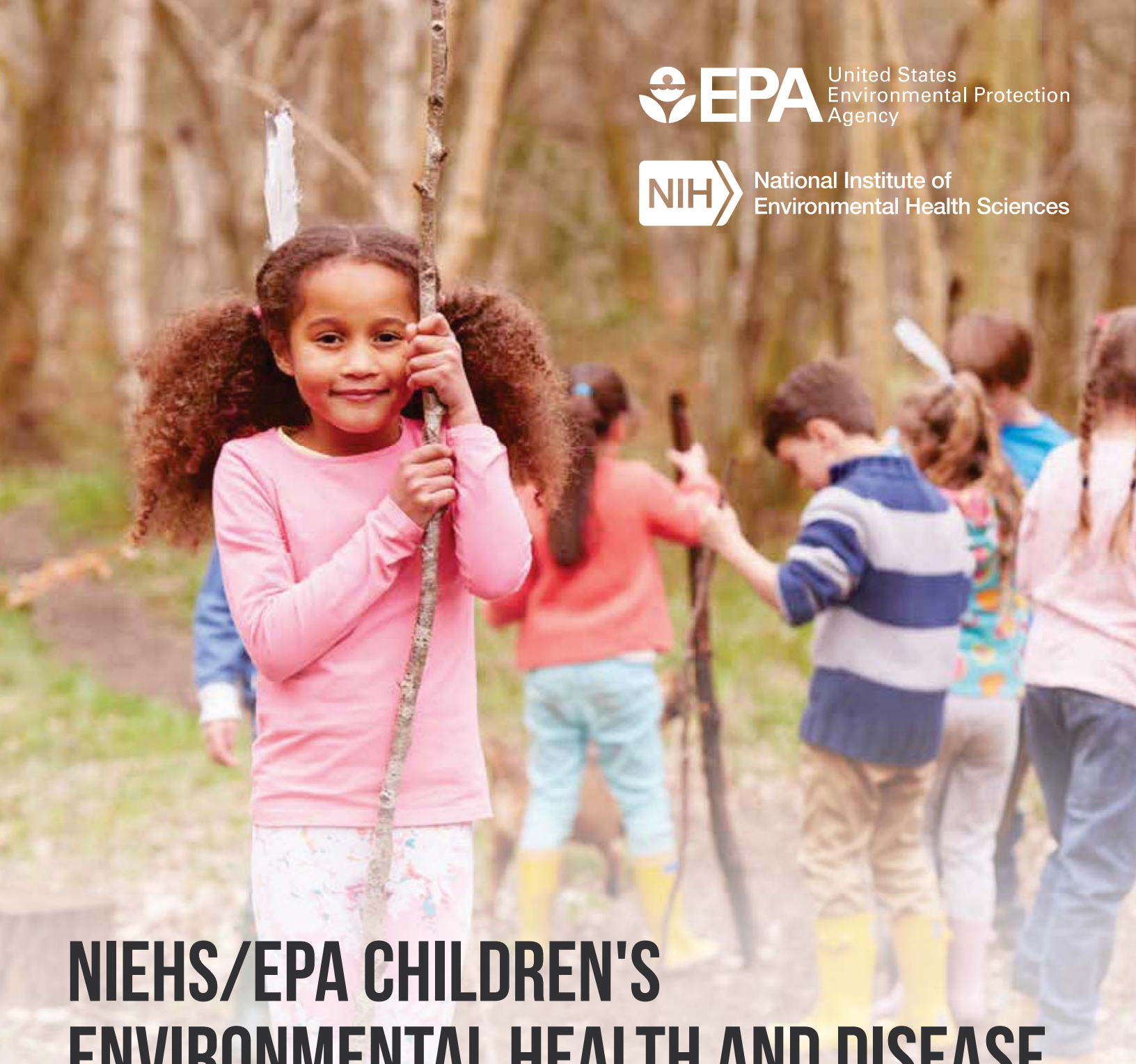


United States Environmental Protection Agency

National Institute of Environmental Health Sciences

NIEHS/EPA CHILDREN'S ENVIRONMENTAL HEALTH AND DISEASE PREVENTION RESEARCH CENTERS

IMPACT REPORT

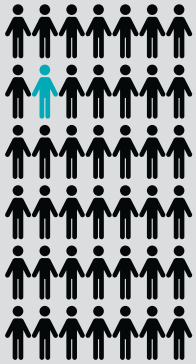
PROTECTING CHILDREN'S HEALTH WHERE THEY LIVE, LEARN, AND PLAY

EPA/600/R-17/407

Children's Health Matters

The number of children diagnosed with leukemia has increased by **35%** over the past 40 years.[1]

8.4% of children in the U.S. have asthma.[2]



1 in 42 8-year-old boys have autism.[3]

Children in the U.S. are at high risk for chronic disease

This may be a result of increasing exposures to environmental toxicants.

Approximately **16,000** premature births per year in the U.S. are attributable to air pollution.[4]

Children in **4 million** U.S. households may be exposed to high levels of lead.[5]

60% of acute respiratory infections in children worldwide are related to environmental conditions.[6]

Genetics were once thought to contribute **90%** to autism, but are now thought to only contribute **41-56%** in boys and **13-16%** in girls.

The role of environmental factors in autism is greater than previously thought.[7]

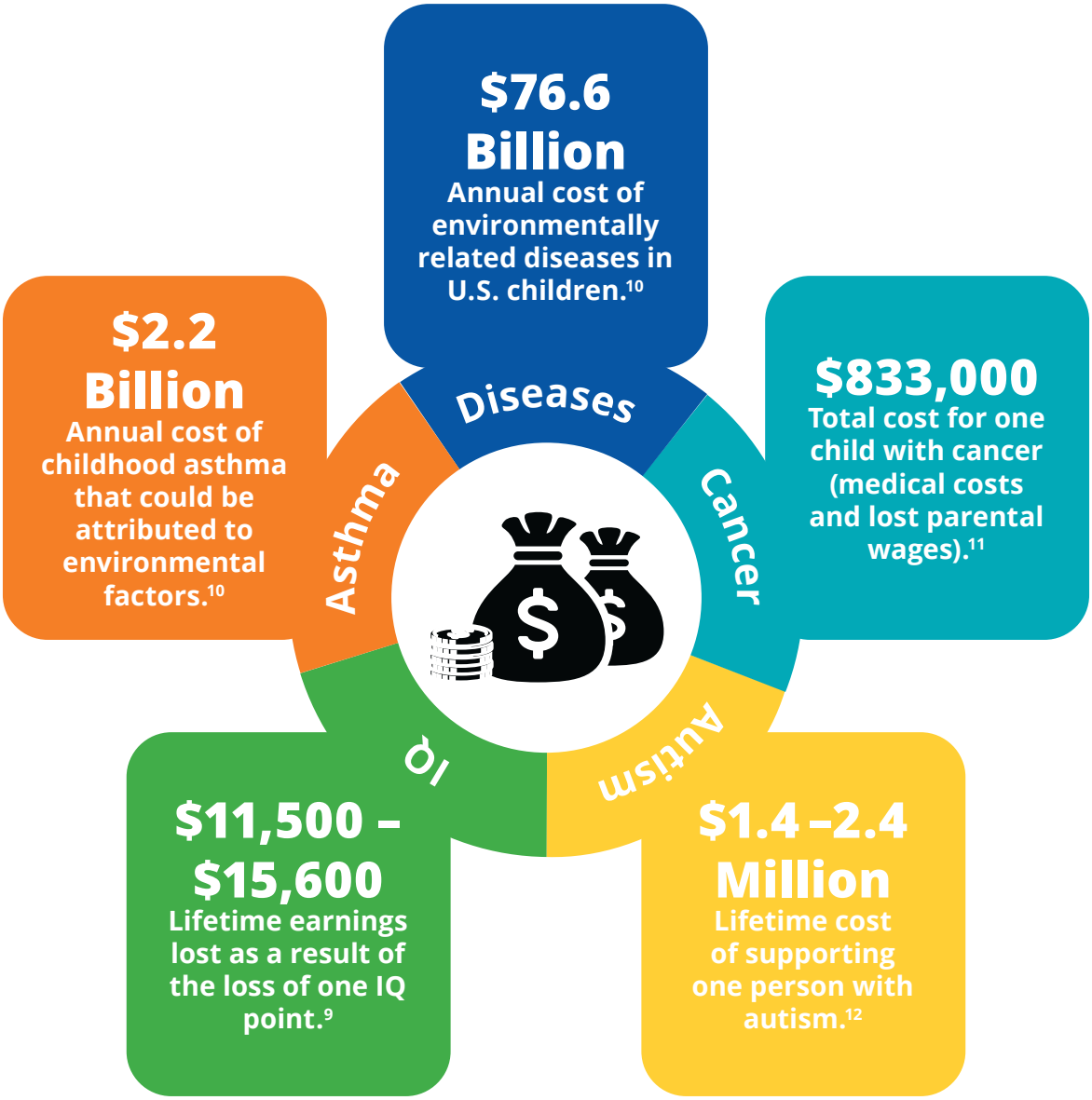
Air pollution contributes to **600,000** deaths worldwide in children under 5 years old.[8]

Children are uniquely vulnerable to environmental risks

Biology. Children's brains, lungs, immune, and other systems are rapidly developing. Their natural defenses are less developed than adults; skin and blood–brain barriers are more permeable, and metabolic and detoxification pathways are not yet fully developed.

Behavior. Children's behavior patterns make them more susceptible to exposure. They crawl and play close to the ground, putting them in contact with dirt and dust. They put their hands, toys, and other objects in their mouths. They eat, drink, and breathe more than adults relative to body mass.

Children's environmental health has a significant impact on society



Environmental exposures in the earliest stages of human development – including before birth – influence the occurrence of disease later in life. Improving the understanding of these **developmental origins of health and disease** is critical to reducing children's health risks and improving the quality of life for children and their families.

DISCLAIMER

The research described in this document has been funded jointly by the U.S. Environmental Protection Agency (EPA) under the Science to Achieve Results (STAR) grants program and the National Institute of Environmental Health Sciences (NIEHS). The information provided does not necessarily reflect the views of the Agency, and no official endorsement should be inferred. Mention of trade names or commercial products does not constitute endorsement or recommendation by EPA for use. The information presented in this summary report is intended to provide the reader with insights about the progress and scientific achievements of STAR research grants. The report lists the grantees whose research is discussed, and it also indicates where more detailed peer-reviewed scientific data can be found. This report is not intended to be used directly for environmental assessments or decision making. Readers with these interests should instead consult the peer-reviewed publications produced by the STAR grants and conduct necessary data quality evaluations as required for their assessments. ICF International provided support under contract with the EPA (contract number EP-C-14-001). EPA and/or its contractor has received permission to use the images within this document.

"As we embark on 17 years of outstanding interagency collaboration, we recognize that we will all gain strength and momentum by working together to protect the most vulnerable population – our children."[13]
– James H. Johnson, Jr., Ph.D., Director, NCER, EPA and Gwen W. Collman, Ph.D., Director, Division of Extramural Research & Training, NIEHS

ACKNOWLEDGMENTS

To the Children's Centers investigators, listed on the right – thank you! Research takes time and all the findings documented in this report are a result of your unrelenting perseverance. Thank you for investing your careers and ingenuity to change the landscape of children's environmental health. Thank you, also, for your significant contributions to this document. It has been awe-inspiring to watch you paint a picture that represents the extensive impact of your work.

I am indebted to Hayley Aja (EPA Student Contractor) and Emily Szwiec (Association of Schools and Programs of Public Health/EPA) who made tremendous contributions to the report with passion, dedication, and determination as both authors and reviewers. I am truly grateful to Patrick Lau for his support, expertise, and drive for excellence. The continued support and guidance from the EPA communications staff, including Kelly Widener, Pradnya Bhandari, Aaron Ferster, and Annie Kadeli were instrumental in preparing this report.

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The development of this report also benefited from the invaluable comments of more than 20 EPA staff across the Agency (listed in Appendix A). Valuable input and constructive recommendations from Martha Berger and the EPA Office of Children's Health Protection, as well as the Children's Health Protection Advisory Committee, provided essential guidance on increasing the impact of the report.

Finally, sincere thanks to the individuals that make this research possible. The American people who have entrusted us to discover ways to better protect our children; the diligent staff in grants, financial, and legal offices at EPA, NIEHS, and the funded institutions; those who have organized and participated in peer reviews; the research support staff at the centers; and the children and parents who invest their time to participate in this research.

Over the last two decades, this program has been skillfully managed by various EPA and NIEHS staff — It has been my privilege to capture a snapshot of the impact of this program. With sincere gratitude,

Nica Louie
Project Officer, Children's Centers program
NCER, ORD, EPA

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CONTENTS

HALLMARK FEATURES 58

APPENDICES

EXECUTIVE SUMMARY

Environmental exposures in the earliest stages of human development—including before birth—influence the occurrence of disease later in life. Since 1997, the U.S. Environmental Protection Agency (EPA) and the National Institute of Environmental Health Sciences (NIEHS) have partnered to investigate new frontiers in the field of children's environmental health research by supporting research devoted to children's environmental health and disease prevention. EPA funding has been provided under the Science to Achieve Results (STAR) grant program. STAR funds research on the environmental and public health effects of air quality, environmental changes, water quality and quantity, hazardous waste, toxic substances, and pesticides.

The Children's Environmental Health and Disease Prevention Research Centers (Children's Centers) program was established through this unique partnership, and continues to be successful in protecting children's health. **46 grants have been awarded to 24 centers through a highly competitive process.**

EPA and NIEHS have together invested more than $300 million in the Children's Centers program to expand our knowledge on the exposures and health outcomes. The partnership has led to tangible results in communities across the country.

This impact report highlights some of the progress the Children's Centers have made toward reducing the burden of environmentally induced or exacerbated diseases placed on children.

EXECUTIVE ORDER 13045 — PROTECTION OF CHILDREN FROM ENVIRONMENTAL HEALTH RISKS

Signed in 1997, this Executive Order requires federal agencies to ensure their policies, standards, and programs account for any disproportionate risks children might experience.[14] With this incentive, EPA and NIEHS executed a memorandum of understanding to jointly fund and oversee a new and impactful research grant program focused on children's health.

Exemplifying the value of partnerships between federal agencies

Approaching the challenge of studying children's environmental health with a unique perspective

A Children's Center is not a pediatric clinic or a physical building — it is the name used to describe a research program investigating the impact of environmental exposures on children's health. Investigators may be located in one building or at one university, however many centers are located across campuses in one or more partnering institutions.

The Children's Centers examine pressing questions with a wide-angle lens, not allowing the boundaries of any particular field to restrict, define, or determine the array of possible approaches. They bring together experts from many fields, including clinicians, researchers, engineers, social scientists, and others. Relying on a diverse set of disciplines has helped the centers successfully bridge the gap between environmental exposures and health outcomes.

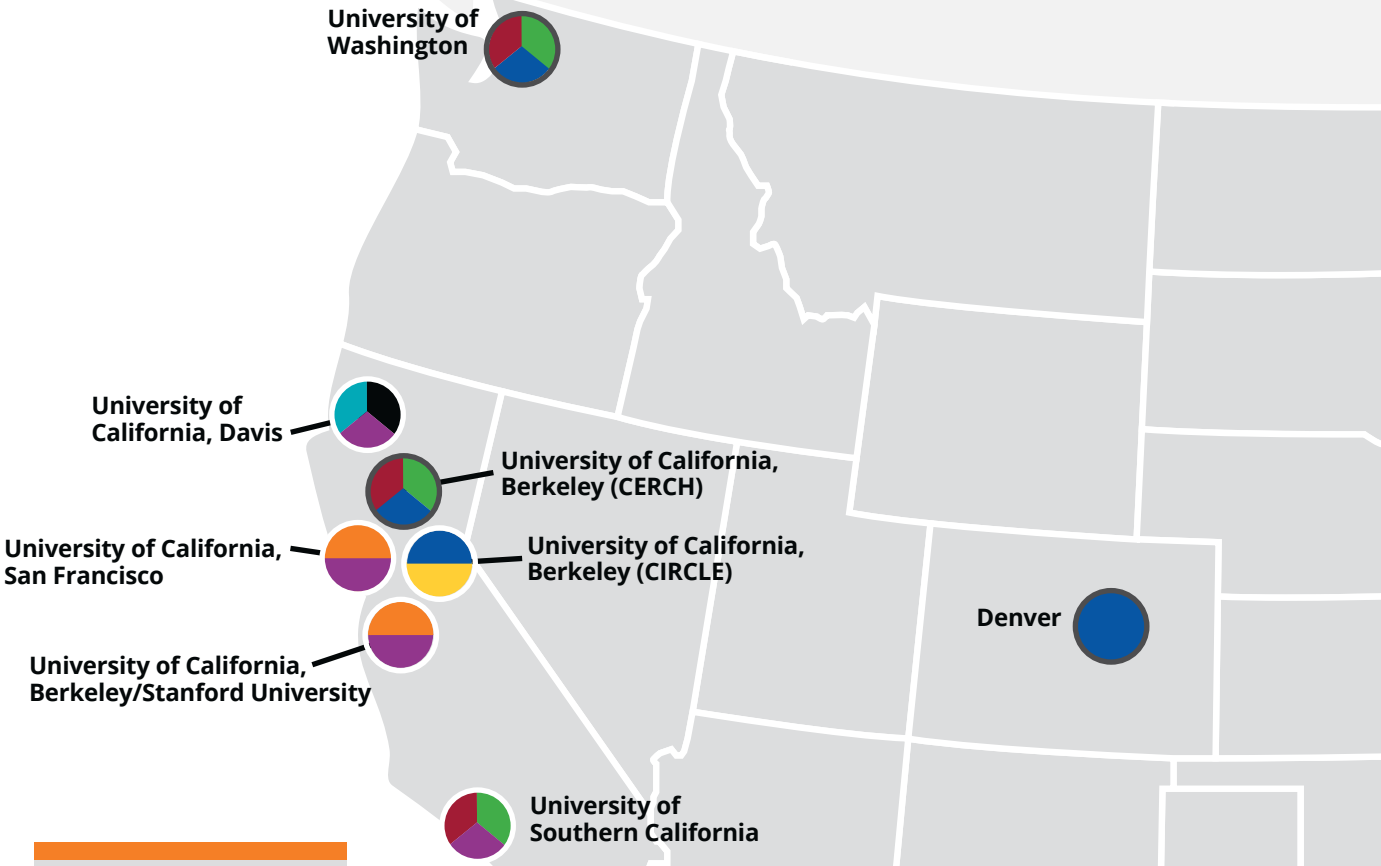
Determining what chemical exposures are toxic to children requires a variety of research approaches. Each center consists of three to four unique but integrated research projects related to the center's theme. Children's Centers are supported by cores that provide infrastructure, services, and resources to the research projects to help them meet their long–term goals. Each center is structured with at least two cores: one that coordinates and integrates center activities, and one that engages with the community and translates scientific findings. A coordinated interrelationship exists between the projects and cores that combine to form a cohesive center with a common theme.

Many Children's Centers follow children from preconception through childhood, enabling a deeper understanding of the effects of environmental exposures on childhood diseases. This approach has also allowed for the collection of biological samples over time. These archives of biological samples serve as a resource for the future and provide critical information on the prenatal and childhood determinants of adult disease.

WANT TO LEARN MORE?

If you are interested in what makes the Children's Centers program unique, see the **Hallmark Features** section.

Leveraging the expertise of researchers across the country

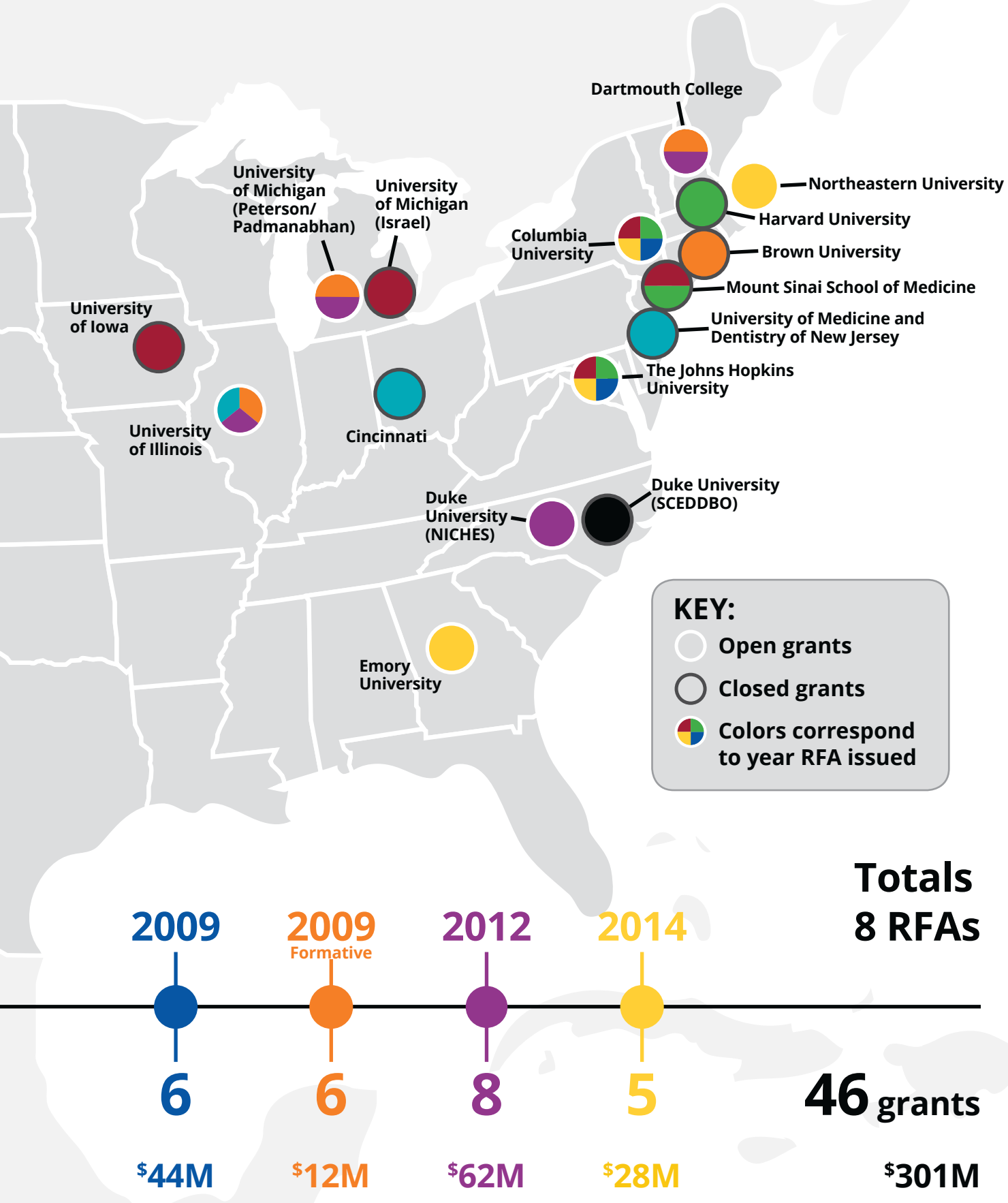


WANT TO LEARN MORE?

See **Appendix B** for more information about each Children's Center.

	1997	2000	2003	2005
Year Request for Application (RFA) Issued				
Grants Funded	8	4	7	2
Approximate Joint Funding (millions)	$60M	$28M	$52M	$15M

Fostering a new generation of leaders in children's environmental health



Totals
8 RFAs

2009	2009 Formative	2012	2014
6	6	8	5
$44M	$12M	$62M	$28M

46 grants

$301M

Leading the field in research that improves the quality of life for children and adults

The Children's Centers have transformed the field of children's environmental health. They have heightened awareness of children's environmental health—both nationally and internationally—and have helped establish it as a distinct field of study. Research from the centers has led to new detection, treatment, and prevention strategies for diseases related to environmental exposures.

Children's Centers research has identified the critical role environmental toxicants play in the development of asthma, obesity, ADHD, cancer, autism, and other childhood illnesses that may set the trajectory of health throughout adult life.

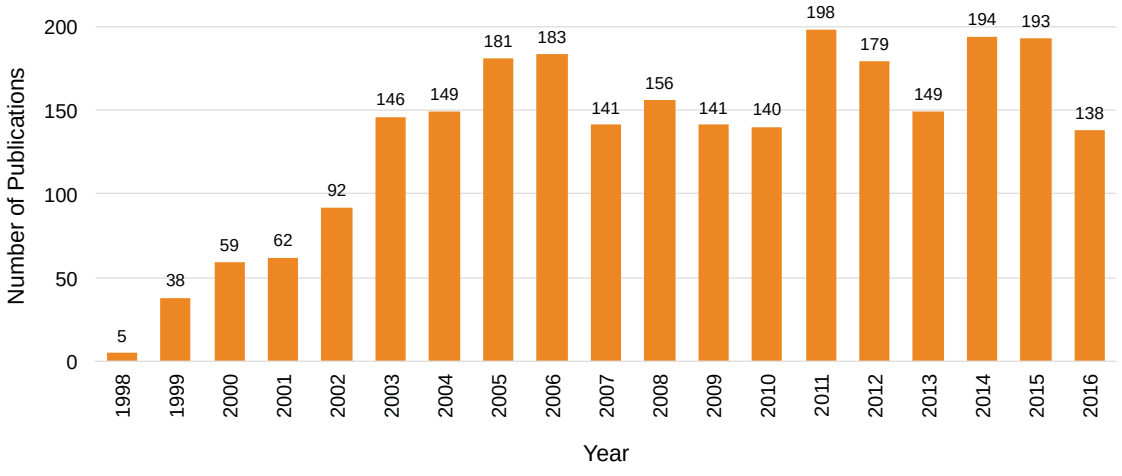
The centers have led the way in clarifying the relationship between exposures in the earliest stages of human development—including before birth—and the occurrence of disease later in life. Improving understanding of the developmental origins of health and disease is critical for developing effective interventions to reduce health risks and improve quality of life for children and adults.

WANT TO LEARN MORE?

If you are interested in a specific disease, see the **Health Outcomes** section.

If you are interested in a specific chemical, see the **Environmental Exposures** section.

Children's Centers Publications by Year (as of June 2017)



2,544 publications, including journal articles and book chapters.

141 publications per year, on average (excluding 1998).

Through their groundbreaking work, the Children's Centers have pushed the boundaries of clinical, field, and laboratory–based research. The research has been disseminated through thousands of publications in diverse and peer–reviewed journals. The research findings lay a critical foundation for reducing health risks and improving quality of life for children and adults.

Serving communities in ways that help protect children and pregnant women

Many times, scientific findings and research results are complex and difficult to understand. Empowered by Children's Centers program requirements[15] to translate and apply research findings to protect children, the Children's Centers successfully translate and communicate scientific findings into actionable solutions. The centers provide the public, community organizations, healthcare professionals, decision makers, and others with practical information about the science linking the environment to children's health.

Innovative partnerships between researchers and the community help drive research design, lead to practical interventions, and create culturally–appropriate communication materials. Through their efforts, the centers empower community members to participate in planning, implementing, and evaluating interventions and public health strategies for healthier children, families, and future generations.

WANT TO LEARN MORE?

If you are interested in the community outreach and research translation efforts by the Children's Centers, see the **Hallmark Features** section.

Research from the Children's Centers has reached thousands of people across the world through various forms of media.*

1,400 news media stories

2,300 Facebook posts

8,000 Tweets

*based on a June 2017 Altmetric analysis of 1,877 Children's Centers publications

Continuing to transform the landscape

The Children's Centers are integral to both EPA and NIEHS' research programs. The centers are one of several commitments to foster a healthy environment for children. They have advanced our understanding of the critical role environmental toxicants play in the development of childhood illnesses that may set the trajectory of health throughout adult life.

While EPA and NIEHS have together invested more than $300 million in the Children's Centers program to better understand the impact of the environment on children's health, there is still much to learn. The relationships between many environmental exposure and health outcomes remain unexplored. More data is needed to reduce or eliminate any uncertainties in associations between environmental exposures and health outcomes.

The work of the Children's Centers program has identified the need for more feasible, simple strategies to prevent environmental exposures and reduce the burden of disease in children.

Future efforts to protect children's health will require collaboration with communities, health professionals, and local, state, and federal governments. The strong relationships that the centers have established will benefit researchers and members of the community in the future.

The future of children's environmental health relies on research that expands knowledge, reduces uncertainty, and furthers collaboration.

# of children's environmental health

The Children's Centers research program addresses a broad range of key issues by:

Stimulating new and expanding existing research on the environmental determinants of children's health and the biological mechanisms that impact health and development.

Using an inter-disciplinary approach to understand the persistent developmental effects of chemicals and other environmental exposures from preconception through childhood and adolescence.

Enhancing communication and accelerating translation of research findings into applied intervention and prevention methods.

COMMONLY USED ACRONYMS

ADHD – Attention–Deficit Hyperactivity Disorder

ASD – Autism Spectrum Disorder

BPA – Bisphenol A

EDCs – Endocrine Disrupting Chemicals

IPM – Integrated Pest Management

NO_2 – Nitrogen Dioxide

OP – Organophosphate

PBDEs – Polybrominated Diphenyl Ethers

PAHs – Polycyclic Aromatic Hydrocarbons

PCBs – Polychlorinated Biphenyls

PM – Particulate Matter

STS – Secondhand Tobacco Smoke

UC – University of California

µg/dL – Micrograms per deciliter

CENTER NAMES AND AFFILIATIONS

Brown University – Formative Center for the Evaluation of Environmental Impacts on Fetal Development*

Cincinnati – Center for the Study of Prevalent Neurotoxicants in Children

Columbia University – Columbia Center for Children's Environmental Health

Dartmouth College – Children's Environmental Health and Disease Prevention Research Center at Dartmouth

Denver – Environmental Determinants of Airway Disease in Children

Emory University – Emory University's Center for Children's Environmental Health

Duke University (NICHES) – Center for Study of Neurodevelopment and Improving Children's Health Following Environmental Tobacco Smoke Exposure

Duke University (SCEDDBO) – Southern Center on Environmentally–Driven Disparities in Birth Outcomes*

Harvard University – Metal Mixtures and Children's Health*

Mount Sinai School of Medicine – Inner City Toxicants, Child Growth, and Development

Northeastern University – Center for Research on Early Childhood Exposure and Development in Puerto Rico

The Johns Hopkins University – Center for the Study of Childhood Asthma in the Urban Environment

University of California, Berkeley (CERCH) – Center for Environmental Research and Children's Health

University of California, Berkeley (CIRCLE) – Center for Integrative Research on Childhood Leukemia and the Environment

University of California, Berkeley/Stanford University – Berkeley/Stanford Children's Environmental Health Center

University of California, Davis – Center for Children's Environmental Factors in the Etiology of Autism

University of California, San Francisco – Pregnancy Exposures to Environmental Chemicals Children's Center

University of Illinois – Novel Methods to Assess Effects of Chemicals on Child Development

University of Iowa – Children's Environmental Airway Disease Center

University of Medicine and Dentistry of New Jersey – Center for Childhood Neurotoxicology and Assessment

University of Michigan (Peterson/Padmanabhan) – Lifecourse Exposures and Diet: Epigenetics, Maturation and Metabolic Syndrome

University of Michigan (Israel) – Michigan Center for the Environment and Children's Health*

University of Southern California – Southern California Children's Environmental Health Center

University of Washington – Center for Child Environmental Health Risks Research

Specific findings from these Centers are not discussed in this report

The Children's Centers have led the way in demonstrating many of the links between environmental exposures and health outcomes. This report outlines some of the important contributions the Children's Centers have made to the field of children's environmental health.

It is often challenging to neatly categorize research findings and you will notice an overlap between the topic areas. For example, findings about air pollution may also be found in the topic area about asthma. To assist readers, an index has been provided that lists the various places where a topic is mentioned.

Are you interested in learning more about a specific disease, like autism or cancer? Or intrigued about how children may be exposed to environmental toxins, like BPA or lead? You will see the report is split into **Health Outcomes** and **Environmental Exposures**. Within each of these sections, the report is organized into topic areas that the Children's Centers have focused on since the inception of the program.

Each topic area includes a brief background, a summary of scientific findings, and examples of impacts in the community or in decision making. Each of these sections can be identified by text box color and location on the topic page.

Interested in scientific research?

Read the research findings boxes at the bottom of each page. These findings are linked to the publication abstracts to help you gain a greater depth of scientific understanding.

Need an overview of children's environmental health?

Focus on the top half of each topic area page, which provides general information.

Interested in impacts in communities?

Read the Impact on Community boxes at the bottom of some of the topic area pages. Also read the Community Outreach and Research Translation topic area in the Hallmark Features section.

Want to know what makes the Children's Centers so successful?

Read the Hallmark Features section to learn about the unique characteristics that have facilitated the program's success.

Infants and children are more vulnerable than adults to the negative effects of environmental exposures. The rapid growth and development that occurs *in utero* and during infancy, childhood, and adolescence makes children especially susceptible to damage. In fact, exposures throughout childhood can have lifelong effects on health.

Many factors contribute to children's health, including genetics, nutrition, and exercise, among others. The adverse health consequences of environmental exposures may occur along with other risk factors, and it is often difficult to determine the extent that the environment contributes to children's health.

The following pages present research from the Children's Centers on increasing rates of common chronic illnesses and the role of environmental exposures.

HEALTH OUTCOMES

ASTHMA

BACKGROUND

In the U.S., 6.2 million children have asthma.[1] Exposure to environmental chemicals can worsen asthma symptoms and can reduce ability to control those symptoms.[2] Asthma affects people of all ages, but most often starts during childhood; it is one of the top reasons that children miss school.[3] Asthma is a chronic disease, and symptoms include wheezing, breathlessness, coughing, and chest tightness.[4] These symptoms can be controlled by medication and by avoiding triggers. However, certain things such as air pollution, mold, and secondhand smoke can worsen symptoms.[3] Since 1980, the number of children with asthma and the severity of symptoms have risen sharply, putting tremendous burden on families and making this issue critically important to communities.[5]

$56 billion:
Yearly cost of asthma in the U.S. (all ages).[6]

Exposure to air pollution is associated with an increased risk of asthma.[7] Traffic-related air pollution (TRAP) includes polycyclic aromatic hydrocarbons (PAHs), particulate matter (PM), nitrogen dioxide (NO_2), and ozone. The levels of TRAP are high near roadways and decline markedly as you move further away. Children who live, attend school, or play near major roadways are more susceptible to asthma.

University of Southern California

- Asthma risk increased in children who lived closer to major freeways, even those with no family history of asthma.[8,9]
- New onset asthma in primary school children could be associated with local TRAP near homes and schools.[7]

UC Berkeley/ Stanford

- Wheezing increased in children with asthma after ambient exposure to PAHs.[10]

University of Michigan

- Increased asthma symptoms and reduced lung function were associated with exposures to ambient PM and ozone in children with moderate to severe asthma.[11]

"When I have an asthma attack, I feel like a fish with no water.
– Jesse, 5 years old.[8]

IMPACT

The Children's Centers have investigated the causes of asthma so that children can maintain a normal quality of life. **Both outdoor and indoor air pollution can pose a risk to children whether they live in inner cities or rural communities.** The Children's Centers research has helped clarify the relationship between air pollution and asthma. The research has also found links between asthma and exposures to other chemicals, such as bisphenol A (BPA) and pesticides. Researchers learned that timing matters too. **Multiple windows of exposure, including during prenatal and postnatal development, can make a difference when it comes to asthma.** Research from the Children's Centers help support an improved understanding of asthma and has helped children and their families better manage this chronic disease. The research has also led to simple, feasible interventions to reduce the severity of asthma symptoms. For example, The Johns Hopkins University Children's Center used portable high efficiency particulate air (HEPA) filters in the homes of children who lived with a smoker, resulting in 33 fewer days per year with asthma symptoms.[13] The Children's Centers research is now moving toward exploring the links between asthma and other emerging factors, including obesity and immune function.

University of Iowa

Children living in rural areas experience different environmental exposures than those living in urban areas. Children in agricultural settings often live, play, and work on farms, with children as young as 5 years old participating in farm chores. The study observed that children in this region were mainly exposed to organic dusts, such as grain and cotton dusts, or dusts generated in dairy barns. Other exposures that influenced asthma development were animal-derived proteins, common allergens, and low concentrations of irritants. The asthma prevalence in rural children rivaled that of children in large Midwestern cities. These results counter the preconceived idea that rural life has a protective effect for childhood asthma.[14]

UC Berkeley (CERCH)

Recent studies found consistent associations between childhood organophosphate (OP) pesticide exposure, increased asthma symptoms, and reduced lung function in children. This finding is consistent with known acute effects of OP pesticide exposure and raises concerns about health impacts in agricultural areas.[15, 16] Researchers also found strong associations between sulfur use in agriculture and poorer respiratory health. Sulfur, which is of low toxicity and approved for conventional and organic agriculture, is a respiratory irritant and the most heavily used pesticide in California.[17]

UC Berkeley/ Stanford

Recent studies about the ways air pollution may exacerbate asthma focused on a particular group of immune cells, called T cells, that are important in controlling immune responses for asthma.[18-20] Researchers identified how PAHs impaired T cell function; in children with asthma, impaired T cell function is associated with increased asthma morbidity and decreased lung function.[18] Additionally, chronic exposures to ambient PAHs cause epigenetic changes that can suppress immune system regulation in children with asthma.[21]

BIRTH OUTCOMES

BACKGROUND

The physical and emotional effects of birth outcomes, such as preterm birth, low birth weight, and structural birth defects, can be overwhelming and the medical costs staggering.[22] In some cases, prenatal exposure to environmental chemicals may be the cause.[23] Many adult diseases are also believed to have their origins in fetal life.[24] For example, a newborn with low birth weight (less than 5.5 pounds) has an increased risk of health problems in childhood and adulthood.[25] These infants also have an increased chance of getting sick in the first six days of life, developing infections, and suffering from long-term problems including delayed motor and social development or learning disabilities.[25]

In the U.S., more than **1 in 10 babies** are born preterm.[26]

UC Berkeley/ Stanford

Maternal exposure to air pollution appears to substantially increase the risk of early preterm birth (less than 27 weeks gestation). These findings are from one of the largest studies of these associations and have extended the understanding of the effects of air pollution.[27-29]

University of Southern California

Maternal exposure to ozone may be associated with reduced birth weight in newborns.[30] The 2013 EPA Integrated Science Assessment for ozone reports that, of all studies considered, the University of Southern California Children's Center provided the strongest evidence for a relationship between ozone exposure and birth weight.[31]

University of Michigan

Maternal exposure to phthalates during pregnancy is associated with decreased fetal growth.[32] These findings were consistent across different growth parameters (head circumference, femur length, fetal weight) and by fetal sex. Maternal phthalate exposure during early pregnancy is also related to birth size and gestational age.[33]

UC Berkeley (CERCH)

Studies suggest that pesticide exposure is higher for resident agricultural families and agricultural workers.[34] Prenatal exposure to organophosphate (OP) pesticides was associated with preterm birth in a population of low-income women living in an agricultural community in California. Increased pesticide exposure later in pregnancy was more strongly associated with shortened gestation.[35]

"You can, as a pregnant woman, decide not to smoke or not to drink, but you can't avoid the air that you breathe."
– Dr. Linda McCauley, Co-Director, Emory University Children's Center.

IMPACT

Adverse birth outcomes can negatively impact health during childhood and adulthood. The Children's Centers research has identified links between preterm birth, air pollution, and pesticides. Researchers also found that exposure to arsenic, ozone, phthalates, and PBDEs contributed to lower birthweight. **The centers have engaged with communities to address concerns about how the environment may be impacting pregnancy.** The Children's Centers continue to improve the understanding of how the environmental contributes to birth outcomes in order to prevent exposures and improve children's quality of life.

Dartmouth College

Prenatal development is a period marked by rapid growth and is therefore highly sensitive to the effects of toxic exposures. Evidence suggests that fetal growth is an important predictor of adult health.[36] Since arsenic can cross the placental barrier, low level exposures may affect fetal growth.[37] Prenatal arsenic exposure was associated with decreased head circumference of newborns and decreased birth weight for baby girls born to overweight or obese mothers.[36,38]

UC Berkeley (CERCH)

Flame-retardant chemicals called polybrominated diphenyl ethers (PBDEs) are used in furniture, vehicles, and consumer electronics. Prenatal exposure to PBDEs was associated with decreased birth weight in a population of low-income women living in California. These findings are consistent with other recent studies. This was the first prospective study to examine fetal growth independent of gestational age at birth.[39]

IMPACT ON COMMUNITIES

The Emory University Children's Center created a short documentary to increase awareness of prenatal environmental exposures and pregnancy outcomes among African American women living in metro Atlanta.[40] The center partnered with its Stakeholder Advisory Board, which includes mothers, grassroots and non-profit organizations, community and environment advocates, breastfeeding counselors, an urban farmer, and state government representatives. The video is helping to raise awareness of food and household hazards within the community and is shared on social media.

CANCER

BACKGROUND

Cancer is the second leading cause of death among children between ages 1 and 14 years old.[41] Leukemia, cancer of the white blood cells, is the most common childhood cancer.[42] The number of children diagnosed with leukemia has increased by about 35 percent over the past 40 years, especially among Latino children as shown in recent studies in the U.S.[43, 44] Part of this increase is likely due to changes in patterns of exposure to chemicals introduced into a child's environment, alone or in combination with genetic susceptibility. [43, 45] Cancer survivors can develop health problems after receiving treatment, known as late complications, but children are of particular concern because cancer treatment during childhood can lead to significant lasting physical, cognitive, and psychological effects.[46] It is therefore critical to understand what causes leukemia in children in order to develop prevention strategies. This way, not only is the incidence of disease reduced, but also the lifelong impacts for children and their families.

More than **10,000** U.S. children under age 15 will be diagnosed with cancer in 2017.

Tragically, **1,190** of these children will not survive.[46]

UC Berkeley (CIRCLE)

Because the majority of childhood leukemias occurs before age 5, it is important to understand the most vulnerable windows of a child's exposure to harmful chemicals.[47] For example, paternal occupational chemical exposures before and after the child's birth are associated with risk of childhood leukemia.

Latino fathers exposed to known or possible carcinogens such as pesticides, polycyclic aromatic hydrocarbons (PAHs) in combustion exhaust, and chlorinated hydrocarbons at work were more likely to have children with leukemia.[48, 49] Chlorinated hydrocarbons are volatile and cannot be tracked back home; thus, paternal exposure during preconception is the most likely susceptible window of exposure.[48, 49] In contrast, pesticides and PAHs are semi-volatile and can be transported from work back home; thus, the susceptible windows of exposure related to paternal occupation may be before and after the child's birth.[48, 49]

IMPACT

Research from the UC Berkeley (CIRCLE) Children's Center has made important strides in uncovering associations between leukemia and exposure to tobacco smoke, pesticides, paint, organic solvents, polychlorinated biphenyls (PCBs), polybrominated diphenyl ethers (PBDEs), and PAHs. The UC Berkeley (CIRCLE) Children's Center's findings on chemical and dietary factors of childhood leukemia provide the scientific basis for prenatal and postnatal prevention efforts directed toward the most vulnerable populations, such as Latino communities exposed to high levels of pesticides and organic solvents.[47] This center also investigates the interplay between genetic, immune, and chemical factors to better understand how chemical exposures may cause leukemia. Researchers are educating clinicians, public health professionals, and parents about the importance of environmental risk factors for childhood leukemia. The long-term goal is to reduce both the incidence of this disease and of neurodevelopmental, respiratory, and other diseases caused by the same environmental exposures.

COLLABORATION

Research to identify risk factors for leukemia requires multi-disciplinary and multi-institutional efforts. In partnership with researchers from all over the world and the International Agency for Research on Cancer, the UC Berkeley (CIRCLE) Children's Center has supported the expansion of the Childhood Leukemia International Consortium (CLIC). CLIC has gathered information from 35 studies in 18 countries on 40,000 children with leukemia and 400,000 controls. With this unparalleled, large number of participating children, CLIC has identified associations of childhood leukemia with multiple chemicals, immune and infectious factors, and fetal growth. (CIRCLE) and CLIC researchers also reported that a healthy maternal diet and vitamin supplementation at the time of conception and during pregnancy reduce the risk of childhood leukemia.[57,50] The evidence-based methodology used in CLIC provides a strong basis to translate research into action that will prevent childhood leukemia.

Exposure to PCBs, PBDEs, and PAHs are potential new risk factors for childhood leukemia.[51-56] Alternative assessment methods developed by the Children's Centers made the discovery of these novel risk factors possible.

UC Berkeley (CIRCLE)

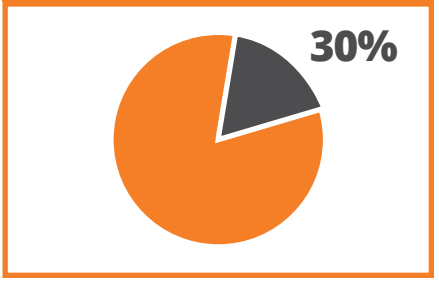
Traditional methods for assessing exposure, such as interviews and questionnaires, yield limited results due to their lack of specificity and possible reporting biases. Researchers developed a novel assessment method: collecting dust samples from households and analyzing them for levels of persistent organic pollutants. They compared the chemical levels in the dust samples to chemical levels in children's and mothers' blood samples. They demonstrated that the mothers and children living in the most highly contaminated households had the highest burden of these chemicals in their bodies.[57, 58]

IMMUNE FUNCTION

BACKGROUND

Prenatal and early life environmental exposures can interfere with the function and regulation of the immune system, which can have harmful effects later in life including neurodevelopmental disorders and cancer.[59] The immune and nervous systems are tightly linked, and there is growing evidence that disturbances in one can have serious consequences for the other. Disruptions to the immune system contribute to autism spectrum disorder (ASD) and other brain development disorders, including lower IQ, problems in social behavior, and poor motor skills.[60] Several genes linked to ASD also have critical roles in immune signaling, activation, and regulation.[61] Dysregulation of the immune system has also been linked to other health outcomes, such as childhood leukemia and atopic disease.[59] Atopic diseases are a group of diseases linked by a shared underlying problem with the immune system and include asthma, allergic rhinitis, and atopic dermatitis (eczema). Rates of atopic diseases have also rapidly increased in prevalence, possibly due to environmentally-mediated epigenetic changes.[62]

Approximately **30%** of people worldwide will suffer from atopic disease at some point in their lives.[63]



Cytokines are proteins that control the immune response and influence the nervous system. Individuals with diseases such as ASD and leukemia and their family members are more likely to experience altered cytokine expression.

UC Davis

- Exposure to PBDEs was linked to asthma and high inflammatory cytokine levels in children with ASD.[64]
- The newborn blood spots of children who were later diagnosed with ASD showed increased inflammatory cytokines IL-1β and IL-4. Early life cytokine production can possibly predict ASD diagnosis.[65]
- Children with ASD had increased levels of pro-inflammatory cytokines and chemokines. High levels of these proteins during development may disrupt the immune system.[66-69]

UC Berkeley (CIRCLE)

- Preliminary results suggest that exposure to polychlorinated biphenyls (PCBs) is associated with decreased cytokine IL-10 levels, potentially linking this chemical to both leukemia risk and loss of immune regulation.[53] Children diagnosed with leukemia have decreased levels of the immunoregulatory cytokine IL-10 at birth, that may later result in more severe responses to common childhood infections.[70, 71]

IMPACT

Exposures to harmful chemicals during prenatal and early childhood development can disrupt normal function of the immune system. **Children's Centers research suggests that disturbances in the immune system may play a role in neurodevelopmental disorders and ASD. Immune dysregulation can also make children more susceptible to atopic diseases such as asthma and allergies, and severely elevate their responses to common childhood infections.** Children's Centers research shows that childhood cancers like leukemia may also be associated with toxic environmental exposures that act on the immune system. The Children's Centers have intensively studied the role of individual chemicals and their influence on health through changes to the immune system, but there is still much to learn.

UC Davis

Maternal immune dysfunction and prenatal environmental exposures can result in ASD and metabolic conditions later in life. Mothers of children with ASD have unique autoantibodies that can bind to neurons and affect behavior.[72, 73] The presence of these ASD-specific autoantibodies in mothers has been linked to decreased immune regulation, cMET polymorphisms, and increased metabolic conditions such as diabetes.[74]

UC Berkeley/Stanford

Immune cells called T cells are key mediators of the adaptive immune system and play critical roles in modulating atopic responses, such as inflammation. Because of this, T cells are a possible target for therapeutic interventions in atopic disorders. The centers have worked to determine the molecular mechanisms where immune dysregulation leads to atopic disease in children exposed to high levels of ambient air pollutants.

- Exposure to air pollution was linked to changes in the DNA of immune cells. These changes may lead to impaired cellular function.[18]
- Exposure to air pollution, including polycyclic aromatic hydrocarbons (PAHs), was associated with decreased regulatory T cell function, increased asthma severity, and lower lung function in children with asthma.[18, 19]
- Exposure to air pollution resulted in epigenetic changes that were sustained over time.[19]
- The damage to the immune system was more pronounced in children with asthma or rhinitis than in children without atopic disease.[75]

NEURODEVELOPMENT: GENERAL

BACKGROUND

At birth, a baby has formed almost all of its brain cells.[76] Exposure to chemicals such as mercury, lead, arsenic, and pesticides can have negative effects on brain development, leading to cognitive delay, attention-deficit hyperactivity disorder (ADHD), lower IQ, higher rates of anxiety and depression, behavior and learning disorders, reduced self-regulatory capacities, and shortened attention span.[77-88] Currently, neurodevelopmental disorders affect 10 to 15 percent of children born annually, and rates of certain disorders have been increasing over the past 40 years.[89, 90] Not only can prenatal exposures to toxins increase the risk of neurodevelopmental disorders at birth, but they can also lead to disorders later in childhood.[89]

The brain reaches approximately **90%** of its adult size by age 6.[91]

Columbia University

Prenatal exposure to airborne polycyclic aromatic hydrocarbons (PAHs) can have negative effects on cognition and behavior in childhood. PAHs are widespread in urban areas largely as a result of fossil fuel combustion, specifically diesel fuel exhaust. The Columbia University Children's Center cohort of mothers and children in New York City was the first human study to examine the effects of prenatal exposure to PAHs on child development. Associations between prenatal PAH exposure and adverse cognitive and behavioral outcomes include:

- Increased likelihood to exhibit signs of cognitive developmental delay at 3 years old. These results suggest that more highly exposed children are potentially at risk for performance deficits in the early school years.[77]
- Lower full-scale and verbal IQ test scores at 5 years old.[78]
- Increased symptoms of anxiety, depression, and attention problems at 6 to 7 years old.[79]
- Slower information processing speed, increased aggression, and other behavioral self-control problems, and increased ADHD symptoms at age 7 to 9 years old.[80]
- Increased behavioral problems associated with ADHD at age 9. This is the first study to report associations between individual measures of early-life exposure to PAHs and ADHD behavior problems.[81]
- Long-lasting effects on self-regulatory capacities across early and middle childhood. These deficits point to emerging social problems with real-world consequences for high-risk adolescent behaviors.[82]

IMPACT

The Children's Centers are exploring associations between brain development and environmental toxicants such as lead, pesticides, phthalates, PAHs, bisphenol A (BPA), and polybrominated diphenyl ethers (PBDEs). **Prenatal exposures to pollutants have shown a relationship to adverse cognitive and behavioral outcomes, demonstrating links to: ADHD, reduced IQ, lessened self-regulatory capacities, anxiety, depression, attention problems, lower memory function, and structural changes to the brain.** Researchers have engaged with parents, childcare providers, and decision makers to encourage changes that reduce exposures and improve children's neurodevelopment. Children's Centers findings have helped develop public health policy and interventions aimed at protecting pregnant women and their babies from toxic environmental exposures. Their findings support the need for additional action.

UC Davis

Phthalates are commonly used in plastics and may affect neurodevelopment in children because they can be released into indoor air and attach to dust particles, that people breathe.

- Phthalate concentrations in indoor dust were higher in houses of children with developmental delay compared to children without developmental delay.[92]
- Among boys with autism spectrum disorder and developmental delay, greater hyperactivity-impulsivity and inattention were associated with higher phthalate concentrations in indoor dust. [92]
- Among children without any developmental delays, impairments in several adaptive skills such as ability to follow directions, written abilities, and language skills were associated with higher phthalate concentrations in indoor dust.[92]

Columbia University

Prenatal exposure to chlorpyrifos can interfere with children's brain development. Chlorpyrifos is a pesticide still widely used in agriculture, however, in 2000 it was banned for almost all homeowner use.[83] In a 1998 sample of pregnant women in New York City, detectable levels of chlorpyrifos were found in all indoor air samples and 70 percent of umbilical cord blood samples.[84, 85] Since the ban, levels in indoor air and blood samples have decreased significantly in study participants. Children exposed to higher levels of chlorpyrifos before birth displayed adverse cognitive and behavioral outcomes compared to children exposed to lower levels, including:

- Significantly lower scores on mental development tests and increased attention problems and symptoms of ADHD at 3 years old;[85]
- Lower full scale IQ and working memory test scores at 7 years old.[86] The effect on working memory was more pronounced in boys than in girls with similar chlorpyrifos exposures.[87]
- Structural changes in the brain in regions that serve attention, receptive language, social cognition, emotion, and inhibitory control, and are consistent with deficits in IQ.[88]

NEURODEVELOPMENT: AUTISM SPECTRUM DISORDER

BACKGROUND

Autism spectrum disorder (ASD) includes a wide range of symptoms and levels of disability characterized by challenges with social skills, repetitive behaviors, speech, and non-verbal communication, along with unique strengths and differences.[93] ASD was previously thought to be mainly due to genetics, however it is now understood that environmental factors play an important role; the estimated genetic contribution to ASD has decreased from 90 percent to 38-60 percent.[94-96] Approximately 1 in 68 8-year-old children have ASD, and it is even more common in boys (1 in 42) than in girls (1 in 189). Rates of ASD have been steadily increasing since 2002.[97, 98] While several factors may contribute to the observed rise in ASD, including changes in the diagnostic criteria, an earlier age of diagnosis, and inclusion of milder cases, these could not account for the full extent of the increase.[99]

Caring for a child with ASD costs about **$17,000 more per year** than caring for a child without ASD. [99]

University of Southern California

Research on the relationship between traffic-related air pollution (TRAP) and ASD suggest that late pregnancy and early life are critical windows of exposure. Measuring residential distance to a major roadway is often used as a marker of TRAP.

UC Davis

- For mothers who lived near a freeway during pregnancy, the risk of having a child with ASD doubled.[100]
- Children who were exposed to higher levels of TRAP in utero and in the first year of life were more likely to develop ASD.[101]

UC Davis

Parental environmental and occupational exposures have been linked to ASD and developmental delay.

- Children were at higher risk for developing ASD if their parents were exposed to lacquer, varnish, and xylene at their jobs.[102]
- Children were at greater risk for ASD and developmental delay if their mothers were residing near pyrethroids insecticide applications just before conception or during the third trimester.[103]
- Children were 60 percent more likely to develop ASD if their mothers resided near agricultural fields where organophosphate (OP) pesticides were applied during their pregnancy. The association was strongest for third-trimester exposures and second-trimester chlorpyrifos applications.[103]

"We hope to identify chemical exposures, maybe not for every autistic child, but for subsets of children that are particularly sensitive to chemicals. If one could identify those chemicals and remove or reduce their prevalence in the environments in which children live, one would be in a position to say that we've reduced the prevalence of autism."
– Dr. Isaac Pessah, Director, UC Davis Children's Center.

IMPACT

The Children's Centers have launched the field of research on environmental contributions to ASD. The centers have made significant advances both in identifying modifiable risk factors and in generating evidence for several mechanistic pathways. **Researchers have identified potential links between air pollution, pesticides, occupational exposures, phthalates, and risk of ASD.** The Children's Centers discovered the first gene-by-environment interactions in the development of ASD. Research at the UC Davis Children's Center led to the development of a biomarker test for early risk of having a child with autism. This technology is now being developed into a commercial test. Thus, since the inception of the Children's Centers program, the landscape has changed; rigorous research is now being published at a steady and increasing rate, pointing to avenues for preventive strategies and treatment options.

University of Southern California

UC Davis

Research has uncovered that interaction between genes and the environment may contribute to ASD. A functional promoter variant in the MET receptor tyrosine kinase gene, that regulates aspects of brain development, might interact with air pollution to increase the risk of ASD. Children with high air pollutant exposures and the variant MET genotype were at increased risk of ASD compared to children who had neither high air pollutant exposures nor the variant MET genotype. Subsequent animal toxicological research strengthened the causal inference and indicated a possible mechanism for air pollution effects.[104]

CHARGE

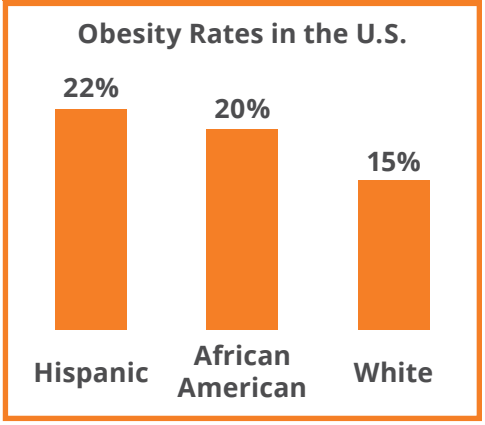
The UC Davis Children's Center initiated the CHARGE (The CHildhood Autism Risks from Genes and Environment) Study, a case-control study of children with and without ASD. CHARGE is the first comprehensive study of environmental causes and risk factors for ASD. Since 2003, the study has enrolled California preschool students with and without autism and other developmental delays. Researchers collected information about chemicals in the environments of these children before and after birth, and assessed children for their stage of social, intellectual, and behavioral development. This study was the first to identify an interaction between genes and the environment that contributes to ASD.

OBESITY

BACKGROUND

Childhood obesity remains a public health concern. While diet and limited physical activity are clear contributors to obesity, other factors, such as genetics and environmental toxicants, may play an important role.[105-110] Although rates of childhood obesity have been declining in certain groups, rates are steadily increasing among others, including Hispanic girls and African American boys. Individuals who are obese as children are more likely to be obese as adults; they are also at a higher risk of developing debilitating and costly chronic diseases later in life, including heart disease, type 2 diabetes, stroke, osteoarthritis, and cancer.[111]

Obesity affects **17%** of U.S. children 2 to 19 years old. However, the rates of obesity are higher in certain racial/ethnic groups.[112]



University of Michigan

Endocrine disrupting chemicals (EDCs), such as bisphenol A (BPA) and phthalates, can interfere with the body's natural hormones. Exposure to EDCs during critical periods of development may play a role in childhood obesity and type 2 diabetes by disrupting metabolic homeostasis.[113, 144] Prenatal exposure to EDCs was associated with several biomarkers of metabolic homeostasis, including leptin, lipids and insulin-like growth factor 1, and measures of insulin secretion and resistance in children 8 to 14 years old.

The Johns Hopkins University

Among children with asthma, being overweight or obese increased susceptibility to indoor air pollutants fine particulate matter ($PM_{2.5}$) and nitrogen dioxide (NO_2). These findings suggest that interventions aimed at weight loss might reduce asthma symptoms in response to air pollution. Additionally, interventions aimed at reducing indoor pollutant levels might be particularly beneficial for overweight children.[115]

University of Southern California

While laboratory studies on rodents have shown a link between air pollution, fat distribution, and insulin resistance, few human studies have investigated whether air pollution contributes to obesity in childhood. Studies from the University of Southern California Children's Center were among the first epidemiological studies to indicate that exposure to air pollution is related to body mass index (BMI) in children. Near-roadway air pollution, secondhand tobacco smoke, maternal smoking during pregnancy, and prenatal exposure to PAHs were all associated with increased BMI in children.[116-118]

"We want to bring another piece into the puzzle of healthy environments, and we sincerely hope that our research will inform better interventions that reduce the risk of obesity in children."
– Dr. Karen Peterson, Director, University of Michigan Children's Center.

IMPACT

Center research findings have demonstrated that prenatal and early childhood exposures to BPA, phthalates, air pollution, and secondhand smoke lead to obesity in childhood, that persists into adulthood. The Children's Centers are advancing how we think about measuring obesity. Since traditional indicators may not be sufficient in the investigation of health effects related to obesity, several Children's Centers are assessing alternative methods of body composition. Working in the community, researchers have engaged parents, families, and teachers to encourage lifestyle changes to reduce obesity and improve children's health across the country.

Columbia University

Traditional measurements, such as BMI, may not be sufficiently sensitive to study body composition in children. Alternative methods are needed to more accurately study the effects of environmental exposures on obesity and metabolic health. For example, results show that prenatal exposure to BPA was associated with fat mass index, percent body fat, and waist circumference, but not with BMI.[119] These findings confirm that traditional indicators that consider only height and weight may not be sufficient in accurately assessing children's health.

Cincinnati

University of Illinois

University of Michigan

The Children's Centers have been on the forefront of using alternative methods to measure obesity both in children and in pregnant women. The University of Michigan and University of Illinois Children's Centers are using bioelectrical impedance, which determines the flow of an electric current through body tissues to estimate fat free body mass. This is especially useful when measuring obesity in pregnant women, when traditional methods such as waist and hip circumference do not apply. The Cincinnati and the University of Michigan Children's Centers are utilizing dual energy x-ray absorptiometry scans to measure bone mineral density and also fat mass and distribution using low levels of x-ray technology.

IMPACT ON COMMUNITIES

More than 200 community members, environmental health and green space advocates, health practitioners, urban planners, and obesity prevention organizations participated in the 2017 "Parks, Pollution & Obesity: Going Beyond Exercise and Eating" meeting. Hosted by the University of Southern California Children's Center, the event advanced a community-oriented discussion of land-use strategies that maximize the benefits of physical activity and minimize potential exposures to air pollution.[120]

REPRODUCTIVE DEVELOPMENT

BACKGROUND

Adolescents may be particularly vulnerable to the effects of toxic chemicals because of the rapid development that occurs during puberty. Adolescence is also an important period of life when children acquire reproductive capability. Evidence suggests that environmental exposures to chemicals such as phthalates can affect the timing of puberty. Children who reach puberty at an early age have been found to be at increased risk of psychological and social issues during adolescence and metabolic, cardiovascular, and endocrine-related diseases and cancers in adulthood.[121, 122]

University of Michigan

Children prenatally exposed to higher levels of phthalates began puberty either earlier or later, depending on sex, compared to those prenatally exposed to lower levels of phthalates.

- Girls 8 to 14 years old with higher prenatal phthalate exposures had alterations in sex hormone levels that indicate earlier pubertal development. Girls also developed pubic hair and started menstruation earlier when prenatal phthalate metabolites were higher.[122, 123]
- Boys 8 to 14 years old with higher prenatal phthalate exposures had alterations in sex hormone levels that indicate later pubertal development. Boys also developed pubic hair later and had lower mature testicular volume when prenatal phthalate metabolites were higher. [124, 125]

Mount Sinai School of Medicine

Girls exposed to higher levels of phthalates at an early age developed breasts and pubic hair at a later age than girls who were exposed to lower levels of phthalates.[126] These findings are from a long-term study that measured levels of phthalate metabolites in urine samples from girls 6 to 8 years old, continuing until they are 12 to 14 years old.

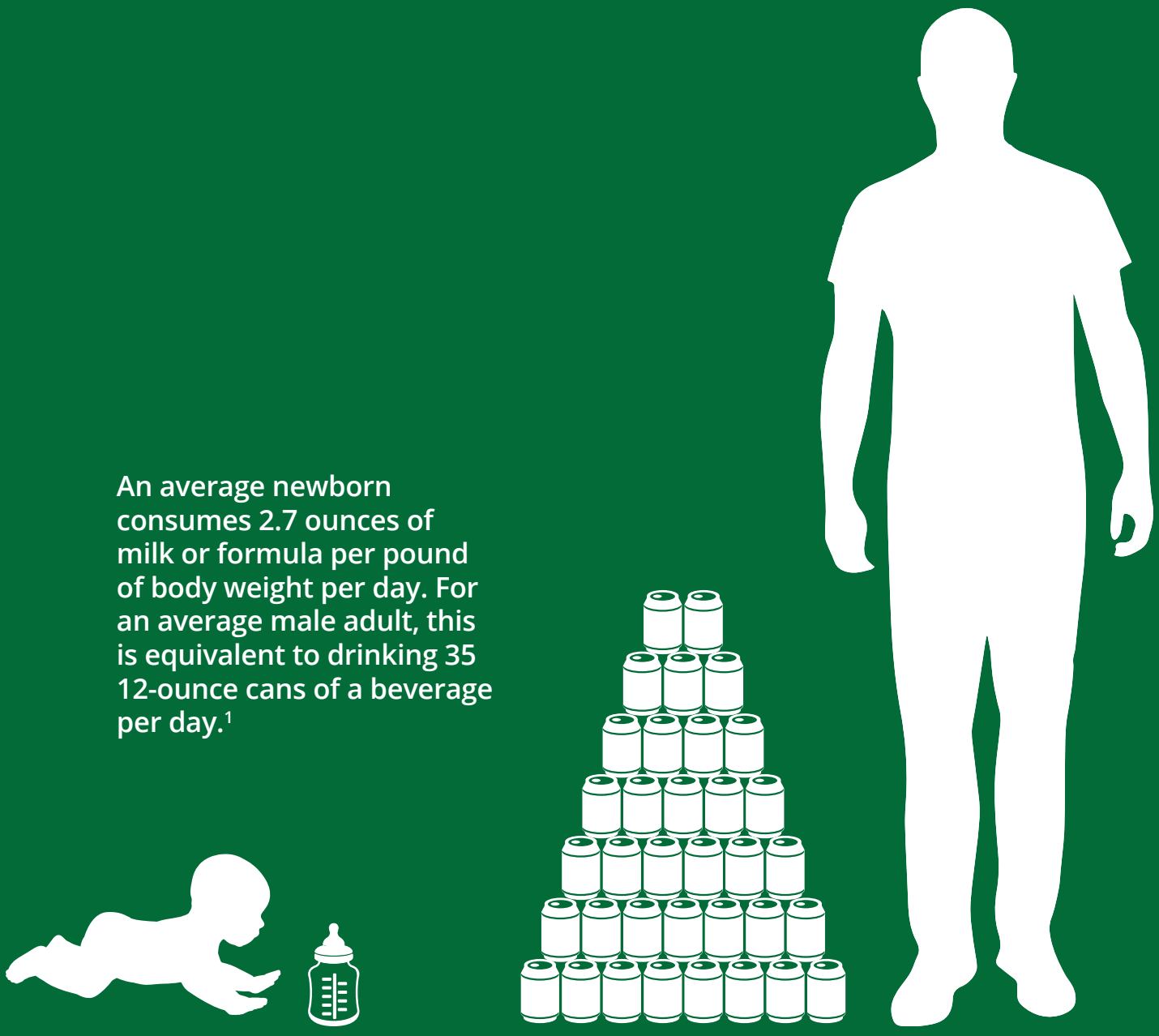
UC Berkeley (CERCH)

Girls prenatally exposed to polybrominated diphenyl ethers (PBDEs) reached puberty earlier than girls not exposed. However, boys prenatally exposed to PBDEs reached puberty later than those not exposed. These results suggest opposite pubertal effects in girls and boys.[127]

Children are exposed to more environmental contaminants than adults because they eat, breathe, and drink more per unit of body weight. They exhibit behaviors such as hand-to-mouth contact and crawling on floors where chemicals accumulate in dust an on surfaces.

The following pages present research findings from the Children's Centers on chemicals and pollutants in the environment children are commonly exposed to through air, water, and food. This section includes the different environments where children can be exposed, including outdoors, indoors at home or at school, urban areas, and rural settings.

An average newborn consumes 2.7 ounces of milk or formula per pound of body weight per day. For an average male adult, this is equivalent to drinking 35 12-ounce cans of a beverage per day.[1]

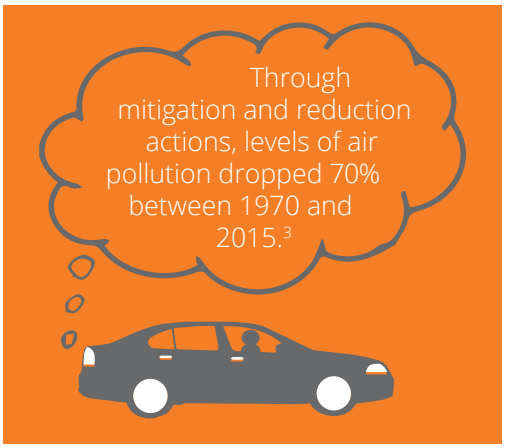


ENVIRONMENTAL EXPOSURES

AIR POLLUTION

BACKGROUND

Exposure to air pollution impacts people of all ages, but infants and children are more vulnerable than adults to the many adverse effects. Children are exposed to more air pollutants than adults because they have higher breathing rates, are more physically active, and spend more time outdoors.[2] Because their lungs and immune systems are immature, children are particularly susceptible to the effects of air pollution. Even a small deficit in lung growth during childhood can accumulate into substantial deficits in lung function in adulthood.[2] Air pollution can affect children's health, especially their respiratory health. Air pollution is known to contribute to upper and lower respiratory infections and asthma exacerbation, and some studies have shown that exposure may also impact infant mortality, weight, and pediatric cancer.[1]



University of Southern California

Lung function is measured by lung volume and air flow and is a marker of respiratory health in childhood. As children grow and develop, their lung function increases. Lung function in childhood can help predict how healthy a person's heart and lungs will be in adulthood.[4]

- Children who lived less than 500 meters (about one-third of a mile) from a freeway had substantial deficits in lung function compared with children who lived more than 1,500 meters (a little less than one mile) from a freeway.[5]
- Abnormally low lung function was five times more common in children living in communities with high levels of particulate matter (PM).[4]
- Lung development was negatively affected in fourth graders exposed to PM, nitrogen dioxide (NO_2), elemental carbon, and inorganic acid vapor. Larger deficits were observed in children who spent more time outdoors.[6]
- Children living near a major roadway were at increased risk for deficits in lung function, even in areas with low regional pollution. These results suggest that children who live close to a freeway in areas with high ambient pollution levels experience a combination of adverse developmental effects because of both local and regional pollution.[5]

PUBLIC HEALTH ACTION

EPA considered over 75 publications from the University of Southern California, Columbia University, and The Johns Hopkins University Children's Centers in its Integrated Science Assessments (ISAs) for air pollutants including ozone, PM, and NO_2.[7-9] The ISAs serve as the scientific foundation for establishing National Ambient Air Quality Standards (NAAQS). Under the Clean Air Act, states must meet the NAAQS in order to protect human health and the environment.[3] Children's Centers findings cited in these ISAs include associations between air pollution and low birth weight, lung development, and asthma.

IMPACT

Since their inception, the **Children's Centers have made important contributions to evidence linking prenatal and early life exposures to air pollution and health effects in infants and children.** The centers have improved the understanding of links between air pollution, preterm birth, low birth weight, birth defects, lung development, asthma, neurodevelopment, and autism spectrum disorder. **This work informed policies that have improved air quality in the U.S., supported clinical interventions that help keep children healthy, and increased the accuracy of methods to measure air pollution**.[7-12] Children's Centers researchers have identified health benefits of cleaner air: when air pollution is reduced, human health improves, especially for children and other sensitive populations.

UC Berkeley/Stanford

Traffic-related air pollution (TRAP) is a potential risk factor for several pregnancy outcomes, including preterm birth and structural birth defects. The UC Berkeley/Stanford University Children's Center has conducted some of the largest studies on the combined effects of air pollution and neighborhood deprivation. This research has substantially extended the knowledge base concerning birth defects that may be associated with gestational exposures to TRAP.[13-17]

- Studies showed that the combination of TRAP and socioeconomic status influenced the risk of neural tube defects, a severe group of birth defects. The combined influence of these factors was not previously demonstrated.[14, 15]
- Exposure to selected air pollutants appears to substantially increase the risk of early preterm birth (less than 30 weeks).[13, 16, 17]

PUBLIC HEALTH ACTION

Studies supported by the University of Southern California Children's Center have provided the scientific foundation for adoption of new policies at the local and state level, including for an ordinance stating that new schools should not be located near freeways with high traffic volumes, as required by California law.[11] A summary of the University of Southern California studies on health effects in proximity to freeway traffic was presented to the Los Angeles City Council before adopting an ordinance that requires multi-family housing units built in the city to have special filters if they are constructed within 1,000 feet of a freeway. The filters capture pollutants and help reduce at-home exposure to TRAP.[12]

AIR POLLUTION CONTINUED

University of Southern California

Reducing air pollution exposure could lead to substantial public health benefits.[5] For example, levels of air pollution decreased in Los Angeles from 1992 to 2011. Studies from this 20-year period show health benefits to children as a result of the improved air quality.[18, 19] When levels of $PM_{2.5}$ and NO_2 were reduced, lung function improved and bronchitis symptoms decreased in children with and without asthma. Reductions in bronchitis symptoms were more pronounced in children with asthma.

The Johns Hopkins University

Placing air cleaners containing high-efficiency particulate air (HEPA) filters in children's bedrooms resulted in a sustained reduction in PM levels. During a randomized, controlled trial, center researchers found that this simple, feasible intervention achieved a substantial reduction in indoor PM levels.[20] Portable HEPA air cleaners were also shown to significantly reduce PM exposure for children living with someone who smokes. Researchers estimate that these reductions could mean that a child is free of asthma symptoms for 33 more days per year.[21]

Columbia University

Prenatal exposure to PAH was associated with adverse effects on child cognitive and behavioral development assessed through age 9 years, [22-26] alone or in combination with material hardship due to poverty.[27] The researchers calculated significant economic benefits from a modest reduction in air PAH levels in New York City.[28]

PUBLIC HEALTH ACTION

Particles from diesel emissions can contribute to asthma onset and asthma exacerbation in children. Columbia University's Children's Center research was cited by community partner WE ACT for Environmental Justice to support an evidence-based campaign that helped New York Metropolitan Transportation Authority (MTA) convert to compressed natural gas buses, hybrid buses, and the use of ultra-low sulfur diesel.[10] Center findings on the harmful impact of diesel soot helped pass New York City Local Law 77, which mandated that all large vehicles, including the MTA bus fleet, convert from dirty to ultra-low sulfur diesel, resulting in vehicles that emit 95 percent less tail pipe pollution.[10]

UC Berkeley/Stanford

Using advanced methodologies for exposure assessment, researchers showed associations between PAH exposure and childhood wheeze, immunological function, and preterm birth.[13, 29-31] This research pushed the field forward by characterizing exposures to criteria pollutants, while also incorporating important non-criteria pollutants such as PAHs, elemental carbon, and endotoxin.

Distribution of PAHs in Fresno, California, based on extensive sampling. Darker areas reflect higher levels of PAHs.[32]

PUBLIC HEALTH ACTION

Heating oil combustion, which is common in New York City for residential heating, releases ambient metals, which can cause respiratory symptoms in young children.[33]

- Columbia Center investigators and community partner WE ACT for Environmental Justice helped to provide education and testimony to inform the debate on the phasing out of dirty heating oils Number 4 (No. 4) and Number 6 (No. 6).
- In April 2011, the New York Department of Environmental Protection adopted a regulation that required all buildings to cease burning No. 4 and No. 6 heating oils by 2015 and 2030 respectively.

ARSENIC

BACKGROUND

Dietary exposure to arsenic is a potential health risk that begins early in life.[34] Arsenic is found in water, soil, and air as a result of naturally-occurring processes and historic and current use in arsenic-based pesticides.[35] While most arsenic-based pesticides were banned in the U.S. in the 1980s, residues of this chemical element are still found in soil.[36] As a result, food and drinking water can contain levels of arsenic that exceed federal health risk targets.[35] Rice-based products can be high in arsenic and are often introduced into a child's diet during infancy.[36] Because young children have less varied diets, it is estimated that they may have two to three times higher arsenic exposure from food than adults.[37] Children are also exposed to more arsenic than adults because they play in the dirt and put their hands in their mouths.[36] Until recently, very little was known about the health impacts of arsenic on children. Research conducted in the past several years has advanced knowledge on dietary sources of arsenic in children and potentially related health effects. Findings included in this report are regarding inorganic arsenic compounds, which are highly toxic.[38]

More than **15 million U.S. households** depend on private wells for drinking water, particularly in rural areas, and may be exposed to high levels of arsenic.[39]

Dartmouth College

Dietary exposure to arsenic is a potential health risk that begins early in life.[34]

- An example of dietary arsenic exposure to infants was organic toddler formula, which contained brown rice syrup. This formula had total arsenic concentrations up to six times the EPA safe drinking water limit.[34]
- Consuming water and food with low levels of arsenic while pregnant may affect fetal growth. Maternal urinary arsenic concentration was associated with a reduction in infant head circumference. Evidence suggests that fetal growth is an important predictor of adult health.[40] This study was one of the first to report an association between low-level arsenic exposure during pregnancy and birth outcomes.[40,41]
- *In utero* exposure to arsenic may alter the fetal immune system and lead to immune dysregulation. Infants prenatally exposed to arsenic were at higher risk for respiratory infection and wheezing. [42-44]
- Prenatal exposure to low levels of arsenic had effects on the infant's epigenome. The epigenome is made up of chemical compounds that can tell human genes what to do, and may be a key mechanism of arsenic's long-term health effects.[45]
- Research has also focused on mechanisms of arsenic toxicity in infants and adults and identified the arsenic transporter AQP9 as a potential fetal biomarker for arsenic exposure.[46]

IMPACT

Given the overall scarcity of studies on the effects of early-life exposure to arsenic, the Dartmouth College Children's Centers research on this topic is essential in protecting children's health. **Findings from this center have provided evidence for associations between arsenic, fetal growth, and immune function**.[34, 40-46] An early draft of the EPA Integrated Risk Information System (IRIS) assessment of arsenic includes research from the Dartmouth College Children's Center on early-life exposure. Once final, the IRIS assessment will be used by other federal, state, and local agencies to assess human health risks from arsenic exposure.[47] This center is also engaging with the community to create educational materials for families to help reduce their arsenic exposure. This research demonstrates the need to continue exploring the effects of arsenic exposure, especially at low levels, on children's health.

PUBLIC HEALTH ACTION

In April 2016, the U.S. Food and Drug Administration (FDA) took its first regulatory action to limit the amount of arsenic in rice products. The proposed limit of 100 parts per billion in infant rice cereal was based on FDA's assessment of the health risks that arsenic in rice and rice products pose. FDA cited several Dartmouth College Children's Center studies examining the effects of arsenic exposure, mechanisms of arsenic toxicity, and the relationship between dietary and drinking water exposure sources.[48]

Research from the Dartmouth College Children's Center informed federal legislation to limit arsenic in rice. As of November 2016, the proposed R.I.C.E (Reducing food-based Inorganic Compounds Exposure) Act has been referred to the House Energy and Commerce Subcommittee of the Health and House Agriculture Committee.[49]

IMPACT ON COMMUNITIES

The Dartmouth College Children's Center is collaborating with a network of primary care physicians and pediatricians to inform families about the potential health effects associated with arsenic exposure and to encourage private well testing. They provide potential strategies for families to reduce arsenic exposure from rice for their infants and children, including diversifying the diet and adopting strategies to minimize exposure.[50] The center has developed an interactive web–based tool that educates parents and the public about sources of arsenic and how they can reduce exposure.[51]

CONSUMER PRODUCTS: BPA

BACKGROUND

Bisphenol A (BPA) is used in a variety of consumer products, including water bottles, baby bottles, toys, food can linings, medical devices, and ATM receipts.[52,53] People are exposed to BPA mainly through eating food or drinking water stored in or processed with BPA-containing plastics. It may also be absorbed through skin or inhaled.[53] There are questions about BPA's potential impact on children's health, since animal studies have shown it is a reproductive and developmental toxicant.[54-56]

While some studies indicate that BPA levels in humans and the environment are below levels of concern for adverse effects, other recent studies describe subtle effects in animals at very low levels, leading to concerns for potential effects on children's health even at low doses.[57]

More than **6 billion pounds** of BPA are produced worldwide every year.[58]

Exposures to BPA during prenatal and early childhood development were associated with multiple measures of body composition, suggesting that BPA may contribute to childhood obesity.

Cincinnati

Children exposed to high levels of BPA had lower body mass index (BMI) at age 2 years, but BMI increased more rapidly from ages 2 to 5 years.[59]

Columbia University

Children with higher prenatal exposures to BPA had a higher fat mass index, percent body fat, and waist circumference at age 7 years.[60]

UC Berkeley (CERCH)

Children exposed to higher levels of BPA showed increased amount of body fat at age 9 years.[61] Higher prenatal exposures showed differences in adiponectin and leptin in 9-year-old children, suggesting that mechanisms of BPA toxicity may interact with metabolic pathways.[62]

University of Michigan

Children with higher exposure to BPA early in life had increased skinfold thickness, as well as higher triglycerides, leptin, and glucose at age 8 to 14 years.[63-65]

IMPACT

Several Children's Centers have conducted research on exposures and related health effects of chemicals commonly found in consumer products, such as BPA, PBDEs, and phthalates, which are explained in more detail in the next sections. **There is growing evidence linking these endocrine-disrupting chemicals to neurobehavioral problems, obesity, and reproductive effects**.[56,59-69] Important findings from the Children's Centers have informed legislative and market actions both nationally and internationally to help reduce exposures and protect children's health. The Children's Centers engage with the community to reduce exposures from consumer products. For example, through a youth participatory research project, the UC Berkeley (CERCH) Children's Center empowered children and teenagers to examine exposures from cosmetics and personal care products.

PUBLIC HEALTH ACTION

The Children's Safe Product Act (CSPA) requires manufacturers to report the concentration of 66 chemicals of high concern in any children's products sold or manufactured in Washington state.[70] The University of Washington Children's Center worked with the Washington State Department of Ecology to prioritize data collected under CSPA. This collaboration resulted in a framework that incorporated both exposure and toxicity factors to identify critical products and chemicals for future monitoring and action.[71]

University of Illinois

Prenatal BPA exposure in mice had negative effects on the development of the reproductive system, even multiple generations after exposure. Investigators studied mice exposed to BPA while pregnant and the resulting reproductive effects on the first (equivalent to children), second (equivalent to grandchildren), and third (equivalent to great-grandchildren) generations.

- The female children and grandchildren of mice exposed to BPA while pregnant showed a reduced ability to maintain pregnancies.[56]
- The female great-grandchildren of mice exposed to BPA while pregnant had more difficulty becoming pregnant.[56]
- The female great-grandchildren of mice exposed to BPA while pregnant reached puberty at a later age.[56]

CONSUMER PRODUCTS: PBDEs

BACKGROUND

Polybrominated diphenyl ethers (PBDEs) are a group of chemicals used as flame retardants in textiles, furniture foam, carpet padding, building materials, upholstery in cars and airplanes, and plastic housings for electronics.[72] Recent evidence suggests PBDE exposure may interfere with the body's natural hormones and disrupt mental and physical development.[72] As furniture and other products age, flame retardants can be released into the surrounding environment where they remain for years. Dust containing PBDE particles is one of the main routes of exposure to PBDEs, especially for young children who put their hands or toys in their mouths.

A northern California study found **100% of women** they tested had been exposed to PBDEs.[73]

UC Berkeley (CERCH)

PBDEs have been linked to unhealthy changes in growth and development, and can negatively impact maternal and child health.[72] Higher PBDE exposure during pregnancy was associated with babies having lower birthweight.[74, 75] Additionally, PBDE exposure was associated with lower levels of maternal thyroid-stimulating hormone during pregnancy, which could have implications for maternal health and fetal development.[76] Women exposed to higher levels of PBDEs also took a longer time to become pregnant, suggesting that PBDEs may affect fertility.[76, 77]

Exposures to PBDEs during prenatal and early childhood, at a time when the brain is rapidly developing, are particularly harmful. When compared to children with lower exposure, children with high prenatal exposure to PBDEs displayed:

Columbia University

- Lower scores on mental and physical development tests at age 1 to 4 years.[66]
- Twice the number of attention problems at ages 3, 4, and 7 years.[67]

Cincinnati

- More hyperactivity problems and a decrease of 4.5 IQ points at age 5 years.[68]
- Poorer behavioral regulation and executive functioning at ages 5 and 8 years.[69]

IMPACT See page 45

PUBLIC HEALTH ACTION

Californians have high exposure to flame retardants because these chemicals were used to meet the state's previous furniture flammability standard.[72] In 2012, California implemented a new flammability standard.[78] Furniture and baby product manufacturers can now meet the new standard without toxic flame retardant chemicals.[79] This action was based in part on findings from the UC Berkeley (CERCH) Children's Center.[80] Although this action effectively eliminated the need for flame retardants in household furnishings, it is not an overall ban.[79]

UC Berkeley (CERCH)

Both prenatal and childhood PBDE exposures were associated with poorer attention, fine motor coordination, and cognition of school-age children.[66, 81] This is one of the largest studies to evaluate cognitive declines in school-aged children exposed to PBDEs. This research contributes to a growing body of evidence suggesting that PBDEs have adverse impacts on child neurobehavioral development.

CONSUMER PRODUCTS: PHTHALATES

BACKGROUND

Phthalates are commonly found in personal care products such as shampoo, perfume, makeup, and lotion. They are also found in plastic products such as toys, shower curtains, medical tubing, car upholstery, food packaging, and many others.[82] Such widespread use means that people are exposed to phthalates every day.[83] Possible adverse health outcomes from phthalate exposures include disruption of the body's natural hormones and impaired brain development. Exposures are particularly harmful during pregnancy, when they can disrupt fetal development.[84, 85] Because many personal care products are designed to be absorbed into the skin and have long lasting fragrances, chemicals can easily enter our bodies.[86] While adults are mainly exposed through using personal care products, eating contaminated food, and inhaling indoor air, infants and toddlers can also be exposed by ingesting indoor dust that is contaminated with phthalates.[87]

17 Products

The average number of personal care products used by a teenage girl per day.* In comparison, an adult woman uses 12 products, and an adult man uses 6 products.[88, 89]

University of Michigan

Prenatal exposure to phthalates negatively impacts pregnant women and birth outcomes.

- Exposure to phthalates and BPA is associated with biomarkers of angiogenesis, or formation of new blood vessels, during pregnancy. This may indicate disrupted placental development and function.[90]
- Exposure to phthalates during pregnancy are associated with increased oxidative stress biomarkers, which can lead to preeclampsia, intrauterine growth restriction, and other pregnancy outcomes.[91]

University of Illinois

Prenatal exposure to phthalates negatively impacts reproductive development in mice, such as:

- Decreased sperm motility and premature reproductive aging in male mice.[92]
- Disruption of several aspects of female reproduction, including ovarian cysts and a disrupted estrous cycle (equivalent to the human menstrual cycle).[93]
- Direct damage to the ovaries, increased uterine weight, decreased anogenital distance, induced cystic ovaries, disrupted estrous cyclicity, reduced fertility-related indices, and some breeding complications at age 3, 6, and months in female mice.[94]

IMPACT See page 45

IMPACT ON COMMUNITIES

As part of the UC Berkeley (CERCH) Children's Center, the Health and Environmental Research in Make-up Of Salinas Adolescents (HERMOSA) Study was led in partnership with youth in Salinas Valley, California, to examine how girls are exposed to hormone disrupters, like phthalates in personal care products.[95] The study was featured in local and national news broadcasts including ABC's Good Morning America[96] and National Public Radio (NPR).[97] Results showed that chemicals in personal care products used by teenage girls are absorbed into their bodies. The study also found that exposures can be reduced when users switch to products that contain fewer chemicals. Through this study, researchers empowered local youth by engaging them in many aspects of research, including design, data collection, analysis, and communicating findings with the community, policy makers, and media. The findings are also important because there is little information about how exposure to hormone disrupting chemicals during adolescence may impact long term health.

"Personally, since the [HERMOSA] study, I've tried to use more natural products. It's hard, especially as a college student who doesn't have a lot of money... I've decided to splurge more on products with fewer chemicals because of the effect in the future."
– Maritza Cardenas, teen researcher and HERMOSA study co-author.[98]

UC Davis

Phthalates found in household dust may have negative effects on children's brain development.

- Higher levels of phthalates in household dust were associated with poorer adaptive functioning and developmental delays in children 2 to 5 years old.[99]
- When researchers restricted their analysis to male children only, they found that phthalates were associated with hyperactivity, impulsivity, and attention problems.[99]

LEAD

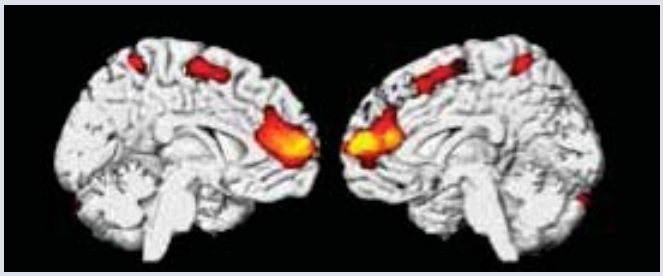
BACKGROUND

Levels of lead in children's blood have declined tremendously since the 1970s.[100,101] While substantial progress has been made to reduce children's exposure to lead, approximately half a million U.S. children 1 to 5 years old still have blood lead levels above 5 micrograms per deciliter (µg/dL) — the reference level that the Centers for Disease Control and Prevention (CDC) recommends public health action.[102] The number of children who continue to be exposed to lead is alarming, since research demonstrates that even low levels of lead exposure can affect IQ, attention, academic achievement, and cause long-term mental and behavioral problems.[103-109] The Children's Centers have been working to better understand the health effects of lead at even the lowest levels of exposure. Research shows that there is no safe level of lead exposure for children, and the most important step that parents, doctors, and others can take is to prevent lead exposure before it occurs.[110]

As a child's blood lead level increases from 1 to 10 µg/dL, a **child may lose anywhere from 3.9 to 7.4 IQ points.**[103] Chronic low level exposure to lead may have an even greater effect on IQ than a single instance of high level lead exposure.

Cincinnati

Lead has significant and long-term impacts on the nervous system. Studies using advanced neuroradiological methods from the Cincinnati Children's Center were the first to document persistent lead-related damage to areas of the brain responsible for cognitive and language functions.



Regions of the brain (in red and yellow) show declines in brain gray matter volume associated with childhood blood lead concentrations.[106]

- Childhood lead exposure impacts brain reorganization and language function. Damage to the primary language areas in the brain's left hemisphere resulted in compensation by the brain's right hemisphere.[104]
- Higher rates of total criminal arrests and arrests for violent offenses during young adulthood have been linked to prenatal and early childhood lead exposure. The likelihood of being arrested for a violent crime as a young adult increased by almost 50 percent for every 5 µg/dL increase in blood lead levels at age 6 years.[105] This study was the first to document the relationship between childhood lead exposure and young adult criminal behavior.
- Reductions in adult gray matter volume in regions of the brain responsible for executive functions, mood regulation, and decision-making were associated with childhood lead exposure. These findings were more pronounced in males.[106]

IMPACT

Children's Centers research is vital to demonstrating and halting the detrimental health effects of lead exposure to children at low levels. EPA cited nearly 40 Children's Centers publications in its Integrated Science Assessment (ISA) of Lead in 2013.[111] The ISA serves as the scientific foundation for establishing National Ambient Air Quality Standards (NAAQS) for lead. Under the Clean Air Act, states must meet the NAAQS in order to protect human health and the environment.[3] EPA cited several Children's Center studies as evidence for a causal relationship between lead and the following effects observed in children: impaired cognitive function, poor fine motor skills, increased risk for criminal behavior, and altered brain structure and function. Simple steps to reduce exposure to lead are essential to protect children's health. The University of Michigan Children's Center collaborated with the Flint Water Task Force to create a training for community members and health workers who provide nutrition education to the Flint community. The training provides nutritional information and guidance on nutrients and culturally relevant foods to reduce lead absorption in young children. The centers have created knowledge essential for effective action and made use of existing knowledge to reduce lead exposure and protect children's health.[112]

Childhood lead exposure has been linked to a number of adverse cognitive outcomes, including reduced performance on standardized IQ tests, neurobehavioral deficits, poorer test scores, and classroom attention deficit and behavioral problems.[107]

Duke University	End-of-grade test scores on elementary school achievement tests were lower for children who had higher blood lead levels. A strong relationship was seen between increased early childhood lead exposure and decreased performance on elementary school achievement tests.[107]
Cincinnati	Intelligence test scores were lower for children who had higher blood lead levels. Findings showed a 3.9 IQ point decrement associated with an increase in blood lead from 2.4 to 10 µg/dL.[108]
University of Michigan	Symptoms related to Attention Deficit Hyperactivity Disorder (ADHD), specifically hyperactivity and restless-impulsivity behaviors, were positively associated with low blood lead levels (equal to or less than 5 µg/dL).[109]

PESTICIDES

BACKGROUND

Studies have demonstrated widespread pesticide exposures for the U.S. population, including pregnant women and children.[113-120] Exposure to pesticides may be linked to adverse developmental, cognitive, and behavioral outcomes. Children are especially susceptible to pesticide exposure because they have higher rates of metabolism, less-mature immune systems, unique diets, and distinct patterns of activity and behavior when compared with adults.[121] For example, children spend more time outdoors on grass and fields where pesticides might be. Children also spend more time on the ground and tend to have more frequent hand-to-mouth contact than adults.[122] Furthermore, children's diets are usually less varied than adults, which could increase their intake of foods containing pesticide residues.[121] Of particular concern are organophosphate (OP) pesticides because of their toxicity and widespread use.[123]

More than **one billion pounds of pesticides** are used each year in the U.S., with more than 700 million pounds used annually in agriculture.[124]

Both the UC Berkeley (CERCH) and the University of Washington Children's Centers have found that farmworkers and their children are exposed to higher levels of pesticides than the general population and therefore, may experience more adverse health effects.[125-133]

UC Berkeley (CERCH)

- Children prenatally exposed to higher levels of OP pesticides exhibited poorer cognitive functioning compared to children exposed to lower levels.[128-130, 134-137]
- Women experienced shorter duration pregnancies.[128]
- Infants showed more abnormal reflexes soon after birth.[129] Children scored lower on tests for psychomotor development at ages 6 and 12 months, and on tests for mental development at ages 12 and 24 months.[130]
- Children were at higher risk for developmental problems at age 2 years.[134]
- Children exhibited attention problems and signs of ADHD at age 5 years. Boys displayed more hyperactive and impulsive behaviors while girls displayed more inattentive-type problems.[135]
- Children scored lower on tests for working memory, processing speed, verbal comprehension, perceptual reasoning, and full-scale IQ at age 7 years. Children at the highest levels of exposure had an average deficit of 7 IQ points.[136, 137]

"The center's research about the exposure of pregnant women and newborns to pesticides motivated Local Law 37 and put New York at the forefront of safer pest control methods in the United States."
– Michael Bloomberg, former New York City Mayor.[138]

IMPACT

The Children's Centers have documented that pre- and postnatal exposure to pesticides is linked to various adverse health effects such as autism spectrum disorder, poorer cognitive function, lower IQ, attention problems, low birth weight, and leukemia in children. **Children's Centers researchers have examined how age, genetics, and environmental factors influence children's susceptibility to the harmful effects of pesticides, which can affect growth, development, and learning.** Center research has led to public health policies designed to better protect children and infants from harmful pesticide exposures. Children's Centers research on pesticides has been translated to farmworkers and their families to reduce exposures and to protect health. While great progress in reducing children's exposure to pesticides has been made, a greater understanding of the exposure pathways of pesticides, the long-term health effects of pesticides, and methods to reduce pesticide exposure remains essential.

Columbia University

Prenatal exposure to chlorpyrifos can interfere with children's brain development (see page 29). Chlorpyrifos was commonly used as an insecticide in residential settings before it was banned for domestic use by EPA in 2001.[139] This action had a positive effect on public health and quickly resulted in reduced levels of chlorpyrifos in the umbilical cord blood of babies, as demonstrated by evidence from the Columbia University Children's Center.[140]

At the heart of the UC Berkeley (CERCH) Children's Center is the center for the Health Assessment of Mothers and Children of Salinas (CHAMACOS) study. CHAMACOS is the longest running longitudinal birth cohort study of pesticides and other environmental exposures among children in a farmworker community. It is also one of the only cohorts focused on low-income, Latino children in a farmworker population. Since 1999, CHAMACOS has enrolled pregnant women living in Salinas Valley, California, one of the most productive agricultural regions in the nation. More than 600 children continue to participate in the study and will be followed until adulthood.

UC Berkeley (CERCH)

Newborns have very low levels of the critical enzyme PON1, which can detoxify OP pesticides. Levels of PON1 remain low through age 7, indicating that childhood is a time of increased vulnerability to pesticide exposure. Some adults may also have lower PON1 enzyme activities and levels, demonstrating differential susceptibility to exposures in adults as well. This was the first study to examine PON1 variability by age and genetics in children.[141-143]

PESTICIDES CONTINUED

PUBLIC HEALTH ACTION

The EPA Worker Protection Standard (WPS) is designed to reduce pesticide exposure and protect farmworker health. In November 2015, EPA updated and strengthened the WPS for pesticides to protect farmworkers and their families. EPA considered research from the UC Berkeley (CERCH) and University of Washington Children's Centers to support the new standard.[131, 144-148] As part of the strengthened WPS, new rules are in place to prohibit children under 18 from handling pesticides. Additional education requirements now address take-home pathway exposures to farmworker families, and pesticide safety training is required every year. The UC Berkeley (CERCH) Children's Center is actively developing opportunities to conduct WPS trainings in agricultural communities throughout California.

When farmworkers go home after work, they may contaminate their cars and homes with pesticide residues from their skin and clothes. Family members may then be exposed to these residues. This route of exposure is called the take-home pathway.

University of Washington

- Studies show that the take-home pathway contributes to pesticide contamination in homes of farmworkers where young children are present.[131-133, 149, 150]
- Concentrations of agricultural pesticides were higher in the homes and vehicles of farmworkers compared to those of non-farmworkers. This suggests that the vehicle used for travel to and from work can be a source of exposure for family members.[131, 149, 151]

UC Berkeley (CERCH)

- The use of protective clothing, gloves, and hand-washing are known to reduce pesticide exposure to workers. However, these protective measures do not address the potential for the take-home pathway. A community-based intervention designed to reduce children's exposure to pesticides through the take-home pathway found that farmworkers can reduce pesticide exposure to their families by wearing gloves and removing work clothes before returning home.[144-145]

PUBLIC HEALTH ACTION

Informed by scientific findings from the UC Berkeley (CERCH) Children's Center, the California Department of Pesticide Regulation is developing new guidelines limiting pesticide applications near schools and day care centers. The new policy would require additional communications between pesticide applicators, school administrators, and parents. Researchers also presented testimony on this subject to the California Senate Environmental Quality Committee.[152]

IMPACT ON COMMUNITIES

The University of Washington Children's Center developed the "For Healthy Kids!" program to reduce the take-home pathway of pesticide exposure in farmworker households. In total, center staff conducted over 1,500 separate activities that reached close to 15,000 people. The program targeted behavioral interventions to specific communities and disseminated information on reducing exposures at health fairs, schools, and home health parties. They distributed "Keep Me Pesticide-free" bibs to newborns, soap kits for washing clothes separately, and many more materials to community members. These activities resulted in modest changes in certain behaviors among farmworkers.[146] Researchers conducted a results analysis of study participants and found that the community supported this style of research messaging.[153]

PUBLIC HEALTH ACTION

Integrated Pest Management (IPM) is an environmentally friendly approach to controlling pests. IPM uses strategies such as identification, monitoring, and prevention to minimize pesticide use. Findings show that IPM practices are successful in reducing pest counts in apartments while also reducing exposure to pesticides.[154, 155] In an effort to reduce the impact of pesticide exposure, New York City lawmakers have passed legislation and revised health codes that encourage the use of IPM. Many of these laws and codes cite the work of the Columbia University Children's Center.

- Neighborhood Notification Law (Intro 328A), 2007. This law created requirements about providing sufficient notice to neighbors about certain pesticide applications.[156]
- NYC Pesticide Reduction Law (Intro 329A, Local Law 37), 2007. This law established requirements related to the use of pesticides and promoted IPM practices.[157]
- NYC Health Code (Article 151), 2008. The revised code includes a section calling for pest management measures other than pesticide use and specifically stated, "Pesticide use should not be the first and only line of defense against pests."[158]

SECONDHAND TOBACCO SMOKE

BACKGROUND

Children have no control over their indoor environment, including where and when adults smoke. Secondhand tobacco smoke (STS) is a complex mixture containing more than 7,000 chemicals.[159] The numerous toxic and carcinogenic compounds found in STS can result in negative health effects, including preterm birth, impaired fetal growth, respiratory illness, and neurological problems, all of which can persist into adulthood.[160-166] Children's Centers research has clarified the relationship between STS and childhood leukemia, asthma, and neurodevelopment.

40% of nonsmoking children 4 to 11 years old had measurable levels of cotinine in their bodies in 2011-2012. Cotinine is created when the body breaks down nicotine found in tobacco smoke.[167]

UC Berkeley (CIRCLE)

STS has been proven to cause cancer in adults.[159] Until recently, little was known about STS exposure at critical periods of development and childhood cancer. This center was one of the first to study the effects of cigarette smoking in both fathers and mothers. Research found that paternal smoking before conception and STS exposure during early childhood can result in acute lymphoblastic leukemia and acute myeloid leukemia.[168] Prenatal paternal smoking and STS were associated with a chromosome abnormality (translocation) caused by a rearrangement of parts between chromosomes 12 and 21. This translocation nearly always occurs in the fetus before birth, often hiding for years before leukemia develops.[168] Identifying chromosome abnormalities allows researchers to better identify types of leukemia associated with specific exposures.

UC Berkeley (CIRCLE)

Poor recall of smoking history may explain why most epidemiological studies have not found an association between maternal smoking during pregnancy and the risk of childhood leukemia. Researchers used methylation biomarkers to better characterize maternal smoking. They found that exposure to STS, particularly from mothers, may alter the DNA of leukemia cells.

The amount of smoke exposure in the environment of the child is positively associated with the numbers of genetic deletions in leukemia cells. This suggests that smoke exposure before and after birth is continuously capable of inducing genetic damage, and removing smoke from a child's environment at any time can potentially stop further damage from occurring.[169]

"Approximately 2 percent of leukemia cases in California could be avoided if children were not exposed to tobacco smoking at any given point."
– Catherine Metayer, M.D., Ph.D., Director, UC Berkeley (CIRCLE) Children's Center.

IMPACT

Multiple Children's Centers have contributed to research on STS, focusing on the relationship to asthma, childhood leukemia, and neurodevelopment. Through their research, the Children's Centers show that STS can affect genes related to asthmatic and allergic responses in children. The centers have provided evidence that STS can exacerbate allergic effects and that exposure to STS can vary by socioeconomic status. The Children's Centers have disseminated their research findings to the community. With each step forward, Children's Centers research continues to identify ways to lessen or prevent effects of STS exposure.

University of Southern California

Maternal smoking during pregnancy can affect the respiratory health of her child. Maternal and grandmaternal smoking during pregnancy increased risk of childhood asthma.[161] Additionally, the risk of asthma onset in adolescents who smoked cigarettes regularly was more pronounced in those whose mothers smoked during pregnancy.[162] Risk of respiratory-related school absences also increased among children exposed to STS, regardless of whether or not they had asthma.[163]

Duke University

The complex mixture of chemicals in tobacco smoke has the potential to affect children's neurodevelopment by a variety of different mechanisms. Exposure to the entire mixture of compounds in STS had long-lasting negative effects on neurodevelopment that were much greater in magnitude than nicotine exposure alone.[164,165] It is important to minimize or eliminate prenatal and childhood STS exposure since efforts to minimize the neurodevelopmental effects of STS have been thus far unsuccessful. These *in vitro* studies included nicotinic receptor blockades, antioxidants, and methyl donors.[166]

IMPACT ON COMMUNITIES

A major health issue in Baltimore is the impact of STS and other air pollutants. Investigators from The Johns Hopkins University Children's Center met with the Baltimore City Health Department to learn about the effectiveness of HEPA air cleaners and educational interventions for STS reduction. The health department then developed a pilot intervention study using HEPA air cleaners, which has been successful in improving air quality in homes of pregnant mothers and babies who live with someone who smokes.

The Children's Centers have collectively pushed the boundaries of clinical, field, and laboratory-based research through novel and interdisciplinary approaches that include both animal and human studies designed to reduce the burden of disease in children.

Following children from preconception through childhood has enabled a greater understanding of the effects of environmental exposures on childhood diseases, and allowed for the collection of samples over time. These archives of biological and environmental samples serve as a tremendous resource for future studies and provide critical information on the prenatal and childhood determinants of adult disease.

The centers have translated scientific findings to provide practical information and actionable solutions leading to healthier children and a healthier society.

The following pages give examples of the unique features that have facilitated the Children's Centers' work and advancements in the field.

HALLMARK FEATURES

COMMUNITY OUTREACH AND RESEARCH TRANSLATION

BACKGROUND

Many times scientific concepts and research results are not easily understood by the general public. Empowered by program requirements[1], the Children's Centers have successfully communicated and applied research findings to protect children. The centers have provided the public, community organizations, healthcare professionals, decision makers, and others with practical information about the science and actionable solutions that link the environment to children's health. These achievements are largely due to the work of their Community Outreach and Translation Cores as well as input and direction from community advisory boards. The center structure and effective partnerships drive research design, lead to practical interventions, and create culturally-appropriate communications and educational resource materials that serve the community. Through their efforts, the centers have mobilized community members to participate in planning, implementing, and evaluating the effectiveness of interventions and public health strategies for healthier children, families, and future generations.

More than **1,500** separate outreach activities that informed **15,000** people about ways to reduce their environmental exposures.

– University of Washington Children's Center.

UC Davis

University of Southern California

Dartmouth College

UC San Francisco

The Children's Centers have developed and disseminated outreach materials that are critical for educating communities about children's environmental health topics. For example, the UC San Francisco Children's Center developed and disseminated a patient-centered series of culturally-appropriate brochures to counsel women and men who are planning a family, as well as pregnant women, on how to prevent harmful exposure to environmental contaminants.[2] The brochures are now being developed into a mobile app. The materials are highly engaging and interactive, such as the web tool developed by the Dartmouth College Children's Center to help families decrease their risk from exposure to arsenic in food and water.[3] Another example is the series of infographics created by the USC Children's Center to communicate risks of air pollution across the life course; these infographics received an award from the National Academy of Science Engineering and Medicine.[4] Many of the Children's Centers, including the center at UC Davis, designed brochures in multiple languages to be distributed in places like community clinics, support groups for Latina mothers, and the Mexican Consulate in Sacramento.

UC San Francisco

The UC San Francisco Children's Center developed the Environmental Health Inquiry Curriculum, an eight-hour in-depth course for all first year medical students. This medical school training is the first of its kind, and covers scientific concepts, critical literature appraisal, and application in clinical settings. The training is part of UC San Francisco's medical school curriculum for 2017.

"Starting today, everything will change. I learned techniques on how to protect my children from pesticides exposure, my family will benefit in addition to people of my community."
– CHAMACOS study trainee.

UC Berkeley (CERCH)

The partnership between the UC Berkeley (CERCH) Children's Center and the farmworker community in Salinas Valley has been the cornerstone of the center's success and impact. This center has pioneered more effective methods to provide individual results to study participants. They have worked closely with community partners for almost two decades to provide information to farmworker families on preventing pesticide and other environmental exposures. The center has given more than 1,000 presentations reaching over 25,000 people and developed brochures to promote healthy homes for farmworkers. They are working with the California Migrant Education Program to expand trainings statewide.

The UC Berkeley (CERCH) Children's Center also collaborated with Clinica de Salud del Valle Salinas to develop an innovative, computer-based prenatal environmental health kiosk: a culturally-appropriate software that teaches pregnant women about environmental health concerns to be aware of during pregnancy. Prenatal environmental health brochures on asthma, allergies, lead, pesticides, and carbon monoxide accompanied the kiosk.

CHAMACOS participant, age 12, showing the t-shirt she was given at birth when she was enrolled in the study.

UC San Francisco

The UC San Francisco Children's Center effectively collaborated with women's health professionals to engage the clinical community in efforts to prevent harmful environmental exposure through clinical, educational, and policy efforts. The leading women's health professional societies in the U.S. and globally called for action to prevent harmful environmental exposures.[5, 6] Eleven Children's Center's studies, including publications from the UC San Francisco Children's Center, were cited by the American College of Obstetrics and Gynecology and the American Society of Reproductive Medicine as evidence that environmental chemicals can adversely impact reproduction. The International Federation of Obstetrics and Gynecology (FIGO) also cited Children's Centers studies in their 2015 opinion paper. The FIGO opinion was amplified by a summit that brought together 50 leaders of reproductive health professional societies from 22 countries to develop an action plan addressing the global threat of environmental chemicals to reproductive health. The plan served as a starting point for the newly formed FIGO Reproductive Developmental Environmental Health Work Group that is carrying the action plan forward.

COMMUNITY OUTREACH AND RESEARCH TRANSLATION CONTINUED

UC Berkeley (CIRCLE)

When people get sick or develop a disability, they often ask their health care providers, "How or why did this happen?" In some cases, the answer is obvious. In others, it's more complicated. A Story of Health is a multimedia e-book told through the lives of fictional characters and their families – Brett, a young boy with asthma; Amelia, a teenager with developmental disabilities; and Stephen, a toddler recently diagnosed with leukemia. Each fictional case features the latest scientific research about disease origin and helpful facts about disease prevention. The e-book can help families explore the risk factors for disease as well as how to prevent disease and promote health. It was developed by the UC Berkeley (CIRCLE) Children's Center, the Western States Pediatric Environmental Health Specialty Unit (PEHSU), Agency for Toxic Substances and Disease Registry (ATSDR), the Collaborative on Health and the Environment, the Office of Environmental Health Hazard Assessment, California Environmental Protection Agency, and the Science and Environmental Health Network. A Story of Health is available online.[7] More than 7,500 health professionals have registered for continuing education credits available from the CDC for completing chapters.

"A Story of Health is compelling, educational and engaging, and will absolutely make a difference."
– Dr. Brian Linde, Pediatric Hospitalist, Kaiser Permanente.

Denver

With guidance from their community advisory board, the Denver Children's Center developed outreach materials for school-aged children and public health professionals. They designed 20 publicly-available lesson plans in environmental education related to air quality with supporting resources that comply with public school education science curriculum requirements.[8] As of August 2017, the Clean Air Projects K-12 website had received more than 7,600 unique visitors. The center's educational efforts help students, educators, and other stakeholders think critically about air quality and health. As a result, the community has been empowered to make informed decisions about these issues.

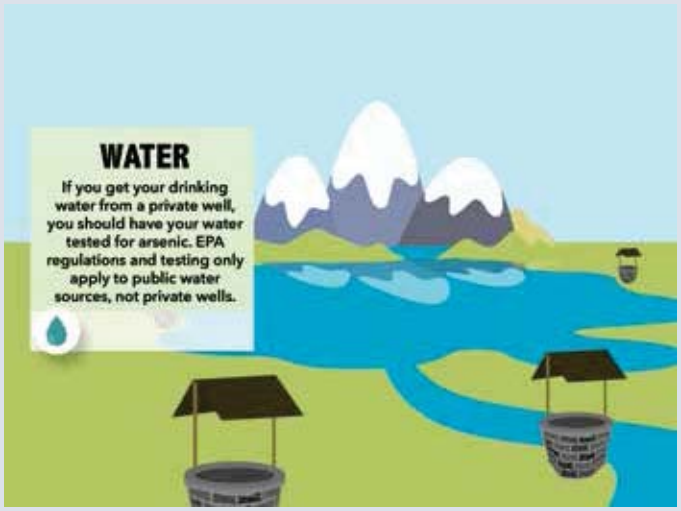
UC Berkeley (CERCH)

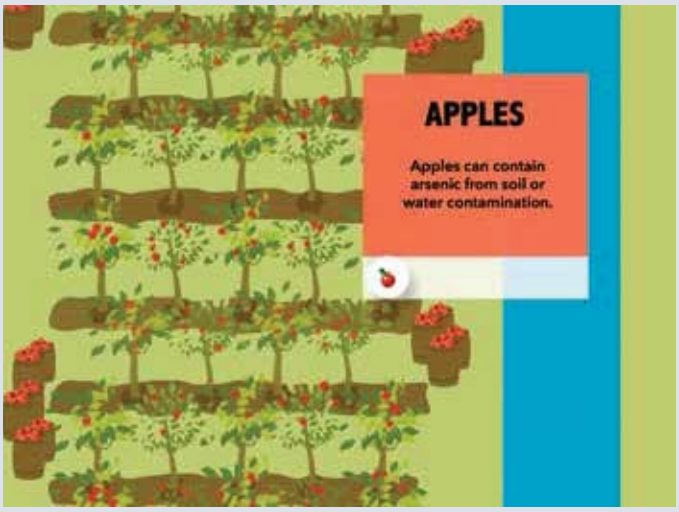
Two toolkits for childcare providers – an Integrated Pest Management (IPM) Toolkit and a Green Cleaning and Sanitizing Toolkit – were developed by the UC Berkeley (CERCH) Children's Center and the UC San Francisco Childcare Health Program.[9, 10] They provided environmental health training to schools and child care centers, in partnership with EPA Region 9 and the Pediatric Environmental Health Specialty Units. The UC Berkeley (CERCH) Center also developed an IPM training program for pest control companies serving schools and child care centers. The course is now a permanent Continuing Education curriculum on the UC Statewide IPM program, and more than 1,160 pest control professionals have been trained (as of 2017).[11]

"I would not consider it outreach; it is a dialogue; it is a community partnership."
– Dr. Elaine Faustman, Director, University of Washington Children's Center.

Dartmouth College

Through their interactive web tool, the Dartmouth College Children's Center disseminates tips for reducing arsenic exposure and preventing adverse health effects. Some of the tips include choosing white rice over brown rice, substituting rice with other grains such as millet and quinoa, soaking and rinsing rice before cooking, limit apple juice or choose other juices, reading food labels closely to avoid sweetener in the form of brown rice syrup, and testing private wells for arsenic levels.[3]





Images from the Dartmouth College Children's Center's web tool on arsenic.

EXPOSURE ASSESSMENT

BACKGROUND

The Children's Centers have developed technologies and used existing methods in new ways to more accurately measure environmental exposures in the places where children spend most of their time. These accurate and creative assessment tools can reveal correlations between environmental exposures and disease outcomes that are missed by conventional methods. The Children's Centers have collected biological and environmental samples across multiple years, allowing for analysis of between- and within-person variability. Between-person variability means comparing the levels of chemicals in different people. Within-person variability means comparing the levels of chemicals in the same person across seasons and years. It also allows for identification of seasonal and long-term trends. Whether it is measuring new contaminants or mixtures of contaminants, improving sampling techniques, or developing new exposure models, the exposure assessment conducted by the centers allows researchers to observe connections between complex environmental exposures and health outcomes not previously seen.

UC Berkeley (CERCH)

The UC Berkeley (CERCH) Children's Center has pioneered methods to measure manganese exposure in children's teeth.[12] While manganese is an essential nutrient, it is also used in some pesticides, and studies indicate that high exposures during development can result in neuropsychological deficits in children.[12] Studies addressing health effects of manganese during prenatal development are hampered by a lack of maternal biomarkers that reflect fetal exposure. Teeth accumulate metals, and their growth proceeds in an incremental pattern similar to growth rings that span the prenatal and postnatal periods. Measuring the distribution of manganese in children's teeth allows researchers to reconstruct exposure to manganese-containing pesticides at specific times during fetal development.[13]

The Johns Hopkins University

The ability to accurately capture children's air pollution exposures is essential to understanding its relationship to asthma. Many studies have focused on exposure to fine particulate matter ($PM_{2.5}$) as a risk factor for asthma, but very few epidemiological studies have assessed the implications of exposure to ultrafine particulate matter (UFP). Traditionally, monitoring UFP has been limited by the cost, size, weight, and upkeep of the equipment. However, The Johns Hopkins University Children's Center used a monitor that is small enough for personal exposure assessment resolution (Partector, CH Technologies). Measuring UFP along with $PM_{2.5}$ and the use of a GPS receiver improves the ability to observe relationships between air pollution and asthma by recording exposure peaks in relation to time and space. The center captured personal exposures at home, school, and in transit by placing these monitors in children's backpacks as they went about their daily activities. This is critical since ambient monitors often used in exposure assessments cannot capture the indoor environments where children spend most of their time.

Denver

The Denver Children's Center has improved the accuracy of measuring air pollution exposure with innovative, wearable exposure monitor samplers. These samplers are used to measure coarse particulate matter (PM_{10}) and its components, including black carbon, brown carbon, and secondhand tobacco smoke. Children wear the samplers along with ozone and nitrogen dioxide passive badges during the school week. Analyses have shown that personal monitors measure respirable pollutant exposures more accurately than conventional stationary monitors.[14, 15] As a result, the personal monitors reveal correlations between asthma severity and air pollutant exposures that are missed by stationary monitors. Understanding the relationship between exposures and asthma severity at the personal level is critical for managing asthma symptoms and for developing effective interventions and therapies.

Personal wearable exposure monitors: MicroPEM™ and Ogawa™ badges.

UC Berkeley (CERCH)

The UC Berkeley (CERCH) Children's Center has partnered with Oregon State University to use silicone sampling bracelets to assess pesticide exposures. These bracelets monitor cumulative pesticide exposures during daily activities, both indoors and outdoors. This approach differs from stationary monitors that can miss important exposure events and result in incomplete measurements. This is one of the first studies to compare measurements of pesticides in the bracelets to pesticides measured in house dust and agricultural pesticide use.

MyExposome wristband monitor.

INTERDISCIPLINARY APPROACHES

BACKGROUND

The Children's Centers approach pressing questions with a wide-angle lens from multiple dimensions, while not allowing the boundaries of any particular field to restrict, define, or determine the array of possible solutions. Experts from across many fields are involved at the earliest stages of developing research hypotheses, and they have been essential in narrowing the gap among environmental health knowledge and its application in our daily lives. Whether it is the synergy between the Emory University's nursing, medicine, arts and sciences, and public health programs, the University of Michigan's collaboration with a medical anthropologist to study neighborhood characteristics, or partnerships between the University of Illinois and the Pediatric Environmental Health Specialty Units (PEHSUs), the Children's Centers leverage the unique expertise of many fields to provide evidence to protect our children.

Dartmouth College

The maternal-infant microbiome study at the Dartmouth College Children's Center has fostered interdisciplinary research that was not realized prior to this program. This collaboration involves maternal–fetal physicians, neonatologists, pediatricians, experts in bioinformatics and statistics, biologists, ecologists, microbiologists, epidemiologists, and toxicologists to structure a pipeline from the clinic to the lab, to the analytics/visualization, and back to clinical outcomes. Additionally, this center is applying elemental mapping, which is an analytical technique in geochemical, environmental, and materials sciences that has only recently been applied to epidemiological studies. This approach can be used to investigate biomarkers and provide mechanistic information, and to investigate the impact of environmental toxins in combination with measures of socioeconomic adversity. These novel approaches facilitate collaboration between behavioral scientists, physicians, neonatologists, and pediatricians.

University of Washington

The University of Washington Children's Center translated research from public health, medicine, and public affairs to answers questions on how, what, where, and when agricultural farmworkers and their families are exposed to pesticides. The center worked with biologically based models for systems biology, *in vitro* models for evaluating impacts on neurodifferentiation, animal models for neurobehavior, exposure scientists, and engineers for air and fugitive dust modeling as well as risk assessors.

"Such centers are critical generators of new knowledge and also incubators for the next generations of leaders in children's environmental health."
– Textbook of Children's Environmental Health.[16]

University of Illinois

Developmental psychologists view the eyes as a window into an infant's world. By studying infant looking behavior, researchers have learned a great deal about early cognitive development. However, this approach is labor intensive because it typically involves manually scoring behavior as infants view stimuli on a computer screen. An important goal of the University of Illinois Children's Center is to adapt and implement methods used by developmental psychologists, allowing them to better study cognitive development during infancy in the epidemiological setting. To achieve this goal, the center partnered with an engineering research group and developed a new software that uses a computer webcam to reliably detect and record the gaze direction of very young infants (1 to 5 weeks of age). This allows for automated assessments of visual attention and visual recognition memory. Previous methods to track looking behavior cannot be used in infants this young, so this new methodology is a breakthrough in the field of children's health. This advancement would not be possible without the kind of interdisciplinary collaboration that is at the heart of the Children's Centers philosophy.

University of Michigan

The University of Michigan Children's Center spans various disciplines in public health. For example, the center is working with a medical anthropologist to examine how neighborhood characteristics, sleep patterns, perceptions of water quality, and diet may interact with toxicants to affect health outcomes. The health outcomes include growth and maturation, telomere length (often a sign of aging and/or stress), and DNA methylation profiles in a longitudinal birth cohort in Mexico City. Due to this collaboration, the center has revised many of their questionnaires and research activities to be culturally relevant and to reflect the daily lives of participants.

NEW METHODS AND TECHNOLOGIES

BACKGROUND

The Children's Centers have pioneered new approaches to study environmental exposures and health outcomes to establish a strong base of science. Novel methodologies, instrumentation, technologies, and tools have been used to more accurately measure and characterize complex exposures and identify early endpoints that are predictive of disease outcomes. Novel approaches to understand the biology of diseases include what are referred to as "-omics", such as genomics, epigenomics, proteomics, adductomics, metabolomics, and microbiomics. By incorporating these innovative methods, the Children's Centers have helped to revolutionize research and clinical practice. Ushering in new paradigms allow for more precise measurement and discovery of new risk factors.

UC Berkeley (CIRCLE)

Since the 1970s, blood spots have been routinely collected from every child at birth and stored for future reference. UC Berkeley (CIRCLE) Children's Center researchers obtained authorization from the California Department of Public Health to access this extensive archive as a valuable resource for discovering early-life exposures that may contribute to disease. By developing and validating new omics techniques, researchers have used blood spots to study the risks of childhood leukemia. These methods measure chemicals extracted from the blood spots, namely, small molecules (metabolomics) and adducts of reactive chemicals with human serum albumin (adductomics).[17-21] Unlike traditional, hypothesis-driven methods that target individual exposures, metabolomics and adductomics focus on broad classes of molecules. Investigators are comparing metabolomic and adductomic profiles between children with and without leukemia in order to find discriminating features that will then be investigated to determine their chemical identities and exposure sources. This novel untargeted approach will allow for discovery of new risk factors for childhood leukemia.

Blood spots that are routinely collected from every child at birth.

Duke University

The Duke University Children's Center developed a model to examine the effects of specific environmental aexposures on the brain. This *in vitro* model helps researchers study environmental exposures and neurodevelopmental health outcomes using primary neural stem cells derived from the neonatal rat brain, which closely resembles the human brain. The center is currently studying exposure of these cells to tobacco smoke extract and its constituents, including nicotine, and testing nutritional supplements for the potential to lessen tobacco-induced health effects.

"Children's Centers have led to an improved understanding of the environmental impacts on child health and development."
– 2017 National Academy of Sciences Report.[22]

Northeastern University

One novel approach used to study central nervous system integrity with infants is by using a custom pacifier device to examine non-nutritive suck patterning. This can serve as a potential biomarker of infant brain injury and be used as a prognostic tool for detecting future developmental delays. The Northeastern University Children's Center is using non-nutritive suck patterning to examine the effect of chemical exposures during pregnancy on the infant brain. This will be the first time it has been used in environmental health sciences.

University of Michigan

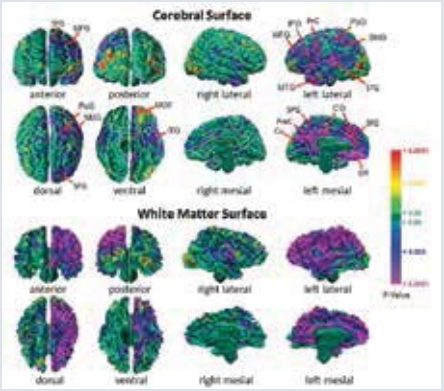
As a leader in epigenetics, the University of Michigan Children's Center is employing both gene-specific and genome-wide approaches to identify toxicant- and diet-induced perturbations to DNA methylation and gene expression underlying adverse health outcomes. Exposures to lead, bisphenol A (BPA), and phthalates at multiple developmental stages (prenatally, early childhood, and pre-adolescence) are associated with blood leukocyte methylation. This suggests that environmental exposures can impact the epigenome during multiple stages of life.[23, 24] The epigenome is made up of chemical compounds that can tell genes what to do. Further, lipids in the maternal bloodstream are associated with epigenetic programming in infants.[25]

University of Washington

The University of Washington Children's Center has developed advanced mathematical models to estimate between- and within-person variability. They also developed a biokinetic model for cortisol. The center has linked parent organophosphate (OP) pesticide compounds in the blood with concentrations in house dust and calculated observed half-lives of parent compounds in the blood.[26, 27] These advanced methodologies put the observed exposures in context.

Columbia University

Incorporating MRI brain imaging into epidemiological studies allows researchers to examine changes to brain structure that may mediate the effects of air pollution exposure on a range of neurodevelopmental, behavioral, and physical outcomes. Researchers have documented associations between specific brain changes and prenatal exposure to polycyclic aromatic hydrocarbons (PAHs) and chlorpyrifos, suggesting a key pathway for the observed neurotoxic effects of these chemicals.



MRI scans from the Columbia University Children's Center study population show correlations of prenatal PAH levels with cerebral surface measures.[28]

POPULATION–BASED STUDIES

BACKGROUND

Cohort studies follow a designated study population over time to establish risk factors for disease. Prospective cohort studies that are designed to follow children from before birth into adolescence or adulthood can provide critical information on prenatal and early childhood determinants of adult disease. The plasticity of the brain during puberty is the same as the first three months of life, and it is important to observe children during both these phases of development. Many Children's Centers have initiated large observational, prospective cohort studies that start during pregnancy or immediately after birth, then follow the children up to young adulthood. Other Children's Centers have utilized cohorts funded through other mechanisms, leveraging major investments that have already been made, such as examples shown below for the Duke University and the University of Michigan Children's Centers.

Columbia University

Starting in 1998, the Columbia University Children's Center enrolled more than 700 Latina and African-American women from New York City for its Mothers and Newborns (MN) cohort. This initial study led to the enrollment of subsequent cohorts, including 130 younger siblings of the MN cohort participants and the Fair Start cohort, that is currently enrolling pregnant women from the same neighborhoods. These prospective cohort studies are examining the impact of prenatal and postnatal exposure to air pollution, bisphenol A (BPA), phthalates, flame retardants, and pesticides on childhood health and development. These studies have been instrumental in the field, finding associations between certain environmental exposures and multiple adverse outcomes including reduced birthweight, obesity, attention-deficit hyperactivity disorder (ADHD), reduced IQ, and anatomical brain changes. The research has also revealed interactions between toxicant exposure and stressors related to poverty.

University of Washington

The University of Washington Children's Center has enrolled and maintained a prospective cohort of farmworkers, nonfarmworkers, and their families living in Yakima Valley, Washington. Families were first enrolled in the study when the children were between ages 2 and 6 years. Over the next 10 years, researchers assessed pesticide exposure in multiple seasons by measuring levels of pesticides in dust, urine, and blood. The study has also assessed biological mechanisms linked with toxicity and disease. A hallmark of this cohort is the frequency of samples, taken multiple times per season, during multiple seasons per year, across multiple years. This structure has allowed researchers to evaluate between- and within-person variability across seasons and years. One unique element of this study is the extensive exposome-based assessments. Not only have researchers measured over 80 pesticides in dust, they have also assessed phthalates, metals, mold, and social stress exposures using biomarkers and questionnaires.

"The Children's Centers have overcome many hurdles to understand the links between environmental exposures and health outcomes or social and cultural factors. Long-term studies [are critically important] to assess the full range of developmental consequences…at different life stages."
– Excerpt from *Lessons learned for the National Children's Study.*[29]

Duke University

The Duke University Children's Center follows a subset of approximately 400 children from a pre-existing Newborn Epigenetics STudy (NEST) cohort. NEST includes 2,000 racially-diverse pregnant women in central North Carolina, and was specifically designed to allow for in-depth investigation of epigenetic mechanisms that link the prenatal environment to children's health outcomes. NEST has assembled a rich repository of biological specimens over time from these mothers and their children as well as medical and epidemiological data that altogether have provided a strong foundation for other studies, including the Duke University Children's Center. This center is specifically investigating how secondhand tobacco smoke exposure during early life increases the risk of developing ADHD during adolescence.

University of Michigan

The Early Life Exposures in Mexico to Environmental Toxicants (ELEMENT) cohort consists of children enrolled at birth in Mexico City beginning in 1994 and followed for more than 22 years. The previously funded cohort is now part of the University of Michigan Children's Center, which investigates the influence of lead exposure on fetal and infant development. Findings from ELEMENT have found relationships between prenatal lead and low birthweight,[30] lower weight and higher blood pressure in young girls,[31, 32] cognition,[33-36] and ADHD[37]; findings have also shown that calcium supplementation during pregnancy can blunt the mobilization of lead stored in bone, thereby reducing fetal exposure.[38-40] Over the long follow-up period, researchers have been able to study exposures to metals other than lead, including fluoride,[41] cadmium,[42] mercury,[43] BPA, and phthalates.[44-49] Studies on additional health outcomes, such as cognition,[50-53] behavior,[50, 54] dental health, sexual maturation,[45, 46, 48, 55] adiposity,[44, 56, 57] and cardiometabolic risk[58] have also been possible. Evidence from ELEMENT has informed U.S. and Mexican lead exposure guidelines, including the 2010 CDC "Guidelines for the Identification and Management of Lead Exposure in Pregnant and Lactating Women", among others.[59]

UC Davis

In addition to the CHARGE study, the UC Davis Children's Center launched a second epidemiologic study of autism spectrum disorder (ASD) in 2006. The Markers of Autism Risk in Babies – Learning Early Signs (MARBLES) study follows mothers with at least one child with ASD before, during, and after their pregnancy. This allows researchers to obtain information about babies' prenatal and postnatal exposures. Infants are enrolled at birth and assessed for neurodevelopmental status until 3 years old. MARBLES has enrolled over 440 mother-child pairs and has conducted longitudinal biological and environmental sampling.

RODENT MODELS

BACKGROUND

Determining what chemical exposures are toxic to children requires a variety of research approaches, including high throughput *in vitro* cell based assays, animal models, and clinical and epidemiological studies. Studying mice in particular allows researchers to mimic how environmental exposures might affect humans. Such animal models provide invaluable information that researchers can use to isolate what chemicals pose the greatest risks, work out the complex mechanisms of toxicity, determine who is at risk for disease, and develop effective treatments. The Children's Centers use animal models alongside epidemiological studies to inform actions designed to reduce the burden of disease in children.

University of Illinois

Animal studies from the University of Illinois Children's Center were the first to determine the long-term and transgenerational consequences of prenatal phthalate exposure on both male and female reproduction. Prenatal exposure to phthalates was found to disrupt several aspects of female reproduction, including a disrupted estrous cycle, ovarian cysts, increased uterine weight, reduced fertility, and direct damage to the ovaries.[60, 61] The chemical mixture used in these animal studies was based on the specific mixture of phthalates identified in the blood of pregnant women enrolled in the center's cohort study. The resulting data represent the first findings from animal studies using an environmentally relevant phthalate mixture.

University of Illinois

Researchers found that exposure to bisphenol A (BPA) during perinatal development and adolescence may alter neuron and glia numbers in the prefrontal cortex of adult rats.[62] Given that the prefrontal cortex is a part of the brain that is critical for learning and memory, changes to the structure and function of this region may have broad implications for health. Studies are also underway to explore the effects of an environmentally relevant mixture of phthalates on the prefrontal cortex. Early findings show that phthalates resulted in impaired cognitive flexibility in adult rats. Researchers have taken anatomical measurements of the prefrontal cortex of the rat brain to establish the neural basis for this deficit.[63]

Columbia University

Researchers used animal models to investigate the epigenetic mechanisms or ways that polycyclic aromatic hydrocarbons (PAHs) and BPA may affect neurodevelopment and obesity.[64-67] High prenatal PAH exposure was found to be associated with weight gain and greater fat mass in mice, as well as more sedentary behaviors.[66, 67] These results parallel the findings in epidemiological studies linking high prenatal PAH exposure with higher risk of childhood obesity.[68]

"We don't do advocacy. We conduct the science and provide it in a way that can empower both the communities and the policymakers to do something about it."
– Frank Gilliland, Director, University of Southern California Children's Center.

Duke University

An animal model was used to examine the effects of preconception, prenatal, and early childhood exposure to tobacco smoke extract and nicotine on neurobehavioral function. Researchers successfully differentiated between the effects of exposure to the complex tobacco mixture and to nicotine alone. These investigators found predominant persistent neurobehavioral impairments with late gestational exposure. However, persisting neurobehavioral effects were also seen with early gestational and even preconceptional exposure.[69] Studying rats allows researchers to analyze effects of exposures that are difficult to study in humans, particularly in different parts of the brain. Because the effects of prenatal exposure in children is usually studied using blood, the genes identified in animals help to determine where researchers should look for similar epigenetic alterations in humans.

University of Michigan

Researchers are utilizing an agouti mouse model to mirror exposures seen in humans. They are investigating the role of perinatal and peripubertal lead, BPA, and phthalate exposures on offspring lifecourse metabolic status, reproductive development, and epigenetic gene regulation. Findings show that perinatal lead exposure in mice was associated with increased food intake, body weight, total body fat, energy expenditure, and insulin response in adult mice, with more pronounced effects in males.[70] In addition, lead exposure immediately before or after birth (perinatal) was associated with changes to gut microbiota that can cause obesity. Perinatal lead exposure also enhanced long-term epigenetic drift in mice.[71, 72]

University of Washington

Using animal models, researchers have conducted neurobehavioral studies to identify how genetic differences and timing of exposure modifies the health effects of pesticide exposure. The use of *in vitro* models that mimic brain development shows the impact of pesticides on signaling pathways and brain disorders. *In vitro* and animal models have demonstrated that organophosphate (OP) pesticides significantly inhibited neural growth, even at low concentrations. These effects appeared to be mediated by oxidative stress, as they were prevented by antioxidants.[75,76] These results suggest potential mechanisms where OP pesticides may interfere with neurodevelopment in children. Understanding these mechanisms may help identify critical windows of susceptibility in children.

SAMPLE REPOSITORY

BACKGROUND

Biological samples such as blood, placenta, urine, baby teeth, hair, and saliva allow researchers to answer questions about environmental exposures over long periods of time. The Children's Centers have been collecting and storing such samples since the inception of the program in 1997. As new environmental exposures of concern are identified, these samples serve as invaluable resources regarding historical exposures and health outcomes (as demonstrated by the Cincinnati Children's Center example below). Epidemiological studies, such as those established and accessed by the Children's Centers, are more valuable when there is capacity to store samples for future analysis. Evolving approaches for processing, extracting, and storing samples allow for downstream high throughput laboratory analyses at a pace not previously considered possible.

220,000 biological and environmental samples collected by the UC Berkeley (CERCH) Children's Center since 1998.

Cincinnati

The Cincinnati Children's Center has utilized archived samples to examine the effects of chemicals that were not included in its original study design. At its inception, the center focused on the effects of lead, pesticides, mercury, polychlorinated biphenyls (PCBs), and tobacco smoke. As time went on, however, community and public health concerns emerged concerning the potential effects of other metals, bisphenol A (BPA), polybrominated diphenyl ethers (PBDEs), phthalates, and other metals on the health of children. Under a different grant, Cincinnati Children's Center researchers were able to test for the presence of these chemicals in the stored biological samples and explore the associations between past exposures and health outcomes.

UC Davis

The UC Davis Children's Center has amassed an enormous repository of biological and environmental samples. More than 200,000 samples, including urine, blood, saliva, hair, baby teeth, placenta, maternal vaginal swabs, breast milk, meconium, and stool samples are now stored in the center's biorepository. Records of this biorepository will be available online where potential collaborators may query.

University of Washington

Since 1998, the University of Washington Children's Center has maintained a biorepository of biological and environmental study samples. These samples were leveraged by the National Children's Study for formative research projects related to social stress, dust pesticide concentrations, and characterization of the impacts of pesticides on the oral microbiome.[75-77] Samples have also been used to quantify the microRNA signal associated with pesticide exposure and occupational status.[78]

"Solid intervention work has been created [by the Children's Centers] along with extended links to the communities served. The continuity of this work has proven successful and should be maintained."
– EPA Board of Scientific Counselors/Children's Health Protection Advisory Committee Review.[79]

UC Berkeley (CERCH)

Starting in 1998, the UC Berkeley (CERCH) Children's Center established an extensive biorepository of more than 220,000 biological and environmental samples from the CHAMACOS studies. The center has collected urine samples from hundreds of children, starting as young as 6 months old.[80] These urine collection protocols have been adopted by cohort studies nationally and around the world. The center has pioneered blood processing and storage techniques and has collected breastmilk, saliva, hair, and deciduous (baby) teeth. Collecting samples from children at very young ages allows researchers to assess the effects of early life exposures on health outcomes later in childhood and young adulthood.

Dartmouth College

The Dartmouth College Children's Center has applied innovative approaches and technologies to expand infant microbiome studies to large scale, molecular epidemiology studies of healthy pregnant women and their infants. The center uses state-of-the-art laboratory techniques including automated archival storage and retrieval, and automated specimen processing. Expanding the application of advanced microbial sequencing and bioinformatics techniques has furthered the investigation of environmental exposures, the developing microbiome, and health outcomes.

EPA-funded research grants adhere to all laws, regulations, and policies supporting the ethical conduct and regulatory compliance of protecting the rights and welfare of human subjects and participants in research. To learn more about EPA's protection of human subjects, visit https://www.epa.gov/osa/basic-information-about-human-subjects-research-0.

A

B

C

D

E

F

INDEX

R

S

T

U

W

REFERENCES

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APPENDIX A

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James H. Johnson, Jr., ORD, NCER

Annie Kadeli, Office of Environmental Information (OEI)

Rick Keigwin, OCSPP, OPP

Christopher Lau, ORD, National Health and Environmental Effects Research Laboratory (NHEERL)

Patrick Lau, ORD, NCER

Sylvana Li, ORD, NCER

Danelle Lobdell, ORD, NHEERL

Sarah Mazur, ORD, Immediate Office of the Assistant Administrator

Jacquelyn Menghrajani, Region 9

Jacqueline Moya, ORD, National Center for Environmental Assessment (NCEA)

Linda Phillips, ORD, NCEA

Patrick Shanahan, ORD, NCER

Maryann Suero, Region 5

Nicolle Tulve, ORD, National Exposure Research Laboratory

Kelly Widener, ORD, NCER

APPENDIX B

SUMMARY OF GRANTS FUNDED UNDER THE NIEHS/EPA CHILDREN'S CENTERS PROGRAM, 1998-2017

This appendix summarizes the 46 grants funded as part of the Children's Centers program. Information provided includes:

BRIEF SUMMARY

Environmental exposures and health outcomes studied by each center for each of their awards, as well as the study populations.

GRANT NUMBERS

Use the grant numbers to access annual and final reports as well as publications on the EPA[1] and NIH[2] websites.

PRINCIPAL INVESTIGATORS (PI)

Some Centers have had been led by the same PI for different awards, others have different PIs for each award. Some centers have also had multiple PIs.

FUNDING INFORMATION

While most centers were funded for 5-year periods, the formative centers were for 3-year periods. These were established in 2010 to expand existing research, stimulate investigation of new research areas, and build capacity in the field of children's environmental health. You can identify these awards by looking for P20 in the NIH grant numbers.

For more information, please visit the Children's Centers website[3].

BROWN UNIVERSITY

Formative Center for the Evaluation of Environmental Impacts on Fetal Development

PI: Kim Boekelheide, M.D., Ph.D.

Study Population: N/A (animal models only)

2010-2014
$2,174,474
R834594
P20ES018169

Focused on correlating biomarkers with exposures to common environmental pollutants and stressors. Studied mechanisms that explain how environmental toxicants may alter prenatal development.

Obesity, lung development, metabolic syndrome

Arsenic, bisphenol A (BPA), endocrine disrupting chemicals (EDCs), phthalates

CINCINNATI

Center for the Study of Prevalent Neurotoxicants in Children

PI: Bruce Lanphear, M.D.

Study Population: Pregnant women and their children living in Cincinnati, Ohio

2001-2006
$7,429,010
R829389
P01ES01126

Examined the effects of low-level exposures to prevalent neurotoxicants. Tested the efficacy of an intervention to reduce lead toxicity. Evaluated new biomarkers to better predict the adverse effects of toxicants on cognition. Studied the mechanisms that explain how potential neurotoxicants contribute to behavioral problems, attention-deficit hyperactive disorder (ADHD), cognitive deficits, and hearing loss.

Growth, neurodevelopment

Lead, mercury, polychlorinated biphenyls (PCBs), secondhand tobacco smoke (STS), pesticides

1 https://cfpub.epa.gov/ncer_abstracts/index.cfm/fuseaction/searchFielded.main
2 https://projectreporter.nih.gov/reporter.cfm
3 https://www.epa.gov/research-grants/niehsepa-childrens-environmental-health-and-disease-prevention-research-centers

COLUMBIA UNIVERSITY

The Columbia Center for Children's Environmental Health

PI: Frederica Perera, Ph.D., Dr.P.H.

Study Population: African-American and Dominican pregnant women and their children in Northern Manhattan and the South Bronx, New York City

2015-2019 $5,795,207 R836154 P50ES009600	Examining how prenatal and early childhood exposures to air pollution disrupt brain development and lead to serious cognitive, emotional, behavioral, and adiposity problems during adolescence. Analyzing magnetic resonance imaging (MRI) scans to see how early PAH exposure adversely affects the structure, function, and metabolism of neural systems known to support the capacity for self- regulation.	ADHD, neurodevelopment, obesity Air pollution, polycyclic aromatic hydrocarbons (PAHs)
2009-2015 $7,660,669 R834509 P01ES009600	Studied the role of EDCs in the development of obesity, metabolic syndrome, and neurodevelopmental disorders in children. Evaluated the epigenetic mechanisms where prenatal and postnatal exposures to BPA and PAHs affect health in adolescence.	Neurodevelopment, obesity Air pollution, BPA, EDCs, PAHs
2003-2010 $7,947,203 R832141 P01ES009600	Studied mechanisms where prenatal exposures to air pollution may increase risk of asthma in children aged 5-7. Designed an intervention and evaluated the efficacy of a comprehensive integrated pest management (IPM) program for public housing.	Asthma, neurodevelopment Air pollution, PAHs, pesticides
1998-2004 $7,080,366 R827027 P01ES009600	Explored the mechanisms where prenatal and postnatal exposures to air pollutants increase the risk of asthma and/or neurodevelopmental impairments in young children. Investigated the impact of community and home-based interventions to reduce toxicant and allergen exposure, as well as risk of asthma.	Asthma, neurodevelopment Air pollution, PAHs, particulate matter (PM), STS

APPENDIX B

SUMMARY OF GRANTS FUNDED UNDER THE NIEHS/EPA CHILDREN'S CENTERS PROGRAM, 1998-2017

DARTMOUTH COLLEGE

Children's Environmental Health and Disease Prevention Research Center at Dartmouth

PI: Margaret Karagas, Ph.D.

Study Population: Pregnant women and their children living in New Hampshire whose household is served by a private well

2013-2018
$6,212,622
R835442
P01ES022832

Aims to understand the effect of arsenic and other contaminants in drinking water and food on child growth, neurodevelopment, and immune response, including infections, allergy, vaccine response, and the microbiome. Exploring the relationship between arsenic, gene expression, and epigenetic alterations in the placenta, and health outcomes.

Growth, immune function, neurodevelopment

Arsenic

2010-2014
$1,971,577
R834599
P20ES018175

Identified sources of arsenic for infants and children living in rural areas. Studied how arsenic interacts with key pathways in human development. Identified placental biomarkers related to prenatal arsenic exposure and to poor health outcomes in children. Determined the mechanisms that explain how arsenic modulates cell signaling.

Immune function, birth defects

Arsenic

DENVER

Environmental Determinants of Airway Disease in Children

PI: David Schwartz, M.D.

Study Population: Children nationwide aged 5 to 12 years with asthma

2009-2017
$7,612,686
R834515
P01ES018181

Studied whether endotoxin exposure, modified by genetics and environment, is associated with inflamed airways and more severe asthma symptoms. Explored whether epigenetic mechanisms contribute to the etiology of allergic airway disease. Tested an intervention to reduce home endotoxin levels and improve asthma.

Asthma, immune function, lung function

Air pollution, endotoxin, ozone

DUKE UNIVERSITY

Center for Study of Neurodevelopment and Improving Children's Health Following Environmental Tobacco Smoke Exposure

PI: Susan Murphy, Ph.D.

Study Population: Pregnant women and their children living in central North Carolina

2013-2018
$6,110,785
R835437
P01ES022831

Investigating mechanistic relationships between STS exposure and developmental neurocognitive impairments including ADHD.Exploring the impact of prenatal and postnatal exposures to environmental pollutants on neurodevelopmental impairments in both human and animal models.

ADHD, neurodevelopment

STS

Southern Center on Environmentally-Driven Disparities in Birth Outcomes

PI: Marie Lynn Miranda, Ph.D.

Study Population: Pregnant women in Durham, North Carolina

2007-2014
$7,735,620
R833293

Determined the mechanisms that explain how environmental, social, and host factors jointly influence rates of low birthweight, preterm birth, and fetal growth restriction in health disparate populations. Explored numerous gene- environment interactions in complementary human and animal models of birth outcomes.

Birth defects, fetal growth restriction, low birthweight, preterm birth, respiratory health

Air pollution, ozone, PM, non-chemical stressors

EMORY UNIVERSITY

Emory University's Center for Children's Environmental Health

PIs: Linda McCauley, Ph.D., R.N., P. Barry Ryan, Ph.D.

Study Population: Pregnant African American women and their children living in metro Atlanta

2015-2019
$5,023,117
R836153
P50ES026071

Assess pregnant women's environmental exposures, the impact on the microbiome, and the subsequent effects of changes in the microbiome on infant and child neurodevelopment.

Microbiome, neurodevelopment, preterm birth, socioemotional development

EDCs, maternal stress, chemical exposures

APPENDIX B

SUMMARY OF GRANTS FUNDED UNDER THE NIEHS/EPA CHILDREN'S CENTERS PROGRAM, 1998-2017

HARVARD UNIVERSITY

Metal Mixtures and Children's Health

PI: Howard Hu, M.D., Sc.D., Joseph Brain, S.D. (Co-PI)

Study Population: Children living in the Tar Creek Superfund site of Oklahoma

2003-2010
$7,184,280
R831725
P01ES012874

Examined biological markers of prenatal and early childhood exposures to metals. Explored the potential effect of stress from living near toxic waste and the modifying effect of stress on the neurotoxicity of metals. Used animal models to address fundamental mechanisms of metal pharmacokinetics.

Growth, neurodevelopment

Cadmium, iron, lead, manganese, stress

THE JOHNS HOPKINS UNIVERSITY

Center for the Study of Childhood Asthma in the Urban Environment (CCAUE)

PI: Nadia Hansel, M.D.; Greg Diette, M.D., Patrick Breysse, Ph.D.; Peyton Eggleston, M.D. (reverse chronological order)

Study Population: African-American children with asthma, living in the inner city of Baltimore

2015-2019
$6,000,000
R836152
P01ES018176

Exploring how exposure to air pollution causes high rates of asthma in the inner city. Investigating whether obese children with asthma are more vulnerable to the effects of air pollution. Studying a variety of mechanisms, including increased inflammation and oxidative stress.

Asthma, obesity

Air pollution, nitrogen dioxide (NO2), PM

2009-2014
$8,180,400
R834510
P01ES018176

Investigated how diet influences the asthmatic response to indoor and outdoor air pollution. Studied the mechanisms that explain how a low anti-oxidant, pro-inflammatory diet impairs the capacity to respond to oxidative stress, thereby increasing susceptibility to exposures.

Asthma

Air pollution, diet

2003-2010
$7,125,443
R8232139
P01ES009606

Examined how exposures to air pollution and allergens may relate to airway inflammation and respiratory morbidity in children with asthma. Explored new ways to reduce asthma symptoms by reducing environmental exposures. Examined the mechanisms where PM may exacerbate an allergen-driven inflammatory response in the airways.

Asthma

Air pollution, PM

1998-2003
$7,773,787
R826724
P01ES009606

Examined the genetic mechanisms for susceptibility to an inflammatory response in airways generated as a result of exposure to ozone. Developed intervention strategies to reduce environmental pollutant and indoor allergen exposures.

Asthma

Air pollution, ozone

MOUNT SINAI SCHOOL OF MEDICINE

Inner City Toxicants, Child Growth, and Development

PI: Mary Wolff, Ph.D.; Phillip Landrigan, M.D.

Study Population: Pregnant African American and Latino women and their children living in inner city New York

2003-2010
$7,919,631
R831711
P01ES009584

Studied children's pathways of exposure to EDCs. Explored relationships among prenatal and early childhood exposures to EDCs and neurobehavioral development in children 6 to 10 years old. Evaluated individual susceptibility factors such as, built environment, diet, physical activity, and genetic variability.

Neurodevelopment

EDCs, lead, non-chemical stressors, PCBs, pesticides

1998-2003
$8,007,874
R827039
P01ES009584

Identified linkages between environmental toxicants and neurodevelopmental dysfunction. Studied mechanisms that explain how environmental toxicants can impair development. Evaluated novel approaches to prevention.

Neurodevelopment

EDCs, lead, PCBs, pesticides

NORTHEASTERN UNIVERSITY

Center for Research on Early Childhood Exposure and Development in Puerto Rico

PI: Akram Alshawabkeh, Ph.D.

Study Population: Young children born to mothers living near Superfund and hazardous waste sites in Puerto Rico during pregnancy

2015-2019
$4,999,537
R836155
P50ES026049

Focusing on the impact of a mixture of environmental exposures on prenatal and early childhood development in an underserved and highly-exposed population. Study the mechanisms that explain how environmental toxicant exposures during pregnancy affect childhood health and development.

Growth, neurodevelopment, preterm birth

Air pollution, consumer products, EDCs, maternal stress, parabens, water quality

APPENDIX B

SUMMARY OF GRANTS FUNDED UNDER THE NIEHS/EPA CHILDREN'S CENTERS PROGRAM, 1998-2017

UNIVERSITY OF CALIFORNIA, BERKELEY

Berkeley/Stanford Children's Environmental Health Center

PI: S. Katharine Hammond, Ph.D. (current); John Balmes, M.D. (Co-PI); Gary Shaw, Dr.P.H. (Co-PI); Ira Tager, M.D.

Study Population: Pregnant women, infants, children, and adolescents living in the San Joaquin Valley and Fresno, California

2013-2018
$7,175,201
R835435
P01ES022849

Understanding the relationship between air pollution and health outcomes throughout childhood. Examining the modifying role of both genetic and neighborhood factors. Studying the underlying immune mechanisms that could be related to environmental exposures and health outcomes. Improving risk assessment in a region characterized by both high air pollution and health disparities.

Asthma, atopy, birth defects, diabetes, immune function, obesity, preterm birth

Air pollution, non-chemical stressors, PAHs

2010-2014
$1,986,370
R834596
P20ES018173

Investigated the effects of prenatal and childhood exposures to air pollution on birth outcomes, immune function, and asthma. Studied the underlying immune mechanisms that could be related to environmental exposures and health outcomes.

Asthma, birth defects, immune function, low birth weight, preterm birth

Air pollution, endotoxin, non-chemical stressors, PAHs

Center for Environmental Research and Children's Health (CERCH)

PI: Brenda Eskenazi, Ph.D.

Study Population: Pregnant women and their children in a primarily low-income, farmworker community in the Salinas Valley, California

2009-2017
$6,179,461
R834513
P01ES009605

Studying exposures and health outcomes in children, focusing on boys age 9-13 year. Focusing on exposure to a mix of chemicals including pesticides, PBDE flame retardants, and manganese fungicides. Assessing the relationship of prenatal and early childhood exposures with neurodevelopment and the timing of pubertal onset. Studying on molecular mechanisms with a focus on epigenetic effects.

Neurodevelopment, reproductive development

Manganese, PBDEs, perfluorooctanoic acid (PFOA), perfluorooctane-sulfonic acid (PFOS), pesticides

2003-2010
$8,431,143
R831710
P01ES009605

Assessed exposures and health outcomes in children age 5-7 years. Conducted specialized pesticide exposure studies to improve understanding of pesticide metabolism. Conducted laboratory studies to investigate responses to mixed exposures to pesticides and allergens.

Asthma, growth, neurodevelopment

PBDEs, PCBs, pesticides

1998-2003
$8,695,541
R826709
P01ES009605

Explored whether chronic, low-level exposures to organophosphate pesticides are potentially hazardous to children's health. Initiated and evaluated the impact of an intervention to reduce pesticide exposure to children.

Asthma, neurodevelopment

Pesticides

UNIVERSITY OF CALIFORNIA, BERKELEY

Center for Integrative Research on Childhood Leukemia and the Environment (CIRCLE)

PI: Catherine Metayer, M.D., Ph.D.(current); Patricia Buffler, Ph.D.

Study Population: Children with leukemia living in California and worldwide

2015-2019
$5,999,999
R836159
P50ES018172

Identifying causes of childhood leukemia in an ethnically diverse population and understand how environmental factors increase risk. Studying specific chemical exposures during pregnancy and the effects on immune system development and risk of childhood leukemia. Investigating the epigenetic mechanisms associated with exposures and leukemia risk.

Leukemia, immune function

PBDEs, PCBs, pesticides, STS

2009-2014
$6,667,762
R834511
P01ES018172

Investigated the effects of prenatal and childhood exposures to chemicals. Investigated the genetic and epigenetic mechanisms associated with exposures and leukemia risk.

Leukemia, immune function

PBDEs, PCBs, pesticides, STS

UNIVERSITY OF CALIFORNIA, DAVIS

Center for Children's Environmental Factors in the Etiology of Autism

PI: Judy Van de Water, Ph.D. (current); Isaac Pessah, Ph.D. and Irva Hertz-Piccioto, Ph.D. (Co-PI)

Study Population: Children living in California with autism or developmental delay

2013-2018
$6,061,423
R835432
P01ES011269

Studying the epigenetic mechanisms of toxicant exposure on immune function. Develop and apply new biomarkers of autism risk. Characterizing the potential health effects of environmental exposures and various life stages. Predicting long-term clinical and behavioral consequences.

Autism spectrum disorder (ASD), immune function

PBDEs, PFOA, PFOS, pesticides

2006-2013
$8,154,371
R833292
P01ES011269

Identified environmental, immunologic, and genetic risk factors contributing to the incidence and severity of ASD. Studied the mechanisms that explain how environmental, immunologic, and molecular factors interact to influence the risk and severity of autism.

ASD, immune function

Mercury, PBDEs, PCBs

2001-2006
$7,395,766
R829388
P01ES011269

Investigated environmental risk factors contributing to the incidence and severity of autism. Conducted the first case-controlled epidemiological study of environmental factors in the etiology of autism. Examined molecular mechanisms underlying neurodevelopmental disorders associated with autism.

ASD, immune function

Mercury, PBDEs, PCBs

APPENDIX B

SUMMARY OF GRANTS FUNDED UNDER THE NIEHS/EPA CHILDREN'S CENTERS PROGRAM, 1998-2017

UNIVERSITY OF CALIFORNIA, SAN FRANCISCO

Pregnancy Exposures to Environmental Chemicals Children's Center

PI: Tracey Woodruff, Ph.D.

Study Population: Pregnant women in northern California

2013-2018
$5,309,618
R835433
P01ES022841

Examining the epigenetic mechanisms that explain how environmental exposures during pregnancy affect early stages of prenatal development. Studying how environmental chemicals may damage the placenta and disrupt prenatal development. Explore whether effects are exacerbated by maternal stress.

Birth outcomes, early development, growth, placental development

BPA, EDCs, non-chemical stressors, PBDEs, perflourinated chemicals (PFCs), PFOA, PFOS

2010-2013
$1,986,370
R834596
P20ES018173

Explored the epigenetic mechanisms that explain how environmental exposures during pregnancy affect early stages of prenatal development. Translated scientific findings to healthcare providers in order to improve clinical care and prevent prenatal exposures to harmful chemical exposures.

Birth outcomes, early development, growth, placental development

BPA, EDCs, non-chemical stressors

UNIVERSITY OF ILLINOIS

Novel Methods to Assess Effects of Chemicals on Child Development

PI: Susan Schantz, Ph.D.

Study populations: (1) Pregnant women and their infants living in Urbana-Champaign, Illinois; (2) Adolescents living in New Bedford, Massachusetts

2013-2018
$6,213,565
R835434
P01ES022848

Investigating how EDCs interact with diets high in saturated fat to impact neurological and reproductive function. Studying the mediating role of oxidative stress and inflammation. Using laboratory rodent studies to examine the mechanisms that explain how BPA causes trans-generational effects on female fertility.

Neurodevelopment, oxidative stress, reproductive development

BPA, EDCs, high-fat diet, phthalates

2010-2014
$2,009,214
R834593
P20ES018163

Assessed prenatal and adolescent exposures to BPA and phthalates. Studied the relationship between environmental exposures, physical development, cognition, and behavior in infants and adolescents. Understand the mechanisms where prenatal BPA exposure affects gonadal development and reproduction in adulthood in mice.

Growth, neurodevelopment, reproductive development

BPA, EDCs, phthalates

FRIENDS (Fox River Environment and Diet Study) Children's Environmental Health Center

PI: Susan Schantz, Ph.D.

Study Population: Hmong and Laotian refugees who consume PCB and mercury-contaminated fish from the Fox River in northeastern Wisconsin

2001-2006
$9,057,170
R829390
P01ES011263

Studied the impact of exposure to PCBs and methylmercury on cognitive, sensory, and motor development. Developed effective educational strategies to reduce exposure to neurotoxic contaminants. Included laboratory rodent studies to better understand the mechanisms that explain how environmental contaminants may induce neurological deficits in children.

Neurodevelopment, reproductive development

Mercury, PCBs

UNIVERSITY OF IOWA

Children's Environmental Airway Disease Center

PI: Gary Hunninghake, M.D.

Study Population: Children 6 to 14 years old living in rural communities in Iowa

1998-2003
$7,175,201
R835435
P01ES022849

Studied mechanisms that initiate, promote, and resolve grain dust-induced inflammation. Estimated asthma prevalence and morbidity and determine differences between farm and nonfarm children. Discovered that endotoxin increases the replication of viruses in airway epithelia.

Asthma, respiratory disease

Endotoxin, grain dust

UNIVERSITY OF MEDICINE AND DENTISTRY OF NEW JERSEY

Center for Childhood Neurotoxicology and Assessment

PI: George Lambert, M.D.

Study Population: Children living in New Jersey with ASD or learning disabilities

2001-2006
$6,179,461
R834513
P01ES009605

Examined the effects of environmental chemicals on neurological health and development. Studied brain development in laboratory animal models. Explored linkages and the underlying mechanisms between environmental neurotoxicants and ASD.

ASD, neurodevelopment

Heavy metals, manganese

APPENDIX B

SUMMARY OF GRANTS FUNDED UNDER THE NIEHS/EPA CHILDREN'S CENTERS PROGRAM, 1998-2017

UNIVERSITY OF MICHIGAN

Lifecourse Exposures and Diet: Epigenetics, Maturation and Metabolic Syndrome

PI: Karen Peterson, D.Sc., Vasantha Padmanabhan, Ph.D.

Study Populations: Pregnant and postpartum mothers and their children living in (1) Mexico City and (2) in Michigan

2013-2018
$5,618,006
R835436
P01ES022844

Researching how obesity, sexual maturation, and risk of metabolic syndrome are affected by the interaction of EDCs with diet during prenatal development and puberty.

Birth outcomes, physical growth, obesity, metabolic syndrome risk, sexual maturation

BPA, cadmium, diet, EDCs, lead, phthalates

2010-2013
$1,919,311
R834800
P20ES018171

Examined how prenatal and childhood exposures to lead and EDCs affect the epigenome, the instruction book that programs the activity of genes, with a focus on key genes regulating growth and maturation; Examined the associations between prenatal and childhood exposures to BPA and phthalates, and health outcomes during adolescence.

Physical growth, obesity, and sexual maturation

BPA, EDCs, lead, phthalates

Michigan Center for the Environment and Children's Health

PI: Barbara Israel, Dr.P.H.

Study Population: Asthmatic children living in inner city Detroit

1999-2003
$7,433,496
R826710
P01ES009589

Studied environmental hazards in houses and neighborhoods with the goal of improving asthma-related health. Examined the effects of daily and seasonal fluctuations in indoor and outdoor ambient air quality on lung function and severity of asthma symptoms.

Asthma, lung function

Air pollution

UNIVERSITY OF SOUTHERN CALIFORNIA

Southern California Children's Environmental Health Center

PI: Robert McConnell, M.D., Frank Gilliland, M.D., Ph.D., Henry Gong, M.D.

Study Population: School-age children living in Los Angeles, California

2013-2018
$6,418,683
R8345441
P01ES022845

Investigating the longitudinal effects of prenatal, early and later childhood TRAP exposure on BMI, obesity, and metabolic dysfunction. Examining the effects of air pollution on adipose inflammation and metabolic outcomes.

Fat distribution, insulin sensitivity, obesity

Air pollution, NO2, PM, traffic-related air pollution (TRAP)

2003-2010
$7,696,613
R831861
P01ES009581

Examined the effects of regional ambient air pollutants and locally emitted fresh vehicle exhaust on asthma and airway inflammation. Assessed genetic variation as a determinant of childhood respiratory susceptibly.

Asthma, inflammation

Air pollution, NO2, PM, TRAP

1998-2003
$7,290,042
R826388
P01ES009581

Explored how host susceptibly and environmental exposures contribute to children's respiratory disease. Studied the biological mechanisms that explain how STS alters normal allergic responses in children.

Asthma, respiratory disease

Air pollution, STS

UNIVERSITY OF WASHINGTON

Center for Child Environmental Health Risks Research

PI: Elaine Faustman, Ph.D.

Study Population: Children in agricultural communities in the Yakima Valley region of Washington state

2009-2016
$7,273,531
R834514
P01ES009601

Studied biochemical, molecular and exposure mechanisms that define children's susceptibility to pesticides. Evaluated age, seasonal, temporal, and gene-environment factors that define within- and between-person variability for organophosphate pesticide exposures and response.

Neurodevelopment
Pesticides

2003-2010
$7,651,736
R831725
P01ES009601

Studied the biochemical, molecular, and exposure mechanisms that define children's susceptibility to pesticides and the implications for assessing pesticide risks to normal development and learning.

Neurodevelopment
Pesticides

1998-2004
$7,102,390
R826886
P01ES009601

Studied biochemical, molecular and exposure mechanisms that define children's susceptibility to pesticides. Developed an intervention to break the take-home pathway of exposure. Incorporated findings into risk assessment models designed to protect children's health.

Neurodevelopment
Pesticides

October 2017
www.epa.gov

U.S. Environmental Protection Agency • Office of Research and Development • National Center for Environmental Research
U.S. Department of Health and Human Services • National Institutes of Health • National Institutes of Environmental Health Sciences