.42 per 1,000 births. Potential causal mechanisms include increased physical activity, stress reduction as a result of contact with green space, and improved social contacts (Donovan, Michael, Butry, Sullivan, & Chase, 2011).*

- *Dadvand et al. (2012) reported that higher levels of greenness near maternal residences were associated with higher birth weight and infant head circumference, particularly in participants with low/moderate education levels. Potential mechanisms include decreased personal exposure to air pollution and increased physical activity.*

Research Activities across the Federal Government

- EPA-Funded Research

- *A joint study between Texas State University, Texas A&M University, Texas Department of State Health Services, and the University of North Carolina at Charlotte is defining new public health indicators linking exposure metrics and birth defects.*
- *EPA is examining water-related exposures and birth defects in a five-county area in Texas.*

- EPA/NIEHS Children's Environmental Health and Disease Prevention Research Centers www.epa.gov/ncer/childrenscenters

- *A study at the University of California at Berkeley is investigating the association between air pollutants, including airborne PAHs, and birth defects and preterm birth.*
- *A study at the University of California at San Francisco is studying the role of endocrine disrupting compounds, perfluorinated compounds, and other chemicals in fetal development and adverse birth outcomes.*
- *A study at the University of Michigan is investigating the association between phthalates, lead, cadmium, and other compounds and adverse birth outcomes.*

- Pregnancy Health Interview Study/Birth Defects Study – NIH, FDA, Private companies, others http://www.bu.edu/slone/research/studies/phis/

- *Multicenter case control study began in 1976 and is investigating a wide range of environmental exposures in pregnancy that may be associated with birth defects and other adverse birth outcomes.*

- NIEHS Research on Cookstoves http://www.niehs.nih.gov/research/programs/geh/cookstoves/
- *NIEHS funded research in Guatemala, Ecuador, Nepal, Pakistan, Ghana, and the United States on the health effects, including low birth weight, of smoke from cookstoves.*

- CDC Birth defects research and tracking http://www.cdc.gov/ncbddd/birthdefects/research.html
- *CDC tracks birth defects, researches factors that might increase or decrease the risk of birth defects, and identifies community or environmental concerns or other factors that need more study.*

Neurodevelopmental Disorders (Autism)

Definition

- Autism spectrum disorder (ASD) is a group of developmental disabilities that can cause significant social, communication and behavioral challenges (Landrigan, Lambertini, & Birnbaum, 2012; National Institutes of Environmental Health Sciences, 2014).

- A diagnosis of ASD now includes several conditions that used to be diagnosed separately: autistic disorder, pervasive developmental disorder not otherwise specified (PDD-NOS), and Asperger syndrome (National Institutes of Environmental Health Services, 2014).

Trends

- Change in percentage of children aged 5–17 years in the United States reported to have ever been diagnosed with autism has increased from 0.1 percent in 1977 to 1.0 percent in 2010 (U.S. Environmental Protection Agency, 2013).
- Globally, after accounting for methodological variations, there is no clear evidence of a change in prevalence for ASD between 1990 and 2010. (Baxter et al., 2014).

Prevalence

- The CDC estimates ASD affects roughly 1 in 68 children in the United States (aged 8 years, period covered 2010) (Centers for Disease Control, 2014).
- ASD is almost 5 times more common among boys (1 in 42) than among girls (1 in 189) (Centers for Disease Control, 2014)
- Globally, the prevalence of ASD is estimated to be 1 in 132 persons (Baxter et al, 2014).

Causes

- Emerging understanding suggests a complex, dynamic system of metabolic and immune anomalies involving many organ systems, including the brain, in association with environmental exposures (U.S. Environmental Protection Agency, 2013).
- Evidence points to pregnancy and the early postnatal period as critical windows of vulnerability (Interagency Autism Coordinating Committee, 2013).
- Understanding of the role of genes has been significantly refined in recent years. Data suggest that approximately 40–60 percent of ASD risk can be attributed to inherited, common variation (single nucleotide polymorphisms [SNPs]); (Sandin et al., 2014).

Evidence for Environmental Risk Factors

- Outdoor Air Pollutants

- *Several studies suggest an increased risk of ASD from air pollution exposure during gestation or early infancy, or both (Becerra, Wilhelm, Olsen, Cockburn, & Ritz, 2013; Volk, Lurmann, Penfold, Hertz-Picciotto, & McConnell, 2013; von Ehrenstein, Aralis, Cockburn, & Ritz, 2014).*
- *Volk et al., (2014) reported that children with a specific genotype and high air pollutant exposures were at increased risk of ASD compared to children who had the same genotype and lower pollutant exposures.*
- *Allen et al. (2014) investigated the mechanism by which exposure to ultrafine particulate matter from air pollution adversely affects central nervous system development in mice.*

- Pesticides

- *Shelton et al. (2014) showed an increased risk of ASD for children of mothers who lived within 1.5 km of an agricultural pesticide application during pregnancy.*

- *Roberts et al. (2007) reported an increased risk for developing ASD with increasing poundage of organochlorine pesticide applied and decreased with distance from the pesticide application sites.*

• Brominated Flame Retardants

- *In a literature review, Messer (2010) suggests that polybrominated diphenyl ethers (PBDEs) may be a risk factor for ASD, while a case-control study that measured 11 PBDE congeners showed no difference in PBDE levels and congeners in children with ASD compared to controls (Hertz-Picciotto et al., 2011).*

Research Activities across the Federal Government

• Interagency Autism Coordinating Committee (IACC)

- *IACC was established in accordance with the Combating Autism Act of 2006, reauthorized 2011 (Public Law 112-32).*
- *Federal members of IACC include the Director of NIH, Director of NIEHS, Director of NICHD, FDA, DOD, HHS, and DOE.*
- *In the Strategic Plan, 2009, updated April 2014, the objectives associated with elucidating causes of ASD emphasize:*
  - *Understanding how environmental risks may differ in vulnerable subgroups*
  - *Applying emerging science in epigenetics, the microbiome, animal models of ASD, and bioinformatics*

• GAO report May 20, 2014 on coordination of federal autism activities

- *GAO found that, apart from federal agencies' participation on the IACC, instances of agency coordination are limited.*
- *Twelve federal agencies have funded 1206 autism research projects.*
- *Five agencies fund 159 research activities focused on elucidating causes of autism, primarily NIH followed by DOD and CDC. EPA is included under the category "other agencies" and funds one activity.*

• BRAIN Initiative

- *On June 5, 2014, NIH released a scientific vision for a 4.5–billion dollar investment over 10 years beginning in 2016.*
- *Early results include application of a 3-D map collating activity of genes in 300 brain regions during mid-prenatal development to demonstrate the relationship between genetic risk factors for ASD and early brain development.*

Metabolic Syndrome

Definition

• Metabolic syndrome incorporates a cluster of adverse health effects, including obesity, hypertension, altered lipid levels, and other metabolic abnormalities, that appear to be caused by common biological mechanisms (U.S. Environmental Protection Agency, 2013).

- Obesity, defined as a high range of weight for an individual of a given height that is associated with adverse health effects, is measured based on a set cutoff point directly related to an individual's body mass index (BMI) (U.S. Environmental Protection Agency, 2013).
- Obesity has been associated with cardiovascular disease, cancer, psychological stress, asthma, and diabetes in childhood and later in life (U.S. Environmental Protection Agency, 2013).

Prevalence

- The prevalence of childhood obesity in the United States has been increasing for several decades, although it has stabilized at approximately 16 percent over the past few years (U.S. Environmental Protection Agency, 2013).
- In 2005–2008, 22 percent of Mexican-American and 20 percent of black non-Hispanic children were obese, compared with 14 percent of white non-Hispanic children and 14 percent of children of "other races/ethnicities" (U.S. Environmental Protection Agency, 2013).
- Among children in the United States, the prevalence of obesity is greater in children with family incomes below poverty level than in those above poverty level (U.S. Environmental Protection Agency, 2013).

Trends

- In 1976–1980, 5 percent of children in the United States were identified as obese; this rate rose until it reached a high of 16 percent in 2007–2008 (U.S. Environmental Protection Agency, 2013).

Causes

- Obesity is primarily due to an imbalance between caloric intake and activity (U.S. Environmental Protection Agency, 2013).
- A number of animal and cellular studies suggest that environmental chemical exposures may contribute to obesity and diabetes (U.S. Environmental Protection Agency, 2013).
- Studies show that obesity is largely determined during early life, including the prenatal period (Janesick and Blumberg, 2011).

Evidence for Environmental Risk Factors

- Outdoor Air Pollutants

- *Several studies have reported that obesity may result in greater susceptibility to the adverse effects of air pollutants, such as particulate matter and ozone, including airway inflammation, cardiovascular effects, and increased particle deposition in the lungs (U.S. Environmental Protection Agency, 2013).*

- Endocrine Disrupting Chemicals

- *Studies suggest that some endocrine disrupting chemicals, such as bisphenol A, phthalates, diethylstilbestrol, and endogenous steroids may be associated with obesity in children (Choi, Eom, Kim, Lee, & Kim, 2014; Karoutsou & Polymeris, 2012).*
- *Janesick & Blumberg (2011) hypothesized that individuals exposed to certain endocrine disrupting chemicals early in life might be predisposed to increased fat mass and obesity.*

- Other Chemicals

- *Smink et al. (2008) reported that prenatal exposure to high levels of hexachlorobenzene was associated with increased weight and BMI in children 6.5 years old.*
- *Verhulst et al. (2009) reported that prenatal exposure to DDE (the main metabolite of DDT) was associated with increased BMI and exposure to PCBs was associated with increased BMI in early childhood.*
- *Scinicariello and Muser (2014) found an association between total urinary PAH metabolites and naphthalene metabolites and higher BMI, obesity, and waist circumference in children 6–11 years of age.*

- Health Promotion: Physical Activity

- *Children who lived in greener neighborhoods were less likely to increase their BMI scores over 2 years compared to those who lived in less-green neighborhoods. The lower BMI scores were likely due to increased physical activity or time spent outdoors (Bell, Wilson, & Liu, 2008).*
- *Wolch et al. (2011) reported that children who had parks or recreation programs close to their homes had lower measured BMIs at age 18 than those without such programs. The authors concluded that this may be because children with better access to parks and recreation programs spend more time in physical activity and thus have reduced BMIs.*
- *Models based on the results from Wolch et al. (2011) suggest that, if all children in the sample were to have average access to parkland and recreation programs near their homes, over 9.5 percent of boys and 8.3 percent of girls would move from being overweight to having normal BMIs, and approximately 2 percent of obese children would become overweight.*

Research Activities across the Federal Government

- EPA-Funded Research

- *EPA is conducting a state-of-the-science literature review to identify chemical and nonchemical stressors related to childhood obesity.*

- EPA/NIEHS Children's Environmental Health and Disease Prevention Research Centers www.epa.gov/ncer/childrenscenters

- *A study at the University of California at Berkeley is investigating the association between pesticides and flame retardants and obesity.*
- *Another study at the University of California at Berkeley is studying the effects of air pollutants on obesity and glucose dysregulation.*
- *A study at the University of Michigan is investigating bisphenol A, phthalates, lead, and cadmium and the risk of metabolic syndrome.*
- *A study at the University of Southern California is studying near-roadway air pollution and its contribution to obesity and metabolic phenotypes.*

- NIH Obesity Research http://www.obesityresearch.nih.gov/

- *NIH seeks to identify genetic, behavioral, and environmental causes of obesity; to understand how obesity leads to type 2 diabetes, cardiovascular disease, and other serious health problems; and to build on basic and clinical research findings to develop and study innovative prevention and treatment strategies.*

- CDC – Overweight and Obesity: Childhood Obesity Facts
  http://www.cdc.gov/obesity/data/childhood.html
- *Presents facts about the prevalence of childhood obesity in the United States*
- CDC – National Collaborative on Childhood Obesity Research (NCCOR)
  http://www.cdc.gov/obesity/data/surveillance.html
- *CDC's Catalogue of Surveillance Systems reviews, sorts, and compares more than 75 surveillance systems with data related to childhood obesity research.*
- *CDC's National Collaborative on Childhood Obesity Research (NCCOR) Measures Registry is a database of diet and physical activity measures used in childhood obesity research.*

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