

# Air Pollutants and Asthma

Children's Environmental Health Centers

Environmental Protection Agency

Asthma, a chronic respiratory disease characterized by airway inflammation, difficulty breathing, wheezing and coughing, affects the lives of millions of Americans. The disease remains one of the leading causes of emergency room visits and school absenteeism for children. The NIEHS/EPA Centers for Children's Environmental Health and Disease Prevention (Children's Centers) are investigating how asthma develops in children, which individuals may be most susceptible (including genetic factors), what environmental triggers may lead to asthma attacks, and how interventions can reduce the severity of asthma symptoms.

**Question 1 (Concerns):** What are the primary **concerns** about exposure to air pollutants and their connection with the development of asthma, and how is EPA addressing these concerns?

**Question 2 (Exposure):** What are the Children's Centers learning about exposure to air pollutants and their connection with the development of asthma, and how is EPA addressing these concerns?

**Question 3 (Susceptibility):** What are the Children's Centers learning about children's **susceptibility** to air pollutants and asthma?

**Question 4 (Effects):** What are the Children's Centers learning about the **effects** of air pollutants on children?

**Question 5 (Prevention):** What are the Children's Centers learning about effective ways to **reduce or prevent** asthma?

**Question 1 (Concerns):** What are the primary concerns about exposure to air pollutants and their connection with the development of asthma, and how is EPA addressing these concerns?

Of the approximately 20 million people in the U.S. with asthma, more than six million are children. From 1980 to 1994, the proportion of Americans suffering with asthma increased by 75%, and in children, the proportion increased by 160% while asthma rates among children remain at historically high levels (CDC 2006). However, the causes of asthma remain uncertain and appear to be complex, so the U.S. government has identified asthma as a top priority for research. The Children's Centers are addressing the etiology of asthma from a number of different perspectives, including the Centers at Columbia, Johns Hopkins, the University of Iowa, the University of Michigan and USC/UCLA.

Columbia: Children's vulnerability and susceptibility to a variety of urban environmental toxins/toxicants, see if exposure to these chemicals is linked to asthma outcomes at ages 6, 7 and 8.

Johns Hopkins and University of Michigan (1998-2005): Particulate matter (PM), vulnerability and susceptibility to air pollution, immune system dysfunction.

University of Iowa (1998-2004): Focus on rural populations, endotoxins, RSV virus in infants and its role in making children more vulnerable to asthma.

USC/UCLA: Air toxics, vulnerability and susceptibility of children to asthma, advantages and disadvantages of a new biomarker for asthma, exhaled nitric oxide (eNO).

To incorporate the role of environmental factors such as airborne particles and gases into the campaign to prevent asthma, EPA's Office of Research and Development (ORD) has developed a targeted asthma research program which identifies significant information gaps, prioritizes research needs, and proposes advisory guidelines indicating how available resources can be utilized to advance scientific knowledge and control environmental factors that contribute to asthma prevalence and severity.

**Question 2 (Exposure):** What are the Children's Centers learning about children's exposure to air pollutants which may lead to the development of asthma or exacerbation of asthma symptoms?

- Children two years or younger living within 75 meters (82 yards) of a major roadway have an increased risk of developing asthma and it appears that children without a family history of asthma may be especially susceptible. This "roadside effect" was more pronounced in girls. This risk of developing asthma decreased to background rates at 150-200 meters (0.12 miles) from a major road (USC/UCLA, McConnell et al. 2006).
- Disadvantaged asthmatic children in urban areas appear to be at increased risk for higher residential allergen and elevated air pollution exposure. This combination of asthma triggers in the home appears to contribute to a disparity in asthma burden between inner-city and non-inner-city children (Johns Hopkins, Breyse et al. 2005).
- The Columbia Children's Center has developed new biomarkers to improve exposure assessment, including epigenetic changes related to pollutant exposure and gene and haplotype analysis to investigate gene-environment interactions.
- Exposure to mouse allergens is strongly associated with asthma symptoms in both inner-city and suburban homes. The Johns Hopkins Children's Center has published a series of papers documenting the importance of mouse allergen as a source of asthma morbidity (disease) for inner-city asthmatic children.
  - Children sensitive and highly exposed to mouse allergen experience more days of symptoms and are more likely to have an unscheduled doctor visit and hospitalization.
  - Exposure to mouse allergens remained a significant factor after adjusting for potential confounders, such as cockroach allergen. (Matsui et al. 2004, Matsui et al. 2006, Matsui et al. 2007).
- Indoor particulate matter (PM, or soot) levels in the bedrooms of inner-city children in Baltimore were found to be remarkably high, as more than 17% of the homes tested would fail the EPA 24-hour ambient PM<sub>2.5</sub> standard.
- Smoking households average much higher PM<sub>2.5</sub> and PM<sub>10</sub> (fine and coarse particle) concentrations. These findings demonstrate (1) that the indoor PM concentration of most homes in the study would exceed the EPA annual limit for ambient PM; (2) there was wide variation in indoor PM levels, which were considerably higher than outdoor levels; and (3) smoking is an important indoor source of PM (Johns Hopkins, Breyse et al. 2005).
- The University of Michigan Children's Center demonstrated how environmental exposure and health effect research could be successfully carried out in a community-based participatory research (CBPR) framework. The Center worked with community members in Detroit to measure PM concentrations in the home. Average personal and indoor home PM<sub>2.5</sub> and PM<sub>10</sub> exposures were found to be significantly greater than the outdoor PM<sub>2.5</sub> and PM<sub>10</sub> concentrations. Researchers found high levels of air pollutants in southwest Detroit from heavy industrial sources and interstate motorways (Keeler et al. 2002).

**Question 3 (Susceptibility):** What are the Children's Centers learning about children's susceptibility to air pollutants and asthma?

- Researchers from the Columbia Children's Center compared fetal and adult susceptibility to polycyclic aromatic hydrocarbons (PAHs) and environmental tobacco smoke (ETS). They observed DNA damage in the fetus from this exposure, providing evidence that a developing fetus is far more susceptible than an adult to the carcinogenic effects of PAHs, which are present in emissions from motor vehicle engines, residential heating, power generation and tobacco smoking. Furthermore, it was suggested that the fetus has less of an ability to repair

damaged DNA as well as a reduced ability to clear ETS components from their system, increasing the fetus's overall susceptibility to these exposures (Perera et al. 2004, Bocskay et al. 2005).

- Early life exposures to traffic-related pollutants in urban environments appear to affect the immune system by increasing allergic responses, leading to respiratory symptoms in children as young as two years of age (Columbia, Al-alem et al. 2006).
- Genetic variations in immune response to air pollutants may offer protection or confer susceptibility to the incidence of asthma. Some of these genetic differences appear to vary significantly between ethnic groups, potentially contributing to health disparities (USC/UCLA, Li et al. 2006; Donohue et al. 2006).
- The USC/UCLA Children's Center found that in utero exposure to maternal smoking has been associated with increased risk of asthma and wheezing among children with the glutathione-s-transferase M1 (GSTM1) null genotype, but not among children with the GSTM1(+) genotype. This demonstrates important long-term effects of in utero exposure to tobacco smoke in genetically susceptible children. This study was one of the first to illustrate the critical need to consider both environment and genes in understanding asthma pathogenesis (USC/UCLA, Gilliland et al. 2002).
- Individuals with the GSTM1 null or GSTP1 I105 wildtype genotypes show greatly enhanced nasal allergic responses in the presence of diesel exhaust particles. Compared with patients with a functional GSTM1 genotype, GSTM1 null patients had a larger immune response (increase in IgE and histamine) after exposure to diesel exhaust particles (DEP) plus allergens. This work paved the way for study of the mechanism of genetic susceptibility to air pollutants and inflammatory response within cohort studies (USC/UCLA, Gilliland et al. 2004).
- Iowa Children's Center researchers have described mechanisms by which respiratory syncytial virus (RSV), a virus that triggers asthma, can escape antiviral mechanisms in the airway and pathways that the virus uses to trigger inflammation. RSV preferentially infects lung airway epithelial cells and is a major cause of illness in young children. Findings indicate that RSV infection in the first year of life increases the risk of subsequent development of asthma.

**Question 4 (Effects):** What are the Children's Centers learning about the effects of air pollutants on children and the development of asthma?

- Research on air pollution and asthma from the Children's Centers has broadened our understanding of the inflammatory process in the lung (Johns Hopkins, Walters et al. 2002) and have shown that the effects of air pollution can be seen in school-age children as increased exacerbation of asthma symptoms and increased days absent from school (USC/UCLA, McConnell et al. 2003; Gilliland et al. 2003).
- A study by the Columbia Children's Center of 60 newborns in New York City showed that prenatal exposure to combustion-related urban air pollutants (PAHs) alters the structure of chromosomes of babies in the womb. This is the first study to show that environmental exposure during pregnancy to PAHs (components of vehicle exhaust and tobacco smoke) can cause a modest but significant increase in chromosomal abnormalities in fetal tissues, which have been linked in other studies to increased risk of cancer in children and adults. (Columbia, Bocskay et al. 2005).
- Prenatal exposure to combustion-related urban air pollutants can adversely affect child development. Investigators at the Columbia Children's Center showed that exposure to PAHs was linked to significantly lower scores on mental development tests and more than double the risk of developmental delay at age 3. Such cognitive delay is indicative of greater risk for performance deficits in language, reading and math for these children in early school years. (Columbia, Perera et al. 2006).
- Prenatal exposure to airborne PAHs, in conjunction with postnatal exposure to ETS, has been associated with respiratory symptoms in young children. Results from this study at the Columbia Children's Center also suggest that ETS worsens these respiratory symptoms. The results of this research suggest the need for community-based interventions to lower the risk of respiratory infections among inner-city populations (Columbia, Miller et al. 2004).

- The Johns Hopkins Children's Center found that particulate matter (PM) can induce asthma-like allergic symptoms in mice along with significant increases in airway hyperresponsiveness. PM seems to react with the "complement" system, immune system proteins that work with antibodies to destroy bacteria in the body and in doing so, induce an inflammatory response. Investigators also identified a susceptibility gene for asthma in a mouse model and showed that mice genetically deficient in complement factor 3 (C3) did not develop airway hyperresponsiveness to PM. Results showed that response from the complement system may be one way in which airborne PM elicits an allergic airway response (Walters et al. 2001, Walters et al. 2002).
- Researchers at the Johns Hopkins Children's Center have shown effects of airborne PM on the growth of dendritic cells (DCs), cells in the immune system that process antigens and then present them on their surface to other immune system cells. They found that PM induces a distinct form of DC maturation that shares some features with lipopolysaccharide (LPS), an endotoxin on the outer membrane of some bacteria, but has a unique signature, including down-regulation of the immune system pattern recognition toll-like receptors TLR2 and TLR4 and the production of Interleukin (IL)-10. Research implicates PM as a novel agent acting on DCs to promote pro-inflammatory Th2-like immune responses, which are a hallmark of allergic asthma. These studies open up a new area of research into how environmental pollutants affect asthma immunology (Johns Hopkins, Williams et al. 2007).
- Exposure to indoor PM from inner-city Baltimore has been significantly associated with asthma symptoms. The Johns Hopkins Children's Center found that elevated indoor PM levels were significantly associated with increased respiratory symptoms and more frequent inhaler medication use. Investigators showed that for each 10 µg/m<sup>3</sup> increase in PM<sub>10</sub> levels (PM that is 10 microns or smaller, the coarse PM fraction), there were more nights with awakening with asthma symptoms, more days with exercise symptoms, a 7% increase in severe wheezing and a 5% increase in beta-agonist (inhaled bronchodilator) use (Johns Hopkins, manuscript in preparation).
- A study by researchers at the USC/UCLA Children's Center showed that B (lymphocyte) cells in the immune system are part of a natural protective mechanism from oxidant pollutants such as diesel exhaust particles (DEPs). The ability of DEP extracts to enhance an inflammatory response was blocked by the induction of protective Phase II enzymes in B cells by the chemical sulforaphane. This suggests that treatment with sulforaphane could prevent the immune response to diesel exhaust, blocking the inflammatory and allergic response (USC/UCLA, Wan et al. 2006, Ritz et al. 2007).
- Researchers at the University of Michigan Children's Center found an association between ambient pollution levels in Detroit and poor lung function in children with asthma. The study showed that while ambient levels of PM<sub>2.5</sub> and ozone were close to or exceeded the National Ambient Air Quality Standards (NAAQS) and PM<sub>10</sub> levels were within current standards, these levels were associated with adverse effects on pulmonary function among at-risk children with asthma. (University of Michigan, Lewis et al. 2005).
- Long-term exposure to air pollutants is associated with significant deficits in lung capacity at age 18. In a study by the USC/UCLA Children's Center, the children with the highest exposure to PM<sub>2.5</sub> (fine particulate matter pollution) were five times as likely to have a diminished lung capacity which is only about 80 percent of normal. The study demonstrates that current levels of air pollution can have chronic, adverse effects on lung development in children from the age of 10 to 18 years, leading to clinically significant deficits in lung capacity as children reach adulthood (Gauderman et al. 2004).

**Question 5 (Prevention):** What are the Children's Centers learning about effective ways to reduce or prevent children's exposure to air pollution and how to prevent asthma?

- The Johns Hopkins Children's Center has tested a combination of behavioral and physical interventions specifically tailored for individual children to reduce indoor particulate matter (PM) concentrations and relevant allergen levels. The researchers have published a series of papers describing the residence-wide environmental treatment designed to reduce airborne PM and indoor allergens in inner-city homes, and found that these interventions were

associated with a modest reduction in a child's daily asthma symptoms (Breysse et al. 2005, Eggleston, Butz et al. 2005, Swartz et al. 2004).

- The Columbia Children's Center has collaborated with New York City agencies to implement a community-based intervention in public housing to lower pest allergen exposure using lower-toxic pest control methods, and is partnering with local community organizations to translate research findings into public policy change by educating policymakers and creating an education campaign recommending ways to reduce children's exposures to environmental toxicants.
- The University of Michigan Children's Center developed mouse model of asthma-like pulmonary inflammation. The original publication has been cited nearly 20 times and the model served as the basis for preclinical studies using tumor necrosis factor inhibitors for the treatment of asthma (Kim et al. 2001).
- The intervention research component of the University of Michigan Children's Center has had a major impact on improving the health of children and the caregivers involved. Trained community health workers provided asthma education, materials such as HEPA-filter vacuum cleaners and allergen-proof mattress covers, integrated pest management (IPM), social service referrals and ongoing support. The intervention was effective in improving measures of lung function, reducing the frequency of coughing, reducing the proportion of children requiring unscheduled medical visits and reporting inadequate use of controller medication. (Parker et al. 2004, Edgren et al. 2005, Parker et al., in press).
- Some studies have shown a protective effect for asthma for children who live in farming communities (the so-called "hygiene hypothesis"). The Iowa Children's Center did find that children who lived on farms were somewhat less likely than those who lived in town to have ever shown symptoms of wheezing. However, this protective effect with farming was only observed in one of the study areas, Keokuk County. A major conclusion of this large, rural study is that asthma prevalence in this population rivals that in large Midwestern cities, casting doubt on a protective effect of rural life for the development of childhood asthma (Chrischilles et al. 2004).
- The USC/UCLA Children's Center has shown a protective role for the Phase II enzymes GSTM1 and GSTP1 from the effects of diesel exhaust particles (DEP), therefore people with low Phase II enzyme response are at increased risk for an inflammatory response. Center studies also showed that cells in the lung lacking GSTM1 produce more Phase II protective enzymes. Researchers are testing whether sulforaphane, which promotes Phase II enzyme production, can block the inflammatory and allergic response to DEP (Gilliland et al. 1999, Ritz et al. 2007).