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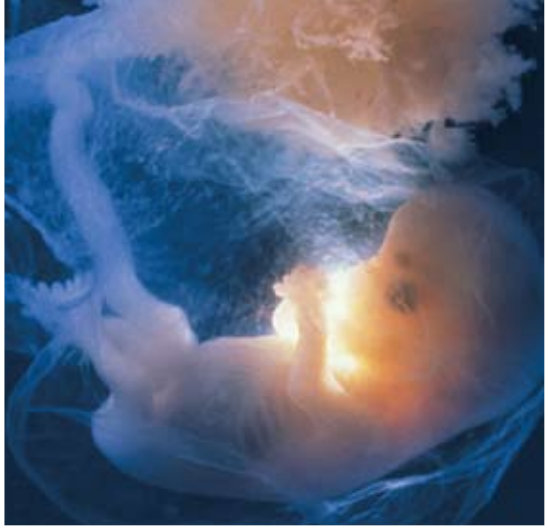

A Decade of Children's Environmental Health Research

Highlights from EPA's Science to Achieve Results Program

SUMMARY REPORT

Office of Research and Development
National Center for Environmental Research

EPA/600/S-07/038

A Decade of Children's Environmental Health Research: Highlights from EPA's Science to Achieve Results Program

U.S. Environmental Protection Agency
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Disclaimer

The research described in this document has been funded wholly by the United States Environmental Protection Agency (EPA) under the Science to Achieve Results (STAR) grant program. 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 synthesis 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 sufficiently detailed nor is it 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.

Acknowledgement

While this document was reviewed by both external and internal EPA reviewers chosen for their contributions to the field of children's environmental health, it was also reviewed by some of the principal investigators whose research is discussed in the report. Dr. Cynthia F. Bearer of Case Western Reserve University under contract to ICF International provided additional review. Rebecca Brown of EPA's National Center for Environmental Assessment; Michael Firestone, Ph.D. EPA's Office of Children's Health Protection; Hugh Tilson, Ph.D. EPA's Office of Research and Development National Program Director for Human Health reviewed the report for EPA.

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Contents

Glossary

Allergic sensitization: Process by which a subject becomes increasingly allergic to a substance through repeated exposure to that substance. As the allergy develops, the response becomes worse with even short exposures to low concentrations eliciting severe reactions.

Arsenic: Heavy metal naturally occurring in the environment in various organic and inorganic forms. Typical sources of exposure to arsenic are from food, drinking water, and pesticides.

Attention Deficit Hyperactivity Disorder (ADHD): A largely neurological developmental disorder characterized by a persistent pattern of inattention or hyperactivity-impulsivity, or both.

Autism: A developmental disability that results from a disorder of the human central nervous system. It is diagnosed using specific criteria for impairments to social interaction, communication, interests, imagination, and activities.

Autism Spectrum Disorder (ASD): A developmental and behavioral syndrome that results from certain combinations of characteristically autistic traits.

Biomarker: A biological substance (blood, DNA, saliva, breast milk, hair, etc.) used to indicate exposure, or early biological effect to an environmental chemical, or susceptibility to disease.

Cell proliferation: Cell growth and multiplication.

CHAMACOS: The Center for the Health Assessment of Mothers and Children of Salinas, a project of the University of California at Berkeley Center for Children's Environmental Health Research.

CHARGE: Childhood Autism Risks from Genetics and the Environment, a project of the University of California - Davis Center for the Study of Environmental Factors in the Etiology of Autism.

Chloropyrifos: Ubiquitous organophosphate pesticide widely used before an EPA ban on household use in 2001.

Community-based participatory research (CBPR): A collaborative approach to research that equitably involves community and academic investigators in the research process and recognizes the unique strengths that each brings, particularly with the goal of achieving social change, to improve health outcomes and eliminate health disparities.

Detoxify: Removing harmful substances from the body through metabolic pathways.

Dichlorodiphenyl dichloroethene (DDE): A metabolite of DDT.

Dichlorodiphenyl trichloroethane (DDT): A synthetic crop pesticide widely used in the 1940s and 1950s and banned in the 1970s due to its harmful effects on wildlife and proclivity for bioaccumulation.

Environmental neurotoxicants: Naturally occurring (e.g., mercury) or synthetic (e.g., pesticides) chemical agents that act specifically on nerve cells.

Environmental tobacco smoke (ETS): Smoke generated from the burning end of a cigarette, pipe, or cigar and smoke that is exhaled by smokers.

Exposure assessment: Evaluates the magnitude, frequency, and duration of human substance exposure.

Genotype: Internally coded, inherited information used as a blueprint to build a living organism.

Inorganic arsenic: See arsenic.

Longitudinal birth-cohort studies: Typically long-term observational studies; often following mothers during pregnancy and/or babies from birth through several stages of the developmental.

Manganese: Toxic metal similar to iron occurring naturally in the environment; exposure linked to cognitive and motor impairments.

Metabolites: Biological by-products of metabolism. Often used as a biomarker to confirm exposure to environmental factors.

Microactivities: Individual, detailed behavioral characteristics comprising part of the exposure pathway.

Neurotoxic pesticides: Pesticides formulated to alter the normal functioning of the nervous system. See also, Environmental neurotoxicants.

Ovalbumin (OVA): A protein commonly used in research to stimulate an allergic reaction.

Ozone: An unstable form of oxygen found naturally in the stratosphere and troposphere. At ground level it is considered an air pollutant having harmful effects upon the respiratory system.

Particulate-matter (PM): The summation of airborne molecules, both solid and liquid, that remain suspended in air. These molecules vary in toxicity due to their size (e.g., PM10, PM2.5) and /or composition.

Pathways: Refers to the numerous channels by which one can become exposed to environmental pollutants.

Pervasive Developmental Disorder (PDD): A group of five disorders (Autistic Disorder, Rett's Disorder, Childhood Disintegrative Disorder, Asperger's Syndrome, and Pervasive Developmental Disorder Not Otherwise Specified) characterized by delays in development.

Pesticide drift: Term used to define the airborne release and distribution of pesticides/insecticides.

Polybrominated diphenyl ethers (PBDEs): A bioaccumulating flame retardant substance found in many household products (e.g., electronics, furniture).

Polychlorinated biphenyls (PCBs): An array of synthetic organic pollutants produced primarily for industrial processes in the 1950-60s and widely released into the environment. PCBs were banned in the US in 1977.

Polycyclic aromatic hydrocarbons (PAH): A carcinogenic organic molecule produced from the burning of organic substances such as coal, garbage, oil, and cigarettes.

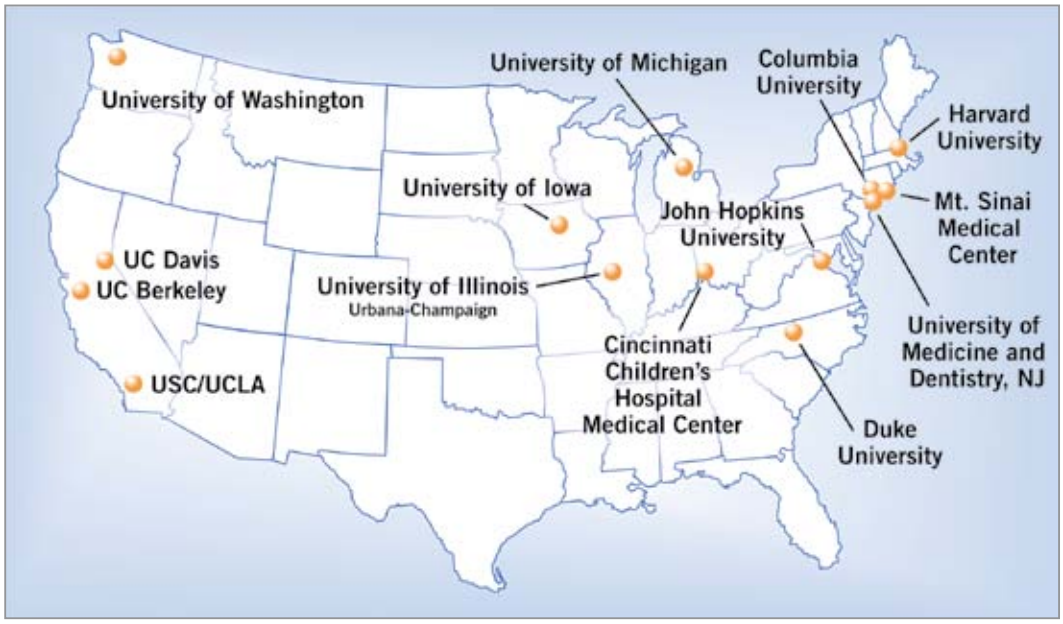
Respiratory syncytial virus (RSV): Virus causing respiratory tract infections, most commonly in infants and children.

Spray Drift: See pesticide drift.

T-helper cell (Th1, Th2): A type of T cell that provides help to other cells in the immune response by recognizing foreign antigens and secreting substances called cytokines that activate T and B cells.

Wheezing: Making a coarse whistling sound due to narrowed or obstructed air passages; symptomatic of asthma and/or reduced lung function.

EPA/National Institute of Environmental Health Sciences (NIEHS)
Centers for Children's Environmental Health and Disease Prevention Research Locations



Executive Summary

In 1997, Federal Executive Order 13045, *Protection of Children from Environmental Health Risks and Safety Risks*, mandated Federal agencies to place a high priority on identifying and assessing risks affecting children and to ensure their policies, standards, and programs address disproportionate risks to children. The Executive Order stimulated a wide array of research supported by the U.S. Environmental Protection Agency (EPA), particularly through the National Center of Environmental Research's (NCER) extramural Science to Achieve Results (STAR) grant program.

In 1998, the STAR grant program, which supports human health, ecology, economics and engineering sciences through grants, centers, and fellowships, initiated a diverse portfolio focused specifically on children's environmental health research. The goal of this research is to better understand children's genetic, life stage, and behavioral susceptibilities. The research also aims to better characterize child-specific harmful chemical exposures and to demonstrate cost effective, protective interventions, particularly at the household and community level. Since 1998, the STAR grant program has issued more than 10 research solicitations and awarded over 60 grants focusing on children's environmental health, including: Centers for Children's Environmental Health and Disease Prevention Research (21 Children's Centers awards—11 currently active); Aggregate Exposure Assessment of Pesticide Exposure (3 grants); Biomarkers for Children's Risks (8 grants); Children's Vulnerability to Toxics (19 grants); Children's Valuation (7 grants); and Early Indicators of Environmentally Related Disease (5 grants). To date, NCER has funded more than a hundred individual projects resulting in more than a thousand peer-reviewed articles in a wide array of scientific publications.

Since the passage of the Executive Order 10 years ago, this research has increased scientific knowledge of many aspects of children's environmental health. For example, studies have shed light on how environmental exposures change across life stages from newborn to school-age children and some of the genetic factors that contribute to children's vulnerability. Research has also provided insight on how to appropriately assess aggregate and cumulative exposures, suggested what biological markers in children's urine or blood tell us about exposure or effects, and indicated what steps need to be taken in order to prevent harmful exposures, including which interventions are effective and sustainable. This is particularly the case for residential pesticide exposure, which was an articulated focus of the STAR grant program during the past 10 years. Some of the major research findings include the following:

- People metabolize pesticides differently based on their genotype; some faster, others slower. This finding is of particular concern during pregnancy, as many babies do not develop the ability to metabolize some pesticides during the first two years of life, putting them at greater risks of health effects.
- Children living close to major roadways in Southern California have a higher risk of asthma.
- EPA's ban on two household pesticides (diazinon and chlorpyrifos) resulted in a rapid decrease in exposures in New York City. Children born after the ban were also healthier.
- Integrated Pest Management (IPM) can be effectively implemented in urban areas to reduce both pesticide and allergen triggers.
- Community partners play a critical role in informing, implementing, and translating children's environmental health research.

While much has been discovered in the last 10 years, there is still much to learn about children's environmental health. Building on the many lessons learned in characterizing pesticide exposures during early development and in investigating the multiple impacts of indoor and outdoor air pollution on childhood asthma, NCER is now broadening its focus. Recently, the STAR grant program has increased its support for research on less characterized, though increasingly common, chemicals (for example, plasticizers and flame retardants) and chronic childhood ailments (for example, autism and other developmental disabilities). The STAR grant program will continue to work closely with Federal, state, and community partners to disseminate these and many other findings in order to create healthier environments and nurture healthier children. The STAR grant program also anticipates continuing, even broadening, Federal partnerships for future research efforts that build upon the progress that has already been made. For more information about NCER and the STAR grant program, please visit **http://www.epa.gov/ncer**. For more information on the Children's Centers, please visit **http://www.epa.gov/ncer/childrenscenters**.

Introduction

Scientists are finding increasing evidence that exposure to some environmental factors jeopardizes children's health and may relate to large increases in the number of children diagnosed with asthma, Attention Deficit/Hyperactivity Disorder (ADHD), autism, and developmental impairment. Evidence is also strong that environmental health risks disproportionately affect children. Their nervous, immune, digestive, and other bodily systems are still developing while they receive disproportionately greater exposure to pollutants. They eat more food, drink more fluids, and breathe more air in relation to their body weight than adults do.

To address the increasingly evident disproportionate environmental health risks for children, President Bill Clinton signed Federal Executive Order 13045, *Protection of Children from Environmental Health Risks and Safety Risks*, on April 21, 1997 (**62 FR 19883**). This Order mandated Federal agencies to place a high priority on identifying and assessing risks affecting children and to ensure their policies, programs, activities, and standards address disproportionate risks to children.

In response, EPA's NCER started a research program focusing on children's environmental health issues through its STAR grant program. In the 10 years since the Executive Order was signed, NCER has developed a research portfolio of more than a hundred individual projects the results of which have appeared in more than a thousand peer-reviewed publications. Policymakers at state and local levels have used STAR grant research results to frame legislation and regulations. These results also have contributed to various approaches used to assess risk, and they have provided guidance to the public in creating safer, healthier environments (**CHPAC-BOSC Workgroup 2007**).

In addition, NCER and NIEHS have established the Centers for Children's Environmental Health and Disease Prevention Research ("Children's Centers"). This multidisciplinary research effort applies community-based, participatory research (CBPR) and innovative techniques in the investigation of environmental stressors on widespread childhood disorders such as asthma, autism, and learning disabilities. This research is also seeking effective strategies to reduce children's exposure to these environmental stressors.

The first eight Children's Centers, established in 1998, set out to study the effects of environmental factors such as pesticides and air pollution on childhood asthma and children's growth and development. In 2001, four more Children's Centers opened to study the basis of neurodevelopmental and behavioral disorders such as autism. Additional Children's Centers began investigations in 2004 and 2007

on how exposure to mixtures of chemicals affects children's health and which environmental pollutants cause disparities in birth outcomes. Since 1998, EPA has awarded 21 Children's Center grants that have fostered a collaborative network of pediatricians, basic scientists, epidemiologists, and community advocates across the United States, seeking to improve the health and environments of children.

This report highlights some important research findings from the STAR research grants, including the Children's Centers during the past 10 years. It also describes how this scientific research is developing ways to improve the health of our nation's children.

How This Report is Organized

To assist implementation of the 1997 Executive Order, the EPA Risk Assessment Forum drafted a document, *Guidance on Selecting Age Groups for Monitoring and Assessing Childhood Exposures to Environmental Contaminants* (Age Grouping Guidance) (EPA 2005) to complement existing EPA guidance and experience aimed at improving the accuracy and consistency of children's exposure assessments. The Age Grouping Guidance describes logical children's age groupings for more uniform monitoring studies and exposure assessments. The document divides age groups according to specific developmental stages (table 1).

Table 1. Recommended Childhood Age Groups for Agency Exposure Assessments (EPA 2005)

Age Groups 1 Year	Age Groups 1 Year
Birth to < 1 month	1 to < 2 years
1 to < 3 months	2 to < 3 years
3 to < 6 months	3 to < 6 years
6 to < 12 months	6 to < 11 years
	11 to < 16 years
	16 to < 21 years

This summary report uses age groups similar to those used in the Age Grouping Guidance to illustrate children's vulnerabilities at different developmental stages and the disproportionate effects of some environmental exposures for children of certain age groups (table 2). This report combines several age groups based on similarities of their exposure characteristics. Additionally, it highlights information from the prenatal lifestage, which is not listed in EPA's Age Grouping Guidance, yet it does not include the adolescent life stage (11 to <21 years) because NCER has yet to fund studies of this age group. Investigators in the Children's Centers are following children from birth throughout the various stages of development in several long-term, longitudinal birth-cohort studies.

> *"At EPA, we are committed to protecting human health and the environment for all our residents, including our most vulnerable citizens. By promoting children's health research, we are working to provide a healthier start for every child born in America."*
>
> *— Stephen L. Johnson, EPA Administrator*

Highlights of NCER-supported findings in basic science, exposure assessment, epidemiology, and intervention for each of the life stages are featured at the end of this section (table 3). The chapters that follow report six case studies illustrating that childhood is a significantly vulnerable period for exposure to environmental factors and that health outcomes can vary with a child's age at exposure. Although the research studies often span multiple life stages, each case study focuses on susceptibility, health outcomes, or interventions at one of the six life stages. Case studies discuss research findings and their implications for public policy in the following key issues:

- Fetal vulnerability, growth, and development related to prenatal pollutant exposure
- Genetic differences in newborns that may contribute to susceptibility
- Immune development, allergic sensitization, and allergic and chemical response during the infant and crawler life stage
- The effect a toddler's behavior has on exposure to pollutants
- Autism, autism spectrum disorder (ASD), and ADHD as health outcomes of pollutant exposure
- The effectiveness of various asthma intervention programs

References to published results in the scientific literature are provided throughout the report and in the References section. In instances where research results have not yet been published, EPA grant numbers (e.g., R831710) have been provided. Full information on these grants may be found by visiting **http://www.epa.gov/ncer** and performing a search on the relevant grant number.

Table 2. Definition of Life Stages and Examples of Exposure Characteristics (EPA 2005)

Life Stage	Age Group	Characteristics Relevant to Oral and Dermal Exposure	Characteristics Relevant to Inhalation Exposure	Anatomy and Physiology Characteristics
Prenatal[a]				
	Before Birth			
Neonatal				
	Birth to < 3 months	• Breast and bottle feeding • Hand-to-mouth activity	• Time spent sleeping • Time spent sedentary	• Rapid growth and weight gain • Increased proportion of body fat • Increased skin permeability • Deficiencies in liver enzyme activity (affecting ability to breakdown chemicals) • Immature immune system functions • High oxygen requirements (increased inhalation rates) • More alkaline stomach fluids (affecting function and digestion) • Increased extracellular fluid • Less kidney function than predicted by surface area
Infant/Crawler				
	3 to < 6 months	• Introduction of solid food • Increased contact with surfaces • Increased object and hand-to-mouth activity	• Breathing zone close to the floor	• Rapid growth and weight gain • Increased proportion of body fat • Deficiencies in liver enzyme activity • Immature immune system functions • Increased extracellular fluid • Kidney function less than predicted by surface area
	6 to < 12 months	• Expanded food consumption • Increased floor mobility (surface contact) • Increased likelihood to put nonfood items in mouth	• Development of personal dust clouds	• Rapid growth and weight gain • Increased body fat begins to level off • Deficiencies in liver enzyme activity (affecting ability to breakdown chemicals) • Immature immune system functions • Rapid decrease in extracellular fluid • Kidney function more predictable by surface area

Life Stage	Age Group	Characteristics Relevant to Oral and Dermal Exposure	Characteristics Relevant to Inhalation Exposure	Anatomy and Physiology Characteristics
Toddler				
	12 to < 24 months	• Consumption of full range of foods • Participation in increased play activity • Demonstration of curiosity accompanied with poor judgment • Cessation of breast and bottle feeding	• Walking upright, running, and climbing • Occupy wider variety of breathing zones • Engage in more vigorous activities	**1 to < 3 years[b]:** • Some liver enzyme activities peak, then fall back to adult range • Most immune system functions mature • Extracellular fluid more consistently related to body size
Preschooler				
	2 to < 6 years	• Onset of wearing adult-style clothing • Decreased hand-to-mouth activities	• Increased time outdoors	**3 to < 8/9 years[b]:** • Relatively stable weight gain and skeletal growth (as opposed to a period marked by growth spurts)
School-Age				
	6 to < 11 years	• Decreased oral contact with hands and objects • Decreased dermal contact with surfaces	• Time spent in school environments • Participation in sports activities	**8/9 to < 16/18 years[b]:** • Rapid skeletal growth • Rapid reproductive and endocrine system changes, including puberty

[a] This life stage was not addressed in EPA's Age Grouping Guidance.
[b] The age categorization of anatomy and physiology characteristics differs slightly from the age categorization for behavioral development.

Table 3. Summary of Relevant Research Findings Across Life Stages

Prenatal	Neonatal: Birth to <3 months	Infant/Crawler
		
• Babies exposed before birth to higher levels of organophosphate (OP) insecticides have a shorter gestation period, smaller birth weight, shorter length, and decreased head circumference, and show delay in neurodevelopment up to age 3 (R827039C004, R831710C001). For example, babies exposed prenatally to chlorpyrifos and diazinon weighed less at birth by an average of 6.6 ounces, which is equivalent to that seen in babies born to women who smoked during pregnancy (R827027C003). • Approximately 40 percent of babies exposed before their birth to a mixture of polycyclic aromatic hydrocarbons (PAHs) primarily from traffic sources and environmental tobacco smoke (ETS) have genetic damage that can be linked with increased cancer risk (R827027C003). • Increases in maternal levels of dichlorodiphenyl trichloroethane (DDT), a pesticide, during pregnancy decrease scores on the Mental Development Index at 2 years of age. Each 10-fold increase in DDT level is associated with a 2- to 3-point decrease in mental development (R831710C001). • Prenatal exposure to lead or tobacco smoke has been implicated as a precursor of Attention Deficit/Hyperactivity Disorder (ADHD) in children, possibly accounting for as many as one in three cases of ADHD in children (R829389). • Maternal levels of ortho-substituted polychlorinated biphenyls (PCBs), one form of the class of compounds that compose PCBs, are associated with reduced weight gain up to 17 years of age in girls but not boys, suggesting that prenatal exposure to PCBs may affect female growth (R831711).	• Human respiratory syncytial virus (RSV) infection in the first year of life increases the risk of asthmatic symptoms later in life. RSV affects the receptors in the airway that interact with environmental agents, which may explain why children with RSV-induced asthma are especially sensitive to their environment (R826711003). • Very low expression of the paraoxonase1 (PON1) enzyme, an enzyme that facilitates the breakdown of pesticides into a less toxic form, is a major predictor of young children's susceptibility to the toxic effects of some OP insecticides (R831709). For example, decreases in the PON1 gene cause some newborns to be 26 to 50 times more susceptible to adverse health outcomes from exposure to certain OP pesticides than other newborns (R831710C003). • Rat pups exposed to PCBs at the same level as babies breast-fed by mothers who live in high-PCB environments have developmental and auditory abnormalities, specifically, the ability for the brain to interpret auditory cues (R829388C005). 	• Children in farmworker families may be particularly vulnerable to pesticides because they often are exposed to these chemicals from multiple pathways such as pesticide drift from agricultural fields, take-home exposure from their parents, and breast milk from mothers who work or have worked in the fields (Bradman et al. 2007; R831710). • Children living within 75 meters of a major roadway have an increased risk of developing asthma. This effect was stronger in girls and in children without a family history of asthma (R831861). • Early life exposures to traffic-related pollutants in urban environments appear to affect the immune system by increasing allergic responses, which can lead to respiratory symptoms in children as young as 2 years of age (Al-alem et al. 2006; R827027). • Developmental exposure to non-coplanar PCBs, one of the many forms of compounds that compose the class of PCBs, increases the chance of a seizure. PCB exposure for autistic children is particularly dangerous because these children have a particularly high rate (about 30 percent) of seizure disorders (R829388). • Placental tissues with higher concentrations of dichlorodiphenyl dichloroethene (DDE), a pesticide breakdown product, showed a correlation with increased levels of type 2 T-helper cells (Th2) cytokines (R830825). Elevated levels of these cells in very young children are a possible indicator for the development of asthma and other immune system disorders.

Toddler: 1 to <2 years	Preschooler: 2 to <6 years	School-Age: 6 to <11 years
		
• About 30 percent of children with Autistic Spectrum Disorder (ASD) exhibit loss of neurological and behavioral function during their first few years of life (12 to 30 months of age). This loss coincides with the onset of children's physical capacity to explore their environment, and, combined with repetitive behavior typical of ASD, it increases their exposure to environmental neurotoxicants. Autistic children also appear to have a different genetic or biochemical susceptibility (R829391). • Toddlers in farmworker communities accumulate more pesticides on their clothing (socks and union suits) compared with younger, crawling children. In addition, toddlers show higher urinary metabolite levels than infants (R826709C003). • Pesticide levels on children's hands are associated with pesticide metabolite levels in their urine, which means that their frequent hand-to-mouth behavior may cause them to ingest chemicals that they come in contact with (R827440). • Exposure to lead during early childhood increases the risk of illegal behavior as an adult. There is a relationship between neuropsychological functioning in adolescence and police contacts in early adulthood, indicating a link between early lead exposure and adult antisocial activities (R829389C004). • Children with iron deficiency retain more lead in their bodies. Childhood iron deficiency modifies behavior such as increasing pica (the desire to eat substances not normally eaten) and hand-to-mouth activity. These modified behaviors can increase children's exposure to environmental lead. Correlation between iron deficiency and blood lead levels is strongest among children aged 1 to 2 years (Bradman et al. 2001; R826709C003).	• Mouse allergen exposure and asthma-related outcomes have a strong and consistent relationship. Children with high exposure to mouse allergens have more asthma-related unscheduled doctor visits, emergency department visits, and hospitalization than unexposed children (R832139C001). • Elevated indoor particulate matter (PM) levels are associated with increased respiratory symptoms in preschool-aged children (R832139C001). • Children with organic diets show lower median OP metabolite levels in their urine than children with conventional diets (Curl et al. 2003; R825171). • Boys who spend the greatest amount of time playing outdoors have the highest pesticide exposure levels of any childhood group. Similarly, children who play extensively in laundry rooms and entryways exhibit higher rates of pesticide metabolites in urine than those who do not play, or play less, in these areas. Additionally, frequent hand washing does little to reduce children's pesticide exposures in households where chemical contamination is readily accessible (R827443). • Floor dust appears to be the major source of exposure to OPs for young children (accounting for 68.8 percent), followed by solid food (18.8 percent) and beverages (10.4 percent). Air and water contribute less than 2 percent to the total aggregate exposure (R825169). • Autistic children showed higher levels of leptin (a hormone that affects the regulation of body weight, metabolism, and reproductive function, and influences the immune system) in their blood when compared to typically developing children (Ashwood et al. 2007; R829388C002).	• An increased risk of respiratory-related school absences occurs in asthmatic and nonasthmatic children exposed to ETS (Gilliland et al. 2003; R831861). • Placing air cleaners containing high-efficiency particulate air (HEPA) filters in inner-city asthmatic children's bedrooms can achieve a substantial, sustained improvement in indoor PM levels, one major cause of respiratory problems in children (Eggleston et al. 2005; R832139C002). • Rural lifestyles may not protect children against developing asthma. Prevalence of asthma in rural areas is comparable to prevalence in large Midwestern cities (R826711C001). • High levels of PM and ozone are associated with worsening pulmonary function and increased asthmatic symptoms among children from Detroit, Michigan, who have moderate to severe asthma (R826710C002). • Disadvantaged asthmatic children in urban areas appear to be at increased risk for higher residential allergen levels, elevated air-pollution exposure, and higher levels of asthma triggers in the home (Breysse et al. 2005; R832139). • Children exposed to manganese and arsenic in the environment score lower on general intelligence tests and tests for memory (Wright et al. 2006; R831725). 

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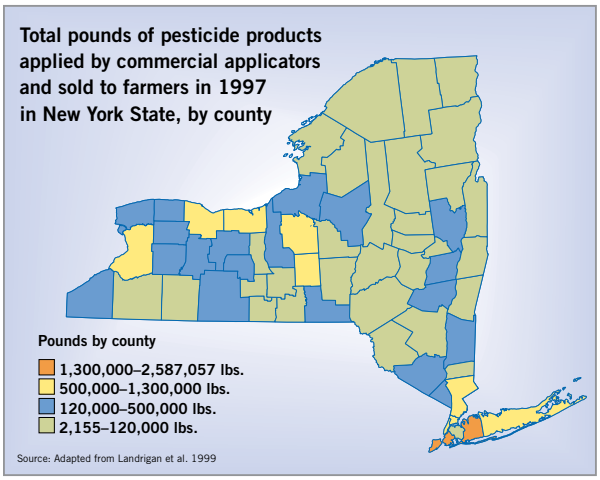
Important Findings Across Life Stages

The six case studies in this section of the report highlight NCER-supported findings for each of the six life stages (table 2).

Prenatal: Pollutant Exposure

Every day, people are exposed to many different environmental pollutants ranging from pesticides used to control cockroaches in the home to particulate matter (PM) generated from combustion engines in vehicles. Pesticides in particular are a major problem. Large quantities are applied in urban communities to control vermin, especially in some low-income areas. For example, the amount of one common insecticide, chlorpyrifos, applied in one urban borough of Manhattan in 1997 exceeded the total amount of all pesticides applied in any other single county in all of New York, including in upstate agricultural regions (Landrigan et al. 1999). Exposure to pesticides is of special concern for certain sensitive groups such as pregnant women, infants, and children.



Prenatal and early postnatal periods are critical life stages, and they require careful assessment for pesticide exposure. In early life, the nervous system is still developing, and it is more susceptible to effects from exposure to neurotoxic pesticides. STAR research results have significantly increased knowledge of prenatal pollutant exposure. For example, one significant finding is that exposure to certain pesticides can have adverse effects on birth size and neurodevelopment (Bradman and Whyatt 2005).

What contributes to fetal vulnerability?

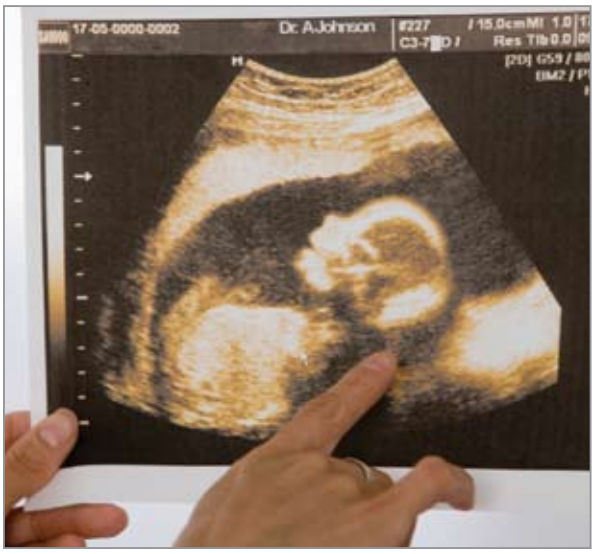
Many physiological characteristics of a growing fetus make it more likely to suffer a health effect from exposure to environmental pollutants. Some metabolic activities such as clearance by the kidneys and enzyme activity in the liver are immature, and these activities often are easily disrupted during development because they are highly variable throughout gestation and following birth (Landrigan et al. 1999, Corrion et al. 2005). Greater absorption or retention rates of toxic substances, a reduced ability to detoxify chemicals and repair damage to DNA, and a higher rate of cell proliferation are other factors that contribute to a fetus's susceptibility to health risks (Perera et al. 2005). STAR research results have demonstrated some of the effects of fetal vulnerability. For example, in one study of a group of minority women and their infants, scientists measured women's exposure to

several pollutants including airborne polyaromatic hydrocarbons (PAHs) (which were monitored during pregnancy) and chlorpyrifos (which was measured from the mother and infant at birth). The results show that exposure to PAHs and pesticides during pregnancy impairs fetal growth and development (Perera et al. 2003). The study results also show that the developing fetus may be 10 times more susceptible to DNA damage from before-birth exposure to PAHs than the mother is (Perera et al. 2004, 2005).

Another study has shown the effect on an infant's growth from exposure before birth to certain pesticides. This study enrolled pregnant women at prenatal clinics in January 1998 and followed them until January 2004, capturing data from a critical period when EPA began to phase out residential use of chlopyrifos in 2001. This study included women exposed to higher levels of pesticides during the phase-out period as well as women exposed after the phase-out period. Infants exposed prenatally to pesticides before the EPA phase-out of chlorpyrifos showed significantly reduced birth weight and shorter length (Whyatt et al 2004, 2005). Other studies showed that infants were born with low activity levels of an enzyme, paraoxonase 1 (PON1), which affects the metabolism and detoxification of pesticides (Furlong et al. 2006). Infants with prenatal pesticide exposure and low PON1 enzyme levels had smaller head circumferences (Berkowitz et al. 2004, Wolff et al. 2007).

These results cause concern because outcomes such as a smaller head circumference correlate with reduced intelligence quotient levels and decreased cognitive function in later years. Study results indicate early-life exposures are more likely to lead to adverse health outcomes than similar exposures encountered later in life. Even more troubling are results that show the deficits sustained in early life may persist throughout life (Landrigan et al. 1999). For example, one study showed that prenatal PAH exposure led to cognitive development issues later in life, including higher risk for performance deficits in language, reading, and math in early school years (Perera et al. 2006).

How do we measure exposures relevant to fetal growth and development?



Measuring exposure to environmental pollutants is difficult for a number of reasons. Exposure can vary widely across age groups depending on factors such as the amount and type of chemical used and daily patterns of life. Exposure can be of different durations and magnitudes such as short-term, high-level pesticide applications versus long-term, low-level pesticide applications. Some pollutants do not persist in the body for a long time, making them hard to measure without frequent sampling (Bradman and Whyatt 2005, Fenske et al. 2005). Because prenatal development is so critical, it is particularly important to assess maternal exposure to environmental chemicals during pregnancy to make subsequent associations with infant health (Fenske et al. 2005).

In general, maternal and infant exposures typically are measured using one or more of the currently available techniques; scientists take the advantages and limitations of each method into account when designing a research study. The techniques currently used include (Bradman and Whyatt 2005, Fenske et al. 2005):

- *Biological monitoring*—Uses biomarkers (biological substances (blood, DNA, saliva, breast milk, urine, hair, etc.) to indicate exposure, or early biological effect to an environmental chemical, or susceptibility to disease) to provide a direct measure of the concentration of a pollutant in the body at a given time.
- *Environmental monitoring*—Uses environmental samples such as air, dust, diet, and drinking water to characterize residential contamination and provide a measure of potential exposure to the pollutant.

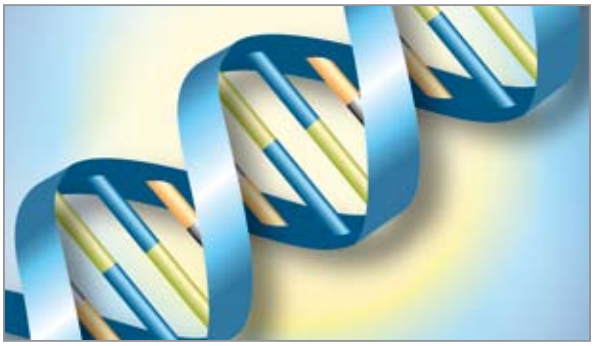
- *Survey questionnaire*—Uses participant surveys to collect general information on a person's habits and use of chemicals (typically conducted as a supplement to biological and environmental monitoring).
- *Ecological methods*—Uses geographic information systems and other techniques to help map the relative locations of populations potentially exposed to pollutant sources.

While biological monitoring appears to be one of the best ways to assess exposure, all biomarkers have limitations, and certain methods may not truly represent the full extent of exposure. For example, pollutants measured in blood represent only a snapshot of exposure because the body constantly metabolizes, redistributes, and eliminates chemicals (Ostrea et al. 2002). Additionally, drawing blood is invasive, especially when children are involved. Some scientists (Corrion et al. 2005) are looking for more innovative techniques that address this problem, such as sampling maternal and umbilical cord whole blood rather than blood serum (because pesticides are more likely to concentrate in red blood cells). One reason blood sampling is attractive for biological monitoring is because, unlike urine, blood is highly regulated, and factors such as water intake are less likely to alter concentrations.

Other studies indicate that meconium, the first set of stools of a newborn, is a useful biomarker of prenatal exposure to pollutants such as pesticides. Meconium is a direct measure of exposure before birth (Ostrea et al. 2006, Whyatt and Barr 2001, Bearer et al. 2005), and the main advantage over other biological measures is that it has a wide window of exposure time. Meconium starts forming at the beginning of the second trimester and is not excreted until after birth. Although it provides a cumulative prenatal measurement, meconium is more difficult to analyze when compared with blood or urine (Ostrea et al. 2006).

Neonatal: Genetic Vulnerability

Like the developing fetus, neonates (birth to <3 months) are more susceptible to health effects from pollutant exposure than adults because they are still developing. Additionally, genetic differences can increase their vulnerability to pollutants such as pesticides, secondhand smoke, and air toxics. Genetic differences may occur either as a difference in a gene itself or in how the information from a gene is processed. Genetic differences can significantly affect metabolism and cause increased susceptibility for children at all life stages, but the neonatal period is unique in that newborns display some genetic characteristics that are different from those observed for adults or even older children.

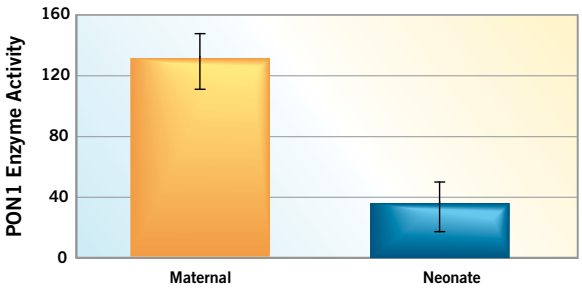


An important example of a genetic difference in neonates involves an enzyme that plays a key role in protecting humans against toxic effects of pesticides. Enzymes are proteins that help to accelerate chemical reactions in the body, and in this case, the enzyme PON1 facilitates the breakdown of pesticides into a less toxic form. For several decades, scientists have shown that high levels of PON1 are protective against nervous system effects associated with exposure to pesticides during development. More recently, researchers have demonstrated that having low levels of PON1 results in greater sensitivity to these harmful effects. By knocking out the PON1 gene in neonatal mice—an animal model often used as a substitute for humans—researchers demonstrated an increase in sensitivity to certain insecticide exposures when compared with mice that still had the PON1 gene (Furlong et al. 2005).

In several Children's Center projects, researchers have shown that the enzyme PON1 is typically not fully functional until after birth. Even after birth, newborns and infants have very low levels of this enzyme. The results of a review of active PON1 levels in humans show that the enzyme levels increase from birth through infancy (Costa et al. 2003). PON1 levels reach a plateau at different ages in individuals anywhere from 15 to 25 months, depending on factors such as the individual's genetic background. Before the levels plateau, an infant is much more vulnerable to health effects resulting from exposure to pesticides.

> *"People have this remarkable difference in enzymes that defend their health from pesticide exposure. In developing regulatory standards for safe levels of exposure, we need to protect the most sensitive in a population, particularly because children and unborn fetuses are involved."*
>
> *— Dr. Nina Holland, UC Berkeley*

Researchers observed variability not only in reaching the plateau, but also in the range of PON1 levels among newborns when compared with their mothers. Levels of this critical enzyme varied by 26-fold in newborns compared with only 14-fold among mothers (Furlong et al. 2006). Even considering the variability among individuals, average PON1 levels in children were four times lower than the PON1 levels in the mothers, demonstrating that infants clearly are a more vulnerable population in their ability to detoxify certain commonly used insecticides (Chen et al. 2003, Furlong et al. 2006). Researchers confirmed the observation that PON1 levels are lower in children, and that the differences between adults and children vary by ethnicity: The average PON1 level in adults compared with newborns was 2.6 times higher for African Americans, 3.6 times greater in the Caribbean Hispanic population, and 4.6 times greater for Caucasians (Chen et al. 2003).



Average PON1 activity for all genotypes and race/ethnicities for mothers and neonates.

Source: Chen et al. 2003 (Tables 2 and 3); median of all values plotted; error bars represent the range in the means for the various genotypes.

In addition to studies that focus on pesticides, some STAR research studies focus on early exposure to environmental tobacco smoke (ETS), air toxics, and other pollutants encountered in the neonatal period. For example, scientists investigated long-term genetic effects of prenatal exposure to ETS through maternal smoking and early life exposures (Gilliland et al. 2001, 2002a, 2002b). The researchers found a candidate gene that reduces the effects of the exposure to ETS by detoxifying some of the harmful chemicals associated with smoking. Because tobacco-related toxins are more harmful to a developing fetus or infant than to the mother, the presence of this candidate gene, glutathione S transferase M1 (GSTM1), may be especially important during the early life stages. More specifically, the adverse effects of prenatal exposure to maternal smoking (e.g., asthma, wheezing) were predominantly observed in children with a variation of GSTM1, the null genotype, which lacks the enzyme that helps to detoxify the pollutants associated with ETS (Gilliland et al. 2002a). Damage during fetal development in particular can permanently alter the structure or function of the lungs, and thus can lead to postnatal vulnerabilities (Gilliland et al. 2003). In addition, large deficits in lung function are found in school-aged children with both early-onset asthma and before-birth exposure to maternal smoking regardless of whether the child had ETS exposure later in life (Gilliland et al. 2001, Gilliland et al. 2003, Li et al. 2005). These results further emphasize the importance of early exposure and confirm that exposure before birth to maternal smoking is a critical risk factor for childhood asthma.

Strikingly, environmental exposures also may change genetic susceptibility. Results from STAR research show a new association between smoking during pregnancy and a child's risk of asthma that extends beyond one generation (Li et al. 2005). These groundbreaking results show an increased risk of asthma across multiple generations, meaning that if a woman smokes during pregnancy, her child's risk of developing asthma increases, and even if that child doesn't become a smoker in adulthood, the next generation (grandchildren) will still have an increased risk. Potentially, this could occur through epigenetic mechanisms (interactions between genes and the environment that produce differences between cells during development before birth, but that do not involve changes to the underlying DNA). The researchers suggest that tobacco products may affect both immune function and pollutant detoxification mechanisms in the offspring by altering DNA patterns in the fetal cells (Li et al. 2005). This alteration would result in an increased genetic susceptibility to asthma affecting one generation to the next.

Infant/Crawler: Early Immune Function

Allergic sensitization and responses to allergies and chemicals have become the focus of much STAR grant research, especially for infants/crawlers (3 to <12 months old) whose immune systems are still in the early stages of development. One reason for this focus is because asthma is the most common chronic disease among children. Asthma is an immune system disorder manifested when the airways in the lungs strongly react to various factors, such as stress, allergens, temperature, exercise, and air pollutants in the air that generally pose no risk to individuals with healthy immune systems. In individuals susceptible to asthma, reaction to these factors can cause the airways to become irritated and inflamed, and may evoke symptoms such as wheezing, coughing, chest tightness, and difficulty breathing. Although a large body of evidence has linked life style and environmental exposures to asthma, the timing of such environmental exposures during early development also may be critical to how children become susceptible to allergens that previously had no effect (that is, allergic sensitization), as well as the later development of asthma.

One way scientists are exploring the relationship between asthma and age is to measure biomarkers that indicate this immune system disorder. Researchers compared levels of type 1 and type 2 T-helper cells (Th1 and Th2) in infants to observe relationships caused by exposure to pesticides, natural toxins, and allergens and compared the data to the resulting incidence of asthma (Duramad et al. 2006). The selected infants were subjects of the Center for Health Assessment of Mothers and Children of Salinas (CHAMACOS) birth-cohort study. The study comprises infants of farm workers in rural areas. Infants in this study population may have experienced greater exposure to pesticides because of their proximity to fields and contact with pesticide residues brought home by their parents. Researchers took blood samples from the infants at 12 and 24 months to measure the amount of Th1 and Th2 cells. The results indicated that infants who live with agricultural workers and whose mothers work in the field had higher levels of Th2 cells than infants who did not meet these criteria. These are important findings because 2-year-old children diagnosed with asthma and wheezing exhibit a significant increase in Th2 levels, which means that elevated levels of these cells in very young children can perhaps indicate the onset of respiratory or other immune system disorders.

Using Biomarkers to Discover Asthma in Children

Biomonitoring is the measurement of a substance—or its breakdown product, known as a metabolite—in biological samples such as blood or urine. Researchers measure biomarkers and then use the data to assess the presence of a pollutant such as a pesticide or a condition such as asthma. Because the balance between Th1 and Th2 cells is important in the development of asthma, scientists have examined the levels of these cells in blood as a possible indicator of asthma in children. These cells are part of the immune system and belong to a group of cells essential to controlling viruses and bacteria. Th1 cells tend to provide general protective immunity; Th2 cells may play an important role in the functional changes of allergic diseases, including asthma.

Animal studies also have concentrated on the importance of age and early immune system development, allergic sensitization, and allergic and chemical response. One such study focused on the

relationship between age and the onset of allergies in mice (Rumold et al. 2001). Investigators for this study examined the effect of age on the response to environmental ETS and its possible role in sensitization to normally harmless substances. Studying how ETS affects infants and crawlers is very important because secondhand smoke exposure causes numerous problems in children, such as slower lung growth, acute respiratory infections, ear problems, and more frequent and severe asthma attacks. In the study, young mice aged 2 to 3 weeks and adult mice aged 6 to 8 weeks received exposure to (1) ETS, (2) a protein called ovalbumin (OVA) that stimulates an immune response but that is typically harmless, or (3) both ETS and OVA. Investigators measured the animal's ability to respond and defend itself based on levels of two immunoglobulins (Ig), IgE and IgG1. IgE is an antibody class that plays a role in allergic responses; it binds to allergens and triggers the release of histamines (important substances involved in many allergic reactions). IgG1 is a subclass of IgG, which provides the majority of antibody-based immunity against invading pathogens. Researchers detected the antibodies in both adult and young mice exposed to both ETS and OVA. Because exposure to ETS and OVA together created an allergic response, but not OVA or ETS exposure alone, results suggest that ETS can create allergic sensitization to otherwise harmless substances. Furthermore, the young mice had significantly higher antibody levels, which may explain why exposure to secondhand smoke is a major risk factor for the development of allergies in young children.

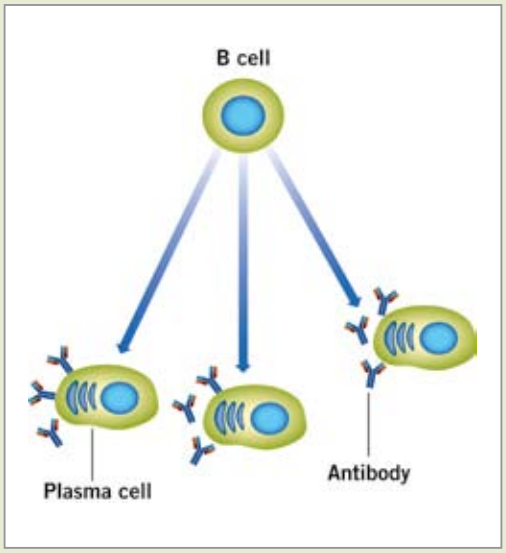
CHAMACOS

CENTER FOR THE HEALTH ASSESSMENT OF MOTHERS AND CHILDREN OF SALINAS

http://ehs.sph.berkeley.edu/chamacos

What is an antibody?

An antibody is a protein whose primary responsibility is defending the body as part of the immune system. In response to bacteria or viruses, mature B cells or plasma cells, make antibodies. In mammals, there are five classes of antibodies. Each class is named with an "Ig" prefix, which stands for immunoglobulin – another name for an antibody. These antibody classes – IgA, IgD, IgE, IgG and IgM – differ in their biologic properties, their function, where they are found in the body, and their ability to interact with various substances that stimulate antibody production.



Toddler: Behaviors that Affect Pollutant Exposure

Children are often exposed to contaminants at levels that are equal to, or greater than, adult levels of exposure (Black et al. 2005; Harnley et al. 2005). Relative to their body weight, children typically eat more food, drink more water, and breathe in more air than adults, and because they are less able than adults to rid their bodies of contaminants or reduce the toxicity of pollutants, the effects in children associated with these exposures can be greater (Eskenazi et al. 1999; Bearer 2000). Children also may have a greater level of exposure to contaminants because they tend to put items in their mouth, they are closer to potentially contaminated floors and surfaces, and they spend more time inside the home.

By spending a significant portion of their time inside, children are exposed to a complex mix of contaminants including pesticides that come from numerous sources such as outdoor air, tracked-in particles, and various indoor sources that can vary in nature by geographic region (Lioy 2006; Akland et al. 2000). For example, researchers have measured pesticide contamination levels in the homes of families living close to agricultural activities (Freeman et al. 2004; Shalat et al. 2003; Eskenazi et al. 1999). In one agricultural community, children had 3.5 to 13 times higher urinary pesticide metabolites than children in the National Health and Nutrition Examination Survey (NHANES) database, a database containing information on the health and nutritional status of adults and children in the United States (Shalat et al. 2003). This exposure to pesticides from agricultural application is a concern for children living in homes adjacent to or in close proximity of agricultural fields and orchards (Ramaprasad et al. 2004).

In addition to the amount of time spent indoors, children's other activities also greatly influence their potential exposure to environmental contaminants (Black et al. 2005). The frequency, duration, and nature of a child's interaction with contaminated media determine the degree of a child's exposure. Young children, through a number of normal activities and behaviors, have the potential to sustain substantial exposure to contaminants such as pesticides. For example, studies demonstrate that toddlers (children ages 12 months to <2 years) have higher levels of pesticides on their clothing, as well as higher concentrations of urinary metabolites, when compared with younger infants (Bradman et al. 2007). Toddlers are extremely susceptible to pesticide exposure in the indoor environment because of their characteristic behaviors. At the toddler stage, children consume a full range of foods because breast- and bottle-feeding cease. They participate in increased play activities, are extremely curious, and exercise poor judgment. Toddlers walk upright, run, climb, occupy a wider variety of breathing zones, and engage in more vigorous activities than younger infants do (EPA 2005).

> *"Pesticide exposure isn't a great idea for adults, but it poses a particular concern in regards to children. These smallest humans, who spend a lot of time close to the floor and with their hands in their mouths, can encounter much higher doses relative to their body weights."*
>
> — *Phillips 2005*

Furthermore, toddlers have several microactivities that help determine their level of exposure. Toddlers frequently insert objects or hands into their mouths; demonstrate poor food handling skills; and use objects such as toys, bottles, pacifiers, and blankets in the home that may affect exposure (Black et al. 2005; Freeman et al. 2001a; Akland et al. 2000). The activity of eating and food contamination is a specific concern (and this finding extends to children 3 years of age as well as toddlers). In fact, research results suggest that poor food handling skills can increase a child's potential for exposure from hand-to-food, food-to-surface, and hand-to-surface contacts to pesticides (Akland et al. 2000). Children spend a significant portion of their waking hours engaged in eating and other activities during which their hands are exposed to contaminated surfaces. For example, Freeman et al. (2001b) reported that 63 percent of toddlers ate food that had been on the floor.

While researchers have evaluated some microactivities, much remains unknown. Identifying the link between a child's behavior and the resulting amount of a contaminant that enters a child's body is an extremely important step in determining the significance of an exposure (Black et al. 2005). A number of novel methods have helped determine the link between behavior and dose. One new approach developed at the University of Washington Center for Child Environmental Health Risks Research involves the use of global positioning system technology for characterizing children's activity patterns (EPA 2007a). Another novel method involves the use of laser-based, real-time measurement of pesticide spray drift, a frequent occurrence in agricultural communities.

Path traveled by one child (6-hour sampling time) on a weekday during school hours.

Why the potential for food contamination while eating is a specific concern for children:

- *Approximately 20 to 80 percent of a child's dietary exposure results from handling his or her food.*
- *A child's hands contact contaminated surfaces up to 32 times during eating.*
- *A child's contaminated hands then contact his or her food 10 to 39 times before it enters his or her mouth during eating.*

Source: Akland et al. 2000.

This tracking technique will help in estimating community residents' and bystanders' exposure to pesticide drift (EPA 2007a; Tsai et al. 2005). A third new approach uses videotaping to capture behaviors and detail needed to quantify exposures. (See text box on page 16.)

As concerns regarding environmental contaminants and their effects on children's health continue to increase, the need continues for more knowledge about how children's activities influence their exposure. This knowledge will help in the development of improved risk assessment models, which subsequently will promote our understanding of the risks environmental contaminants pose to children's health. In turn, policymakers will have more information when designing strategies to reduce exposure to contaminants and developing methods to protect children's health. If communicated effectively, this increased knowledge will help members of the public protect themselves and their children from pollutant exposures.

Preschooler: Neurological Disorders

The number of preschoolers diagnosed with neurodevelopmental disorders such as autism, ASD, Pervasive Developmental Disorder (PDD), and ADHD has been increasing recently. In California alone, a 210-percent increase in the number of diagnosed cases of profound autism in children has been recorded in the past 10 years. Centers for Disease Control and Prevention (CDC) data released in 2007 show a high number of cases of ASD in several particular areas in the United States—approximately 1 in 150 children in those areas are diagnosed with an ASD by the time they are 8 years old.

This sudden rise in the number of children exhibiting neurodevelopmental disorders is worrisome because scientists have little understanding of the causes and contributing environmental factors. The preschooler group, 2 to <6 years of age, is of particular significance because the symptoms associated with ASD generally begin before 3 years of age. Consequently, the scientific community is examining numerous factors such as environmental influences to find an explanation for the increasing trend in this age group (CDC 2007).

One environmental influence under study by researchers is early exposure to pesticides, an area that may reveal important information about neurodevelopmental disorders in children. For example, researchers are exploring the relationship between chlorpyrifos (a pesticide used in homes to kill cockroaches until 2001 when it was banned from residential sales) and neurodevelopmental disorders in preschool children through 3 years of age (Rauh et al. 2006). The investigators are finding that children who were exposed to high levels of chlorpyrifos before birth have greater developmental delays in motor and mental skills when compared with children who received low exposures. Researchers assess motor skills by examining endpoints like crawling, walking, reaching, and grasping; and cognitive development by studying how a child perceives, thinks, and gains an understanding of the world. By 3 years of age, children with high exposure to pesticides before birth were 11 times more likely to have attention problems, 6.5 times more likely to have ADHD diagnosis, and 5 times more

Videotaping: A Tool Capable of Capturing Children's Microactivities (Freeman et al. 2001a)

Children's microactivities are not well documented, and understanding how exposures occur requires recording how children behave during specific activities. Detailed information about microactivities is difficult to obtain from questionnaires because many microactivities are behaviors that caretakers barely notice and cannot recall. A potential solution is to get information on microactivities from direct or videotaped observations.

For example, during the Minnesota Children's Pesticide Exposure Study (MNCPES)—a population-based study in the National Human Exposure Assessment Survey—researchers videotaped 19 of the 102 children for four consecutive hours of normal daily activities. The purpose of the MNCPES was to characterize children's exposure to residential pesticides and evaluate the contribution of children's activities to their exposures.

Observational data from MNCPES expanded the existing microactivity database of observational studies, including the knowledge that most of children's frequent contacts with the environment are short (typically less than 5 seconds in duration). Although the MNCPES observed children older than 3 years, the videotaping method is applicable for children of all ages. Improved understanding of the variability of microactivities will help protect the most vulnerable children.

likely to have PDD diagnosis than children with low exposure. These results show that not only is there an association between prenatal exposures to high levels of pesticides and neurodevelopmental delays, but also that symptoms of these delays begin to present strongly during preschool years.

Types of Neurodevelopmental Disorders

Autism—A developmental disability that results from a disorder of the human central nervous system. It is diagnosed using specific criteria for impairments to social interaction, communication, interests, imagination, and activities.

Autism Spectrum Disorder—A developmental and behavioral syndrome that results from certain combinations of characteristically autistic traits.

Pervasive Developmental Disorder—A group of five disorders (Autistic Disorder, Rett's Disorder, Childhood Disintegrative Disorder, Asperger's Syndrome, and Pervasive Developmental Disorder Not Otherwise Specified) characterized by delays in development.

Attention Deficit Hyperactivity Disorder—A largely neurological developmental disorder characterized by a persistent pattern of inattention or hyperactivity-impulsivity, or both.

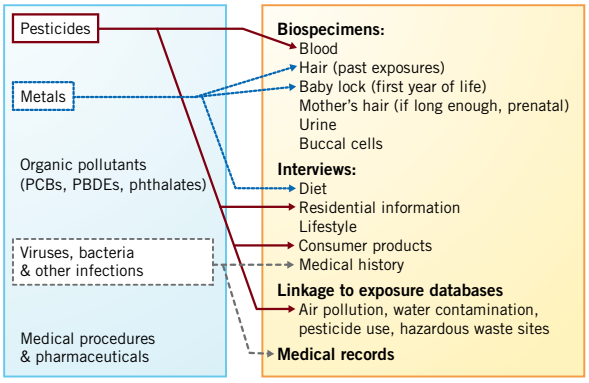
CHARGE

http://beincharge.ucdavis.edu/

To better understand autism and its underlying causes, investigators at UC Davis are conducting a large-scale study called CHARGE (Childhood Autism Risks from Genetics and the Environment), examining potential genetic and environmental causes and triggers of autism (Hertz-Picciotto et al. 2006). The CHARGE investigators are particularly interested in studying the role the immune system plays in autism. The study enrolled children 2 to 5 years of age in Northern California diagnosed with autism. One of the key findings of this study showed higher levels of the hormone leptin in their blood (Ashwood et al. 2007). Leptin, a hormone known for its important effects on regulating body weight, metabolism, and reproductive function, also influences the immune system. When the body has too little of this hormone, the immune system is less responsive. Researchers identified children in the study who were diagnosed with early onset autism and regressive autism. Early onset autism refers to children with early delays in the development of language or social skills, or both; regressive autism refers to children who develop some language or social skills, or both, but who, between the ages of 18 to 24 months, lose those skills. Children diagnosed with early onset autism had significantly higher blood levels of leptin as compared with children diagnosed with regressive autism. This finding is important because leptin may be the first biomarker to distinguish children with early onset autism from children with regressive autism. Because of its role in the immune system, leptin also may be an important biomarker of susceptibility to environmental triggers such as pollutants and pesticides.

Because the early interplay between toxic exposures, immune function, and neurological development appear to be strongly linked, the CHARGE investigators are evaluating blood samples from autistic children for other biomarkers of the immune system. Investigators found that children with autism have significantly lower levels of certain antibodies, show a significantly decreased response to some vaccinations for prevention of bacterial diseases, and have significantly increased levels of certain proteins that help amplify inflammatory reactions (EPA Grant Number R829388C002). The blood samples also show that autistic children have higher levels of natural killer cells and CD8 cells, which play similar roles in the immune system (EPA Grant Number R829388C003). Both cell types attack and destroy many foreign cells—natural killer cells kill right away; CD8 cells are more specific and follow a process before attacking and killing the foreign cell. The observed different levels of antibodies and cells in the immune systems of autistic children are significant because they indicate that autism may be linked to environmental triggers affecting the immune system.

Environmental Exposures Assessed in the CHARGE Study



School-Age: Asthma Intervention Programs

Asthma is the most common chronic disease of childhood in the developed world. In the United States, pediatric asthma affects approximately five million children under the age of 18 (Keeler et al. 2002). Furthermore, the prevalence rate of pediatric asthma (under 18 years of age) in the United States increased by 61 percent from 1982 to 1994 (Keeler et al. 2002), and the mortality rate from pediatric asthma increased by 78 percent from 1980 to 1993 (Keeler et al. 2002; Clark et al. 1999). Children in urban areas, especially poor and minority children, represent a sensitive subpopulation because they spend a significant portion of their time indoors where irritating and allergenic substances are prevalent. This indoor exposure to allergens may increase a child's susceptibility to allergic sensitization, respiratory symptoms, and ultimately the development of asthma (Limb et al. 2005; Perera et al. 2002). While the consequences for the current U.S. population afflicted with pediatric asthma are unknown, large deficits in lung function persist into adulthood. The extent of the deficits associated with asthma is greater than it is with smoking (Berhane et al. 2000).

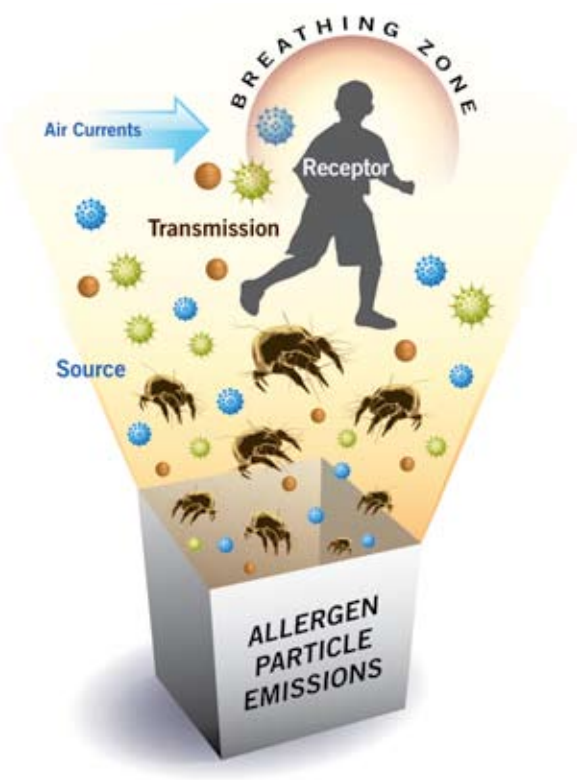
Children and Asthma Video

"Each year, asthma kills more than 600 American children, and since 1980 the incidence of the disease has doubled and now affects over 5 million children in the U.S. Low-income children living in urban areas are at highest risk, but the disease cuts across socioeconomic and geographic boundaries."

View the video:

http://www.epa.gov/ncer/childrenscenters/multimedia.html#child_asthma

Research results indicate that in addition to genetic disposition, demographic variables, and psychosocial stressors, indoor environmental exposures may contribute significantly to the worldwide increase of asthma (Eggleston et al. 2005; Keeler et al. 2002; Rauh et al. 2002). In fact, 80 to 90 percent of asthmatic children become sensitized to airborne environmental allergens beginning at school age (6 years of age and less than 11 years of age) (Zeldin et al. 2006). Some of the strongest associations between asthma and indoor allergen exposure have been found with dust mites, rodents, pets, and cockroaches (Zeldin et al. 2006; Kinney et al. 2002; Rauh et al. 2002). Exposure to ETS during childhood also appears to play an important role in asthma causation and aggravation (Zeldin et al. 2006).



While investigators have identified environmental allergens as a potential cause for childhood asthma, the actual concentration of allergens that a child is exposed to remains uncertain (Zeldin et al. 2006). "Exposure dose" is dependent on both the concentration inhaled and the duration of exposure (Eggleston 2005). The most effective method of reducing exposure dose is to remove the source of the contaminant (Eggleston 2005). To achieve adequate source removal, it is necessary to conduct further research to better understand and address the sources of indoor and outdoor pollutants (Keeler et al. 2002).

Research in this area is making progress. For example, studies have demonstrated that more than three-quarters of U.S. homes have detectable concentrations of mouse allergen. Although mouse allergen is almost ubiquitous in inner-city homes and occurs in approximately 75 percent of middle-class suburban homes, analyses of settled dust concentrations of mouse allergen indicate that indoor levels are 10-fold higher in inner-city homes than suburban homes (Matsui et al. 2005). Studies have suggested that the distribution of cockroach allergen is dependent on the built environment and that cockroach allergen persists for months after successful pest control (Eggleston 2005; Eggleston 2003). While it is impossible to make indoor environments allergen free, proven effective intervention methods for reducing most indoor allergens have been developed based on this increasing knowledge base (table 4). It is important to recognize that each intervention method requires a somewhat different approach.

Table 4. Allergen Characteristics and Possible Exposure-Reduction Methods

Dust Mite • Carried on relatively large particles (10 to 30 micrometers) that do not remain airborne for long • Infestation on fabrics, especially bedding	• Fitting allergen-proof encasings to the mattress and pillow • Vacuuming, cleaning, and washing all bedding regularly • Relocating the bedroom • Applying pesticides designed to kill mites • Dehumidifying • Removing wall-to-wall carpeting
Pet • Carried on small particles that remain airborne and are extremely adherent to surfaces and clothing	• Using air filters • Removing pet • Removing carpets, furniture, and other reservoirs • Purchasing new bedding

Allergen Characteristics	Exposure-Reduction Methods
Rodent • Carried on particles that are small and remain airborne • Widely distributed and commonly found in homes that are not infested with mice	• Applying Integrated Pest Management (IPM) to reduce exposures by combining nonchemical approaches, education, and information on the life cycles of pests and their interactions with the environment • Removing basic rodent survival elements such as air, moisture, food, and shelter by sealing cracks and crevices • Carefully placing least-toxic baits and gels • Maintaining properties • Sanitizing properties to remove the allergen • Educating residents • Specially training professionals to conduct interventions
Cockroach • Resembles mite allergens with up to 80 percent of aeroallergens carried on larger particles (>10 micrometers) that are detectable mainly after vigorous activity and settle rapidly • Highly mobile; therefore, spreads widely throughout the home, especially in bedding and kitchens • Concentrates behind appliances and in cracks and crevices	• Using IPM • Cleaning to remove food sources, grease, food debris • Storing food in plastic containers kept in a refrigerator
Environmental Tobacco Smoke • Widespread exposure—approximately 15 million children in the United States are exposed to environmental tobacco smoke (ETS) • Restricts lung growth and development, which results in reduced pulmonary function	• Removing sources of cigarette smoke from the indoor environment

Sources: Apter and Eggleston 2005; Brenner et al. 2003; Clark 1999; Eggleston 2005; Gilliland et al. 2000; Matsui et al. 2005; Phipatanakul et al. 2004

While these personal-level interventions are helpful, researchers recognize that to successfully combat the rising pediatric asthma prevalence rate, more community-based participatory approaches to interventions are needed. Urban environments are complex; they consist of a network of factors that potentially contribute to environmental allergens. Urban areas often contain multifamily residences, a high density of grocery stores and restaurants, substandard housing maintenance, and an inadequate sanitation infrastructure. All of these factors potentially could increase the prevalence and concentrations of environmental allergens; therefore, it is important to target asthma interventions at the community level (Chew et al. 2003). Researchers are beginning to recognize the value of including the intended beneficiaries in the planning, implementation, and evaluation of research (Parker et al. 2003; Clark et al. 1999). Involving community partners in collecting, analyzing, interpreting, and disseminating the research results, as well as developing, implementing, and evaluating household-, community-, and policy-level strategies aimed at reducing exposures and improving children's health, will help make interventions successful (Keeler et al. 2002; Clark et al. 1999).

Several CBPR projects (some completed, some in progress) have actively involved community members in the research. The following projects investigated multiple exposures and susceptibility factors that may disproportionately affect children and the interactions between community members:

- **Community Action Against Asthma (CAAA)**: The overall goal of this CBPR project is to better understand environmental triggers and psychosocial factors such as family tensions, physical activity, anxiety and stress, and friends and peer pressure on children with asthma. Understanding this cause-and-effect relationship will help reduce various asthma triggers through household- and neighborhood-level interventions. Specifically, the CAAA study conducts research on the effects of environmental exposures on the residents of Detroit, Michigan, through a CBPR process. Participants and researchers are involved in all aspects of the design and conduct of research, and all parties involved receive the study results. The study uses the research to design, in collaboration with all partners, interventions to reduce identified environmental exposures (Keeler et al. 2002).
- **Inner-City Asthma Study**: The overall goal of this project was to design intervention strategies to reduce allergen and particulate exposures. Results show that airborne particulates and allergens affect asthma synergistically. The intervention involved the following approaches: home-based education, cockroach and rodent extermination, mattress and pillow encasings, and cleaning with high-efficiency particulate air (HEPA) filters. The research results indicate that an intervention that combines strategies to reduce indoor pollutants and allergens simultaneously with education of residents in inner-city homes substantially reduces exposure levels of particulate matter and allergens. The research results also indicate modest reductions of symptoms in asthmatic children who live in homes treated with this combination intervention (Eggleston et al. 2005).
- **National Cooperative Inner-City Asthma Study**: This study consisted of a family-focused asthma intervention for low-income, inner-city children with moderate to severe asthma and their family members. The research focused on both problem solving and asthma education so that participants would have an improved understanding of the disease and gain the skills to avoid asthma triggers. The study demonstrated how common environmental allergens are in inner-city homes and how strongly sensitization and asthma morbidity relate to exposure. The current preferred approach is using IPM combined with pesticide application, accompanied with family education and maintenance of the built environment (Chew et al. 2003; Eggleston 2003; Rauh et al. 2002).
- **Integrated Pest Management Study in East Harlem, New York City**: This study was a two-pronged prevention and intervention program to test whether IPM techniques in combination with education targeted at the household level could reduce cockroach allergens and decrease reliance on chemical pesticides in the urban home. Although the study demonstrated that IPM techniques are effective and relatively economical, success depends on direct involvement of the community residents in the development and implementation phases and education and guidance from pest control experts. Building managers, superintendents, and others who provide services to urban residences also must support the IPM efforts (Brenner et al. 2003).

Columbia University Center for Children's Environmental Health has been honored with an Excellence Award from the EPA Office of Children's Health Protection for its Integrated Pest Management interventions. This program trains and educates tenants to use IPM practices, which include reducing the levels of toxic pesticide use inside their homes and sealing cracks and crevices, as well as reducing asthma-triggering pet allergens.

Although researchers have made progress in establishing the causes of the rising rate of pediatric asthma, the need continues for a better definition of susceptible populations and a better understanding of the effect of allergens on susceptible individuals. Protecting children's health will require identifying preventable risks and rapidly translating this knowledge into protective policies and interventions (Perera et al. 2002). Continued CBPR will give researchers and policymakers a better understanding of the interactions between multiple exposures and susceptibility factors that disproportionately affect certain populations (Perera et al. 2002), and CBPR can help make policymakers aware of susceptible populations when they formulate new standards and policies (Lewis et al. 2005; Clark et al. 1999). For example, researchers using CBPR could address the fact that asthma is especially prevalent in urban and minority populations (Keeler et al. 2002; Kinney et al. 2002; Clark et al. 1999). Researchers and policymakers using CBPR could develop effective and sustainable strategies for communities with susceptible populations such as disproportionately high levels of exposure to ETS and allergens and people who lack access to medical care, financial resources, and social support to effectively manage the disease long-term (Clark et al. 1999).

Children's Health and The Environment:
Emerging Trends, Current Work, And Future Directions

Over the past fifty years, the trends in health threats to the Nation's children have changed significantly. By creating safer drinking water and healthier environments, we have made tremendous progress in reducing childhood infectious diseases and infant mortality. Science-based policies have brought public health successes in certain areas of environmental health. For example, lead exposure prevention programs have reduced the average blood lead levels of children in the United States. Additionally, advances in asthma research have enabled pediatricians to detect the warning signs of respiratory distress earlier and to intervene through environmental and clinical management. Today, scientists now face increasingly complex questions and must deal with chronic health challenges affecting children, including impairments in growth and development, increased rates of preterm birth and low birth weight (LBW) babies, childhood obesity, Type 2 diabetes, and poorly understood developmental disabilities such as autism. Identifying the potential role of the environment in the development or progression of these diseases is further complicated by the emergence of many new chemicals in both domestic and international markets that are increasingly ubiquitous at low levels.

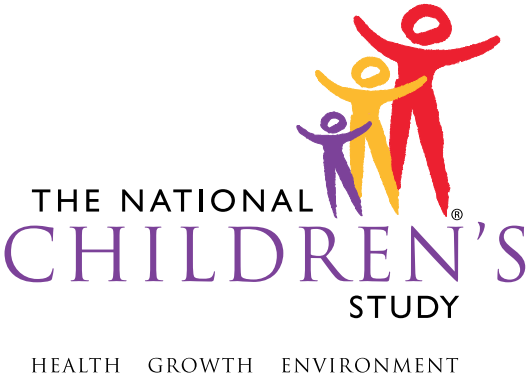
As discussed in this report, STAR research is starting to address these more complex questions. For example, EPA-funded researchers are providing cutting edge epidemiology and basic science insights to answer questions about:

- **LBW and Preterm Birth**: LBW babies and babies born before term (preterm birth) are at increased risk for various health problems (Stevens et al. 2002). Despite overall improvements in prenatal care in the United States, rates of LBW and preterm births continue to rise (**Hamilton, et al 2006**). STAR researchers have published scientific findings on the association between certain environmental exposures (e.g. organophosphate pesticides and air pollution) in the womb and increased risk of preterm birth and low birth weight babies. Furthermore, in 2007, EPA launched a new Children's Center at Duke University that seeks to understand the disparities in adverse birth outcomes, particularly in the American South as they relate to environmental exposures, complex genetic interactions, and community-level influences.
- **Childhood Obesity**: Rates of childhood obesity in America are increasing; an estimated 17 percent of children and adolescents aged 12-19 years are overweight (**CDC 2007**). Obesity is a complex issue related to lifestyle, environment, and genes. Recent data have shown that there are plausible biological mechanisms through which chemical exposures can disrupt hormonal processes. STAR research is investigating the links between early life exposures to endocrine disrupting chemicals and childhood obesity, early pubescent development, and Type 2 diabetes.
- **Autism Spectrum Disorder**: Once reported to have an incidence rate in the single digits per 1000, ASD today affects one out of every 150 children (**Rice 2007**). Researchers are at the starting point in understanding how genetics, environmental exposures, maternal infections, and other factors can impact child neurodevelopment. For example, the summer of 2007 marked the initiation of the EPA/NIEHS supported *Markers of Autism Risks in Babies—Learning the Early Signs* (MARBLES) study. The lead investigators of MARBLES will monitor the environmental and genetic influences on pregnancies at higher risk of autistic outcomes (**http://marbles.ucdavis.edu/**).

> *"In the South, there is a unique social, economic, and demographic context in which environmental exposures play out. Poor birth outcomes aren't just an immediate problem -- the effects can be very long lasting. Survivors of poor birth outcomes are at increased risk for serious illnesses later in life."*
>
> *— Dr. Marie Lynn Miranda, Duke University Children's Center Director*

As the science from the past ten years is reviewed, it is clear that EPA-funded research has led to important advances in understanding how environmental factors affect children's health. This robust body of work has also informed policies that protect public health. As EPA looks to the future, however, it is equally clear that important work remains to be done. EPA,

along with several other Federal Agencies, will begin working together to answer some of these more complex questions through a landmark study – the National Children's Study – that will examine the effects of environmental influences on the health and development of more than 100,000 children across the United States, following them from before birth until age 21. This study defines the term "environment" broadly by considering natural and man-made environmental factors, biological and chemical factors, physical surroundings, social factors, behavioral influences and outcomes, genetics, cultural influences, and geographic locations. The NCS will be one of the richest information resources available for answering questions related to children's health and development and will form the basis of child health guidance, interventions, and policy for generations to come.



http://www.nationalchildrensstudy.gov

While EPA-funded research will provide some of the foundation for this major landmark study by advancing the science and creating the tools needed for conducting longitudinal epidemiology studies, NCER's STAR program will also continue to work in major emerging areas of scientific inquiry such as advanced methods for interpreting biomonitoring data and community-based risk assessment.

Interpreting Human Biomonitoring Information

Human biomonitoring data is collected as a way of assessing exposure, susceptibility, and effects by researchers involved in many types of environmental health studies, including long term studies of the association between human exposure to environmental chemicals and resulting health effects. Advances in measurement technology have made biomonitoring more popular as a way to track health and monitor trends in exposure or disease. There are efforts at the Federal and State levels to collect information on human exposure to environmental chemicals and also to use biomonitoring data to assess the public health impacts of policy decisions. There are still data gaps, however, in our understanding of what certain biomarkers actually mean in terms of exposure and dose. STAR research is starting to fill some of these knowledge gaps through a program designed to develop methods and models to interpret and understand biomonitoring data. Using sophisticated, state-of-the-science modeling techniques, STAR researchers are making headway into this important area of science. These results will be informative for scientists and policy makers who rely on biomonitoring data – including those researchers working in children's environmental health. A better understanding of biomarker data will help us more accurately assess a child's exposure and risk and can eventually contribute to broader knowledge of children's environmental health. This program will help answer questions like what exposure must have occurred to create the measured biomonitoring level and, based on the measured biomonitoring level, how much of this chemical reached a point in the body where it could potentially do harm.

Community-Based Risk Approaches: Exploring Interactions between Chemical and Nonchemical Stressors

An important emerging area of environmental health science is investigating how chemical and nonchemical stressors – in combination – can impact health outcomes. NCER is leading an effort to explore the opportunities and challenges of this question in greater detail by initiating a program on conducting risk assessments that take into account both chemical and nonchemical stressors in a community and the potential health impact of those stressors when combined. It is likely that STAR research will fill an important role in this emerging area. It is anticipated that specific research needs will be identified in the areas of: (1) methods to measure chemical and nonchemical stressors, susceptibility factors, and health outcomes at the community level; (2) the physiological impacts on nonchemical stressors and the impact on health outcomes associated with environmental chemical exposures; and (3) statistical methods for assessing community and cumulative risk.

The ability to conduct community-level risk assessments that account for the many chemical and nonchemical stressors faced by the population relies on the use of well-developed tools and methods to accurately understand exposures to all stressors, the interactions between stressors, the biological impacts

of those stressors, and the best way to combine and analyze the information in a way that is useful for risk assessors and managers. This type of assessment will move the science of risk assessment and environmental health forward.

Epilogue

Ten years ago, scientists were just beginning to answer pressing health and policy questions such as: How do children's behaviors impact exposure to environmental toxins? How do children's behaviors and exposures change over time? Can we identify biological susceptibilities that increase risk of health effects in children? Do exposures in the womb lead to health effects in children, and if so, to what extent? Are there effective ways to reduce children's exposures to environmental chemicals? Can these effective interventions actually improve children's health outcomes?

During the past ten years, with the emergence of biological monitoring, advanced exposure methods, and the rapidly proliferating science of human DNA analysis, STAR-supported researchers and community partners began answering these questions. Moreover, many scientists participated directly or indirectly in creating more protective policies based on sound science for children at the state and local levels.

Yet many of our most daunting challenges in children's health protection may lie ahead. In the future, increasingly complex questions are likely to arise as the trends in low dose chronic exposures to multiple new chemicals continue across life stages. Additionally, global warming, nanotechnology, and urbanization each present potential risks for children's health. Yet they also present an opportunity to design safer, more sustainable environments.

NCER's STAR program will continue to build upon the successes of the past ten years by supporting the scientific leaders of tomorrow. Together with our federal, academic, and community partners, EPA will step boldly toward answering the questions that will help create a cleaner environment and healthier communities for the Nation's children.

Links to Additional Information

For more information on the Children's Centers and NCER's STAR grant program, see the links below. Other important sources for children's health information are also provided.

EPA. Children's Centers. Available online at http://www.epa.gov/ncer/childrenscenters/ or http://www.niehs.nih.gov/research/supported/centers/prevention/.

The Children's Centers are funded jointly by EPA's STAR grants, NIEHS, and CDC to conduct laboratory, clinical, and behavior studies on the environmental factors influencing children's health.

EPA. NCER. Available online at http://www.epa.gov/ncer/.

NCER supports scientific research across the country on a wide variety of environmental issues. Researchers use these results to develop and support national environmental policies and goals. The NCER STAR grant program partially funds the Children's Centers and provides other grants to focus on children's health.

CDC. Pediatric Environmental Health Specialty Units (PEHSUs). Available online at http://www.atsdr.cdc.gov/HEC/natorg/pehsu.html.

Funded by the Agency for Toxic Substances and Disease Registry (ATSDR) and EPA, PEHSUs consist of representatives from pediatric and environmental clinics who provide education and consultation to health professionals in the field of children's environmental health. Currently, 13 PEHSUs are in operation across the United States, Canada, and Mexico.

Children's Environmental Health Network (CEHN). Available online at http://www.cehn.org/.

CEHN is a nonprofit organization that, among other endeavors, promotes research in the field of children's health. CEHN stimulates research in five priority research areas: asthma and respiratory diseases, childhood cancer, neurodevelopmental effects, endocrine and sexual disorders, and cross-cutting issues.

EPA. Office of Children's Health Protection (OCHP). Available online at http://yosemite.epa.gov/ochp/ochpweb.nsf/content/homepage.htm.

OCHP works with other EPA Offices and other Federal Agencies to promote scientific research in children's environmental health, including the Toxicity and Exposure Assessment for Children's Health (TEACH) program and the National Children's Study.

EPA. TEACH. Available online at http://www.epa.gov/teach/.

The TEACH Web site and database include information on scientific research and Federal regulations relating to children's environmental health. Currently, TEACH provides nonbiased information from numerous sources on 18 chemicals of concern.

EPA. Voluntary Children's Chemical Evaluation Program (VCCEP). Available online at http://www.epa.gov/oppt/vccep/.

VCCEP was developed in response to the Chemical Right-to-Know Initiative, and compiles information from companies that manufacture and import products that contain one or more of the 23 chemicals identified as risks to children.

National Institutes of Health (NIH). National Children's Study. Available online at http://www.nationalchildrensstudy.gov/.

Beginning this year, the National Children's Study will track the physical and mental health of more than 100,000 children from before birth until age 21 in an effort to determine the environmental factors that affect children's health.

World Health Organization (WHO). Child and Adolescent Health and Development (CAH). Available online at http://www.who.int/child-adolescent-health/.

CAH gathers data on children from birth through 19 years of age, focusing on the burden of disease and the effectiveness of public health interventions

References

Akland, G.G., Pellizzari, E.D., Hu, Y., Roberds, M., Rohrer, C.A., Leckie, J.O., and Berry, M.R. 2000. Factors influencing total dietary exposures of young children. *Journal of Exposure Analysis and Environmental Epidemiology* 10(6 Pt 2):710–722.

Al-alem, U., Lendor, C., Kong, J., Garfinkel, R., Chew, G., Perzanowski, M., Camann, D., Whyatt, R.M., Kinney, P., Perera, F., and Miller, R.L. 2006. Association of mouse, cockroach and dustmite IgE levels at age 2 with traffic-related air pollution exposure and respiratory symptoms in an inner city birth cohort. *Journal of Allergy and Clinical Immunology* 117(2): S178.

Apter, A.J. and Eggleston, P.A. 2005. Controlling the environment of asthmatic children: benefits and limitations. In: Szefler, S.J. and Pederson S., eds. *Childhood Asthma*. New York, NY: Taylor & Francis, Chapter 8, pp. 187–212.

Ashwood P., Kwong C., Hansen R., Hertz-Picciotto I., Croen L., Krakowiak P., Walker W., Pessah I.N., and Van de Water J. 2007. Brief report: Plasma leptin levels are elevated in autism: association with early onset phenotype? *J. Autism Dev. Disord. Advanced online publication* (DOI 10.1007/s10803-006-0353-1).

Bearer, C.F., Santiago, L.M., O'Riordan, M.A., Buck, K., Lee, S.C., Singer, L.T. 2005. Fatty acid ethyl esters: quantitative biomarkers for maternal alcohol consumption. *J Pediatrm* 146(6):824–830.

Bearer, C.F. 2000. The special and unique vulnerability of children to environmental hazards. *Neurotoxicology* 21:925–934.

Berhane, K., McConnell, R., Gilliland, F., Islam, T., Gauderman, W.J., Avol, E., London, S.J., Rappaport, E., Margolis, H.G., and Peters, J.M. 2000. Sex specific effects of asthma on pulmonary function in children. *American Journal of Respiratory and Critical Care Medicine* 162(5):1,723–1,730.

Berkowitz, G.S., Wetmur, J.G., Birman-Deych, E., Obel, J., Lapinski, R.H., Godbold, J.H., Holzman, I.R., and Wolff, M.S. 2004. In utero pesticide exposure, maternal paraoxonase activity, and head circumference. *Environmental Health Perspectives* 112(3):388–391.

Black, K., Shalat, S.L., Freeman, N.C., Jimenez, M., Donnelly, K.C., and Calvin, J.A. 2005. Children's mouthing and food-handling behavior in an agricultural community on the US/Mexico border. *Journal of Exposure Analysis and Environmental Epidemiology* 15(3):244–251.

Bradman, A., Whitaker, D., Quirós, L., Castorina, R., Henn, B.C., Nishioka, M., Morgan, J., Barr, D.B., Harnly, M., Brisbin, J.A., Sheldon, L.S., McKone, T.E., and Eskenazi, B. 2007. Pesticides and their metabolites in the homes and urine of farmworker children living in the Salinas Valley, CA. *Journal of Exposure Science and Environmetnal Epidemiology* 17(4):331-349 (Cited as a secondary reference from EPA 2007b).

Bradman, A. and Whyatt, R.M. 2005. Characterizing exposures to nonpersistent pesticides during pregnancy and early childhood in the National Children's Study: a review of monitoring and measurement methodologies. *Environmental Health Perspectives* 113(8):1,092–1,099.

Bradman, A., Eskenazi, B., Sutton, P., Athanasoulis, M., and Goldman, L.R. 2001. Iron deficiency associated with higher blood lead in children living in contaminated environments. *Environmental Health Perspectives* 109(10): 1079-1084.

Brenner, B., Markowitz, S., Rivera, M., Romero, H., Weeks, M., Sanchez, E., Deych, E., Garg, A., Godbold, J., Wolff, M.S., Landrigan, P.J., and Berkowitz, G. 2003. Integrated pest management in an urban community: a successful partnership for prevention. *Environmental Health Perspectives* 111(13):1,649–1,653.

Breysse, P.N., Buckley, T.J., Williams, D., Beck, C.M., Jo, S.J., Merriman, B., Kanchanaraksa, S., Swartz, L.J., Callahan, K.A., Butz, A.M., Rand, C.S., Diette, G.B., Krishnan, J.A., Moseley, A.M., Curtin-Brosnan, J., Durkin, N.B., and Eggleston, P.A. 2005. Indoor exposures to air pollutants and allergens in the homes of asthmatic children in inner-city Baltimore. *Environmental Research* 98(2):167-176.

CDC. 2007. Overweight and obesity: childhood overweight. Centers for Disease Control, Division of Nutrition, Physical Activity and Obesity. Available online at: **http://www.cdc.gov/nccdphp/dnpa/obesity/childhood**. Last accessed: December 19, 2007.

CDC. 2007. Surveillance summaries. *Morbidity and Mortality Weekly Report* 56(SS-1). Available online at: **http://www.cdc.gov/mmwr/PDF/ss/ss5601.pdf**. Last accessed: November 27, 2007.

Chen, J., Kumar, M., Chan, W., Berkowitz, G., and Wetmur, J.G. 2003. Increased influence of genetic variation on PON1 activity in neonates. *Environmental Health Perspectives* 111(11):1,403–1,409.

Chew, G.L., Perzanowski, M.S., Miller, R.L., Correa, J.C., Hoepner, L.A., Jusino, C.M., Becker, M.G., and Kinney, P.L. 2003. Distribution and determinants of mouse allergen exposure in low-income New York City apartments. *Environmental Health Perspectives* 111(10):1,348–1,351.

Children's Health Protection Advisory Committee-Board of Scientific Counselors (CHPAC-BOSC) Workgroup. 2007. *Review of the Research Translation of the EPA/NIEHS Children's Research Centers: Accomplishments and Opportunities for the Future*. Available online at: **http://yosemite.epa.gov/ochp/ochpweb.nsf/content/CEHRC_Findings.htm/$file/CEHRC%20Findings.doc**. Last accessed: November 20, 2007.

Clark, N.M., Brown, R.W., Parker, E.A., Robins, T.G., Remick, D.G., Philbert, M.A., Keeler, G.J., and Israel, B.A. 1999. Childhood asthma. *Environmental Health Perspectives* 107(S3):421–429.

Corrion, M.L., Ostrea, Jr. E.M., Bielawski, D.M., Posecion, N.C., and Seagraves, J.J. 2005. Detection of prenatal exposure to several classes of environmental toxicants and their metabolites by gas chromatography-mass spectrometry in maternal and umbilical cord blood. *Journal of Chromatography B Analyt Technol Biomed Life Sci.* 822(1–2):221–229.

Costa, L.G., Cole, T.B., Jarvik, G.P., and Furlong, C.E. 2003. Functional genomic of the paraoxonase (PON1) polymorphisms: effects on pesticide sensitivity, cardiovascular disease, and drug metabolism. *Annual Review of Medicine* 54:371–392.

Curl, C.L,, Fenske, R.A,, and Elgethun, K. 2003. Organophosphorous pesticide exposure of urban and suburban preschool children with organic and conventional diets. *Environ Health Perspect.* 111(3):377–382.

Duramad, P., Harley, K., Lipsett, M. Bradman, A., Eskenazi, B., Holland, N.T., and Tager, I.B. 2006. Early environmental exposures and intracellular Th1/Th2 cytokine profiles in 24-month-old children living in an agricultural area. *Environmental Health Perspectives* 114(2):1,916–1,922.

Eggleston, P.A., Butz, A., Rand, C., Curtin-Brosnan, J., Kanchanaraksa, S., Swartz, L., Breysse, P., Buckley, T., Diette, G., Merriman, B., and Krishnan, J.A. 2005. Home environmental intervention in inner-city asthma: a randomized controlled clinical trial. *Annals of Allergy, Asthma, and Immunology* 95(6):518-524.

Eggleston, P.A. 2005. Improving indoor environments: reducing allergen exposures. *Journal of Allergy and Clinical Immunology* 116(1):122–126.

Eggleston, P.A. 2003. Cockroach allergen abatement in inner-city homes. *Annals of Allergy, Asthma & Immunology* 91(6):512–514.

EPA. 2007a. Children's Environmental Health Centers: University of Washington Center for Child Environmental Health Risks Research. Available online at: **http://www.epa.gov/ncer/childrenscenters/washington.html**. Last accessed: November 27, 2007.

EPA. 2007b. Children's Environmental Health Centers: University of California at Berkeley Center for Children's Environmental Health Research. Available online at: **http://www.epa.gov/ncer/childrenscenters/berkeley.html**. Last accessed: November 27, 2007.

EPA. 2005. Guidance on Selecting Age Groups for Monitoring and Assessing Childhood Exposures to Environmental Contaminants. EPA/630/P-03/003F. Risk Assessment Forum, Washington, DC.

Eskenazi, B., Bradman, A., and Castorina, R. 1999. Exposures of children to organophosphate pesticides and their potential adverse health effects. *Environmental Health Perspectives* 107(S3):409–419.

Fenske, R.A., Bradman, A., Whyatt, R.M., Wolff, M.S., Barr, D.B. 2005. Lessons learned for the assessment of children's pesticide exposure: critical sampling and analytical issues for future studies. *Environmental Health Perspectives* 113(10): 1,455–1,462.

Freeman, N.C., Shalat, S.L., Black, K., Jimenez, M., Donnelly, K.C., Calvin, A., and Ramirez, J. 2004. Seasonal pesticide use in a rural community on the US/Mexico border. *Journal of Exposure Analysis and Environmental Epidemiology* 14(6):473–478.

Freeman, N.C., Jimenez, M., Reed, K.J., Gurunathan, S., Edwards, R.D., Roy, A., Adgate, J.L., Pellizzari, E.D., Quackenboss, J., Sexton, K., and Lioy, P.J. 2001a. Quantitative analysis of children's microactivity patterns: The Minnesota Children's Pesticide Exposure Study. *Journal of Exposure Analysis and Environmental Epidemiology* 11(6):501–509.

Freeman, N.C., Sheldon, L., Jimenez, M., Melnyk, L., Pellizzari, E., and Berry, M. 2001b. Contribution of children's activities to lead contamination of food. *Journal of Exposure Analysis and Environmental Epidemiology* 11(5):407–413.

Furlong, C.E., Holland, N., Richter, R.J., Bradman, A., Ho, A., and Eskenazi, B. 2006. PON1 status of farmworker mothers and children as a predictor of organophosphate sensitivity. *Pharmacogenet Genomicsn 16(3):183–190.*

Furlong, C.E., Cole, T.B., Jarvik, G.P., Pettan-Brewer, C., Geiss, G.K., Richter, R.J., Shih, D.M., Tward, D.A., Lusis, J.A., and Costa, L.G. 2005. Role of paraoxonase (PON1) status in pesticide sensitivity: genetic and temporal determinants. *Neurotoxicology* 26(4):651–659.

Gilliland, F.D., Berhane, K., Li, Y.F., Rappaport, E.B., and Peters, J.M. 2003. Effects of early onset asthma and *in utero* exposure to maternal smoking on childhood lung function. *Am J Respir Crit Care Med* 167(6):917–924.

Gilliland, F.D., Li, Y.F., Dubeau, L., Berhane, K., Avol, E., McConnell, R., Gauderman, W.J., and Peters, J.M. 2002a. Effects of glutathione S-transferase M1, maternal smoking during pregnancy, and environmental tobacco smoke on asthma and wheezing in children. *Am J Respir Crit Care Med* 166(4):457–463.

Gilliland, F.D., Rappaport, E.B., Berhane, K., Islam, T., Dubeau, L., Gauderman, W.J., and McConnell, R. 2002b. Effects of glutathione s-transferase P1, M1, and T1 on acute respiratory illness in school children. *Am J Respir Crit Care Medn 166(3):346–351.*

Gilliland, F.D., Li, Y.F., and Peters, J.M. 2001. Effects of maternal smoking during pregnancy and environmental tobacco smoke on asthma and wheezing in children. *Am J Respir Crit Care Med* 163(2):429–436.

Gilliland, F.D., Berhane, I., McConnell, R., Gauderman, W.J., Vora, H., Rappaport, E.B., Avol, E., and Peters, J.M. 2000. Maternal smoking during pregnancy, environmental tobacco smoke exposure and childhood lung function. *Thorax* 55(4): 271–276.

Hamilton, B.E., Martin, J.A., and Ventura, S,J. 2006. Births: Preliminary data for 2005. *Health E-Stats*. Available online at: **http://www.cdc.gov/nchs/products/pubs/pubd/hestats/prelimbirths05/prelimbirths05.htm**. Last accessed: December 19, 2007.

Hertz-Picciotto, I., Croen, L.A., Hansen, R., Jones, C.R., van de Water, J., and Pessah, I.N. 2006. The CHARGE study: an epidemiologic investigation of genetic and environmental factors contributing to autism. *Environmental Health Perspectives* 114:1119-1125.

Keeler, G.J., Dvonch, T., Yip, F.Y., Parker, E.A., Israel, B.A., Marsik, F.J., Morishita, M., Barres, J.A., Robins, T.G., Brakefield-Caldwell, W., and Sam, M. 2002. Assessment of personal and community-level exposures to particulate matter among children with asthma in Detroit, Michigan, as part of Community Action Against Asthma (CAAA). *Environmental Health Perspectives* 110(S2):173–181.

Kinney, P.L., Northridge, M.E., Chew, G.L., Gronning, E., Joseph, E., Prakash, S., and Goldstein, I. 2002. On the front lines of environmental asthma intervention in New York City. *American Journal of Public Health* 92(1):24–26.

Landrigan, P.J., Claudio, L., Markowitz, S.B., Berkowitz, G.S., Brenner, B.L., Romero, H., Wetmur, J.G., Matte, T.D., Gore, A.C., Godbold, J.H., and Wolff, M.S. 1999. Pesticides and inner-city children: exposures, risks and prevention. Environmental Health Perspectives 107(3):431–437.

Lewis, T.C., Robins, T.G., Dvonch, J.T., Keeler, G.J., Yip, F.Y., Mentz, G.B., Lin, X., Parker, E.A., Israel, B.A., Gonzalez, L., and Hill, Y. 2005. Air pollution-associated changes in lung function among asthmatic children in Detroit. *Environmental Health Perspectives* 113(8):1,068–1,075.

Li, Y.F., Langholz, B., Salam, M.T., and Gilliland, F.D. 2005. Maternal and grandmaternal smoking patterns are associated with early childhood asthma. *Chest* 127(4):1,232–1,241.

Limb, S.L., Brown, K.C., Wood, R.A., Wise, R.A., Eggleston, P.A., Tonascia, J., Hamilton, R.G., and Adkinson, N.F. Jr. 2005. Adult asthma severity in individuals with a history of childhood asthma. *Journal of Allergy and Clinical Immunology* 115(1):61–66.

Lioy, P.J. 2006. Employing dynamical and chemical processes for contaminant mixtures outdoors to the indoor environment: the implications for total human exposure analysis and prevention. *Journal of Exposure Science & Environmental Epidemiology* 16(3):207–224.

Matsui, E.C., Simons, E., Rand, C., Butz, A., Buckley, T.J., Breysse, P., and Eggleston, P.A. 2005. Airborne mouse allergen in the homes of inner-city children with asthma. *Journal of Allergy and Clinical Immunology* 115(2):358–363.

McConnell, R., Berhane, K., Yao, L., Jerrett, M., Lurmann, F., Gilliland, F., Künzli, N., Gauderman, J., Avol, E., Thomas, D., and Peters, J. 2006. Traffic, susceptibility, and childhood asthma. *Environmental Health Perspectives* 114(5):766–772.

Ostrea, E.M., Bielawski, D.M., and Posecion, N.C. 2006. Meconium analysis to detect fetal exposure to neurotoxicants. *Archives of Disease in Childhood* 91(8):628–629.

Ostrea, E.M., Morales, V., Ngoumgna, E., Prescilla, R., Tan, E., Hernandez. E., Ramirez, G.B., Cifra, H.L., and Manlapaz, M.L. 2002. Prevalence of fetal exposure to environmental toxins as determined by meconium analysis. *Neurotoxicology* 23(3):329–339.

Parker, E.A., Israel, B.A., Brakefield-Caldwell, W., Lewis, T.C., Ramirez, E., Rowe, Z., and Keeler, G. 2003. Community Action Against Asthma: examining the partnership process of a community-based participatory research project. *Journal of General Internal Medicine* 18(7):558–567.

Perera, F.P., Rauh, V., Whyatt, R.M., Tsai, W.Y., Tang, D., Diaz, D., Hoepner, L., Barr, D., Tu, Y.H., Camann, D., and Kinney, P. 2006. Effect of prenatal exposure to airborne polycyclic aromatic hydrocarbons on neurodevelopment in the first 3 years of life among inner-city children. *Environmental Health Perspectives* 114(8):1,287–1,292.

Perera, F., Tang, D., Whyatt, R., Lederman, S.A., and Jedrychowski, W. 2005. DNA damage from polycyclic aromatic hydrocarbons measured by benzo[a]pyrene-DNA adducts in mothers and newborns from Northern Manhattan, the World Trade Center area, Poland, and China. *Cancer Epidemiology Biomarkers & Prevention* 14(3):709–714.

Perera, F.P., Tang, D., Tu, Y.H., Cruz, L.A., Borjas, M., Bernert, T., and Whyatt, R.M. 2004. Biomarkers in maternal and newborn blood indicate heightened fetal susceptibility to procarcinogenic DNA damage. *Environmental Health Perspectives* 112(10):1,133–1,136.

Perera, F.P., Rauh, V., Tsai, W.Y., Kinney, P., Camann, D., Barr, D., Bernert, T., Garfinkel, R., Tu, Y.H., Diaz, D., Dietrich, J., and Whyatt, R.M. 2003. Effects of transplacental exposure to environmental pollutants on birth outcomes in a multiethnic population. *Environmental Health Perspectives* 111(2):201–205.

Perera, F.P., Illman, S.M., Kinney, P.L., Whyatt, R.M., Kelvin, E.A., Shepard, P., Evans, D., Fullilove, M., Ford, J., Miller, R.L., Meyer, I.H., and Rauh, V.A. 2002. The challenge of preventing environmentally related disease in young children: community-based research in New York City. *Environmental Health Perspectives* 110(2):197–204.

Phillips, M.L. 2005. Children's Centers Study Kids and Chemicals. *Environmental Health Perspectives*, 113(10):A664-8.

Phipatanakul, W., Cronin, B., Wood, R.A., Eggleston, P.A., Shih, M.C., Song, L., Tachdjian, R., and Oettgen, H.C. 2004. Effect of environmental intervention on mouse allergen levels in homes of inner-city Boston children with asthma. *Annals of Allergy, Asthma & Immunology* 92(4):420–425.

Ramaprasad, J., Tsai, M-Y., Elgethun, K., Hebert, V.R., Felsot, A., Yost, M.G., and Fenske, R.A. 2004. The Washington aerial spray drift study: assessment of off-target organophosphorus insecticide atmospheric movement by plant surface volatilization. *Atmospheric Environment* 38(33):5,703–5,713.

Rauh, V.A., Garfinkel, R., Perera, F.P., Andrews, H.F., Hoepner, L., Barr, D.B., Whitehead, R., Tang, D., and Whyatt, R.W. 2006. Impact of prenatal chlorpyrifos exposure on neurodevelopment in the first 3 years of life among inner-city children. *Pediatrics* 118(6):e1,845–1,859.

Rauh, V.A., Chew, G.R., and Garfinkel, R.S. 2002. Deteriorated housing contributes to high cockroach allergen levels in inner-city households. *Environmental Health Perspectives* 110 (S2):323–327.

Rice, C. 2007. Prevalence of Autism Spectrum Disorders—Autism and Developmental Disabilities Monitoring Network, 14 Sites, United States, 2002. Morbidity and Mortality Weekly Report 56(SS01):12-28. Available online at: **http://www.cdc.gov/MMWR/preview/mmwrhtml/ss5601a2.htm**. Last accessed: December 19, 2007.

Rumold, R., Jyrala, M., and Diaz-Sanchez, D. 2001. Secondhand smoke induces allergic sensitization in mice. *Journal of Immunology* 167(8):4,765–4,770.

Shalat, S.L., Donnelly, K.C., Freeman, N.C.G., Calvin, J.A., Ramesh, S., Jimenez, M., Black, K., Coutinho, C., Needham, L.L., Barr, D.B., and Ramirez, J. 2003. Nondietary ingestion of pesticides by children in an agricultural community on the US/Mexico border: preliminary results. *Journal of Exposure Analysis and Environmental Epidemiology* 13(1):42–50.

Stevens, L.M., Lynm, C., Glass, R.M. 2002. Low birth weight. *The Journal of the American Medical Association* 287:270.

Tsai, M-Y., Elgethun, K., Ramaprasad, J., Yost, M.G., Felsot, A.S., Hebert, V.R., and Fenske, R.A. 2005. The Washington aerial spray drift study: modeling pesticide spray drift deposition from an aerial application. *Atmospheric Environment* 39(33):6,194–6,203.

Wolff, M.S., Engel, S., Berkowitz, G., Teitelbaum, S., Siskind, J., Barr, D.B., and Wetmur, J. 2007. Prenatal pesticide and PCB exposures and birth outcomes. *Pediatric Research* 61(2):243–250.

Whyatt, R.M., Camann, D., Perera, F.P., Rauh, V.A., Tang, D., Kinney, P.L., Garfinkel, R., Andrews, H., Hoepner, L., and Barr, D.B. 2005. Biomarkers in assessing residential insecticide exposures during pregnancy and effects on fetal growth. *Toxicology and Applied Pharmacology* 206(2):246–254.

Whyatt, R.M., Rauh, V., Barr, D.B., Camann, D.E., Andrews, H.F., Garfinkel, R., Hoepner, L.A., Diaz, D., Dietrich, J., Reyes, A., Tang, D., Kinney, P.L., and Perera, F.P. 2004. Prenatal insecticide exposures and birth weight and length among an urban minority cohort. *Environmental Health Perspectives* 112(10):1,125–1,132.

Whyatt, R.M. and Barr, D.B. 2001. Measurement of organophosphate metabolites in postpartum meconium as a potential biomarker of prenatal exposure: a validation study. *Environmental Health Perspectives* 109(4):417–420.

Wright, R.O., Amarasiriwardena, C., Woolf, A.D., Jim, R., and Bellinger, D.C. 2006. Neuropsychological correlates of hair arsenic, manganese, and cadmium levels in school-age children residing near a hazardous waste site. *Neurotoxicology* 27(2):210-216.

Zeldin, D.C., Eggleston, P., Chapman, M., Piedimonte, G., Renz, H., and Peden, D. 2006. How exposures to biologics influence the induction and incidence of asthma. *Environmental Health Perspectives* 114(4):620–626.

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