United States
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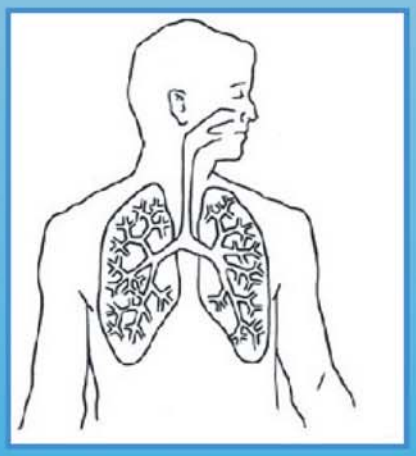
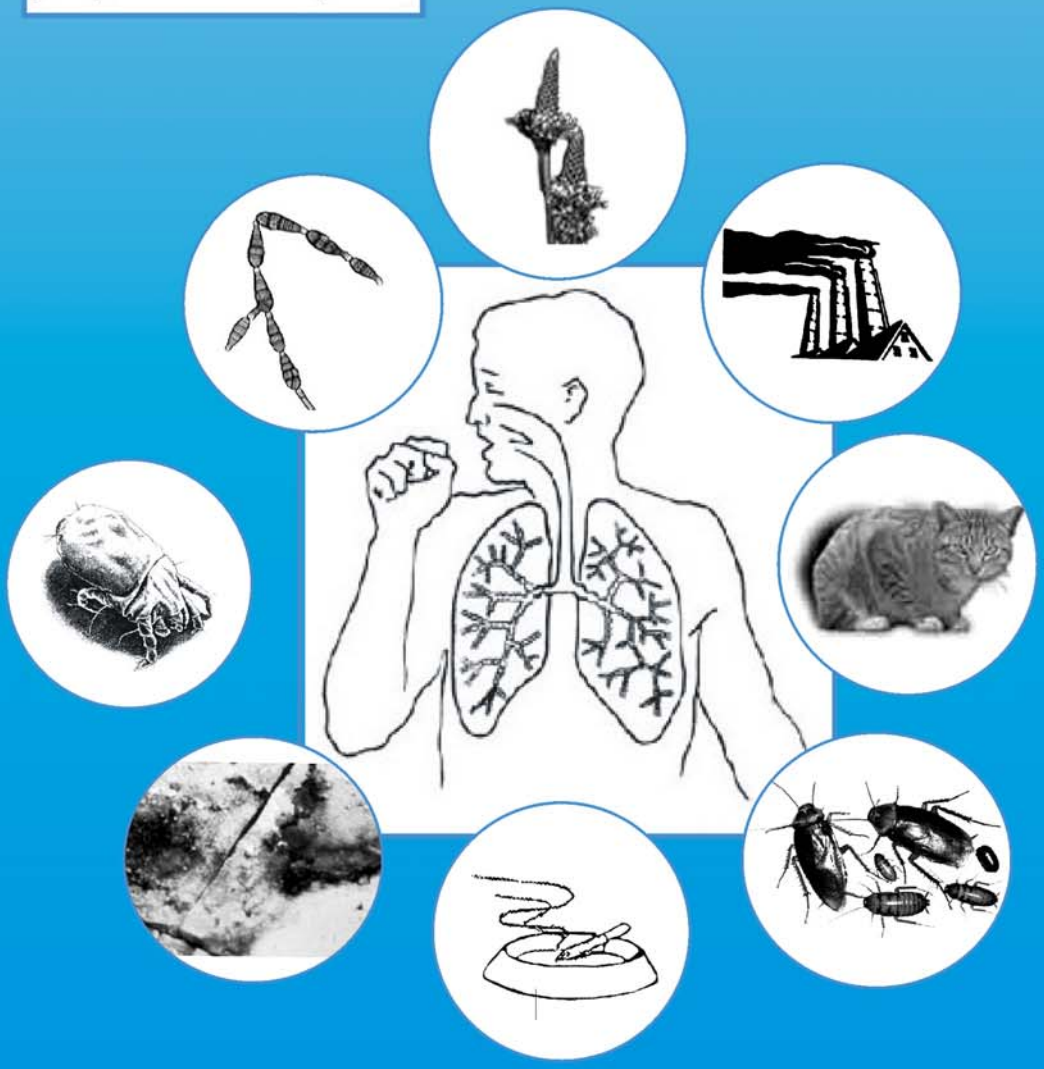


Asthma Research Strategy



On the Cover: Asthma is a disease characterized by reversible airway obstruction, chronic inflammation, and airway remodeling. Susceptibility factors for asthma include the genetic background and overall health status of a person, as well as lifestyle, socioeconomic status, residential location, and overall exposure history, especially the potential for exposure to allergic inducers and nonallergic triggers. The majority of asthma is associated with allergic responses to common aeroallergens in our indoor and outdoor environment, such as house dust mites, cockroaches, animal secretions, pollens, and molds. Exacerbation of asthma may occur with subsequent re-exposure to allergens, or by exposure to a number of nonspecific triggers of lung inflammation and airway obstruction, such as respiratory viruses, tobacco smoke, or certain air pollutants.

EPA 600/R-01/061
September 2002

Asthma Research Strategy

Office of Research and Development
U. S. Environmental Protection Agency
Washington, DC 20460

DISCLAIMER

This document has been reviewed in accordance with U.S. Environmental Protection Agency policy and approved for publication. Mention of trade names or commercial products does not constitute endorsement or recommendation for use.

Dear Reader,

The United States Environmental Protection Agency (EPA) is pleased to present our *Asthma Research Strategy*. The U.S. Environmental Protection Agency (EPA) is committed to preventing pollution and reducing risk from environmental health hazards in communities, homes, workplaces, and ecosystems. According to the 1997 asthma surveillance estimate from the Centers for Disease Control and Prevention released in March of 2002, 26.7 million people reported having had physician-diagnosed asthma during their lifetime. Many recent scientific journal articles and editorials have noted the increasing rates of asthma, particularly in children, and the need for further study. By following the goals detailed within the *Asthma Research Strategy*, EPA scientists will lead a coordinated research effort to address environmental pollutants that influence the incidence and severity of asthma. The strategy supplements and expands on other U.S. agency efforts to better understand this complex disease.

This *Asthma Research Strategy* identifies and prioritizes the research needed to provide information to close the gaps in our knowledge and to control environmental factors that contribute to the disease. It serves to guide the planning of EPA research efforts, led by the Office of Research and Development (ORD), to address the significant issues of exposures, effects, risk assessment, and risk management of environmental pollutants relevant to asthma through the fiscal year 2009.

Pollutants were considered for investigation if they influenced the incidence or exacerbation of asthma and warranted further study. Four environmental pollutant classes were identified by EPA scientists: combustion related products, bioaerosols, air toxics, and pesticides. Additional areas of study detailed in the *Strategy* are: susceptibility factors contributing to asthma (e.g., genetics, health status, socioeconomic status, residence and exposure history, and lifestyle and activity patterns); and risk assessment and risk management of environmental pollutants relevant to asthma.

Sincerely,

Paul Gilman, PhD
Assistant Administrator
Office of Research and Development
U.S. Environmental Protection Agency

AUTHORS AND CONTRIBUTORS

This research strategy was produced by a team of representatives from several laboratories of the U.S. Environmental Protection Agency (EPA), Office of Research and Development, and the Office of Air and Radiation.

Hillel S. Koren, Ph.D.—National Health and Environmental Effects Research Laboratory, U.S. Environmental Protection Agency, Research Triangle Park, NC 27711

Bob Axelrad, Ph.D.—Office of Air and Radiation, U.S. Environmental Protection Agency, Washington, DC 20460

Lawrence Folinsbee, Ph.D.—National Center for Environmental Assessment, U.S. Environmental Protection Agency, Research Triangle Park, NC 27711

Stephen Gavett, Ph.D.—National Health and Environmental Effects Research Laboratory, U.S. Environmental Protection Agency, Research Triangle Park, NC 27711

Bruce Henschel, M.S.—National Risk Management Research Laboratory, U.S. Environmental Protection Agency, Research Triangle Park, NC 27711

Laura Kolb, M.P.H.—Office of Air and Radiation, U.S. Environmental Protection Agency, Washington, DC 20460

Suzanne McMaster, Ph.D.—National Health and Environmental Effects Research Laboratory, U.S. Environmental Protection Agency, Research Triangle Park, NC 27711

Lucas Neas, Sc.D.—National Health and Environmental Effects Research Laboratory, U.S. Environmental Protection Agency, Research Triangle Park, NC 27711

Judith Nelson, M.B.A.—Office of Prevention, Pesticides, and Toxic Substances, U.S. Environmental Protection Agency, Washington, DC 20460

William Steen, Ph.D.—National Exposure Research Laboratory, U.S. Environmental Protection Agency, Research Triangle Park, NC 27711

Kevin Teichman, Ph.D.—Office of Science Policy, U.S. Environmental Protection Agency, Washington, DC 20460

Stephen Vesper, Ph.D.—National Exposure Research Laboratory, U.S. Environmental Protection Agency, Cincinnati, OH

PEER REVIEW

Peer review is an important component of research strategy development. The peer review history for the *Asthma Research Strategy* follows.

ORD Science Council Review

Final Review Date: August 31, 2001

Lead Reviewers:

Elaine Z. Francis, Ph.D.—Associate Director for Health, National Center for Environmental Research, U.S. EPA, Washington, DC
Herman J. Gibb, Ph.D.—Associate Center Director, National Center for Environmental Assessment, U.S. EPA, Washington, DC
Lester D. Grant, Ph.D.—Acting Associate Director for Health, National Center for Environmental Assessment, U.S. EPA, Research Triangle Park, NC
Harold Zenick, Ph.D.—Associate Director for Health, National Health and Environmental Effects Research Laboratory, U.S. EPA, Research Triangle Park, NC

External Peer Review:

ASTHMA RESEARCH STRATEGY PEER REVIEW
December 12-13, 2000
Chapel Hill, North Carolina

External Peer Review Panel Members:

Henry Gong, M.D.—Department of Medicine, Rancho Los Amigos National Rehabilitation Center, Downey, CA
David M. Mannino, M.D.—Air Pollution and Respiratory Health Branch, Centers for Disease Control and Prevention, Atlanta, GA
James A. Merchant, M.D., Dr.P.H., Dean—College of Public Health, University of Iowa, Iowa City, IA
Swati Prakash, M.P.H.—Director of Environmental Health and Community-Based Research Programs, West Harlem Environmental Action, New York, NY

Peer Review Coordinator:

The review was facilitated by Dr. Robert Menzer—National Center for Environmental Research, U.S. EPA, Washington, DC

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Executive Summary

Asthma is a complex, multifactorial disease characterized by chronic airway inflammation, mucus secretion, airway remodeling, and reversible airway obstruction. Both genetic and environmental factors influence the development and exacerbation of asthma. More than 17 million people in the United States had asthma in 1998, double the incidence in the previous 20 years. Because the increase in asthma incidence cannot be reconciled by changes in diagnostic categorization or by alterations in the gene pool, associations between asthma and the environment have attracted increasing attention. Since the Environmental Protection Agency (EPA) is required to set pollutant standards to protect susceptible populations such as asthmatics, a coordinated research effort to study environmental pollutants that influence the incidence and severity of asthma is needed. Therefore, this Asthma Strategy is designed to help plan intramural and extramural efforts by the Office of Research and Development (ORD) to address the significant issues of exposures, effects, risk assessment, and risk management of environmental pollutants relevant to asthma.

The ORD has the expertise to conduct asthma research in the following areas: (1) induction and exacerbation of asthma; (2) susceptibility factors contributing to asthma; and (3) risk assessment issues related to induction, exacerbation, and susceptibility. Four classes of environmental pollutants that may influence the induction and exacerbation of asthma were identified as needing additional research: (1) combustion-related products (CRPs) formed from the burning of organic fuels; (2) bioaerosols, including molds and other allergens; (3) air toxics or hazardous air pollutants, HAPs; and (4) pesticides. Susceptibility factors that may influence the induction and exacerbation of asthma also were identified. These are (1) genetic susceptibility, (2) health status, (3) SES, (4) residence and exposure history, and (5) lifestyle and activity patterns. For each topic, research agenda items were developed to address specific research needs; within the asthma induction and exacerbation research area, research needs were listed for exposure, effects, and risk management.

Multiple clinical, epidemiologic, and animal studies suggest that CRPs exacerbate existing asthma. Exposure research agenda items include assessment of relative exposures from indoor and outdoor sources and development of exposure models. Effects research agenda items include examination of CRP-specific asthma outcomes, acute exposure-exacerbation response relationships, effects on allergen sensitization, and cellular and molecular mechanisms of asthmatic responses. Finally, risk management studies should include the characterization of indoor and outdoor sources of CRPs with an emphasis placed on developing models to define these sources and on the development of appropriate prevention and control approaches and technologies.

Because bioaerosols, especially fungal allergens, are tremendously important in the induction and exacerbation of asthma, and because little is known about the degree of exposure to major asthma-related fungal allergens, further research is needed in this area. Additionally, there is a need to develop innovative measurement protocols with which to assess the degree of exposure to fungal allergens. Research concerning the effects of bioaerosols is also needed to examine the spectrum of fungal sensitivity, to clinically test bronchoprovocation in mold-sensitive asthmatics, and to examine the adjuvant effects of toxic compounds produced by bioaerosols. Risk management needs include the development of basic models characterizing the

sources of indoor bioaerosols and of techniques to reduce bioaerosol exposure and the assessment of technique effectiveness in reducing bioaerosol exposure in outreach programs in affected communities.

Thirty-three hazardous air pollutants referred to as "air toxics," are recognized as posing the greatest threat to public health in the largest number of urban areas (Environmental Protection Agency, 1999). Research agenda items concerning exposure to these toxics include the monitoring of personal exposures to asthma-associated air toxics; the characterization of the major sources, pathways, and routes of exposure; and the development of exposure models for key air toxics. Research agenda items concerning the effects of hazardous air pollutants include studies of asthma prevalence and respiratory effects in relation to air toxics exposures, definition of exposure-response relationships for asthma induction and exacerbation, and development of practical test methods for assessing allergenicity of air toxics. Needed risk management studies include characterization of emissions from priority indoor and outdoor hazardous air pollutants sources and development of technologies for reducing emissions from the most important sources.

Published studies suggest that certain pesticides may affect neurological and immune function in a manner which may favor the development or exacerbation of asthma. Research is needed to determine levels of pesticide exposure and usage in populations with different asthma incidence rates. Immunologic and neurologic mechanisms of responses to pesticides need to be examined; screening methods to determine pesticide effects on asthma need to be developed; and the prevalence and severity of asthma associated with exposure to pesticides need to be better quantified. To better minimize the risks associated with pesticides, improved models of pesticide emissions, transport, and fate of these emissions in the indoor environment are needed. Additionally, alternatives for reducing pesticide exposures associated with induction and exacerbation of asthma need to be developed.

Biological responses to air pollutants in clinical studies of healthy volunteers are heterogeneous among the population, yet consistent within an individual, suggesting a genetic basis for responses among healthy individuals and, presumably, asthmatics. Research is needed to determine the genetic basis of susceptibility to asthma: phenotypic differences in responses of asthmatics and healthy individuals to environmental pollutants need to be defined, and a DNA bank of samples associated with phenotypic markers of response in asthmatics and healthy individuals needs to be established to identify genetic markers of susceptibility. In vitro approaches and genetically-defined animal model studies can and should be utilized to examine the effects of specific genes.

Responsiveness to environmental pollutants may depend on the severity of the disease in asthmatics and the presence of co-morbid conditions. Research agenda items related to health status include modeling dose-response relationships in asthmatics with a broad range of asthma severity, examining of the influence of asthma severity and recent respiratory infections on responses to air pollution episodes, and studying animal models of cardiopulmonary disease to understand mechanisms of enhanced responses to pollutants.

Lower socioeconomic status (SES) may be correlated with increased exposure to various indoor allergens and pollutants. Research is needed to examine gradients of SES in relation to

asthma incidence, severity, and ambient and indoor air pollution levels. Residence and exposure history, including building factors and residence in highly polluted areas or near point sources of pollutants, may also be related to asthma incidence and severity. Research is needed to assess the history of environmental exposure in asthmatics, to develop biomarkers of exposure to pollutants, to define patterns of asthma prevalence and severity relative to area and point sources of pollutants, and to quantify building and structural factors relative to asthma incidence. Additionally, urban or western lifestyle is often correlated with increasing asthma rates. Consequently, research is needed to assess the factors that may account for this disparity (e.g., reduced air exchange in tightly constructed modern buildings, reduction of physical activity, and increased time spent indoors).

Risk assessment research needs related to asthma induction include improvement of exposure information for bioaerosols, pesticides, and air toxics in indoor, occupational, and agricultural settings; development of improved exposure/activity profiles for susceptible populations; and assessment of asthma induction in an occupational setting for key chemicals of interest at ambient levels of exposure. Risk assessment research on asthma exacerbation is needed to develop tools to assess the unique risk of bioaerosols and to determine the relationship of asthma severity to dose-response relationships for asthma exacerbation by CRPs, air toxics, and pesticides. To evaluate the risks of mixtures of chemicals, data on exposure to chemical mixtures in well characterized asthmatics and in validated animal models are required.

Because limited funds make it impossible to address all of the research topics described in this Asthma Strategy, it was necessary to prioritize the research needs. The following factors were used in this prioritization: risk-based planning, relevance to EPA's mission, and public health importance.

Arbitrary scores were assigned for each area for each of the three factors; the scores were summed; and the relative ranking was determined. Of the three research areas, induction and exacerbation of asthma received the highest score, followed by susceptibility factors, and then risk assessment. Within the induction/exacerbation research area, the research topics were ranked in the following order: CRPs > bioaerosols > air toxics > pesticides. Within the susceptibility factors research area, the research topics were ranked in the following order: residence/exposure history > genetic susceptibility > health status > lifestyle/activity > socioeconomic status. Within the risk assessment research area, the research topics were ranked in the following order: asthma exacerbation > asthma induction.

The priority scores were used to generate a timeline to show the sequence and relative level of effort that will be devoted to the research areas and associated topics over an eight year period [fiscal years (FY) 2001 through 2009], depending on available resources. The timing and level of effort in this scale are intended to serve as general advisory guidelines indicating how available resources could efficiently advance scientific knowledge and control environmental factors that contribute to asthma prevalence and severity. An early peak effort in bioaerosols research is indicated, followed a year later by maximal efforts in CRPs and air toxics. Research topics in susceptibility factors peak in FY 2004-05, while risk assessment research, which is dependent on data from research conducted in the first two research areas, peaks in FY 2005-06 and extends through FY 2009.

1. Introduction

1.1. Factors in the Development of Asthma

Asthma is a disease characterized by reversible airway obstruction, chronic inflammation, and airway remodeling. The majority of asthma is associated with allergic responses to common airborne allergens such as house dust mites, pollens, animal dander, and molds. Additionally, the disease has a definite genetic component. In genetically predisposed individuals, exposure to allergens can lead to immunologic sensitization (Figure 1). Sensitization involves the production of antibodies that belong to the immunoglobulin E (IgE) class. Upon re-exposure to allergens, immediate and delayed (late-phase) responses may occur in a subpopulation of sensitized individuals. These responses include airway inflammation (characterized by the presence of inflammatory cells such as eosinophils and activated T-helper lymphocytes) and airway obstruction that is reversible either spontaneously or with appropriate medication.

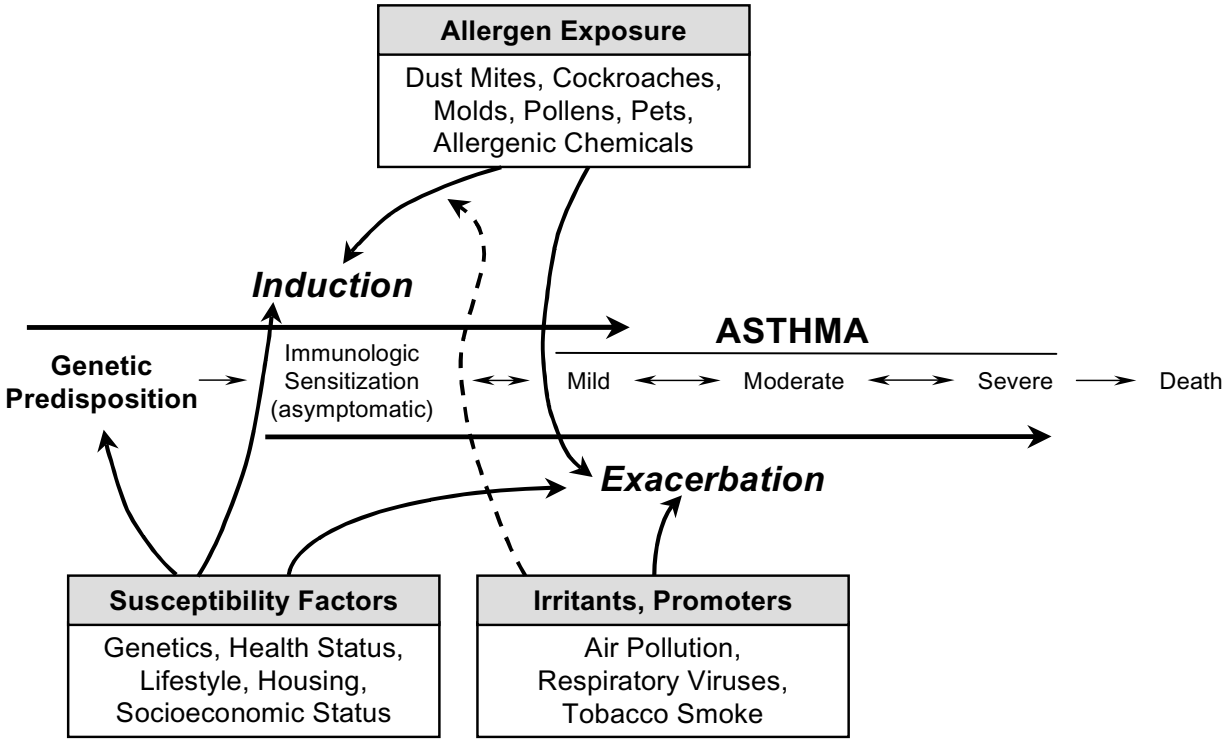

Figure 1. Induction of asthma may occur in genetically susceptible individuals upon exposure to common allergens or certain chemicals. Nonspecific irritants and promoters may facilitate induction through injury and increased uptake of allergens or by modulating immune responses (dashed arrow). Both allergens and irritants may exacerbate existing asthma. Inflammation and airway obstruction in asthma are reversible. Consequently, severity of the disease is variable (double-headed arrows) depending on environmental influences as well as susceptibility factors as indicated here.

Induction of asthma refers both to the acquisition of immunologic sensitivity to allergens and the progression to a clinically detectable disease that is indicated by reversible airway obstruction. Exacerbation of asthma may occur with subsequent re-exposure to allergens or by exposure to a number of nonspecific triggers of lung inflammation and airway obstruction, such as respiratory viruses, tobacco smoke, or certain air pollutants. It also has been suggested that some of these triggers facilitate the induction of asthma by increasing sensitization to allergens. This may occur via modulation of immune responses or injury to airway epithelium–effects that allow allergens to penetrate the immune system barrier and to be taken up by antigen-processing cells.

Susceptibility factors that are indicative of the potential for exposure to allergens and nonallergic triggers include, not only the genetic component and overall health status, but also lifestyle, SES, residential location, and overall exposure history.

1.2. Overview of Environmentally-Related Asthma

The prevalence of asthma in the United States has doubled in the last twenty years (Mannino et al., 1998). More than 17 million people now report having the disease (Centers for Disease Control and Prevention, 1998). Asthma has increased most rapidly in children less than 14 years old, who also account for the highest overall rates of asthma among the population at large. Higher rates of asthma are also reported among minorities and inner-city poor populations. Although asthma-related deaths are infrequent (< 6000 in 1997; Centers for Disease Control and Prevention, 1998), mortality rates have increased 66% since 1980. Illness associated with asthma accounts for an estimated 10 million patient visits and 470,000 hospital admissions annually; this translates to an estimated loss of three million work days and 90 million days of restricted activity for asthmatics. The costs related to this disease are enormous, with an estimated cost in the U.S. in 1996 of $14 billion. Trends toward increased prevalence, deaths, and costs of the disease have also been observed in many other countries. The increase in asthma incidence cannot be reconciled simply by changes in diagnostic categorization, and it has been too rapid to be explained by alterations in the gene pool. For these reasons, there has been a growing interest in the association between the environment and asthma.

Genetic background may determine whether individuals are susceptible to developing asthma while exposure to various environmental factors may determine the onset and progression of the disease. Genetic susceptibility, viral and parasitic infections, diet, lifestyle, air pollution, and allergic status are related to asthma incidence or severity (Koren, 1997). Other studies suggest that the increased prevalence of allergy and asthma is related to the lowered incidence of bacterial infections resulting from increased immunizations, decreased numbers of siblings, less crowding, and overall improvements in hygiene (Romagnini, 2000; Cookson and Moffatt, 1997). Combined with increased exposure to some allergens, these conditions may lead to an imbalance between the T-helper lymphocyte subsets responsible for fighting infections (Th1) and those responsible for promoting allergy (Th2) and may redirect the immune response towards asthma-related allergens. However, the decrease in infections has occurred since the 1960s while the increase in asthma is more recent. The levels of exposure due to indoor and outdoor allergens may have increased, both occupationally and even community-wide. Early childhood exposures to dust mites, cockroaches, cat secretions, mold spores, and pollen also may have increased. The recent Institute of Medicine (IOM) report on Indoor Air and Asthma (Institute of Medicine,

2000) found sufficient evidence of a causal relationship or an association between indoor exposures to house dust mites or environmental tobacco smoke and the development and exacerbation of asthma. The report also found sufficient evidence of a causal relationship between indoor exposure to a number of other biogenic allergens (e.g., mold and cockroach) and the exacerbation of asthma. Other research has looked at lifestyle causes, such as the lack of time spent outdoors, particularly engaged in vigorous activity. Data have shown that living on a farm provides protection from asthma; this may mean that most children spend excessive time indoors which increases their exposure to indoor pollutants. However, none of these factors alone can be considered the primary cause of the recent increase in asthma prevalence.

Several pollutants cause serious health problems for people with asthma. Increases in ambient levels of ozone (O_3), sulfur dioxide (SO_2), nitrogen dioxide (NO_2), and particulate matter less than 10 microns aerodynamic diameter (PM_{10}), as well as suspended sulfates, have been correlated with emergency department visits and hospital admissions for asthma. Brief exposure to SO_2 causes dramatic bronchoconstriction accompanied by shortness of breath and wheezing in many subjects with asthma while similar exposures cause no effects in healthy subjects. In addition, indoor exposure to NO_2 has been associated with the development or exacerbation of asthma (Institute of Medicine, 2000). A study performed in Kanawha County, West Virginia showed an association on a city-wide scale between volatile organic compounds (VOCs) and other traffic-related pollution and asthma (Ware et al., 1993). Toxicology studies by Gilmour et al. show that pre-exposure to NO_2 can increase the severity of allergen sensitization (Gilmour et al., 1996) and suggest that common air pollutants might play a role in asthma induction.

While there is no doubt that air pollution exacerbates existing asthma (Koenig, 1999), data linking air pollution to the incidence of asthma reveal that this relationship is complex and not simply causal. For example, the dramatically cleaner air that resulted from the shutdown of many pollutant sources in the former East Germany did not change asthma rates. While eastern Germans have more bronchitis and wheeze associated with airborne irritants, they also experience lower rates of asthma and hay fever than western Germans. Additionally, New South Wales, Australia has high rates of asthma but a relatively clean environment. In most U.S. cities over the past twenty years, ambient levels of the air pollutants O_3, SO_2, NO_2, and PM_{10} have decreased while asthma cases and severity have increased. Finally, the Harvard study of air pollution and health in six U.S. cities revealed that bronchitis, not asthma, was associated with increasing air pollution (Dockery et al., 1989). Based on these studies, it seems air pollutants may play a greater role as an exacerbator of asthma (by increasing sensitization to antigens and bioaerosols) than as direct causal agents. Although societal and housing factors may be significant inducers of asthma, a role for air pollutants in the development of asthma cannot be ruled out. Consequently, additional toxicological and epidemiological research is needed to clarify the relationships between air pollutants and asthma induction and exacerbation.

1.3. Preview of ORD Research Approach

Conducting research on asthma is consistent with the mission of the EPA to protect public health and safeguard and improve the natural environment upon which life depends. Consequently, the EPA ORD is committed to supporting the principles outlined in the Federal strategy *Asthma and the Environment: A Strategy to Protect Children* (Asthma Priority Area Workgroup, 2000). These principles include a commitment to eliminate the disproportionate

impact of asthma on minorities and the poor; to implement effective environmental, medical, and educational community-based programs and partnerships; to set measurable and consistent goals for childhood asthma as called for in the Healthy People 2010 program; and to identify and implement strategies effective in reducing asthma. In addition, the ORD recognizes the need to address environmentally related aspects of asthma as they apply to adults.

There are several research approaches to the study of asthma which are well within the scientific capability of the EPA and can provide data to fulfill EPA's mission to protect human health. Each approach provides a unique type of data needed to understand the environmental causes of asthma and to effectively manage the risk of exposure to asthma-inducing and/or exacerbating compounds.

ORD Asthma Research Areas

- Induction and exacerbation of asthma
- Susceptibility factors contributing to asthma induction or exacerbation
- Risk assessment

The ORD will focus its asthma research on three areas: (1) the induction and exacerbation of asthma, (2) susceptibility factors contributing to asthma induction or exacerbation, and (3) risk assessment issues related to induction, exacerbation, and susceptibility factors. Specific inducing and exacerbating agents to be studied include bioaerosols, pesticides, hazardous air pollutants, and combustion-related products. Factors that will be evaluated for their potential to affect susceptibility include genetics, health status, SES, residence and exposure history, and lifestyle.

2. Background

2.1. Regulatory Context

Under the Clean Air Act (CAA), the EPA establishes National Ambient Air Quality Standards (NAAQS) for criteria pollutants (ozone, lead, particulate matter, sulfur dioxide, nitrogen oxides, and carbon monoxide). The primary NAAQS are set to protect human health, including the health of sensitive members of the population such as asthmatics, and are required to be reevaluated every five years. Therefore, EPA research on the responses of asthmatics exposed to these air pollutants provides crucial information for the Agency's standard-setting activities. The EPA also is responsible for regulating major industrial sources of large quantities of 188 air toxics. Some air toxics (e.g., diisocyanates, anhydrides, metals) are known to cause or worsen asthma in occupational settings, so data collected at job sites may prove useful to EPA's regulatory efforts. The CAA also addresses area and mobile sources of air toxics that contribute or may contribute to asthma prevalence and severity. In addition, the EPA conducts research and educates the public about indoor air pollutants, such as bioaerosols, that are important in initiating asthma and in posing recurrent exposure risks to people with asthma. EPA's research and educational activities are consistent with the recommendations of the recent IOM report on asthma and indoor air (Institute of Medicine, 2000). This report concluded that several indoor

allergens and pollutants are significant factors in the development and exacerbation of asthma. It also found that effective mitigation strategies are available and can be employed presently and that additional research is needed to assess the role of the environment in the development of asthma, effective interventions to prevent asthma attacks, and the characteristics of a healthy indoor environment.

Because a dominant objective of the EPA is to examine the effects of environmental pollutants on susceptible subpopulations (asthmatics constitute 6.4% of the U.S. population), it is incumbent on the ORD to ensure that carefully collected data is used to reduce the uncertainty in risk assessment and to set standards that protect asthmatics. Additionally, because asthma disproportionately affects people of low SES and certain racial and ethnic minorities, research aimed at understanding asthma induction and exacerbation is consistent with EPA's role in ensuring environmental justice. In this context, the objective of this strategy is to articulate important research areas and ORD's capabilities in this arena in order to provide a road map for ORD's research program development over the next few years. In addition, the research strategy will aid ORD's coordination and communication with other EPA offices, Federal entities, and outside groups conducting asthma research.

2.2. Public Health Goals

2.2.1. Federal Goals

At the Federal level, the cabinet-level Presidential Task Force on Environmental Health Risks and Safety Risks to Children has developed several specific goals related to the Asthma and the Environment Strategy (Asthma Priority Area Workgroup, 2000). These goals, pursued through the efforts of multiple Federal Agencies, include the following:

- By the year 2005, the number of households in which children are regularly exposed to secondhand smoke will be reduced by 15%;
- By the year 2010, asthma hospitalization rates in children will have fallen to no more than 10 hospitalizations per 10,000 people;
- By the year 2010 emergency department visits will be reduced to no more than 46 per 10,000 people;
- By the year 2010, no more than 10% of children with asthma will experience activity limitations.

2.2.2. EPA Goals

The ultimate goals of the EPA are to prevent new cases of asthma caused by environmental factors and to reduce the number and severity of attacks experienced by individuals already diagnosed with asthma. Significant uncertainties and gaps exist in our understanding of environmental factors contributing to current asthma-related statistics in the U.S. Consequently, the ORD needs to develop a cross-paradigm research effort. The efforts outlined in this strategy will provide a substantive foundation to further the federal goals of reducing and mitigating the consequences and occurrence of asthma and asthma-related illnesses. Working within the EPA goal of Sound Science, Improved Understanding of Environmental Risk and Greater Innovation to Address Environmental Problems (Government Performance and Results Act of 1993), the

ORD will develop and apply the best available science to improve understanding of the factors causing asthma susceptibility, induction, and exacerbation. Additionally, ORD's efforts in this area will help reduce the reliance on current health risk assessments and assumptions specific to asthma-related prevalence in U.S. populations. The ORD will focus its attention on identifying the contributions of chemical and biological sources and on developing a database of mitigation strategies and exposure and effects information. This robust database subsequently can be used to assess the risks within specific population sectors and to develop mitigation strategies aimed at reducing the chemical and biological factors associated with asthma induction and exacerbation. ORD's cross-paradigm research efforts in this area are unique: both short- and long-term results of the recommended research will lead directly to intervention strategies aimed at reducing risks of asthma in the U.S. Asthma research projects currently funded through intra- and extramural programs within ORD are tabulated in Appendix B.

2.3. Linkage to Other Federal Agency Asthma-Environment Research

A number of Federal entities besides the EPA ORD are active in asthma research. These include the National Heart Lung and Blood Institute (NHLBI), the National Institute of Allergy and Infectious Diseases (NIAID), the National Institute of Environmental Health Sciences (NIEHS), the Agency for Toxic Substances and Disease Registry (ATSDR), the Centers for Disease Control's National Center for Environmental Health (CDC/NCEH), and the National Center for Health Statistics (NCHS). These federal efforts have been summarized (Department of Health and Human Services, 2000). EPA scientists are already working with some of these organizations to ensure that EPA research supplements and expands current research efforts into the causes of asthma, asthma triggers, and effective intervention strategies. The EPA is also represented in various coordinating bodies that address the subject of asthma. For example, the ORD is represented in the NIOSH/NORA (National Institute for Occupational Safety and Heath's National Occupational Research Agenda) partnership team on asthma and chronic obstructive pulmonary diseases. Most recently, the ORD is supporting an air pollution extension to the Inner-City Asthma Study (ICAS), a multi-center intervention trial among moderate to severe asthmatic children in seven cities through an interagency agreement with NIAID and NIEHS. As part of the air pollution extension to ICAS, researchers in ORD's National Health and Environmental Effects Research Laboratory (NHEERL) and National Exposure Research Laboratory (NERL) are evaluating the role of PM and O_3 in the daily variation of peak expiratory flow and respiratory symptoms among asthmatic children. The objectives of these collaborations are to leverage resources and to enhance other Federal efforts by bringing the expertise and facilities unique to the EPA. The EPA ORD is the only U.S. organization that has in-house capabilities for toxicological, clinical, and epidemiological research combined with extensive in-house capabilities for ambient air and personal exposure measurement.

The ORD can assist the other participants in ICAS in identifying the most appropriate and cost-effective asthma risk management approaches for the inner city environment and in designing protocols for intervention studies in order to determine the effectiveness of these risk management approaches in helping inner-city children. The relationship between these research topics and those covered by other ORD strategy documents [e.g., Particulate Matter Research Program (U.S. Environmental Protection Agency, 1996)], Research on Environmental Risks to Children (U.S. Environmental Protection Agency, 1999)] was an important consideration in the formation of this document.

3. Research Needs

Research addressing the health effects of specific criteria air pollutants on asthmatic individuals has been, and will likely remain, an important component of ORD's pollutant-specific research strategies. However, these pollutant-specific research strategies treat asthma only tangentially and are not aimed specifically at a full understanding of the health effects of air pollutants on asthmatics. (For example, ORD's PM research strategy does not address the genetic basis for differential susceptibility to ambient exposures in asthmatics.) The ORD research strategy for asthma presented here will provide an integrative framework for scientific research specifically directed towards improving understanding of the induction and exacerbation of asthma across the full range of environmental factors without duplicating or replacing research on specific criteria pollutants that is conducted under ORD's pollutant-specific research strategies. Based on the unique capabilities of EPA researchers and the opportunity to reduce scientific uncertainties, this Asthma Research Strategy presents an approach that focuses on the following areas: 1) induction and exacerbation of asthma in relation to four classes of pollutants; 2) susceptibility factors contributing to asthma; and 3) related risk assessment issues. Within Research Area 1, the pollutant classes which merit further study are CRPs, bioaerosols, air toxics, and pesticides. A brief synopsis of these four classes of pollutants and the rationale for their selection is described below. Thereafter, an introduction to the four areas selected for additional study as part of Research Area 2, Susceptibility Factors, is provided. Chapter 4 provides details concerning each of the three research areas and highlights suggested research agenda items.

3.1. Research Area 1: Induction and Exacerbation of Asthma

Research Area 1: Induction and Exacerbation of Asthma

- Combustion-Related Products
- Bioaerosols
- Air Toxics
- Pesticides

CRPs are compounds formed by the combustion of fossil fuels or by secondary transformation reactions. Contributing components include diesel exhaust and criteria air pollutants such as NO_2, O_3, ultrafine or fine particulate matter ($PM_{2.5}$), and SO_2. Current evidence does not support a significant role for CRPs (except possibly for diesel exhaust) in the induction of asthma because ambient levels of all the criteria air pollutants have generally declined while asthma prevalence has increased over the past twenty years. However, the composition of CRPs in the atmosphere has changed over time with the increasing prevalence of diesel exhaust. Consequently, an interaction of CRPs with common allergens in the induction of asthma cannot be ruled out. Multiple clinical, epidemiologic, and animal studies suggest that these pollutants exacerbate existing asthma. These findings need to be extended to further understanding of interactions with allergens and exposure response relationships and to develop effective risk management techniques for both indoor and ambient sources of CRPs.

Bioaerosols include the clinically relevant allergens (e.g., molds, pollens, dust mites, and pet secretions) that are known to induce asthma in genetically susceptible individuals. For many bioaerosols, the antigens responsible for sensitization have been characterized. However, almost

none of the mold allergens have been characterized, despite their widespread distribution and apparent importance in the induction and exacerbation of asthma.

Air toxics include volatile and semi-volatile organic compounds, some metals, and other inorganic compounds which were listed in the 1990 amendment to the Clean Air Act. Except for a few chemicals in occupational settings, little is known about the contribution of air toxics to the development or worsening of asthma. Research is needed to more accurately assess exposures and biological effects and to manage the risks associated with individual air toxics or combinations of compounds, especially those which have been shown to induce or exacerbate asthma and are included in the list of 33 urban hazardous air pollutants.

Some reports suggest that certain classes of pesticides may be associated with induction or exacerbation of asthma (O'Malley, 1997). Pesticide exposure may be particularly harmful in children because their developing immune systems may be more sensitive to pesticide effects. Epidemiological studies of pesticide exposure levels and asthma prevalence are critically important in this regard. Increased exposure assessment, investigation of toxicologic effects, and control strategies for different classes of pesticides are warranted.

3.2. Research Area 2: Susceptibility Factors

As previously stated, asthma is caused by a multitude of factors—none of which is completely understood. Consequently, the second major area in which additional research is needed is the area of susceptibility factors. Factors known to contribute to susceptibility are genetics, gene-environment interactions, health status, and environmental influences. Environmental influences include SES, residential location, total exposure history, and lifestyle. Several of these factors, including genetics, SES, and residential location, have been recommended to be studied in relationship to indoor air quality and asthma (Institute of Medicine, 2000).

Research Area 2: Susceptibility Factors

- Genetic Susceptibility
- Health Status
- Socio-Economic Status
- Residence and Exposure History
- Lifestyle / Activity Patterns

Recent data indicate that responses of both healthy and asthmatic people to environmental pollutants is influenced by genetic background. Identification and characterization of those genetic polymorphisms which influence responsiveness to environmental agents will provide risk assessment tools with which to identify people who are susceptible to these agents

Research is needed on how asthma severity, age, and the presence of other co-morbid conditions may alter uptake and deposition of environmental pollutants in the respiratory tract and how these factors affect the dosimetry of air pollutants and their interactions with asthma.

The relationships between SES and the incidence and severity of asthma in the context of general air pollution levels needs to be assessed and clarified.

Residential location relative to area point sources on a small scale and geographic regions on a larger scale, as well as building age and structure type appear to influence asthma severity and needs to be studied further. Also, the exposure history of asthmatics to defined allergens and air pollutants is an important factor in the development of asthma and requires additional study.

Physical activity, time spent indoors, and nutrition influence allergen and air pollution exposure and effects. The relationship of these factors to subsequent asthma outcomes needs to be more adequately addressed.

4. Research Approach

The research approach of this strategy tests the general hypothesis that environmental factors influence the induction and exacerbation of asthma, and that these factors can be controlled.

4.1. Research Area 1: Induction and Exacerbation of Asthma

4.1.1. Combustion-Related Products

Ambient levels of most CRPs have declined over the past twenty years while asthma prevalence has increased, suggesting that CRPs are not responsible for the increase in asthma prevalence. However, recent evidence suggests that both diesel exhaust and environmental tobacco smoke (ETS) may increase the incidence of asthma, and stronger evidence indicates that they can exacerbate existing asthma. Indoor air levels of some CRPs may be increasing due to tighter construction of homes and less ventilation with outdoor air and may be contributing to the increased prevalence of asthma. Recent human studies suggest that some CRPs, particularly diesel exhaust, may facilitate allergic sensitization. Hence, a role for CRPs in the induction of asthma may be implicated (Diaz-Sanchez et al., 1997; Gilmour et al., 1996; Lambert et al., 1999). There is strong evidence from both human and animal studies that CRPs can exacerbate existing asthma, but mechanisms for these effects and dose-response relationships are not clearly defined.

Exposure

While the measurement of ambient air CRPs is extensive, the role of CRPs in asthma-related problems must be distinguished from other factors. To this end, the monitoring of fine PM is being expanded to allow better definition of its effects on sensitive populations. The relationship between indoor and outdoor PM concentrations needs further investigation. The relationship between exposure to NO_2 and asthma severity is not fully understood; however, an association between NO_2 and asthma exacerbation has been shown to exist (Institute of Medicine, 2000). The time course of asthmatic responses to allergens in relation to CRP exposure also requires further study as increases in ambient CRP levels may occur minutes, hours, or days prior to or following acute allergen exposures. Finally, the CRPs in ETS and diesel exhaust contain toxic low molecular weight compounds that require study, particularly because these compounds and their metabolites can serve as useful biomarkers of exposure.

Research Agenda Items: *CRPs Exposure*

- **Determine exposures to CRPs from outdoor and indoor sources**
- **Develop exposure models linking source to exposure and ambient to indoor air concentrations.**
- **Determine distributions of peak and mean personal exposure to NO_2 and the relationship between NO_2 exposure and asthma.**

Effects

Epidemiologic studies should continue to be performed to determine whether acute exposure to CRPs increases doctors visits, emergency room visits, and hospitalizations. These studies will improve understanding of the conditions of exposure that lead to asthma exacerbation. For example, asthma exacerbation may occur following exposure to a single high exposure or after chronic exposure to lower levels of CRPs. Clinical studies are needed to determine whether short-term exposure to ambient CRPs leads to an increase in acute exacerbation of asthma or use of medication and to determine the exposure-response characteristics. Despite the inverse correlation between CRP levels and asthma prevalence, CRPs may be important in asthma induction by facilitating sensitization to common allergens. CRPs such as residual oil fly ash (an emission source surrogate of PM) and NO_2 can amplify the induction of allergic airways responses to dust mite allergen in rats. These types of sensitization studies should be expanded to examine diesel exhaust and other forms of ambient PM and other allergens that may be important in urban environments. Similar studies should be carried out in atopic humans. Previous studies have been conducted to examine the effects of nasal instillation of diesel exhaust particles on local allergic responses (Diaz-Sanchez et al., 1997). The possibility that viral infection may further enhance allergic responses following exposure to CRPs could also be investigated in animal studies or controlled clinical studies. Finally, the cellular and molecular mechanisms by which CRPs exacerbate airway responsiveness and allergic responses in animal models or controlled human exposures of asthmatics should be determined.

Research Agenda Items: *CRPs Effects*

- **Examine exposure to CRPs (especially fine PM) in relation to asthma outcomes (e.g., symptoms, pulmonary function, medication use, doctors visits, ER visits, hospitalizations, quality of life).**
- **Determine acute exposure-exacerbation response relationships in clinical and animal studies.**
- **Examine whether fine PM or other CRPs enhance sensitization to common allergens.**
- **Study cellular and molecular mechanisms of inflammatory and physiological responses.**

Risk Management

The risk management efforts for CRPs should consider both indoor and outdoor CRP sources (fine PM in particular). As determined by priorities, the ongoing characterization of CRP emission sources under the PM program could be expanded to provide more complete and accurate emission factors and source models. For fine PM, this expanded characterization could also lead to a better understanding of particle size distribution and chemical composition. Drawing from these refined characterization results, experimental and engineering studies could be conducted to develop and improve the appropriate control technologies for CRPs.

Outdoor sources of CRPs to be considered include a wide array of stationary sources (e.g., industrial and utility boilers, wood and biomass combustion) and mobile sources (e.g., diesel trucks). Studies of PM should address the characterization and control of both primary PM (i.e., PM that is released in the particulate form) and secondary PM (i.e., releases compounds such as sulfur oxides that can react in the atmosphere to form PM and that, in their unreacted gaseous form, can independently contribute to asthma symptoms).

Indoor sources of CRPs to be considered include indoor combustion sources, PM re-suspension, creation of fine PM through indoor air chemistry, and entry from outdoors. These sources could be characterized through test chamber and test house experiments and associated modeling studies. Modeling the physical processes involved with the sources and fates of CRPs (emission mechanisms, deposition/sorption, re-suspension/desorption, etc.) as a function of source parameters and building parameters (e.g., ventilation) over extended periods would be useful and could serve as input to the assessment of exposures. This information is required to effectively design a risk management program that reduces CRPs in indoor air.

Research Agenda Items: *CRPs Risk Management*

- **Continue to characterize the indoor and outdoor sources of selected CRPs, emphasizing the development of basic models defining these sources.**
- **From these results, develop appropriate prevention and control approaches and technologies.**

4.1.2. Bioaerosols

Several classes of bioaerosols induce allergic asthma in susceptible individuals. Antigens from dust mites, cockroaches, pets, and several pollens have been well characterized and are routinely measured. Bacterial antigens, such as those present in enzyme preparations of *Bacillus subtilis* or biopesticides like *B. thuringiensis*, have also been associated with the induction of asthma (Pepys, 1992; Bernstein, 1999). Mold growth (including *Aspergillus, Penicillium, Alternaria, and Cladosporium*) in damp buildings appears to be an important risk factor for induction of asthma and other respiratory illnesses (Rylander, 1999; Institute of Medicine, 2000). Although much attention has focused on inner city populations exposed to high levels of cockroach allergens, poor housing conditions which promote the growth of molds may pose the greatest risk of asthma development and exacerbation. However, no federal agency has any significant research program focusing on the role of fungal allergens in asthma induction and exacerbation. Therefore, the ORD will concentrate its research efforts on exposure, health effects, and risk management related to fungal bioaerosols. Research on other bioaerosols (e.g., dust mites, cockroaches) should be considered where there is evidence of interactions with other pollutants (e.g., CRPs, air toxics) causing an increase in the incidence of asthma or exacerbating asthma symptoms.

Exposure

There are no widely available methods for quantitation of fungal allergens; accordingly, very few fungal allergens have been identified. Molecular probes specific for fungal allergens are needed to identify the allergens responsible for health effects. Fungal allergens can then be biochemically characterized, and quantitative enzyme-linked immunosorbent assays (ELISA) for these allergens in environmental samples can be developed.

Indoor fungal allergens are probably more significant in asthma induction and exacerbation than outdoor fungal allergens, especially in damp, poorly-ventilated buildings; however the relative contributions of each type are unknown. To improve understanding of the factors that contribute to asthma induction and exacerbation, dampness, carpeting, and air exchange rates should be compared between homes of asthmatics and healthy individuals. Threshold concentrations for increased risk of asthma symptoms and hospitalization could then be established for common fungal allergens. Geographical differences in fungal exposures among cities and regions may be significant relative to other allergens such as dust mites, cockroaches, and pollens. Exposure assessments of other bioaerosols, such as cat, dog, rodent, and cockroach allergens should also be completed, particularly in areas where they appear to significantly contribute to asthma prevalence and severity and where interactions with other common air pollutants (such as CRPs and air toxics) may enhance asthmatic symptoms.

Research Agenda Items: *Bioaerosol Exposure*

- **Characterize the degree of exposure to major fungal allergens that have been shown to induce sensitization and airway obstruction.**
- **Develop innovative methods and measurement protocols for characterizing and quantifying bioaerosols identified as major contributors to asthma related health outcomes.**
- **Examine building environment factors (e.g., dampness, ventilation) which contribute to fungal exposure.**
- **Assess the relative exposures to indoor and outdoor sources of molds.**
- **Examine the importance of regional differences in fungal exposures as a factor in the prevalence of asthma.**
- **Assess the importance of exposure to mold allergens relative to better studied allergens.**

Effects

Exposure assessment, detailed questionnaires, and clinical testing are needed to estimate the dose of fungal allergen that causes sensitization or exacerbation of asthma symptoms. The doses of defined bioaerosol antigens which exacerbate clinical symptoms and airway hyper-responsiveness in sensitized individuals are poorly characterized and likely depend on various susceptibility factors. Because performance of tasks in school or at the workplace by allergen-sensitive individuals can be adversely affected by exposure to indoor bioaerosols, new measures of these effects are needed.

Immunomodulatory agents such as (1→3)-β-D-glucan, a component of mold cell walls, and mycotoxins, such as those produced by the toxigenic mold species *Stachybotrys chartarum*, may promote nonspecific inflammation which contributes to clinical symptoms and allergic pathophysiology. These adjuvant effects may be studied in appropriate animal models which respond to fungal allergens with allergic airway diseases characteristic of human asthma. Although animal models do not replicate all conditions of human asthma, especially with respect to chronicity of the disease, they are useful for determination of cause-effect and dose-response relationships between bioaerosol exposure and immune, inflammatory, and physiological endpoints. Such models are also useful for testing interactions with other allergens, viruses, and other pollutants. These interactions may be additive, synergistic, or inhibitory. Cellular and

molecular mechanisms of allergic responses to fungal allergens may be determined using whole animal models and human or animal cell culture systems.

Research Agenda Items: *Bioaerosol Effects*

- **Examine the spectrum of fungal allergen sensitivity in asthmatics in the home and workplace.**
- **Carry out allergen bronchoprovocation of clinically-identified mold-sensitive asthmatics to determine dose-response relationships.**
- **Examine the adjuvant effects of toxic compounds produced by bioaerosols on induction and exacerbation of asthma-related responses.**
- **Examine the interactions of bioaerosols with viruses or environmental agents such as CRPs.**
- **Analyze mechanisms of responses with appropriate cell culture or animal models.**

Risk Management

Significant testing of bioaerosol risk management techniques has been reported in the literature. However, to date, even the more promising techniques have provided only modest clinical benefits for asthmatics, indicating that additional, focused studies are needed to develop new risk management techniques or to improve the implementation of the existing ones.

Test chamber and test house experiments and associated modeling studies are needed to more effectively characterize the sources of indoor bioaerosols (including bioaerosols entering from outdoors). The resulting basic source models would define the physical processes associated with the source and the fate of the bioaerosols as a function of source parameters and building parameters (e.g., relative humidity, ventilation rate). This improved understanding of sources would enable definition of risk management strategies to most effectively reduce exposure, and the basic source models would serve as input to exposure assessment. The full range of bioaerosols (i.e., aerosols associated with dust mites, pets, roaches, and fungi) should be considered in accord with the determined priorities.

Techniques recommended for initial attention include improved building materials, furnishings, and mechanical system components that are resistant to biological growth; improved, more durable, or better-verified products (such as mattress encasements or "anti-allergenic" vacuum cleaners); methods for controlling indoor conditions (such as relative humidity) that inhibit the growth of fungi, mites, and roaches; improved maintenance techniques; and improved source treatment measures (such as encapsulation). These source management techniques warrant primary attention because they offer the potential for significant reductions in exposure and are not being fully addressed by other investigators.

Risk management techniques involving ventilation and indoor air cleaners/filters would likely be a secondary research focus. Based on the results from the characterization of exposure pathways, and, in conjunction with such efforts, studies should be conducted to assess the performance and effectiveness of ventilation and air cleaning on selected bioaerosols.

Research Agenda Items: *Bioaerosol Risk Management*

- **Develop improved understanding and basic models characterizing the sources of indoor bioaerosols.**

- **Improve, develop, and demonstrate source management techniques to reduce bioaerosol exposure, such as mold-resistant materials and environmental controls, and define their effectiveness in outreach programs in affected communities.**
- **Assess the effectiveness of improved ventilation and indoor air cleaning and filtration in reducing bioaerosol exposure.**

4.1.3. Air Toxics

The 1990 Clean Air Act Amendments provide the foundation for EPA's air toxics program. It listed 189 compounds (one was removed so the current number is 188) as hazardous air pollutants (HAPs) to be regulated. In 1999, 33 HAPs were selected as posing the greatest threat to public health in the largest number of urban areas (Federal Register, 1999) and 30 compounds were selected as having the highest impact on asthma and respiratory health (Leikauf et al., 1995). These compounds were selected based on their ability to induce or exacerbate asthma, their allergic potential, or their irritant potential. Seven compounds (acetaldehyde, acrolein, formaldehyde, hydrazine, and cadmium, chromium, and nickel compounds) were selected for inclusion in both lists (EPA, 1999; Leikauf et al., 1995) and are prime candidates for initial study. Additionally, six organic acids (three diisocyanates and three acid anhydrides) are known to cause asthma in occupational settings or are structurally related to such compounds and are suitable for clinical studies, as is chlorine which is not a known or suspected carcinogen. Both diesel exhaust and ETS are mixtures of various CRPs and air toxics which may interact to enhance asthma incidence or severity.

Exposure

One of the most significant problems in the study of air toxics and asthma is the lack of information on the ambient air concentrations of these compounds (Leikauf et al., 1995). Data on personal exposures to air toxics are needed to more accurately determine associated risks and measurements of ambient levels of urban HAPs. An expansion of efforts to fully evaluate key determinates of exposure to air toxics within urban and occupational settings is of paramount importance in efforts to understand the relationships between ambient and indoor sources and the characterization and quantification of major exposure pathways and routes. Exposure research will focus on addressing major factors contributing to asthma-related illnesses from exposure to air toxics through better evaluation and characterization of pathways, activity pattern measurements, and development of quantitative multipathway models for predicting the contributions from and exposures to air toxics. In addition to industrial area sources, products such as paints and carpets used in indoor environments may be significant sources of asthma-associated air toxics. In areas with high asthma prevalence, testing for asthma-related air toxics, in addition to the previously mentioned compounds, may be warranted.

Research Agenda Items: *Air Toxics Exposure*

- **Monitor personal exposures to asthma-associated air toxics in different environments.**
- **Characterize major pathways and routes of exposure to key air toxics, evaluate key determinants of exposure, and characterize important activities leading to enhanced exposures in different population sectors (i.e, children, elderly)**

- **Characterize sources of asthma-related air toxics, and develop multimedia/ multipathway aggregate exposure and exposure-to-dose models for key air toxics used in source to dose estimations.**

Effects

Quantitative prospective cohort epidemiologic studies with exposure measurements are needed to determine whether concentrations of air toxics affect asthma rates or severity on a local or regional basis. Relationships between occupational exposure to air toxics and asthma incidence and clinical symptoms are still poorly defined. Occupational environment air toxics measurements would allow definition of exposure-response relationships and relationships between occupational and environmental exposures. Controlled clinical studies of asthmatic volunteers exposed to air toxics at levels found in the urban/occupational environment would also contribute to knowledge of exposure-response relationships. Other epidemiologic studies could examine whether air toxics facilitate the induction of responses to common allergens.

Air toxics may be directly allergenic or may amplify inflammation and airway hyper-responsiveness induced by allergens. Animal models can be utilized to develop test methods for assessing the potential allergenicity of air toxics and to determine whether air toxics increase sensitization to common allergens. Exacerbation of inflammation and reactivity may also be examined in allergic or virus-infected animals, and the pathogenetic mechanisms of irritant-induced asthma can be examined in these models.

Research Agenda Items: *Air Toxics Effects*

- **Conduct studies of asthma prevalence and respiratory effects in relation to air toxics exposures.**
- **Define exposure-response relationships for asthma induction/exacerbation using occupational data and clinical studies.**
- **Develop practical test methods for assessing the allergenicity of air toxics.**
- **Determine whether air toxics induce hyper-responsiveness or exacerbate responses in animal models sensitized to common allergens.**
- **Study interactive effects of air toxics and CRPs.**

Risk Management

Continuing experimental and analytical studies should be conducted to characterize and model the emissions of air toxics from selected indoor and outdoor sources. Among the outdoor sources of primary concern are architectural coatings that emit HAPs such as formaldehyde and acetaldehyde. Indoor sources of concern include building materials, furnishings, interior paints, consumer products, and office equipment, all of which emit formaldehyde and/or other compounds of concern to asthmatics. To allow the risk management effort to be focused on those sources contributing the most to the cumulative exposure, the relationship between indoor versus outdoor air toxics concentrations and the possible interactions between indoor air pollutants (e.g., reactions between indoor VOCs and ozone) require further study. Supported by this characterization work, appropriate experimental and analytical studies should be undertaken on selected sources in order to develop the technology needed to prevent or reduce emissions of air toxics. For indoor sources, the initial emphasis should be on pollution prevention measures (e.g., development of low-emitting materials); for outdoor sources, the focus should be on pollution prevention measures or on add-on controls, depending upon the source.

Research Agenda Items: *Air Toxics Risk Management*

- **Characterize emissions from priority indoor and outdoor air toxics sources, emphasizing the development of basic models defining these sources.**
- **Develop approaches and technologies for preventing or reducing emissions from the most important sources.**

4.1.4. Pesticides

Pesticide exposures may induce systemic and local reactions, such as irritation of the respiratory tract and asthma-like reactions in some individuals (O'Malley, 1997). Young children may be particularly sensitive to the effects of pesticides due to their rapidly developing nervous and immune systems (Eskenazi et al., 1999). Some adverse reactions to pesticides are probably nonspecific responses to low molecular weight organic vehicle components (such as mercaptans). Exposure to carbamate pesticides has been associated with increased incidence of asthma in Canadian farmers (Senthilselvan et al., 1992). Organophosphates and N-methyl carbamates inhibit acetylcholinesterase, lead to reduced enzymatic degradation of acetylcholine, and parasympathetic responses that may include bronchoconstriction. Pyrethrum insecticide may contain sesquiterpene lactones which have been shown to induce allergic rhinitis and may exacerbate asthma. Little is known about the specific effects of organochlorine insecticides on people with asthma.

Exposure

The prevalence of asthma in relation to levels of pesticides encountered outdoors or in homes has not been established. Considerable difficulties exist, not only in identifying individuals who have been exposed to pesticides, but also in identifying the pesticides and exposure levels that may be responsible for observed effects. The concentrations of pesticides in the air, water, or soil and the duration of exposure may affect both clinical symptoms and the level of sensitization to common allergens. These relationships between allergen exposure, pesticide levels, and asthma incidence and clinical symptoms are not well defined. The routes (ingestion, inhalation, or dermal absorption), as well as the sources (indoor versus outdoor) of exposure to pesticides, are important factors to consider. Additionally, factors contributing to children's increased allergen sensitivities/susceptibility resulting from a combination of pesticide exposure should be better understood.

Where analyses of hospitalizations and emergency room visits for asthma have been completed, retrospective exposure assessments of pesticide levels in the home may provide unique opportunities for assessing the types and levels of pesticides associated with asthma exacerbation. The development of biomarkers of exposure to pesticides in blood or urine samples may also be useful in this regard.

Research Agenda Items: *Pesticide Exposures*

- **Examine levels of pesticide exposure and usage in geographic regions and demographic groups with different asthma incidence rates.**
- **Develop biomarkers for exposure to pesticides.**

Effects

The health effects of pesticide compounds must be segregated from those of the VOCs used as vehicle components in the formulation of the product. For example, low molecular weight pesticide compounds may act as haptens, binding to larger proteins and inducing sensitization to the pesticide. Pesticide exposure may also facilitate sensitization to common allergens by increasing serum IgE antibodies to these allergens. The increased levels of IgE may serve as a biomarker of exposure to pesticides, as well as a possible mechanism for increased incidence and exacerbation of asthma. Some pesticides may also cause dysregulation of the autonomic nervous system, which may cause direct effects on respiration or modulate immune responses. Animal toxicology studies can be used as a screening tool to decide which pesticides to examine in epidemiologic studies. The effects of acute pesticide exposure on airway responsiveness and allergic inflammation in animal models may also be tested.

Sensitization to common allergens and subsequent induction of asthma may be enhanced by exposure of infants and children to pesticides. In order to test this hypothesis, epidemiologic studies can be performed to determine incidence of new asthma in children and corresponding pesticide exposure levels. Pesticide levels associated with increased incidence will likely vary depending on the class (organochlorines, carbamates, organophosphates) and mechanism of action. Studies are being conducted to determine whether acute exposure to pesticides increases asthmatic symptoms or acute attacks in children. Toxicology studies can also be used to determine whether fetal or neonatal exposure to various classes of pesticides facilitates induction of responses to common allergens. Finally, new studies of asthma in workers with high exposures to pesticides could facilitate understanding of exposure-response relationships and interactions between occupational and environmental exposures.

Research Agenda Items: *Pesticide Effects*

- **Examine immunologic and neurologic mechanisms of responses to pesticides, and distinguish from the effects of vehicle compounds.**
- **Develop methods for screening pesticides for potential to cause or exacerbate asthma**
- **Determine whether pesticide exposure facilitates induction of asthma or responses to common allergens.**
- **Examine asthma prevalence, incidence, and severity associated with exposure to pesticides.**

Risk Management

For any major class of pesticides (e.g., organophosphates, organochlorines, or carbamates) that becomes linked to the induction or exacerbation of asthma, a detailed source characterization effort should be conducted involving test chamber and test house experimental studies. This effort should include computer modeling of the physical processes involved during application of the pesticide and occurring for an extended period afterwards. The relevant physical processes include airborne emissions from the wet and dried pesticide film, transformation of the semi-volatile constituents between the aerosol and gaseous phases, transport to surfaces, deposition (or sorption) on surfaces, re-suspension (or desorption) from surfaces. This modeling should take into account pesticide characteristics and building parameters (e.g., ventilation), and should address both the active ingredients in the pesticide and other constituents (e.g., co-solvents) of possible concern to asthmatics.

Drawing upon these improved models for pesticides, a focused study can be undertaken to develop pollution prevention and other alternatives for reducing indoor pesticide exposure. Possible examples of such risk management alternatives include definition of the appropriate ventilation strategy to reduce exposure based on the emission pattern from wet pesticide films; re-formulations that could result in a lower-emitting product while maintaining pesticide performance; optimal maintenance/cleaning approaches; integrated pest management, educational campaigns, usage reduction, and proper use and application.

Research Agenda Items: *Pesticide Risk Management*

- **Develop improved models characterizing the airborne emissions resulting from pesticide use and the transport and fate of these emissions in the indoor environment.**
- **Develop pollution prevention and other alternatives for reducing pesticide exposures associated with induction and exacerbation of asthma.**

4.2. Research Area 2: Susceptibility Factors

4.2.1. Genetic Susceptibility

Previous clinical and epidemiologic studies indicate that responses to environmental exposures are heterogeneous among individuals. For example, the magnitude of functional and inflammatory responses to ozone exposures can differ significantly among subjects, while this trait appears to be consistent for a given individual. These observations suggest that human susceptibility to environmental insults is influenced by the genetic background of healthy individuals. It follows that there may also be a genetic basis for differential susceptibility to ambient exposures in asthmatic patients. The goal of research in this area is to identify and characterize genetic polymorphisms that influence responsiveness to environmental agents in order to improve the risk assessment tools used to predict the percentage of the population that is susceptible to environmental exposures. A critical phase in genetic susceptibility research is identification of phenotypic differences of asthmatics and healthy individuals by defining the range of responsiveness to a given exposure under controlled conditions. These phenotypic differences can then be correlated with the genetic profile of each subject to determine genotypic differences. To this end, a DNA bank of samples from asthmatic and healthy volunteers in clinical or epidemiological studies needs to be established. Once this bank is established, opportunities for conducting genetic analysis experiments will exist.

A "top-down, bottom-up" approach can be used to discover genetic markers of susceptibility to air pollutants which define differences in responses of asthmatics and healthy individuals. In this approach, genetic analysis of chromosome regions linked to phenotypic differences is combined with study of candidate genes associated with asthma. Candidate genes may be proposed based on clinical or animal toxicology studies. This approach is distinct from the environmental genome project or the National Health and Nutrition Examination Survey's (NHANES') genetic retrospective in that phenotypic responses to controlled pollutant exposures have been identified in subjects studied by ORD investigators. In vitro approaches may also be used to compare gene expression by airway epithelial cells from asthmatics and healthy humans. Finally, mutant genetic animal models may be utilized to examine environmental interactions with defined genetic differences.

Research Agenda Items: *Genetic Susceptibility*

- **Define differences in responses of asthmatics and healthy individuals to environmental pollutants as a step towards quantifying genotypes common to asthmatics.**
- **Establish DNA bank of samples associated with phenotypic markers of response in asthmatics and healthy individuals for use in conducting genetic analysis experiments to identify genetic markers of susceptibility.**
- **Utilize in vitro studies and animal models to examine effects of specific genes.**

4.2.2. Health Status

Responsiveness to environmental pollutants may depend on the severity of disease and presence of co-morbid conditions. For example, individuals with more severe asthma have greater decrements in pulmonary function in response to SO_2 and O_3. Age and the concurrent presence of other cardiopulmonary diseases can also affect responsiveness. Asthma severity may alter uptake and deposition of environmental pollutants in the respiratory tract and may subsequently influence tissue and physiological responses. The objectives of research in this area are to understand how asthma severity affects dosimetry of air pollutants and subsequent effects and to determine how age and disease status affect responsiveness. Human studies may be carried out to explore the effects of asthma severity on dosimetry, and epidemiological studies can be used to study the responses of mild and severe asthmatics to air pollution episodes. Finally, animal models of cardiopulmonary disease may be used to examine the effects of coexposure to allergens and pollutants such as air toxics and CRPs.

Research Agenda Items: *Health Status*

- **Perform dosimetry and dose-response studies on asthmatics with a broad range of asthma severity with representative compounds.**
- **Develop mathematical models to understand the effect of asthma severity on dosimetry of gaseous and particulate air pollutants.**
- **Examine the influence of asthma severity and recent respiratory infections on responses to air pollution episodes.**
- **Study models of cardiopulmonary disease to understand mechanisms of enhanced responses to pollutants.**

4.2.3. Socioeconomic Status

In general, low SES is highly correlated with asthma prevalence and severity but is less well-correlated with ambient air pollution levels. Low SES, common in inner city populations, may be indicative of increased exposure to indoor air pollutants such as nitrogen oxides, bioaerosols, and pesticides, or stationary or mobile sources of CRPs (Northridge et al., 1999). The relationships between SES and the incidence and severity of asthma need to be clarified. Gradients of SES may be examined in the context of asthma and air pollution levels. In addition to its interest from a health perspective, epidemiological studies should be performed to examine the relationship between SES and asthma prevalence as a social justice issue.

Research Agenda Items: *Socioeconomic Status*

- **Examine gradients of SES in relation to asthma incidence and severity with emphasis on their relationship to ambient and indoor air pollution levels.**

4.2.4. Residence and Exposure History

The totality of exposure history to defined allergens, air pollutants, pesticides, and other chemical stressors appears to influence asthma prevalence. Key factors contributing to exposure history include activity patterns, uptake rates, frequency and duration of the exposures, and potential dose metrics. Understanding the linkages between these key factors and their relationship to asthma incidence rate and prevalence is important. Consequently, the exposure history of asthmatics should be investigated to determine whether asthma prevalence is related to patterns of exposure to indoor allergens, molds, air toxics, pesticides, and CRPs. Additionally, biomarkers of exposure to environmental pollutants may be useful in defining the contribution of individual pollutants to asthma induction.

Residence near area sources of pollutants increases the likelihood of exposure. To assist in risk assessment, patterns of asthma prevalence and severity should be defined relative to area sources and geographic regions (e.g., rural versus urban). These studies may also provide insight into the relative role of indoor versus outdoor pollution. In addition, residential location near point sources on smaller scales needs to be considered (e.g., proximity to dry cleaners on ground floor of apartment building or to unventilated garages in housing units). Building age, structural issues, and multiple-dwelling versus single-family buildings are additional factors which may influence allergen and environmental pollutant exposures and require further research.

Research Agenda Items: *Residence and Exposure History*

- **Assess environmental exposure history in asthmatic patients.**
- **Develop biomarkers of exposure to pollutants to assess the potential contribution of individual pollutants.**
- **Define patterns of asthma prevalence and severity relative to area and point sources of pollutants in residential locations.**
- **Compare existing geographic information system (GIS) data on the location of sources and their emission inventories to patterns of asthma prevalence and severity.**
- **Define the building and structural factors associated with living in an urban environment that contribute to the high incidence of asthma among inner-city residents.**

4.2.5. Lifestyle / Activity Patterns

Urban or western lifestyle appears to be correlated with increasing asthma rates. However, the factors that account for the increased rates are not clear. The time, duration, and frequency of exposures to air pollutants are key factors to be considered when assessing asthma prevalence. The tight construction of modern buildings reduces ventilation from outside air and may increase exposures to indoor allergens and exacerbate the effects of indoor air pollutants. Reduction of physical activity and increased time spent indoors may also be important factors contributing to higher asthma rates. Exercise and outdoor activity increase ventilation and the inhaled dose of

ambient pollutants and may also promote higher rates of asthma. Specifically, the deposition and dose of SO_2 and particles is increased at higher breathing rates and higher flow rates as is the depth to which these pollutants penetrate into the lung. Nutritional factors, including vitamin C intake, also appear to be significant determinants of asthma severity.

Research Agenda Items: *Lifestyle / Activity Patterns*

- **Examine the balance of lifestyle factors, including physical activity, time indoors, and nutrition, which influence allergen and air pollution exposure and their relationship to subsequent asthma outcomes.**

4.3. Risk Assessment

In addition to advanced research into the factors responsible for the prevalence and exacerbation of and susceptibility to asthma, risk assessment is a high priority for the ORD. The following two sections describe specific areas in which additional risk assessment measures are needed.

4.3.1. Asthma Induction Associated with Environmental Exposures

To assess the risk of asthma induction, human exposure studies, epidemiology studies, occupational studies, and animal toxicology studies must be utilized. Animal toxicology studies must be extrapolated to human health effects and compared to human equivalent exposures to complete the risk assessment cycle and provide the basis for risk assessment. The development of an assessment approach would be similar for CRPs, bioaerosols, pesticides, or air toxics. The pattern, timing, and quantification of exposures is likely to be a key issue in determining risk for asthma induction from environmental chemicals or combinations of environmental chemicals and biological factors. An understanding of temporal factors such as the frequency and duration of exposure and the timing of exposures with respect to age and time of day and season is required to assess exposure risks. Additionally, a determination also must be made as to whether induction and/or resensitization occurs as a result of a few high level exposures, numerous low level exposures, or both types of exposures.

Another major issue central to assessing the risk of asthma induction is the prevalence of phenotypes and genotypes that are susceptible to induction as it is likely that a combination of genetic susceptibility and environmental exposure is required for induction. Methods for combining susceptibility with exposure information need to be developed to assess the risk for induction. Since adequate human exposure-response information is presently lacking for many chemical and biological agents of concern, it will be necessary to utilize validated animal-to-human extrapolation models to develop dose response assessments as well as to utilize epidemiological studies to identify key inducers and cofactors.

The induction of asthma generally requires genetic susceptibility, appropriate timing, exposure to susceptibility-enhancing or adjuvant chemicals (e.g., diesel exhaust particles), and adequate exposure to an inducer or combination of inducers. Activity and associated ventilation rates determine bulk flow of gases and particles and influence the extent and pattern of particle deposition. Because environmental levels vary during the day, the juxtaposition of activity and exposure may play an important role in induction. Consequently, simultaneous exposure/activity

information in a susceptible population, preferably across age, would be useful for risk assessment.

Occupational studies may provide a good model for a simplified risk assessment of induction for the following reasons: exposure information can be provided for the workplace (likely the primary source of exposure); activity can be observed and ventilation monitored or estimated; the duration of exposure can be adequately characterized (both cumulative and acute); internal dose or effect surrogates can be developed; whether or not new workers were naive to exposure could be determined; and, with ongoing development of tools to evaluate human genetic characteristics, the contribution of genetics could be evaluated. These types of studies may be especially useful in assessing the effects of air toxics. In addition, information on the presence of cofactors such as other environmental chemicals, smoking habit, and infectious respiratory disease would likely be available. Furthermore, specific challenges can be administered to determine if an individual in whom asthma has been induced is indeed sensitive to chemicals that are present in the workplace. In similar fashion, the occupational environment also provides a setting for the evaluation of biomarkers of exposure, effect, or susceptibility that would be useful for validation of laboratory animal models by providing data to establish the degree of human homology. If satisfactory risk estimates could be developed under such a scenario, it could serve as a model for other assessment formulations in places where information may be less abundant.

Research Agenda Items: *Asthma Induction*

- **Improve exposure information for bioaerosols, pesticides, and toxics in focused areas of concern (e.g., indoors, occupational, and agricultural settings).**
- **Develop improved exposure/activity profiles for susceptible populations (e.g., children of asthmatic parents).**
- **Examine induction of asthma in an occupational setting for key chemicals of ambient interest.**

4.3.2. Asthma Exacerbation Associated with Environmental Exposures

Bioaerosols

In order to assess the risk of exacerbation of asthma due to exposure to specific agents, the prevalence of the sensitivity to this agent must be known. This information is likely to be location specific (the quantitatively predominant allergens in a specific region are more likely to be the most significant triggers) or perhaps occupation-specific; whereas, dose-response relationships are likely to have a high degree of variability. Furthermore, asthma exacerbation by specific stimuli typically involves both an early phase (0-3 hours) and a late phase (4-10 hours). The late phase may occur in combination with an early phase, may occur in isolation, or may not occur to any significant degree. The likelihood of occurrence of an early phase, late phase, or the combination is poorly understood and complicates the assessment of the risk posed by specific stimuli. A dose-response assessment for a specific stimulus (e.g., *Stachybotrys* or platinum salts) is only valid for people who are responsive to that stimulus. Additionally, certain non-exposure factors (such as humidity, ventilation systems and their operation) in indoor environments can contribute to the problems caused by bioaerosols. In light of these complicating factors, tools need to be developed that can aid in assessing the risk posed by biological agents. Risk

assessment for exacerbation of asthma by biological agents would only be feasible for the most common allergens causing asthma (e.g., dust mite, cockroaches).

Combustion-Related Products, Pesticides, and Air Toxics

The risk assessment approach for asthma exacerbation will likely be simpler in the case of the non-specific stimuli CRPs, pesticides, and air toxics as compared to that for specific bioaerosols. Although the extent of exposure to agents such as SO_2 and O_3 is well quantified, the breadth of this information in the temporal and spatial domains is limited. For other chemicals, limited dose-response information exists, but the range of doses and the variability of sensitivity among asthmatics to these chemicals is poorly understood. The use of exposure models needs to be expanded to provide estimates of exposure to chemicals for which less extensive data is available. Assessments of combined exposures are also needed in order to assess modifications of dose-response relationships to one chemical by prior, simultaneous, or subsequent exposure to another. Studies controlling for the influence of exercise and cold air on ventilation rates must also be conducted to assess the risk of exposure to specific and non-specific agents. Risk assessment studies for CRPs, pesticides, and air toxics should include the use of activity diaries to better understand the relative contribution of indoor and outdoor agents.

Another factor that must be taken into account in estimating risk of exacerbation of asthma for both specific and non-specific stimuli is the severity of the disease. Little information exists on the variability of response to environmental chemicals across the spectrum of asthma severity. In some cases, environmental exposures, particularly to specific biologic agents, can be life threatening. To assess the risk of life threatening responses to environmental chemicals, much better dose-response information is needed.

Research Agenda Items: *Asthma Exacerbation*

- **Develop risk assessment tools to assess risk of bioaerosols.**
- **Clarify the relationship of asthma severity to dose-response for asthma exacerbation by CRPs, Toxics, and Pesticides.**
- **Collect better data on population exposure and the prevalence of sensitivity.**
- **Evaluate the risks of mixtures of chemicals using data on exposure to mixtures (simultaneous or sequential) in well characterized asthmatics and in validated animal models.**

5. Research Prioritization and Timeline

The research topics identified in this strategy are broad in scope. In anticipation of funding limitations, the following decision-making criteria were used to set research priorities:

Risk-Based Planning:	Research that addresses an element of the risk assessment paradigm and is designed to reduce the greatest uncertainties is of the highest priority.
Scientific Excellence:	The quality of the science selected for support is of critical importance to both the regulatory application of the resulting information and the overall credibility of the Agency.

Programmatic Relevance:	The degree to which a research project addresses a specific statutory requirement will be an important ranking factor.
Research Coordination:	It is important to determine whether research that will provide equivalent or complementary information is underway or planned elsewhere. A high priority will be given to projects that leverage resources within or outside the Agency.
Capabilities and Capacities:	The likelihood that research can be implemented within a reasonable period of time using existing facilities, expertise, and available resources will be considered when ranking competing projects. This criterion applies to work conducted intramurally, as well as in situations where EPA expertise is needed to oversee the completion of work conducted through a cooperative agreement, contract, or grant.
Sequence of Research:	The value of some research, regardless of its priority ranking on other criteria, is dependent upon the completion of other work. Research that is dependent upon completion of otherwise equally ranked work will receive a lower priority. Such time dependency requires that periodic review of progress is made in order to move to the next stage.

5.1. Prioritization Tables

Since this is a research strategy document rather than a research plan, research areas that have been outlined in this document, rather than specific research plans, have been prioritized. This prioritization will be useful in evaluating research proposals written in response to future RFAs (request for applications). Because EPA's mission differs from that of other public health agencies, prioritization decisions made here will depend most significantly on two of the listed criteria: risk-based planning and programmatic relevance. The potential of proposed research to promote human health also will be a strong determinant of assigned priority.

In Tables 1-4, scores were assigned for each research area (Table 1) and topic (Tables 2-4) relative to risk-based planning, programmatic relevance, and public health importance. The scores range from + to +++, signifying a range from lowest to highest importance. The scores were summed to indicate the overall importance of the research area or topic. These scores do not indicate quantitative differences among area/topics, but allow discrimination of rank importance, which is indicated in the last line of each table. These overall rankings informed the scientific discussions about individual asthma research proposals reviewed by the Asthma Research Strategy Team and were used in the final decision process to grade these proposals.

The first step was to assess the relative priority of the three research areas discussed in this document: induction and exacerbation, susceptibility factors, and risk assessment. This approach is shown in Table 1. The scores range from + to +++ signifying a range from lowest to highest in terms of importance of each of the three criteria. The scores reflect the need for data in these research areas and the importance of the risk assessment. Taking these criteria into

account, the importance of the three research areas is as follows: (1) Induction/Exacerbation, (2) Susceptibility Factors, and (3) Risk Assessment.

TABLE 1. PRIORITIZATION OF THE RESEARCH AREAS

Criteria	Induction / Exacerbation	Susceptibility Factors	Risk Assessment
Public Health Importance	+ +	+	+ +
EPA Mission	+ + +	+ +	+ +
Risk-Based Planning	+ +	+ + +	+
Score	7	6	5
Ranking	1	2	3

Table 2 describes the prioritization process as applied to research topics under the induction/exacerbation research area. Prioritization ranks the research topics as (1) CRPs, (2) Bioaerosols, (3) Air Toxics, and (4) Pesticides. CRPs ranked first because of their relevance to EPA's mission and the need for risk assessment data. Bioaerosols on the other hand scored high in terms of the public health importance. Both air toxics and pesticides were judged to be of less importance with respect to asthma-related public health importance.

TABLE 2. INDUCTION / EXACERBATION

Criteria	CRPs	Bioaerosols	Air Toxics	Pesticides
Public Health Importance	+ +	+ + +	+	+
EPA Mission	+ + +	+	+ +	+ +
Risk-Based Planning	+ +	+ +	+ +	+
Score	7	6	5	4
Ranking	1	2	3	4

CRPs = Combustion-Related Products

Table 3 describes the prioritization of research topics under the susceptibility factors research area as (1) Residence and Exposure history, (2) Genetic Susceptibility, (3) Health Status, (4) Lifestyle and Activity Patterns, and (5) Socioeconomic Status. Residence and exposure history ranked highest because of the relatively high programmatic relevance and the need for data for risk assessment overlaid by the fact that it is an important public health issue.

TABLE 3. SUSCEPTIBILITY FACTORS

Criteria	Genetic Susceptibility	Health Status	Socio-conomic Status	Residence/ Exposure History	Lifestyle/ Activity Pattern
Public Health Importance	+ + +	+ + +	++	+ + +	+ +
EPA Mission	+	+	+	+ +	+
Risk-Based Planning	+ + +	+ +	+	+ + +	+ +
Score	7	6	4	8	5
Ranking	2	3	5	1	4

Table 4 describes the prioritization process as applied to research topics induction and exacerbation of asthma under the risk assessment research area. Because very few pollutants are thought to be responsible for the induction of asthma, they are not perceived as a critical public health issue. In contrast, many pollutants are known to exacerbate asthma and, therefore, are a public health threat. As a result, risk assessment for exacerbation of asthma by environmental pollutants ranked higher than risk assessment for induction of asthma.

TABLE 4. RISK ASSESSMENT PRIORITIZATION

Criteria	Induction	Exacerbation
Public Health Importance	+ +	+ + +
EPA Mission	+ +	+ +
Risk-Based Planning	+	+
Score	5	6
Ranking	2	1

5.2. Timeline of Research Activity

The preceding prioritization tables were used to project the sequence and level of effort devoted to the research areas and associated topics (Table 5). The numbers in this timeline indicate the relative level of effort proposed in FY 2001-2009 for each of the research topics within the research areas, with 1 representing the lowest level of effort and 8 representing the highest. These levels, and the total level of effort for each research topic and for each fiscal year, represent arbitrary units. This scale is not intended to be a precise tool for dictating research activity and distribution of resources, but rather is intended as a general guideline indicating how available resources can most efficiently advance scientific knowledge and control environmental factors contributing to asthma prevalence and severity.

TABLE 5. TIMELINE OF RESEARCH ACTIVITY

	FY01	FY02	FY03	FY04	FY05	FY06	FY07	FY08	FY09	Total
CRPs	3	3	7	7	5	6	6	4	2	43
Bioaerosols	2	8	8	6	4	4	4	2		38
Air Toxics	1	1	4	4	3	4	3	1		21
Pesticides			1	2	3	3	1			10
Induction/Exacerbation Total	**6**	**12**	**20**	**19**	**15**	**17**	**14**	**7**	**2**	**112**
Genetic Susceptibility	1	3	4	3	3	3	2	2	2	23
Health/Disease Status		2	2	4	4	3	3	1		19
Socioeconomic Status			1	2	2	2	1			8
Residence, Exp. History	1	2	4	5	4	4	4	2		26
Lifestyle/Activity Pattern				2	3	2	2	1		10
Susceptibility Factors Total	**2**	**7**	**11**	**16**	**16**	**14**	**12**	**6**	**2**	**86**
Induction			2	3	5	5	4	3	3	25
Exacerbation			4	5	6	5	5	3	3	31
Risk Assessment Total	**0**	**0**	**6**	**8**	**11**	**10**	**9**	**6**	**6**	**56**
Total Effort	**8**	**19**	**37**	**43**	**42**	**41**	**35**	**19**	**10**	**254**

The total level of effort for each research topic is consistent with the ranking of the topics in the prioritization tables. Similarly, the total effort for each research area is consistent with the ranking of the areas in Table 1. The level of effort for the research topics in each fiscal year follows a logical sequence in which an early peak effort on bioaerosols (FY 2002-03) is followed by maximal efforts in CRPs and air toxics a year later. Research on susceptibility factors generally peak in FY 2004-05. Since risk assessment research is dependent on data from research conducted in the first two research areas, the level of effort in this area peaks in FY 2005-06 and extends through FY 2009. These guidelines for research funding should provide a balanced and equitable sharing of resources and will facilitate an understanding of how environmental factors contribute to the development and exacerbation of asthma.

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Appendix A

Abbreviations and Acronyms

CAA	Clean Air Act
CDC/NCEH	Centers for Disease Control and Prevention's National Center for Environmental Health
CRP	Combustion related product
ELISA	Enzyme-linked immunosorbent assays
EPA	Environmental Protection Agency
ETS	Environmental tobacco smoke
FY	Fiscal year
GIS	Geographic information system
HAP	Hazardous air pollutant
ICAS	Inner-City Asthma Study
IgE	Immunoglobulin E
IOM	Institute of Medicine
NAAQS	National Ambient Air Quality Standards
NCHS	National Center for Health Statistics
NERL	National Exposure Research Laboratory
NHANES	National Health and Nutrition Examination Survey
NHEERL	National Health and Environmental Effects Research Laboratory
NHLBI	National Heart Lung and Blood Institute
NIAID	National Institute of Allergy and Infectious Diseases
NIEHS	National Institute of Environmental Health Sciences
NIOSH/NORA	National Institute for Occupational Safety and Heath''s National Occupational Research Agenda
NO_2	Nitrogen dioxide
O_3	Ozone
ORD	Office of Research and Development
PM	Particulate matter
PM_{10}	Particulate matter with an aerodynamic diameter $\leq$ 10 μm
$PM_{2.5}$	Particulate matter with an aerodynamic diameter $\leq$ 2.5 μm
RFAs	Request for Applications
SES	Socioeconomic status
SO_2	Sulfur dioxide
VOCs	Volatile organic compounds

Appendix B

U.S. Environmental Protection Agency
Office of Research and Development
Inventory of Asthma Research

Preface to the Appendix

This inventory is a compilation of the asthma research currently funded through intra- and extramural programs within the U.S. Environmental Protection Agency's (EPA) Office of Research and Development (ORD). It was prepared by the Asthma Research Strategy Workgroup and represents the collective efforts of ORD's National Health and Environmental Effects Research Laboratory (NHEERL), National Exposure Research Laboratory (NERL), National Risk Management Research Laboratory (NRMRL), National Center for Environmental Research (NCER), and the National Center for Environmental Assessment (NCEA).

A number of other Federal entities are active in asthma research, including the National Heart Lung and Blood Institute (NHLBI), the National Institute of Allergy and Infectious Diseases (NIAID), the National Institute of Environmental Health Sciences (NIEHS), the Agency for Toxic Substances and Disease Registry (ATSDR), the Centers for Disease Control and Prevention's National Center for Environmental Health (CDC/NCEH), and the National Center for Health Statistics (NCHS). These federal efforts have been summarized in the *Inventory of Federal Asthma Activities* prepared by the Federal Liaison Group on Asthma. Scientists from the EPA are already working with some of these organizations to ensure that EPA research supplements and expands current research efforts into the causes of asthma, asthma triggers, and effective intervention strategies. Additionally, the EPA is represented on various coordinating bodies that address the subject of asthma to enhance other Federal efforts by bringing the expertise and facilities unique to the EPA to previously-initiated asthma research.

This inventory is organized by the source of funding: specific intramural research projects are presented first, followed by extramural research grants and fellowships funded through the program *Science to Achieve Results* (STAR) and, lastly, by other ORD research on ambient air pollutants that takes into consideration health risks to sensitive subpopulations with asthma.

Introduction

Conducting research on asthma is consistent with the mission of the EPA to protect public health and safeguard the natural environment—air, water, and land—upon which life depends. The EPA ORD is committed to supporting the principles outlined in the Federal strategy: (1) eliminating the disproportionate impact of asthma on minorities and the poor; (2) increasing reliance on community-based programs and partnerships to successfully implement effective environmental, medical, and educational programs; (3) setting measurable and consistent goals for childhood asthma as set forth in the Healthy People 2010 program; and (4) identifying strategies that are effective in reducing asthma so they may be implemented. In addition, the ORD recognizes the need to address environmentally related aspects of asthma as they apply to adults.

The following asthma research to be conducted by the ORD focuses on the three primary areas identified in the *Asthma Research Strategy*: (1) induction and exacerbation of asthma, (2) susceptibility factors contributing to asthma induction or exacerbation, and (3) risk assessment. Specific agents studied will include bioaerosols, pesticides, hazardous air pollutants and combustion related products. Factors to be evaluated for their influence on susceptibility include genetic susceptibility, health status, socio-economic status, residence and exposure history, and lifestyle.

ORD Intramural Asthma Research Program

The three national laboratories (NHEERL, NERL, NRMRL) and the NCEA within the ORD are undertaking an intramural asthma research program (see Table B-1) to characterize the role of various environmental factors (e.g., molds and gaseous and particulate pollutants) in asthma and to better understand the mechanisms of allergic sensitization and asthma exacerbation. The general hypothesis is that environmental factors influence asthma onset and exacerbation and that these factors can be controlled. The program will also assess the relative role these pollutants play in the indoor versus outdoor environments and study the efficacy of various intervention protocols. Several projects address adult populations as part of epidemiological studies and in controlled clinical exposure studies. Children are specifically targeted in various epidemiology studies around the U.S. The ORD is a partner in the Inner City Asthma Study (ICAS), a multi-center intervention trial among moderate to severe asthmatic children in seven cities, through an Interagency Agreement with two NIH institutes, the National Institute of Allergy and Infectious Diseases and the National Institute for Environmental Health Sciences.

National Center for Environmental Research: Science to Achieve Results Grants Program

The mission of the NCER within the ORD is to stimulate the research community to provide high quality, innovative ideas and solutions to protect human health and the environment. The NCER program, *Science to Achieve Results* (STAR), funds research grants and fellowships in environmental science and engineering.

In 1998, NCER began a five-year partnership with the National Institute of Environmental Health Sciences (NIEHS) and the Centers for Disease Control and Prevention (CDC) to sponsor

eight Centers for Children's Environmental Health and Disease Prevention Research (see Table B-2). The centers have undertaken multi-disciplinary basic and applied research in combination with community-based prevention research. These efforts support studies on the causes and mechanisms for children's disorders having an environmental etiology, including asthma and respiratory illnesses. One program investigates how exposures to environmental pollutants and allergens exacerbate asthma and relate to other lung diseases in children living in the inner city, while another is studying causes of airway disease in children from rural communities. Research on effective neighborhood and household interventions to reduce risks of asthma is also an important focus of the centers' program. In addition to the centers' grants, NCER, in partnership with NIEHS, is supporting two environmental justice grants to develop effective community-based environmental interventions to help combat asthma in the urban environment.

Another major priority for the STAR program has been research related to particulate matter air pollution. Particulate matter (PM) is the general term used for a mixture of solid particles and liquid droplets found in the air. Particulate matter exists in a wide range of sizes (from fine to coarse) and originates from many different stationary and mobile sources, as well as from natural sources. Fine particles can accumulate in the respiratory system and are associated with numerous health effects including the aggravation of asthma. In recognition of this potential public health problem, NCER awarded five-year funding to five university-based PM Research Centers which are undertaking integrated programs of health research (see Table B-3). Exposure studies are being conducted to better understand and characterize personal exposures to PM (e.g., size and composition of PM, indoor air versus outdoor air contribution). Controlled clinical studies in humans and animal toxicology studies will help identify the constituents or properties of PM that are most responsible for human health effects and help explain how these effects occur. The research centers also are developing dosimetry models that take into account the amount of PM deposited into the lungs of exposed individuals. This will help elucidate the relationship between personal exposure to PM and the health responses of sensitive populations, such as those with asthma. In addition, epidemiological studies are underway to examine the health effects of PM exposure in susceptible subpopulations.

In addition, the STAR program has awarded a number of individual grants to investigators examining environmental influences on asthma (see Table B-4). Examples range from the relationship between exposure to PM and exacerbation of asthma to effective means of controlling dust mites, a cause of asthma in susceptible individuals. For more information on the NCER grants programs, visit the web site: http://es.epa.gov/ncerqa/.

EPA Ambient Air Research

The EPA is funding three research centers to conduct ambient air research on the induction and exacerbation of asthma in the population (see Table B-5). Specific studies include effects of PM on childhood asthma and the induction of airway inflammation, mechanisms of environmental lung diseases, and the effects of air toxics on people with preexisting respiratory problems including asthma.

The EPA is conducting a risk analysis for PM as part of the National Ambient Air Quality Standards (NAAQS) review. As part of the total risk assessment, the review includes a look at hospital admissions for respiratory causes and the risk of asthma symptoms for children exposed

to ambient particulate matter. The EPA also anticipates conducting a risk assessment for the ozone NAAQS review, which will include looking at the increased risk of childhood asthma at higher ambient ozone levels.

In addition, the EPA is conducting research on sulfur dioxide (SO_2), a suspected asthma trigger. As announced in the Federal Register on January 9, 2001, the EPA plans to propose an integrated monitoring strategy to revise the minimum requirements for ambient monitoring in compliance with the SO_2 NAAQS. The EPA also intends to issue SO_2 monitoring guidelines to assist state and local air pollution control agencies in evaluating their networks and the appropriateness of revising such networks to better address the issue of short-term (five minutes) peaks of SO_2 that have been shown to cause breathing difficulty in sensitive people with asthma. Finally, the EPA is seeking support and participation from the states and industry to develop plans for collecting additional five-minute air quality monitoring data. This effort is expected to take about two years including planning, coordination, data collection, and analysis and to provide important new information on the likelihood and nature of five-minute peak SO_2 concentrations that may occur around various types of industrial facilities. The monitoring information will help inform decisions in the next periodic review of the SO_2 NAAQS.

Healthy People 2010 Objectives:

24-2 Hospitalizations for asthma
24-3 Hospital emergency department visits for asthma
24-7 Appropriate asthma care

EPA Contacts:

Mary Smith, OECA/ORE/AED, representative for EPA asthma programs and interagency committees
Jim Raub, ORD/NCEA/NCEA-RTP, representative for ORD asthma research strategy and tracking

TABLE B-1. ORD INVENTORY OF INTRAMURAL ASTHMA RESEARCH PROJECTS

Project Title	OMIS Task No.[1]	Status	Lab/Center[2]	Investigators	Project Period
1. Develop test methods to access the potential allergenicity of environmental contaminants	126	Active	NHEERL	Selgrade, MJ	
2. Characterization of the allergenicity of *Stachybotrys chartarum* and other molds in the indoor environment and risks to children	126	Active	NHEERL NERL	Selgrade, MJ; Ward, M Vesper, S	
3. Influence of environmental factors on allergic sensitization to dust mite allergy	126	Active	NHEERL	Gilmour, I	
4. Enhancement of allergic responses in mice by particulate matter	131	Active	NHEERL	Gavett, S	1998-2002
5. Interactions of particulate matter air pollution with lung sensory nerves	131	Pending postdoc	NHEERL	Gavett, S	1999-2001
6. Neurophysiology links between sensory irritation and cardiac function	131	Active	NHEERL	Costa, D	1999-2002
7. Effect of allergen challenge on surfactant function and oxygen saturation	131	Active	NHEERL	Wiester, MJ	
8. Use of induced sputum to determine differences in response of normal and asthmatic subjects	115	Active	NHEERL	Devlin, R	
9. Exposure of asthmatics to concentrated ambient particles (CAPS)	115	Active	NHEERL	Kehrl, H	
10. Differences in gene expression between cells from normal and asthmatic subjects	115	Active	NHEERL	Devlin, R	
11. Exacerbation of asthma by particulate matter	1434	Active	NHEERL	Neas, L	
12. National Children's Study		Pending start-up	NHEERL	Mendola, P	

TABLE B-1 (cont'd). ORD INVENTORY OF INTRAMURAL ASTHMA RESEARCH PROJECTS

Project Title	OMIS Task No.[1]	Status	Lab/Center[2]	Investigators	Project Period
13. Effects of short-term ozone exposure upon asthma status	391	Completed	NHEERL	McDonnell, W	
14. Long-term ozone exposure and incidence of asthma in adults	391	Completed	NHEERL	McDonnell, W	
15. Long-term exposure to air pollutants and incidence of respiratory disease in children	391	Active	NHEERL	McDonnell, W	
16. Short-term exposure to ozone and rates of hospitalization	391	Active	NHEERL	McDonnell, W	
17. A pilot home asthma intervention study in Boston public housing	5542	Completed	NRMRL	Howard, B	1999-2002
18. Characterization of indoor VOC/air toxics emissions from sources controlled by internal diffusion	5543	Active	NRMRL	Chang, J	
19. Ability to reduce indoor exposure to VOC air toxics from photocopiers through judicious selection of toner	3848	Active	NRMRL	Henschel, DB	1999-2002
20. Development of guidance to reduce the exposure of children with respiratory problems to airborne irritants while in school ("Buy Clean")	6381	Active	NRMRL	Henschel, DB	2000-2002
21. Performance of ozone generators sold as indoor air cleaners, and the potential role of ozone in creating air toxics through indoor air chemistry	4910 9744	Active	NRMRL	Mason, M	1998-2003
22. Home design and operation to reduce exposure of occupants to fine PM infiltrating from outdoors	2127	Active	NRMRL	Mosley, R	1997-2002

TABLE B-1 (cont'd). ORD INVENTORY OF INTRAMURAL ASTHMA RESEARCH PROJECTS

Project Title	OMIS Task No.[1]	Status	Lab/Center[2]	Investigators	Project Period
23. Characterization of indoor fine PM emission sources	5547	Active	NRMRL	Guo, Z	1999-2002
24. Impact of home construction, operation, and furnishings on occupant exposure to gaseous combustion-related pollutants (CRPs) infiltrating from outdoors	11191	Pending start-up	NRMRL	Mosley, R	2002-2003
25. Effectiveness of air cleaners for reducing risk from indoor pollutants	9746	Pending start-up	NRMRL	Sparks, L	2001-2003
26. Source characterization and risk management options to reduce airborne exposure to *Stachybotrys chartarum* and other microbiologicals	6171	Active	NRMRL	Menetrez, M	1999-2003
27. Risk management options for indoor microbiologicals	6382	Pending start-up	NRMRL	Menetrez, M	2001-2002
28. Development and demonstration of improved methods for sampling and analysis of fine indoor bioaerosols, and assessment of the extent to which indoor bioaerosols infiltrate from outdoors	9748	Active	NRMRL	Menetrez, M	2001-2002
29. Validation of improved methods for sampling and analysis of fine indoor bioaerosols for use as a protocol for the National Children's Study		Pending start-up	NRMRL	Menetrez, M	2002-2003
30. Risk assessment and risk management for indoor mold	80201	Active	NERL NCEA-WA NHEERL NRMRL	Vesper, S	1999-2001
31. Ambient PM exposure and respiratory health in four Chinese cities		Active	NCEA-RTP	Chapman, R	

TABLE B-1 (cont'd). ORD INVENTORY OF INTRAMURAL ASTHMA RESEARCH PROJECTS

Project Title	OMIS Task No.[1]	Status	Lab/Center[2]	Investigators	Project Period
32. Effect of endogenous nitric oxide production on ozone exposure dosimetry and response in asthmatic subjects		Active	NCEA-RTP UNC/CEMLB	Raub, J	1998-2001

[1] ORD Management Information System (OMIS)

[2] Key to ORD Laboratories and Centers: NHEERL = National Health and Environmental Effects Research Laboratory; NERL = National Exposure Research Laboratory; NRMRL = National Risk Management Research Laboratory; NCEA = National Center for Environmental Assessment.

TABLE B-2. EPA/NIEHS CENTERS OF EXCELLENCE IN CHILDREN'S ENVIRONMENTAL HEALTH AND DISEASE PREVENTION RESEARCH: Asthma Research Projects[1]

Project Title	EPA Grant	Status	Center	Investigators/Institutions	Project Period
1. Asthma in children: a community-based intervention project	R826708	Active	Children's Environmental Health Center	Gong, H; Jones, C; McConnell, R (University of Southern California)	1998-2002
2. Children's susceptibility to air pollution	R826708	Active	Children's Environmental Health Center	Gong, H; Jones, C; McConnell, R (University of Southern California)	1998-2002
3. Children's exposure to environmental tobacco smoke: changes in allergic response	R826708	Active	Children's Environmental Health Center	Gong, H; Jones, C; McConnell, R (University of Southern California)	1998-2002
4. Multi-component intervention study of asthma in children from rural communities	R826711	Active	Airway Disease in Children from Rural Communities	Schwartz, D; Merchant, J (University of Iowa)	1998-2002
5. Mechanisms that initiate, promote, and resolve grain dust/LPS- induced inflammation	R826711	Active	Airway Disease in Children from Rural Communities	Schwartz, D; Merchant, J (University of Iowa)	1998-2002
6. Role of RSV infection and endotoxin in airway inflammation	R826711	Active	Airway Disease in Children from Rural Communities	Schwartz, D; Merchant, J (University of Iowa)	1998-2002
7. A model to study the development of persistent environmental airway disease	R826711	Active	Airway Disease in Children from Rural Communities	Schwartz, D; Merchant, J (University of Iowa)	1998-2002
8. A community-based intervention to reduce environmental triggers for asthma among children	R826710	Active	Michigan Center for the Environment and Children's Health	Israel, B; Parker, E (University of Michigan)	1998-2002
9. Indoor and outdoor air contaminant exposures and asthma aggravation among children	R826710	Active	Michigan Center for the Environment and Children's Health	Israel, B; Parker, E (University of Michigan)	1998-2002
10. Chemokines in the pathogenesis of asthma	R826710	Active	Michigan Center for the Environment and Children's Health	Israel, B; Parker, E (University of Michigan)	1998-2002

TABLE B-2 (cont'd). EPA/NIEHS CENTERS OF EXCELLENCE IN CHILDREN'S ENVIRONMENTAL HEALTH AND DISEASE PREVENTION RESEARCH: Asthma Research Projects[1]

Project Title	EPA Grant	Status	Center	Investigators/Institutions	Project Period
11. A randomized, controlled trial of home exposure control in asthma	R826724	Active	The Johns Hopkins University Center for the Asthmatic Child in the Urban Environment	Eggleston, P (Johns Hopkins University)	1998-2002
12. The relationship of airborne pollutants and allergens to asthma morbidity	R826724	Active	The Johns Hopkins University Center for the Asthmatic Child in the Urban Environment	Eggleston, P (Johns Hopkins University)	1998-2002
13. Mechanisms of particulate-induced allergic asthma	R826724	Active	The Johns Hopkins University Center for the Asthmatic Child in the Urban Environment	Eggleston, P (Johns Hopkins University)	1998-2002
14. Genetic mechanisms of susceptibility to inhaled pollutants	R826724	Active	The Johns Hopkins University Center for the Asthmatic Child in the Urban Environment	Eggleston, P (Johns Hopkins University)	1998-2002
15. Community-based intervention: reducing risks of asthma	R827027	Active	Columbia Center for Children's Environmental Health	Perera, F (Columbia University)	1998-2002
16. Research on asthma: prenatal and postnatal environmental exposure	R827027	Active	Columbia Center for Children's Environmental Health	Perera, F (Columbia University)	1998-2002
17. Research project on growth and development	R827027	Active	Columbia Center for Children's Environmental Health	Perera, F (Columbia University)	1998-2002
18. The epidemiological investigation of the effects of pesticide exposure on neurodevelopment, growth, and respiratory health of farmworker children	R826709	Active	Center for Research on the Exposures and Health of Farm Worker Children in California	Eskenazi, B (University of California at Berkeley)	1998-2002

[1] ORD Management Information System (OMIS) No. 4924.

TABLE B-3. ORD/NCER PARTICULATE MATTER RESEARCH CENTERS: Asthma Research Projects[1]

Project Title	EPA Grant	Status	Center	Investigators/Institutions[2]	Project Period
1. Asthma exacerbation study: PM enhancement of the antigen-specific IgE response	R827352	Active	Southern California Center for Airborne Particulate Matter	Froines, JR; Colome, SD; Turco, RP (UCLA, UCI, and UCR; CIT; USC, RLAMC)	1999-2004
2. Allergic inflammation study: adjuvant effects of PAH and redox-active quinones in PM	R827352	Active	Southern California Center for Airborne Particulate Matter	Froines, JR; Colome, SD; Turco, RP (UCLA, UCI, and UCR; CIT; USC, RLAMC)	1999-2004
3. Airborne PM and quinone study: reaction with tissue nucleophiles	R827352	Active	Southern California Center for Airborne Particulate Matter	Froines, JR; Colome, SD; Turco, RP (UCLA, UCI, and UCR; CIT; USC, RLAMC)	1999-2004
4. Comprehensive exposure and health effect assessment in susceptible subpopulations	R827355	Active	Northwest Research Center for Particulate Air Pollution and Health	Koenig, JQ; Liu, L-J; Covert, DS; Claiborn, C (University of Washington; Washington State University)	1999-2004
5. Ultrafine particle: characterization, health effects, and pathophysiological mechanisms: clinical studies	R827354	Active	Rochester PM Center (U. of Rochester; CIT; UCR; GSF- NRCEH; RTI; SUNY at Buffalo; UNM)	Utell, M; Frampton, M (University of Rochester)	1999-2004
6. Ultrafine particle: characterization, health effects, and pathophysiological mechanisms: in vitro mechanisms	R827354	Active	Rochester PM Center	Finkelstein, J	1999-2004
7. A prospective study of asthma susceptibility to PM: epidemiologic investigations of key PM components and biomarkers of effects	R827351	Active	New York University PM Center	Thurston, GD; Reibman, J (New York University)	1999-2004
8. Ambient particle effects: exposure, susceptibility, and mechanisms	R827353	Active	Harvard PM Center	Koutrakis, P; Godleski, JJ; Schwartz, J et al. (Harvard University)	1999-2004

[1] ORD Management Information System (OMIS) No. 6044

[2] Key to Institutions: UCLA = University of California at Los Angeles, UCI = University of California at Irvine, UCR = University of California at Riverside, CIT = California Institute of Technology, USC = University of Southern California, RLAMC = Rancho Los Amigos Medical Center,GSF-NRCEH = GSF- National Research Center for Environment and Health (Neuherberg, Germany), RTI = Research Triangle Institute, SUNY = State University of New York, UNM = University of New Mexico.

TABLE B-4. SCIENCE TO ACHIEVE RESULTS (STAR) GRANTS: Air Pollution Research Projects on Asthma

Project Title	EPA Grant	OMIS Task No.[1]	Status	Institutions	Investigators	Project Period
1. Particulate air pollution and initiation of asthma	R826779	4918	Active	Harvard University	Kobzik, L; Koutrakis, P; Shore, S; Gonzalez-Flecha, B	1998-2001
2. Mechanisms of age-dependent ozone induced airway dysfunction	R827447	5625	Active	Harvard School of Public Health	Shore, S	1999-2002
3. School-based study of complex environmental exposures and related health effects in children: Part A-exposure	R825813	2310	Active	University of Minnesota	Sexton, K; Adgate, J; Greaves, I; Church, T; Ramachandran, G	1998-2001
4. Health effects of HAPs among inner urban school children	R826789	4917	Active	School of Public Health, University of Minnesota	Greaves, I; Sexton, K; Church, T; Adgate, J	1998-2001
5. Human health effects of exposure to ultrafine particles	R826781	4918	Active	University of Rochester School of Medicine and Dentistry	Frampton, M; Utell, M; Oberdorster, G; Marder, V; Zareba, W	1998-2001
6. Airborne particulate matter-induced lung inflammation	R826782	4918	Active	University of Texas, Houston Health Science Center	Holian, A; Morandi, MT; Parsley, E	1998-2001
7. Effects of inhaled ultrafine particles on asthma	R826785	4918	Active	Lovelace Respiratory Research Institute	Bice, DE; Redman, TK; Nikula, KJ; Barr, EB; Cheng, YS	1998-2001
8. Ultrafine particles in urban and respiratory health among children with respiratory symptoms	R825265	1021	Active	Harvard University	Schwartz, J	1996-1999
9. Factors controlling the dust mite population in the indoor environment	R825250	1255	Completed 11-30-00	Wright State University	Arlian, LG	1997-2000
10. Effect of ammonium bisulfate and carbon black particles inhaled alone and in combination on airway reactivity in sensitized brown Norway rats	R826778	4918	Completed 4-30-01	Lovelace Respiratory Research Institute	Benson, JM; Cheng, Y-S; Powell, QH; Bice, DE; Barrett, EG	1998-2001
11. Acidic PM and daily human mortality in three U.S. cities	R825264	1021	Completed 11-17-00	New York University School of Medicine	Thurston, G; Ito, K; Gwynn, RC; Lall, R; Lippmann, M	1996-2000
12. Cellular mechanisms of pulmonary inflammation by environmental particles	R824790		Completed 9-30-99	Harvard School of Public Health	Kobzik, L; Shore, S; Godleski, J	1996-1999

TABLE B-5. TARGETED RESEARCH CENTERS: Air Pollution Research Projects on Asthma

Project Title	EPA Grant	OMIS Task No.[1]	Status	Institution	Investigators	Project Period
1. Acute exposure to particulate air pollution and childhood asthma	R824702	2307	Active	National Jewish Medical and Research Center	Mason, R; Rabonovitch, N; Worthen, S; Gelfand, E.; White, C.	1998-2002
2. Asthma-related projects: particle-induced lung inflammation; effects of diesel particles on development of allergic asthma; role of SP-A and SP-D; mechanism of NO_2 toxicity	R824702	2307	Active	National Jewish Medical and Research Center	Mason, R; Rabonovitch, N; Worthen, S; Gelfand, E.; White, C.	1998-2002
3. Effects of urban air toxics in an elderly population of asthmatics		2087	Active	Mickey Leland National Urban Air Toxics Research Center	Campion, R	2001-2004
4. Health effects of environmental pollutants and mechanism of disease	R828112	1235	Active	Health Effects Institute	Greenbaum, D	2000-2005

[1] ORD Management Information System (OMIS).

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