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Asthma Research Results Highlights

RESEARCH AND DEVELOPMENT

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Asthma Research Results Highlights

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Foreword

In 2002, the U.S. Environmental Protection Agency (EPA) released its Asthma Research Strategy. Since then, scientists have made significant strides in advancing our understanding of how and why asthma is on the rise and our understanding of what induces and exacerbates the disease. EPA research has focused on three areas: asthma triggers, susceptibility factors, and intervention strategies. This document provides an overview of the advances in these areas and highlights studies that are particularly noteworthy because of their contribution to applications that reduce asthma suffered by individuals. This research reflects EPA's commitment to addressing the serious public health threat that is posed by the growing asthma epidemic. While we are proud of the accomplishments of EPA's Asthma Research Program to date, significant uncertainties remain. We need to learn more about the causes and triggers of asthma, as well as how to manage this disease.

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Introduction

Asthma, a chronic respiratory disease characterized by difficult breathing, wheezing, and coughing, is disrupting the lives of an increasing number of Americans. In 2001, more than 20 million Americans had asthma, 6.1 million of which were children. From 1980 to 1994, the proportion of Americans suffering from asthma increased by 75%; in children, the proportion grew by 160%. Asthma also affects some minorities and low-income populations disproportionately.

Because of asthma's increasing incidences, the U.S. government has identified asthma as a top priority for research. *Healthy People 2010*, a guiding document for the Department of Health and Human Services, identified asthma as a "serious and growing health problem" in need of action; and the President's Task Force on Environmental Health and Safety Risks to Children selected asthma as one of four childhood diseases to target. In response, a coalition of U.S. government agencies has launched a cooperative effort to combat asthma. In addition to improving treatment and education for people with asthma, government agencies seek to determine the "how" and "why" of asthma induction (development of new cases) and exacerbation (worsening of existing cases) in order to develop better methods for prevention. Researchers believe that multiple factors are responsible for asthma induction and exacerbation; exposure to environmental factors is a likely contributor. EPA's asthma research focuses on these environmental factors.

Airborne particles and gases, present in different combinations in both indoor and outdoor environments, can exacerbate asthma: they influence the biological processes that trigger asthma attacks and increase the severity of symptoms in people with the disease. EPA researchers are investigating whether exposure to pollutants may also contribute to the initial emergence of asthma in some individuals, especially children. Because allergies can lead to asthma attacks in many people, EPA studies often focus on how environmental factors affect allergic responses.

To incorporate the role of environmental factors into the campaign against asthma, EPA's Office of Research and Development developed a targeted asthma research program outlined by the *2002 Asthma Research Strategy*. Researchers in EPA labs, as well as EPA-funded investigators at universities and other organizations, are currently conducting studies to address three high-priority areas in asthma research. Because some types of air pollution may play greater roles in inducing and exacerbating asthma, the first area focuses on studying these different pollutants and their effects. EPA research focuses primarily on pollutants arising from fuel combustion and bioaerosols, a category that includes indoor molds as well as particles that come from dust mites and cockroaches.

Evidence also suggests that different groups of people tend to have higher risks of either developing asthma or having their symptoms exacerbated because of air pollution. EPA's second area of asthma research deals with susceptibility or factors that increase risk for subgroups of Americans. Because where a person lives in part determines what is in the air he or she breathes, residence history is a priority for research in the susceptibility area. Genetic factors, which may interact with environmental exposures, are also a primary focus.

A third major area of research deals with interventions. Scientists in this area test methods for reducing the risks from environmental factors; e.g., by controlling cockroaches and other types of infections, improving indoor air quality, and providing educational opportunities to affected communities. Although this document categorizes EPA asthma research into these three areas, many projects and objectives span multiple categories.

This publication is intended to give the reader an accessible overview of EPA's asthma research program and its accomplishments. Throughout this document, "Research Highlights" will spotlight EPA research efforts that have made significant contributions to science and real-world applications to improve understanding and associated prevention and treatment strategies of asthma.

Specific Pollutants and Their Ability to Induce or Exacerbate Asthma

EPA's research examines four general types of pollutants: combustion-related products, bioaerosols, air toxics, and pesticides. Research on each pollutant focuses on questions about exposure, effects, and risk management. Exposure questions have to do with what people are actually breathing in – for instance, some studies focus on discovering the relationship between pollution levels inside buildings and outdoor (also known as ambient) levels because measurements are usually taken outside. Effects questions get at the ways the human body responds when exposed to different pollutants. Research on health effects comes from many different fields. For example, epidemiologists might ask whether more people experience asthma exacerbations on days with high levels of a certain pollutant; while molecular biologists might study the chemicals that a lung cell produces when exposed to the same pollutant, providing a biological basis for what the epidemiologist observes. Lastly, questions about risk management aim to improve our ability to prevent negative outcomes, for example, by identifying the source of an asthma trigger so that we may modify the source to reduce levels of the pollutant, irritant, or allergen.

Combustion-Related Products

Burning – whether the fuel is petroleum, coal, tobacco, or a host of other combustibles – releases a mixture of pollutants into the air that includes gases as well as tiny particles. Current EPA studies address the exposures and effects of diesel exhaust, tobacco smoke, and smoke from wildfires, as well as other combustion-related products. Diesel exhaust has come under particular scrutiny. Diesel exhaust now makes up a greater proportion of motor vehicle pollution than in the past, and recent EPA studies indicate that it can exacerbate existing asthma and possibly cause new cases.

One of many challenges in determining the relationship between combustion-related products and asthma is that people breathe in a mixture of different gases and particles. This makes it difficult for scientists to link specific components with biological reactions. Studies show that particulate matter, ozone, and nitrogen dioxide can exacerbate asthma. Researchers are currently working to determine whether these pollutants play a role in the development of asthma. It also seems likely that inhaling a combination of these pollutants may produce a reaction different from the response to any single component.

While acutely smoggy or smoky days may send more asthma sufferers to the emergency room, the role of chronic or low-level exposure also seems to be important. Scientists believe that breathing combustion-related products over time may lead to changes in our immune systems that make people more sensitive to asthma triggers that they encounter every day; e.g., molds, pollens, animal dander, or particles arising from dust mites.

Research Highlight: Development of Asthma and Long-Term Ozone Exposure

Regions of southern California have some of the highest levels of ozone and other traffic-related pollutants in the country. EPA has helped support two significant southern California studies that indicate that ground-level ozone can actually contribute to asthma development in otherwise healthy people.

EPA epidemiologists conducted research as part of the Adventist Health and Smog Study which collected data from over 3,000 southern California adult Adventists between 1977 and 1992. Interestingly, Adventists provided scientists with a unique opportunity for research because the religious group's dietary and lifestyle habits expose them to fewer everyday risks than the general population. The investigators asked each person whether he or she had ever been diagnosed with asthma, taking special note of individuals who were diagnosed with asthma after the initial 1977

survey. Using information about each subject's home and workplace, the investigators determined how much traffic pollution the individual had been exposed to on a regular basis. Then, they used statistical methods to determine whether long-term exposure to ozone, a widespread pollutant produced when emissions from motor vehicles and other sources react in the atmosphere, could be linked to increased incidence of asthma. Results showed that for adult males, but not females, chronic exposure to ozone is associated with asthma development.

In a second study that EPA supported in conjunction with the California Air Resources Board and the National Institute of Environmental Health Sciences, a team of scientists at the University of Southern California recruited a group of 3,535 school-age children who did not have asthma and followed them for 5 years. By the end, 265 of the participants had developed asthma. The scientists measured levels of ozone and other traffic-related pollutants in the California communities where the children lived and observed whether the participants played team sports (because outdoor exercise can lead to greater exposures to pollutants when air quality is poor). The results showed that children who play team sports in communities with high-ozone levels were more likely to develop asthma, while children who play sports in low-ozone areas were not at higher risk.

A smoggy day in California

These studies indicate that living in a high-ozone area can put children and adults at greater risk of developing asthma and support the hypothesis that ozone can cause new cases of asthma, not just make symptoms worse for people already suffering from the disease.

(McDonnell et al. 1999, McConnell et al. 2002)

Research Highlight: Studies Show That Diesel Exhaust Particles Trigger Asthma Attacks in Animals

An EPA-funded research team at the University of California, Los Angeles, School of Medicine, studied mice to determine whether particles from diesel exhaust alone could trigger asthma attacks. Past studies showed that inhaling diesel exhaust particles in combination with an allergen could make a person much more sensitive to that allergen by activating the person's immune system in a process called adjuvancy. However, although adjuvancy could increase asthma prevalence in the long term, scientists observed asthma flare-ups only hours or minutes after exposure to high concentrations of particles. The University of California, Los Angeles, researchers set out to establish the biological basis for this immediate effect.

The researchers faced the challenge of making a mouse's lungs highly sensitive to pollutants so that they would resemble the lungs of people with asthma, prone to swelling that narrows the airways. Scientists often approach this problem by sensitizing the animals' lungs with an allergen called ovalbumin. The University of California, Los Angeles, team also used a novel approach involving mice bred with a genetic mutation that made their lungs highly sensitive. When exposed to diesel exhaust particles, these mice showed signs of airway inflammation even though they had not been exposed to ovalbumin or any other allergen. Study results support the assertion that diesel exhaust particles alone could trigger asthma flare-ups in mice, and these findings are an important indicator for use in additional asthma research.

As a next step, researchers point to the need to confirm that diesel exhaust particles has similar effects in humans. Related projects at the Southern California Particulate Matter Center and at EPA facilities address the specific processes in the cells that underlie these allergic responses.

(Hao et al. 2003)

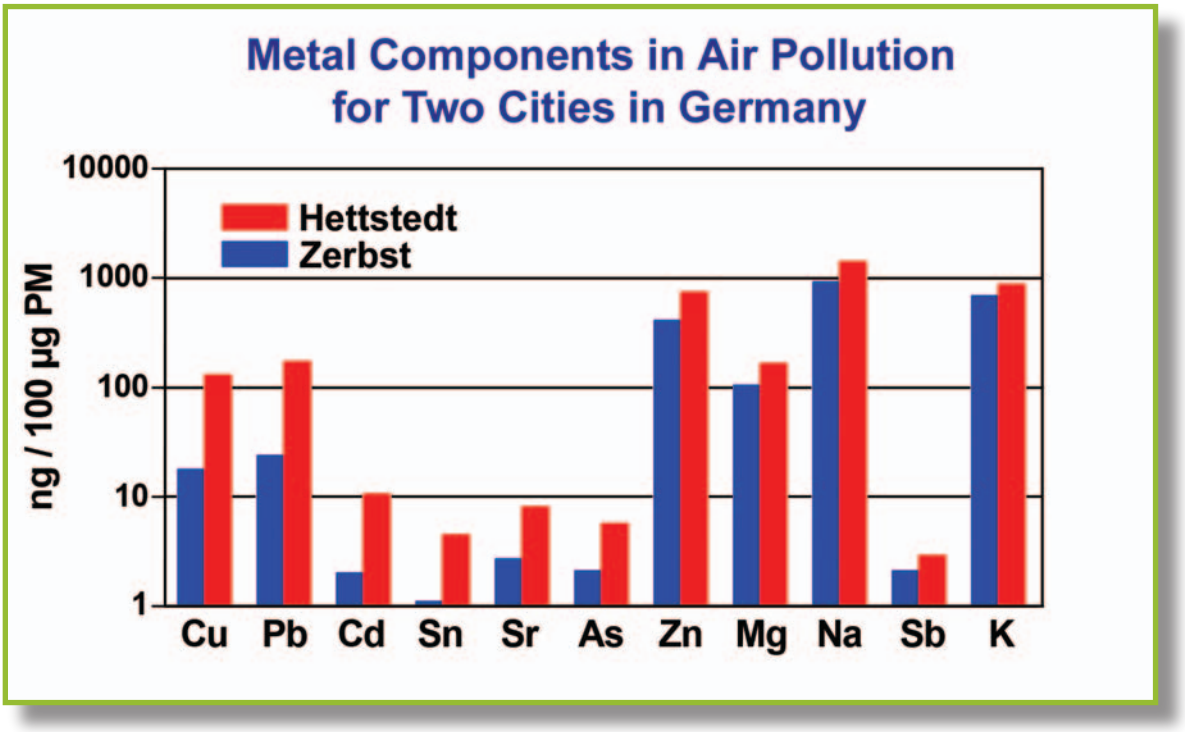
Research Highlight: Metal Components of Air Pollution and Effects on Asthma

Researchers at EPA's National Health and Environmental Effects Research Laboratory showed that a kind of particulate matter called residual oil fly ash, which arises from oil combustion in power plants, causes immune system changes that make mice more sensitive to dust mite allergens. Because residual oil fly ash is made up of many components, it is unclear which of these cause allergic sensitization.

Evidence suggests that metals such as nickel can exacerbate asthma. Residual oil fly ash often contains nickel as well as the metals vanadium and iron. EPA researchers tested the effects of these metals on mice that commonly develop allergies because some mice – like some human beings – have immune systems that are more likely to react to allergens. They exposed the mice to the metals and "challenged" them by exposing them to dust mite allergen. The results showed that each metal, or a combination of them, could cause the mice to develop a stronger allergy to dust mites.

The sensitization process observed in animal studies may partially explain why some geographic regions have higher rates of asthma. Epidemiologists at the National Research Center for Environment and Health in Munich, Germany, compared two regions in Germany and found that children in Hettstedt, a region with metal-rich air pollution (see figure below), had higher rates of asthma and allergies than those in Zerbst. In collaboration with National Research Center for Environment and Health scientists, investigators from EPA collected samples from air filters in each of these regions. When they exposed allergic mice to these samples, the mice exposed to the metal-rich pollution from Hettstedt had the more severe allergic response. This provides further evidence that the metal components in air pollution increase sensitivity to allergens. EPA scientists are also working to discover the cellular processes involved in allergic sensitization caused by air pollution.

(Lambert et al. 2000, Gavett et al. 2003)



Rodents exposed to the metal rich pollution had more severe allergic reaction

Bioaerosols

Airborne particles originating from dust mites, cockroaches, pets, pollens, bacteria, and household molds can trigger allergic responses and lead to asthma attacks. In addition, research shows that dust mite allergens can cause new cases of asthma, and studies suggest that other bioaerosols may also play a role in asthma induction. Many researchers further speculate that interactions between bioaerosols and other factors, such as combustion-related products or infections including the common cold, can cause or worsen asthma.

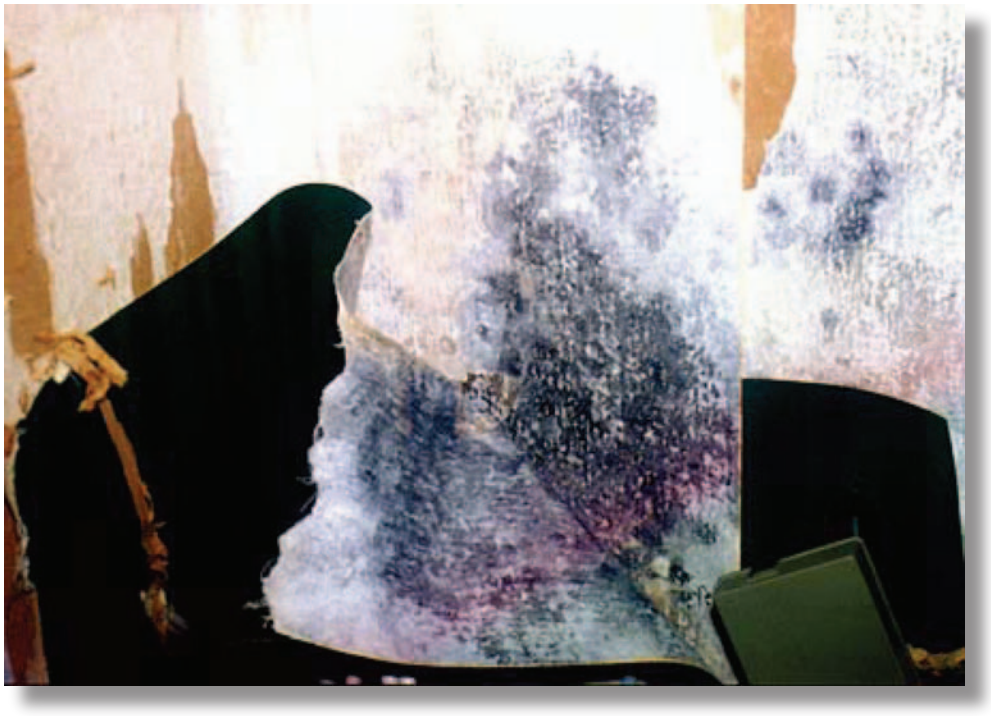
A number of research institutions have studied the effects of cockroach allergens on asthma in inner cities. Cockroach allergen is a potent asthma trigger and an important focus for research because roaches are commonly found in inner-city buildings. In addition, EPA scientists and other researchers think that household molds and the damp conditions that foster mold growth may also put residents at great risk of asthma development or exacerbation. Because of the potential importance of mold research and because few other agencies and research organizations have supported research in this area, EPA has made mold, or fungal bioaerosols, a major focus of its asthma research program.

EPA researchers are currently working to identify and describe the many different molds commonly present in household environments. They hope to determine which molds pose the greatest risks to allergic individuals and whether any has the capacity to cause asthma. Identifying the sources of molds, which may grow in damp basements, carpets, dirty air filters, and a number of other places, will also help in developing interventions.

Scientists also intend to determine how much mold a person must inhale in order for it to have an effect. Inhaling just a few particles may sensitize people's lungs, making them more likely to react to future insults. Genetic variations between people may cause their cells to respond differently, perhaps explaining why mold and other allergens cause or exacerbate asthma in some people but not in others. EPA researchers are working to determine the specific ways in which cells and organs respond to molds and other environmental insults.

Research Highlight: Effects of Household Molds on Asthma

Stachybotrys chartarum, a type of black mold or fungus, received media attention recently when its uncontrolled growth rendered several houses uninhabitable. This mold grows on damp walls, is widespread geographically, and has been associated with a range of health problems including asthma. However, few hypotheses about mold exposure, its influence on asthma, or methods for prevention have been tested scientifically. In order to fill these scientific gaps, investigators from multiple EPA research laboratories collaborated to conduct studies aimed at improving understanding and preventing health problems associated with molds like *Stachybotrys*.



Black mold growing beneath wallpaper in a home

EPA researchers exposed mice to samples of *Stachybotrys* taken from homes and looked for immune system responses typical of allergies as well as inflammation and functional changes in the animals' lungs. The results showed that the mold can indeed cause a disease analogous to asthma in mice.

Meanwhile, other EPA scientists have developed sophisticated procedures for identifying *Stachybotrys* and other molds in indoor environments, making it possible to determine which molds are present in a given household. These procedures include methods for rapidly quantifying the amounts of different fungi present in dust, as well as measuring a biomarker that when found in a person's blood indicates exposure to *Stachybotrys*. The mouse and exposure studies set the stage for further research that would help determine that humans are responding to the same allergens as mice and whether these responses can be associated with asthma.

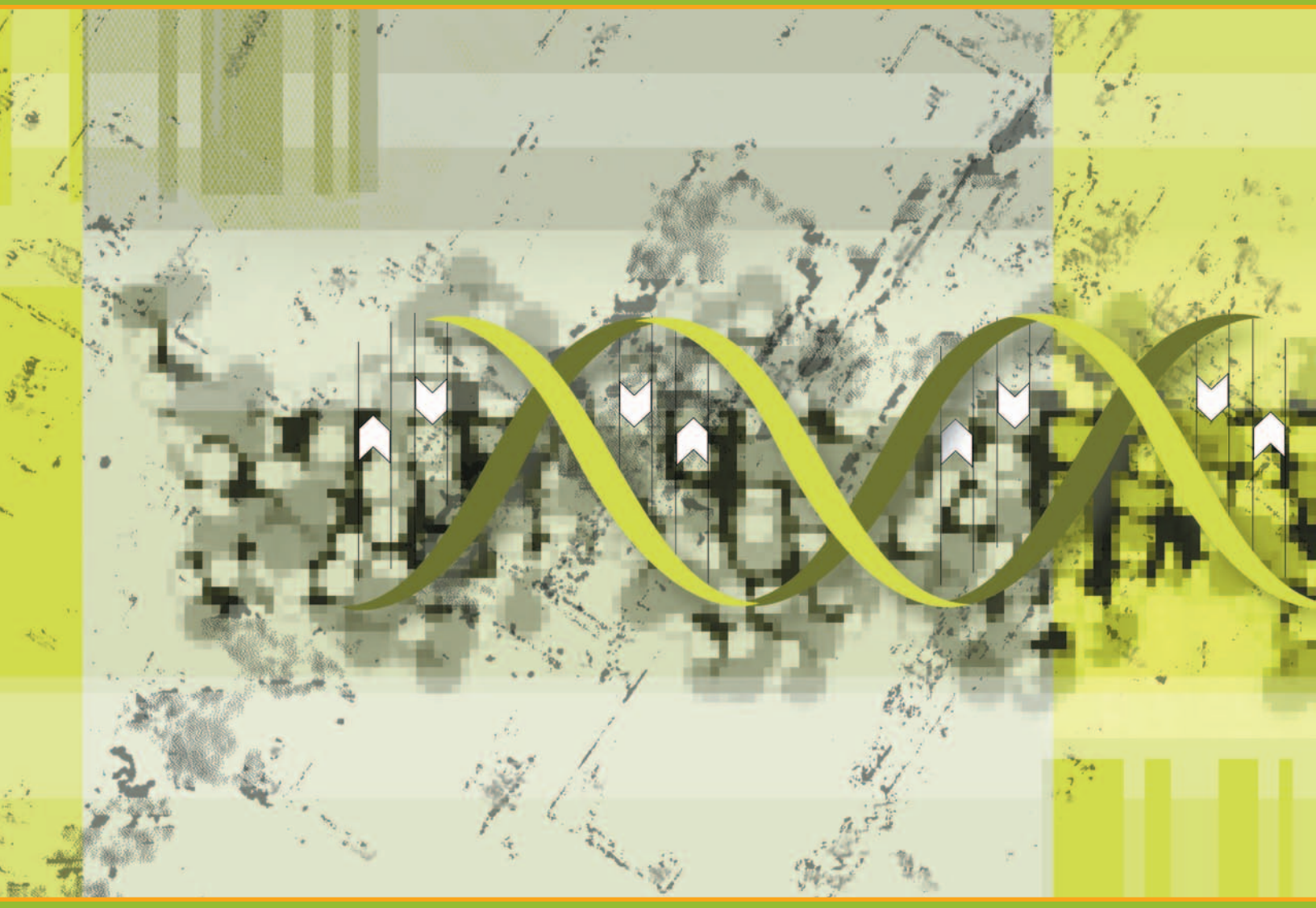
EPA investigators have also been evaluating strategies for preventing mold growth. Strategies include applying antifungal sealants for fiberglass and galvanized steel used in heating and air conditioning systems. Studies show that sealants can reduce mold growth on fiberglass and can completely prevent growth on galvanized steel.

EPA has used a multidisciplinary approach to study *Stachybotrys* and the hazard it creates. EPA researchers are also studying other mold species that may pose a risk in indoor environments.

(Viana et al. 2002, Foarde et al. 2002)

Air Toxics

Hazardous air pollutants include 188 chemicals, many of which are respiratory irritants. A diverse array of chemical classes is contained in the hazardous air pollutants list, including several metals which have been previously shown to have a role in the induction and/or exacerbation of asthma. Another chemical class of abundant hazardous air pollutants is carbonyl compounds, including aldehydes and ketones. The sources of carbonyls in the air are varied and include direct emissions from some industrial processes and from the combustion of diesel fuel. Carbonyls can also be derived from complex photochemical transformations of organic chemicals in the troposphere. EPA is investigating the toxicity of the carbonyls derived from the hazardous air pollutants list, along with those found in combustion sources, to determine whether this class of compounds alters cellular processes leading to asthma or an asthma-like condition. These studies are carried out in rodent exposure systems and use isolated lung cells. In terms of exacerbating asthma symptoms, it is known that inhalation of the hazardous air pollutants acetaldehyde by asthmatics can induce bronchoconstriction, while such responses do not occur in normal healthy individuals. This suggests that asthmatics are a sensitive subpopulation. The findings show that at least one carbonyl compound can induce asthmatic symptoms, but it is uncertain whether other carbonyls can cause similar effects. To address that issue, research will also investigate whether all carbonyls are equally potent in inducing effects such as bronchoconstriction or whether different potencies exist. These studies will use data empirically generated in controlled exposure studies as well as structure-activity modeling of the responses. If exposure to different carbonyls results in different potencies, then the chemical structures can be used to explain the reason behind the unequal potencies. This approach will help the Agency pinpoint which carbonyls are the most potent and should be better managed to prevent asthma attacks.



Factors That Make Certain People More Likely to Be Affected by Asthma

Some groups of people are at higher risk of developing asthma or of having environmental factors worsen their asthma. Many of the five factors that EPA identifies as increasing susceptibility to asthma interact with one another. For instance, place of residence and socioeconomic status are linked in many cases. People living in inner-cities are often exposed to a disproportionately high number of environmental risk factors and have a high incidence of asthma. It is also easy to imagine how health status and a person's genetic make-up or health status and activity patterns might be related. However, none of these factors overlaps completely. Income, for example, cannot explain many characteristics of one's home. Consequently, an effort has been made to separate these different risk factors in order to gain a complete understanding of the reasons why different people face different levels of risk.

Residence and Exposure History

If exposure to environmental factors can worsen asthma, people who live, work, or play in areas with a high concentration of allergens, air pollutants, pesticides, or other offending agents are probably at higher risk. The conditions in homes are particularly important because, on average, people spend 70% of their out-of-work time at home.

People inhale a variety of pollutants and allergens commonly present in the air inside their homes and outside in their neighborhoods. EPA studies have focused on people who move into a new neighborhood or a new residence to discover which residential factors influence asthma. After a move, people may be exposed to a different environment of pollutants and allergens and may develop new allergies or respond to changed levels of pollutants. In addition to the outdoor air, factors that can change when a person moves include ventilation, air conditioning, building age, water damage and dampness, indoor combustion sources, and consumer products. By examining changes in residence and exposure history, researchers have been able to identify new hazards and assess the importance of known hazards.

Researchers collect much of the above information by surveying people and supplementing surveys by going into the field to make observations and measurements. In order to test more directly whether a person has been exposed to a certain chemical, scientists look for molecules called biomarkers in the person's blood or other biological samples. Biomarkers can simply be a component of the inhaled product that enters the blood stream (an exposure biomarker) or can arise from a more complicated chain of events involving interactions between chemicals and the body's cells (biomarker of early response). As an example, skin test reactivity to common allergens is an excellent biomarker of sensitivity that is much better than attempting to identify allergies through a patient's recall of reactions.

Research Highlight: Air Pollution and Asthma Symptoms in Seattle-Area Children

EPA has the responsibility to protect the most sensitive populations when creating regulations for outdoor air pollutants. Children with asthma constitute a group at greater risk. To gather better information about the effects of air pollution on this group, researchers at the University of Washington's Northwest Research Center for Particulate Pollution and Health studied the relationship between certain air quality measures and asthma symptoms in Seattle-area children.

All of the 133 children, ages 5 to 13 years, who participated in the study were enrolled in the Childhood Asthma Management Program sponsored by the National Heart, Lung, and Blood Institute. Each had mild to moderate asthma. The University of Washington scientists asked participants to keep daily diaries; every morning and evening, participants recorded any asthma symptoms they had experienced. The researchers then compared the diary information with air quality measures, including measures of particulate matter, carbon monoxide, and sulfur dioxide. Using statistical models, the researchers concluded that higher levels of carbon monoxide and particulate matter were associated with greater aggravation of asthma symptoms, increased risk of more severe asthma attacks, and higher use of asthma medication.

Because the specific geography and development in a region can influence air quality, these results depend in part on the distinctive make-up of air pollutants in Seattle. Levels of sulfur dioxide in the region are generally low, so sulfur dioxide does not act as a major asthma trigger in Seattle though it does in other regions where concentrations are higher. Carbon monoxide, on the other hand, is not known to trigger asthma symptoms itself. Scientists believe that monitoring carbon monoxide, one of many products of combustion, indirectly measures the levels of other combustion products that exacerbate asthma, such as nitrogen oxides, ozone, and particulate matter.

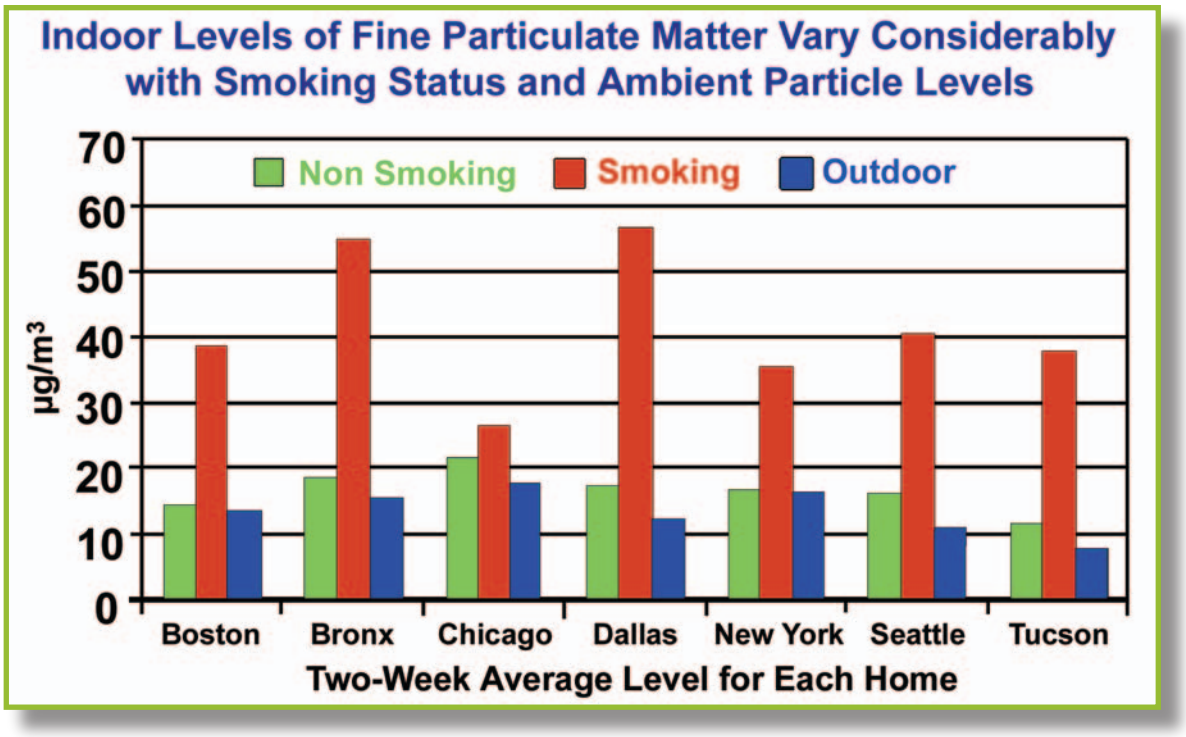
Because the make-up of air pollution differs from region to region, conducting studies in various locations provides more complete information about the effects of air pollution on children with asthma. EPA researchers and university scientists supported by EPA are working to gather related information in several U.S. cities, including Detroit, El Paso, and Los Angeles.

(Yu et al. 2000, Slaughter et al. 2003)

Research Highlight: Particulate Matter Levels and Asthma in Inner-City Children

EPA scientists collaborated with scientists at the National Institute of Environmental Health Sciences and the National Institute of Allergy and Infectious Diseases to undertake the Inner-city Asthma Study, an effort focusing on children with asthma in seven U.S. cities.

As a first step in the environmental portion of this study, investigators determined the relationship between indoor and outdoor pollution levels and identified indoor sources of pollutants. The researchers took continuous measurements of particulate matter levels inside 294 homes for two weeks each. They then compared the data for indoor particulate matter levels with measurements for outdoor concentrations and used a questionnaire to relate indoor levels with different activities in the homes. Taking continuous rather than daily measurements of indoor particulate matter allowed the researchers to observe variations in pollution levels throughout the day. For example, researchers observed consistently low levels late at night when people were sleeping and higher levels during mealtimes from cooking and in the evening from smoking.



The impact of smoking and outdoor particle concentration on indoor levels of fine particulates

The research team found that particulate matter concentrations inside the homes of children in the inner-city asthma study tend to be about twice as high as outdoor concentrations. This percentage can vary depending on people's activities and house characteristics. In the study particulate matter from outdoor sources made up approximately 25% of that found indoors; the rest came from indoor sources, including activities such as frying or burning food, burning incense, and especially smoking. Homes of people who smoke have dramatically higher levels of particulate matter (see figure previous page). Additionally, the researchers found that indoor particulate matter levels are not substantially different from city to city which makes the science emerging from this study applicable in cities nationwide.

Scientists are currently working on the subsequent steps in this study, which include comparing pollution levels with information about asthma severity to examine the relationship between the two. We observed an association between adverse health effects (missed school days and lower lung function) and combustion products, even in cities where ambient pollution levels are generally low.

(Wallace et al. 2003)

Genetic Susceptibility

Different people respond differently to the same environmental exposures. Scientists believe that a large part of this heterogeneity has a genetic basis. Current EPA studies aim to identify genes that influence asthma susceptibility and to characterize the responses to pollutants and allergens that correspond with these genetic differences.

EPA researchers use various approaches to answer questions about genes and asthma. Using clinical studies, they examine how people with a known genetic make-up respond to controlled amounts of environmental stressors such as ozone. Researchers use these trials to identify which genes may be correlated with differences in responses. EPA researchers use *in vitro* studies – those done in test tubes – to observe the role of different genes in the cells of people with asthma. Scientists also use *in vitro* methods to study the step-by-step processes or mechanisms by which chemicals produce their effects. A third mode of EPA research on genetic susceptibility involves laboratory animals; scientists observe how animals with specific genetic mutations respond to environmental exposures.

Health Status

People with more severe asthma and those who suffer from other heart and lung conditions seem to respond differently to environmental pollutants than healthy individuals. For instance, a small amount of a pollutant may trigger an asthma attack in a person with severe asthma, but it may take a higher dose to affect a healthier individual. In order to better protect the populations at greatest risk, scientists are seeking to understand the interaction between the presence of disease and response to pollutants and allergens. EPA researchers have pursued this question using epidemiological field studies to compare people with different severities of asthma, clinical studies to compare people with asthma and healthy people, and studies involving laboratory animals with characteristics that mimic human diseases.

Research Highlight: Inhaled Pollutants Affect People with Asthma More Severely

To build upon epidemiological evidence showing that people with asthma are more susceptible to air pollution than healthy people, EPA researchers and EPA-supported university scientists studied volunteers in carefully controlled laboratory environments to determine the biological basis for this difference. Though these clinical studies vary with regard to the specific pollutants and outcomes tested, one fact has become clear: study participants who have asthma are more affected than their healthy counterparts.

One group of studies that EPA scientists conducted in cooperation with University of North Carolina researchers examined the effects of ozone. The scientists exposed volunteers to ozone and then tested their ability to exhale air forcefully, a measure commonly used to determine whether a person's lungs are functioning normally. The healthy volunteers responded to ozone with a decreased ability to rapidly exhale; scientists concluded that this response arose because ozone interfered with the healthy subjects' ability to take a deep breath. The subjects with asthma also experienced a decrease in pulmonary function; but for these volunteers, the decrease stemmed from an actual narrowing of the lungs' airways – a much worse situation. In addition, inhaling medication designed to open constricted airways did not effectively combat the airway constriction triggered by ozone. Related research efforts showed that exposure to the pollutant causes the lungs to become inflamed in all subjects. However, scientists observed that the cells causing inflammation differ between people with asthma and healthy people and that the cells that cause inflammation in people with asthma can potentially exacerbate their disease.

In addition to ozone, EPA-funded researchers have also examined the effects of particulate matter on people with and without asthma. For example, researchers at the University of Rochester found that greater amounts of air pollution particles deposit in the airways of people with mild asthma. The increased particle deposition in the lungs of people with asthma may partially explain why they are more susceptible to some air pollutants.

These studies show that ozone and particulate matter affect people with asthma more severely than healthy people. They help explain the epidemiological evidence by elucidating some of the specific biological mechanisms that underlie this difference. Further research at the cellular and genetic levels will help to explain what causes greater susceptibility in people with asthma.

(Horstman et al. 1995, Peden et al. 1995, Peden et al. 1997, Pietropaoli et al. 2004)

Research Highlight: Exploring the Connections between Genes, Environment, and Asthma

Studies show that people with asthma are more susceptible to many more air pollutants than healthy people are. EPA scientists are trying to determine whether the genetic makeup of people with asthma plays a role in this susceptibility and, if so, which genes and proteins are involved.

Research has shown that certain proteins found attached to white blood cells and floating free in blood and fluid surrounding lung cells are involved in a person's reaction to a common bioaersol called endotoxin, which comes from bacteria and adheres to many air pollution particles. Although this compound causes inflammation in everyone, people with asthma tend to be more sensitive to endotoxin. This may be because a protein called CD14, which is found on the surface of immune system cells and to which endotoxin binds, is present in higher levels in people with asthma.

In one study, EPA researchers in collaboration with University of North Carolina scientists examined 8 healthy people and 10 people with asthma in order to investigate the relationship between CD14 and severity of response to endotoxin. They measured levels of certain proteins and cells – those that indicate the level of inflammation – in samples of the participants' sputum collected both before and after the exposure. These experiments showed a correlation between levels of CD14 and the severity of the inflammatory response; when levels of CD14 were high before exposure to endotoxin, the inflammation was more severe. Because levels of CD14 are easily measured, these findings suggest that scientists can predict the severity of a person's response to endotoxin by this simple test.

The gene responsible for producing CD14 protein is present in different variations or alleles. Some of these variations are known to cause a higher concentration of CD14 protein on immune cells. EPA scientists are currently performing studies to determine whether people with asthma who have genetic variations that produce greater amounts of CD14 are more susceptible to pollutants than those with variations that do not affect the level of the protein.

(Alexis et al. 2001)

Lifestyle and Activity Levels

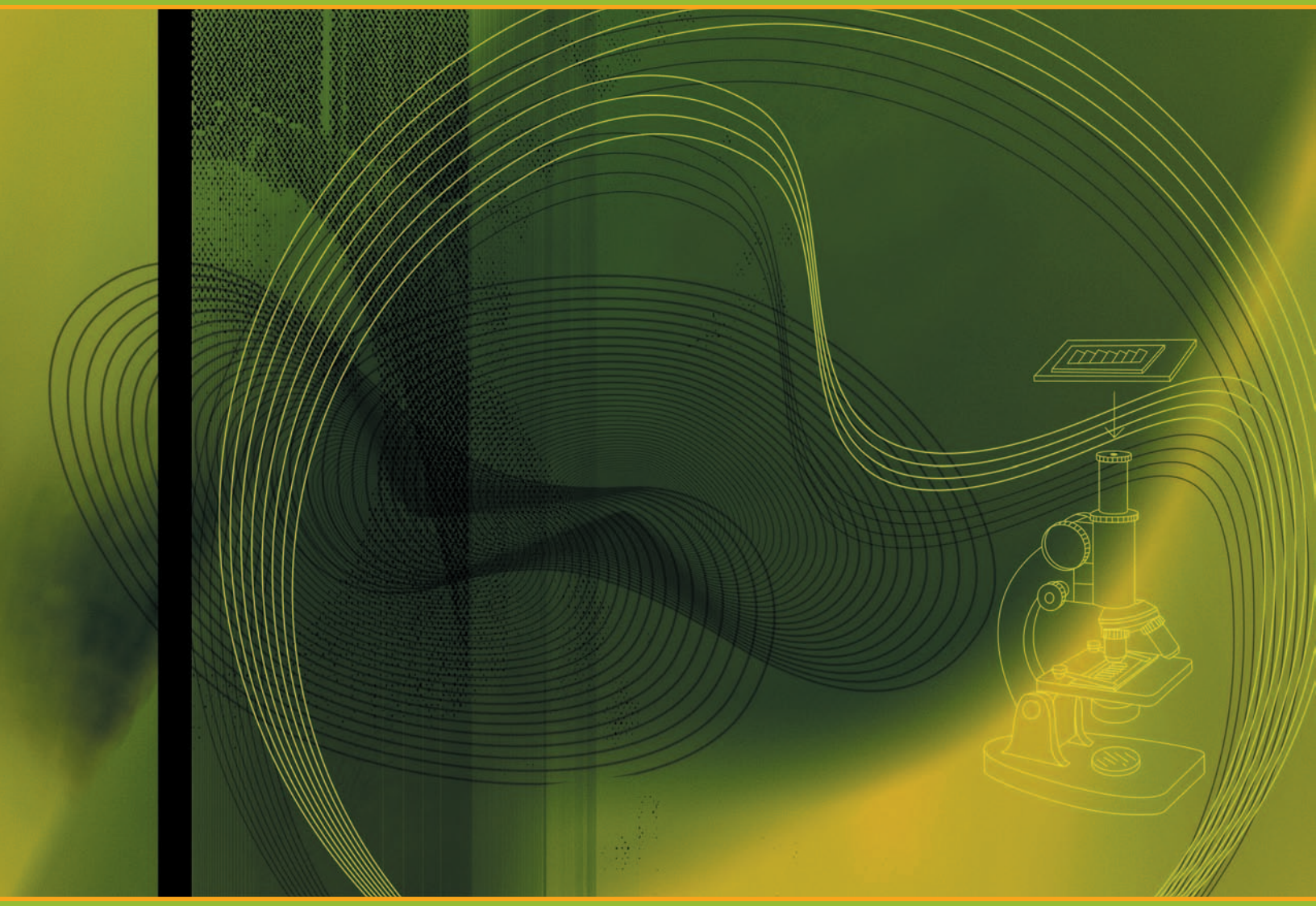
Though urban lifestyle seems to be correlated with higher asthma rates, scientists do not know which elements of these lifestyles influence asthma. Low levels of physical activity and increased time spent indoors may be important contributors, especially because urban buildings tend to be constructed in ways that restrict ventilation with outdoor air.

Though a sedentary lifestyle may be a risk factor for asthma and other health problems, exercising outside on bad air quality days can increase exposure to air pollutants. Heavier breathing while practicing an outdoor sport, for example, means that more ozone, particulate matter, and other pollutants enter the active person's lungs.

When small children play outdoors, crawl on the floor, or engage in other normal, child-like behaviors, they can increase their exposure to certain pollutants and allergens. However, these activities are not the only elements placing children at higher risk. There are biological differences between children and adults as well because children's organs and immune systems are still developing. EPA research suggests that environmental exposures can have different, and often more severe, effects on children than on adults.

Socioeconomic Status

The relationship between socioeconomic status and asthma is an important issue in terms of social justice as well as public health. In terms of both prevalence and severity, people with low socioeconomic status are more likely to be affected by asthma. Though outdoor air pollution levels are not as well correlated with socioeconomic status, scientists believe that exposure to indoor air pollutants and allergens may provide a partial explanation. Low socioeconomic status homes and buildings in inner-cities such as Detroit, Baltimore, Los Angeles, and New York City have documented poor indoor air quality. These cities also have high prevalence of asthma. Other factors, such as nutrition, may also be involved. Studies funded by EPA at the University of Southern California involving inner-city children ask whether the amount of vitamin C and other antioxidants can influence asthma.



Interventions to Reduce the Burden of Asthma

Effective actions to prevent environmental factors from inducing or exacerbating asthma must succeed in the context of real-world complexities. In order to have an effect, interventions must incorporate social elements in addition to good science. EPA researchers have been working in regions with high asthma rates, including Detroit, New York, Baltimore, and Los Angeles, to design and test such interventions.

The ideal way to minimize risk from pollutants or allergens is to stop them at their source. Studies that determine which sources produce the most harmful pollutants and how emissions from sources relate to what people actually breathe provide the foundation for interventions. Strategies for addressing these sources include employing new technologies, changing habits, or modifying regulations. Indoors, finding effective ways to manage cockroaches and eliminating tobacco smoke are two interventions with the potential to drastically affect asthma. Other possibilities for improving indoor air quality might include converting to low-emissions building materials and eliminating the dampness that leads to mold growth. Lowering levels of offending pollutants in outdoor air involves reducing emissions from vehicles and industrial facilities.

Beyond targeting sources, air filtration and other secondary measures for controlling air quality present additional strategies for lowering concentrations of pollutants and allergens. An EPA-funded study conducted in Boston public housing found that mattress and pillow covers lower the levels of dust-mite allergens in bedrooms. However, air filtering did not lower levels of particulate matter in homes, and industrial cleaning reduced levels of mouse and cockroach allergens only temporarily. To prove the effectiveness of any intervention method, tests must show that the method not only lowers the concentrations of such agents, but also reduces asthma incidence or exacerbation as a result.

Social aspects are an important area of focus for intervention research. Intervention strategies have been designed for both single-household and community-wide applications. Many have included elements of education in addition to specific actions that aim to reduce allergen levels in homes. Education and community involvement are important because knowing that an action can alleviate asthma only helps if people are motivated to take that action. Home interventions must also be cost-effective in order for people to use them. A team of EPA-funded economists is currently working to determine how much people are willing to pay to avoid the discomfort and inconvenience that asthma imposes – an exercise that will provide guidelines for designing cost-effective prevention methods.

In addition to its research efforts, EPA has launched an asthma education and outreach campaign. The Indoor Environments Division informs Americans about actions they can take to improve indoor air quality. Public health information about outdoor air pollution can be found at www.epa.gov/airnow.

Research Highlight: Controlling Cockroaches in East Harlem

Cockroaches pose a serious risk because allergens from roaches can trigger asthma attacks in people with cockroach allergies. The Inner-city Asthma Study revealed that as many as 68% of inner-city children with asthma are allergic to cockroaches. However, applying chemical pesticides to control roaches can also be risky, especially because this can expose children to harmful chemicals. To address this problem, a group of scientists at the Mount Sinai Children's Environmental Health and Disease Prevention Research Center worked in collaboration with two East Harlem community health organizations to develop a cockroach control program using a method called integrated pest management. Integrated pest management combines non-chemical approaches with education in order to control pests.

The Mount Sinai researchers went to prenatal clinics to recruit two groups of women for the study: a control group and an intervention group. All of the study participants lived in East Harlem. At the outset, about 80% of homes in both groups had cockroaches although the majority of households used pesticides. For six months, the researchers monitored cockroach levels in the homes of both control and intervention group participants; and, for the intervention group only, researchers worked with the participants to institute integrated pest management practices. The interventions included repair services to seal cracks through which roaches enter, training in better sanitation and housekeeping, and minimal application of pesticide gels rather than sprays when necessary. At the end of the six-month period, half of the intervention homes that started out with cockroaches lowered their roach count to zero (see figure above); in contrast, there was no change for households in the control group. Additionally, integrated pest management methods were no more expensive than traditional methods relying on heavy pesticide application.

The percentage of positive cockroach monitors was significantly reduced in intervention households over a six-month period

These results suggest that integrated pest management can be an effective, less toxic way of controlling cockroaches in urban environments. Because the Mount Sinai study demonstrated the great promise of integrated pest management, researchers at the Columbia University Center of Excellence in Children's Environmental Health and Disease Prevention Research are currently working in collaboration with the New York City Department of Health and the New York City Housing Authority to develop a more expansive study to test the effectiveness of integrated pest management techniques, including measuring the implications for people with asthma.

(Brenner et al. 2003)

Conclusion

EPA's asthma research provides the science upon which EPA bases air quality regulations and supports the Agency's public health programs, helping to decrease the incidence of asthma in the U.S. In addition to contributing to the decision-making process at EPA, many of the findings have applications at community and household levels. Methods developed and evaluated by EPA researchers for controlling cockroaches or preventing mold growth may be used by homeowners. Parents may also use information about the risk of playing sports on bad air quality days when planning their children's activities. With its focus on environmental factors of the disease, EPA's research program adds an important component to asthma research pursued by other government agencies and private institutions.

Additional information on EPA's asthma-related publications and resources is available at: www.epa.gov/asthma/ and www.epa.gov/ord.

Future Directions for EPA's Asthma Research Program:

Asthma poses a public health challenge that EPA and other government agencies will continue to address. In the future, EPA's asthma research will seek to:

Improve understanding of who suffers the impacts of environmental exposures on asthma.

- Define the relationship between exposure to environmental pollutants and the induction of disease in children and severity of asthma in children and adults.
- Understand gene-environment interaction in asthma induction and exacerbation and determine susceptibility and environmental factors that can be modified to reduce the initiation and severity of asthma.

Reduce uncertainties in risks assessments for air pollutants that induce or exacerbate asthma.

- Conduct studies designed to understand the mechanisms by which air pollutants induce or exacerbate asthma.

Develop new and better strategies to prevent environmentally related asthma induction and exacerbation and to protect the populations at greatest risk.

- Define the role of molds and other bioaerosols in the induction or exacerbation of asthma, particularly in susceptible populations, as well as their potential synergistic interaction with other pollutants.

- Develop strategies to remediate risk from exposures to environmental pollutants.

These areas of research will help EPA to continue to protect Americans by providing a sound scientific foundation upon which to base air pollution regulations. In addition, these ongoing efforts will provide information about asthma risk factors and prevention methods that will help consumers, parents, homeowners, and others to make everyday decisions.

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