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A Review of the Impacts of Climate Variability and Change on Aeroallergens and Their Associated Effects

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PREFACE

The Environmental Protection Agency's Global Change Research Program (GCRP) is an assessment-oriented program within the Office of Research and Development that focuses on assessing how potential changes in climate and other global environmental stressors may impact air quality, water quality, ecosystems, and human health in the United States. The Program's focus on human health is consistent with the *Strategic Plan* of the U.S. Climate Change Science Program—the federal umbrella organization for climate change science in the U.S. government—and is responsive to the research agenda developed in the Health Sector Assessment of the First National Assessment of the Potential Consequences of Climate Variability and Change on the U.S.

Since 1998, the National Center for Environmental Assessment within the Office of Research and Development has assessed the consequences of global change on weather-related morbidity, on vector- and water-borne diseases, and on airborne allergens and ambient pollutants, especially tropospheric ozone and fine particles. Through its assessment projects, this Program has provided timely scientific information to stakeholders and policy makers to support them as they decide whether and how to respond to the risks and opportunities presented by global change.

Because health is affected by a variety of social, economic, political, environmental, and technological factors, assessing the health impacts of global change is a complex challenge. As a result, health assessments in the Global Change Research Program look beyond epidemiological and toxicological research to develop integrated health assessment frameworks that consider the effects of multiple stresses, their interactions, potential adaptive responses, and location-specific impacts. This report assesses the state of the scientific literature and examines the potential effects of climate variability and change on aeroallergens and their associated health outcomes in the United States.

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EXECUTIVE SUMMARY

This report presents a survey of the current state of knowledge of the potential impacts of climate change and variability on aeroallergens – pollens, mold, and indoor allergens – in the United States and the allergenic illnesses associated with them. Allergies are highly prevalent in the U.S. and impose substantial economic and quality-of-life burdens. A recent nationwide survey reported that 54.6 percent of people in the U.S. test positive for one or more allergens (American Academy of Allergy Asthma and Immunology, 1996-2005). Among specific allergens, dust mite, rye, ragweed, and cockroaches caused sensitization in approximately 25 percent of the population (Arbes et al., 2005).

Allergies are the sixth most costly chronic disease category in the United States, collectively costing the health care system approximately $21 billion annually (American Academy of Allergy Asthma and Immunology, 1996-2005). The three main allergenic illnesses that have been associated with exposure to aeroallergens – allergic rhinitis (hay fever), asthma, and atopic dermatitis (eczema) – individually impose large economic burdens. The direct medical costs of asthma and allergic rhinitis (hay fever) are estimated to be $12.5 billion and $6.2 billion per year, respectively (in 2005 dollars, American Academy of Allergy Asthma and Immunology, 1996-2005); the direct medical costs of atopic dermatitis (eczema) are estimated to be $1.2-$5.9 billion per year (in 2005 dollars) (Ellis et al., 2002).

While limited data suggest that aeroallergen levels have apparently so far remained relatively stable, the prevalence of allergenic illnesses in the U.S. has increased over the last 30 years, a trend that appears to be mirrored in other countries as well. The causes of this upward trend are as yet unclear. Because the economic impacts of allergenic illnesses associated with aeroallergens and the quality-of-life impacts on those individuals who suffer from them are already substantial, any climate change-induced enhancement or continuation of this trend in the United States would be of particular concern.

General predictions of climate change and its potential impacts on aeroallergens

Although climate change prediction is still considered an uncertain science, there have been many attempts to derive future climate scenarios, based on projected concentrations of greenhouse gases and models that simulate atmospheric circulation. The United Nations Intergovernmental Panel on Climate Change (IPCC) projects that by the year 2100 the average

global temperature may rise by 2.0°C, within a range of 1.4 to 5.8°C over the period 1990 to 2100 (Climate Change 2001: Synthesis Report, p. 8). Along with increasing temperatures, other effects of climate change, such as changes in precipitation and increases in extreme weather events, have also been anticipated. These changes, including increased CO_2 concentrations, could impact the production, distribution, and dispersion of aeroallergens along with the allergen content and the growth and distribution of the weeds, grasses, trees, and mold that produce them. Shifts in aeroallergen production and, subsequently, human exposures, may result in changes in the severity and possibly prevalence of symptoms in individuals with allergenic illnesses.

The literature does not provide definitive data or conclusions, however, on how climate change might impact aeroallergens and subsequently the severity or prevalence of allergenic illnesses in the U.S. This is in part because studies are of necessity often narrowly defined, and a single study is unlikely to encompass the broad subject of weather, aeroallergens, and allergenic illness. There is also an inherent uncertainty as to how the climate will change, especially at a regional level. In addition, the etiology of allergic diseases, especially asthma, is complex and has a gene environment interaction that is poorly understood. Finally, there are numerous other factors that affect aeroallergen levels and the severity and prevalence of associated allergenic illnesses, such as changes in land use, air pollution, adaptive responses, and modifying factors, many of which are difficult to assess.

Nevertheless, some tentative conclusions can be drawn about the potential impact of climate change on aeroallergens and the associated allergenic illnesses through inferences regarding the links between (1) climate change and the characteristics of aeroallergens and (2) those aeroallergen characteristics and the associated allergenic illnesses. Projections for the global climate change models utilized by the National Assessment Synthesis Team suggest that possible changes in annual precipitation across the U.S. are generally mixed. Results from the two models used in the National Assessment tend to agree that there is likely to be an increase in precipitation in the southwestern U.S. as Pacific Ocean temperatures increases, but do not provide a clear indication of the trend in the southeastern U.S (MacCracken et al., 2001).

Other research has shown that preseason temperature and precipitation have been consistently important predictors of pollen and mold production. Overall, experimental and observational data as well as models indicate the following likely changes in aeroallergen production, distribution, dispersal, and allergen content as a result of climate change in the United States:

- Pollen production is likely to increase in many parts of the United States, with the possible exception of the Southeast;

- Phenologic advance is likely to occur for numerous species of plants, especially trees (Root et al., 2003);

- There will likely be changes in the distribution of pollen producing species, including the possibility of extinction in some cases (Joyce et al., 2001);

- Intercontinental dispersal (e.g., of pollen) is possible, facilitating the introduction of new aeroallergens into the United States (Husar et al., 2001); and

- Increases in allergen content, and thus, potency, of some aeroallergens are possible (Beggs, 2004; Beggs and Bambrick, 2005).

Research on the potential effects of climate change on tree and grass pollen production in the United States is limited. In general, the literature to date suggests that preseason temperature and precipitation are important predictors of both tree and grass pollen production. To the extent that climate change results in changes in these two meteorological variables, then, we would expect corresponding changes in tree and grass pollen production, all else equal. The evidence to date suggests that the nature of the changes may be region and species-specific. Although this does not necessarily imply increased pollen production, a consistent finding from international research is earlier start dates for pollen seasons, especially in trees (Clot, 2003).

Among weed pollens, common ragweed (*Ambrosia artemisiifolia* L.) is recognized as a significant cause of allergic rhinitis (hay fever) in the U.S. and there is relatively more research on the response of this weed to climatic variables, especially in the context of climate change. Several researchers have used controlled environments to examine ragweed response to carbon dioxide levels and temperature, the two covariates for which models reliably predict increased levels in the future. The experimental results have consistently demonstrated that doubling carbon dioxide levels from current (350 umol/mol) to predicted future levels (700 umol/mol) would result in a 60 to 90 percent increase in ragweed pollen production (Ziska and Caufield, 2000; Wayne et al., 2002). A field study demonstrated ragweed grew faster, flowered earlier, and produced significantly greater aboveground biomass and ragweed pollen at urban locations than at rural locations (Ziska et al., 2003). Because urban locations are warmer and have higher concentrations of CO_2 than rural locations, all else equal, this may have implications for the impact of climate change on ragweed pollen production overall. In summary, studies of ragweed

in controlled environments and in field studies clearly show that pollen production can be expected to increase with increased temperature and carbon dioxide levels.

There is limited but inconsistent evidence of increasing trends in mold production. Assessment of mold production in response to climate change is derived mainly from observational analyses of long-term data sets. An analysis in Denver, Colorado showed *Cladosporium* increasing, but not co-occurring mold such *Alternaria* or *Epicoccum* (Katial et al., 1997). An observational study in Derby, UK showed *Alternaria* increasing (Corden and Millington, 2001). Another U.S. study observed increases in mold counts after an El Niño event (Freye, 2001). It is unclear whether climatic factors have any impact on mold production or what other mechanisms may be responsible for variations observed locally.

Long-term responses to climate change (over 50 to 100 years) are likely to include species' range or distribution shifts, and in some cases possible extinction. Some ecological models suggest that the potential habitats, and thus distribution, for many tree species in the U.S. are likely to change, in some cases dramatically, by the end of the 21st century. Trees favoring cool environments, such as maple and birch, are likely to shift northward, possibly out of the U.S. entirely, thus altering the pollen distribution associated with them (Joyce et al., 2001). The habitats of alpine, subalpine spruce/fir, and aspen communities are likely to contract significantly in the U.S. and largely shift into Canada (Joyce et al., 2001). Potential habitats for oak/hickory, oak/pine, ponderosa pine, and arid woodland communities are likely to increase in the U.S. (Joyce et al., 2001). Under certain model scenarios, the Southeast will experience significant warming trends leading to an expansion of savannas and grasslands at the expense of forest, again altering the presence of major aeroallergens in large regions of the country Note however, conclusions about projected shifts in the distribution of major vegetation types, as plant species move in response to climate change, depends on an implicit assumption in the biogeography models that assume vegetation will be able to move freely from location to location. This assumption "may be at least in part unwarranted because of the barriers to plant migration that have been put in place on landscapes through agricultural expansion and urbanization (Melillo et al., 2001, p. 82)."

There has been only limited research on how climate change could affect the dispersal of pollen and mold, but there are cases of both pollen and dust being dispersed long distances from their release sites, and the frequency of such cases may be increased by climate change. One study, for example, suggests that in Europe increased strength of westerly winds due to climate change will enhance the long-range transport of birch pollen already observed to take place from

north and central Europe to Scandinavia (Emberlin, 1994). Transcontinental transport of dust particulates has also been observed. To the extent that climate change increases the frequency of weather events that facilitate such transcontinental transport, it could increase the likelihood of additional aeroallergens being introduced into the United States. Whether long-range transport of pollen may instead decrease aeroallergen concentration and distribution so as to decrease human exposures has not been reported.

The links to allergenic illnesses

Shifts in phenology are one of the most consistent findings in studies of plant pollen production. Alterations in the timing of aeroallergen production in response to weather variables have been clearly demonstrated for certain tree species, but less so for grass and weed pollens and mold. Analyses of trends in allergenic illness are based on annual prevalence and generally do not document the seasonal timing of these illnesses within the year. In sensitized individuals, however, exposure clearly leads to allergic response; thus it is reasonable to expect that changes in the timing of production of seasonal aeroallergens would result in corresponding changes in the timing of the associated seasonal allergenic illness. Thus the NAST (Bernard et al., 2001) notes that climate change may affect the timing or duration of seasonal allergies such as hay fever. However, shifts in the timing of asthma and atopic dermatitis in response to changes in phenology are not as predictable.

Increases in aeroallergen production and/or allergen concentration could impact the severity and possibly prevalence of allergenic illness via sensitivity and response pathways. On the basis of model projections by the NAST (Mellilo et al., 2001), pollen production, and possibly allergen content, in many areas of the country will increase at least through the mid-21st century. Exposures to higher concentrations of allergens may lead to more severe allergic responses (Nielsen et al., 2002). In addition, exposure to elevated pollen and mold concentrations during sensitization may lead to a greater likelihood of development of allergies such as rhinitis. Finally, as noted above, additional aeroallergens might be introduced if long-range transcontinental transport of pollens and/or mold is facilitated by climate change-induced factors.

Although there is substantial evidence suggesting a causal relationship between aeroallergens and allergenic illnesses, it remains unclear which aeroallergens are more highly associated with causing sensitization and subsequent disease development primarily because of the cross-reactivity of aeroallergens – the ability of two or more aeroallergens, due to

biochemical similarities, to elicit an allergic response in an individual who may be sensitized to only one of them. Multiple studies have found cross-reactivity among the aeroallergens implicated in causing allergenic illnesses.

Not only the type, but also the amount of aeroallergen to which an individual is exposed is influential in the development of an allergenic illness. Similar to what is observed in most disease causation scenarios, a dose-response relationship between aeroallergen exposure and sensitization and exacerbation of disease has been observed – i.e., sensitized patients are more likely to have more severe disease if exposure to allergens is high.

There are thus at least three causal pathways for climate change-induced impacts on aeroallergens to alter the severity and possibly the prevalence of allergenic diseases. First, a longer exposure during sensitization may lead to greater likelihood of the development of allergy. Second, a higher dose during sensitization may lead to a greater likelihood of development of an allergy. Third, a higher dose during subsequent exposures (post-sensitization) may lead to a more severe allergic response.

However, as noted earlier, the etiology of allergic diseases, especially asthma, is complex and has a gene-environment interaction that is poorly understood. There are numerous other factors that affect aeroallergen levels and the severity and prevalence of associated allergenic illnesses, such as changes in land use, air pollution, adaptive responses, and modifying factors, many of which are difficult to assess.

Future research

Further progress must be made in documenting and understanding aeroallergen response to climate, the role of aeroallergens in disease development, and the willingness to pay to avoid the intangible costs of these allergic diseases. A review of the literature indicates there is limited data on aeroallergen trends in the United States. Integrated long-term data series on all aeroallergens is necessary to clearly document future changes in aeroallergen production and distribution, as well as allergen content. Additional research on the response of mold and indoor allergens to climate change would be of particular value. In addition, further experimental and field studies are needed to examine how allergen content and distribution of aeroallergens may be altered in response to climate change (Beggs, 2004).

There is a need for better understanding of the role of aeroallergens in disease development, especially asthma. Specifically, what is the relative contribution of different aeroallergens to the development of asthma? There is a need to know what levels of allergen

exposure constitute a risk for asthma development. There is also a need for standardized approaches for measuring exposures and outcomes in epidemiologic studies (Selgrade et al., 2006). Finally, the potential synergistic effects of aeroallergens and air pollutants on the development or exacerbation of allergenic illnesses is an important area for future research.

Based on a review of the cost of illness (COI) literature on allergic rhinitis, asthma, and atopic dermatitis, it is clear that an important research gap is the current lack of assessment of – and, in particular, estimation of willingness to pay to avoid – the intangible costs of these diseases. In addition, better methodologies are needed to address productivity losses, aeroallergen avoidance, and over-the-counter medication use. Finally, a disease or condition may also contribute to increased costs as a secondary diagnosis, or as a risk factor for other diseases and conditions. These hidden costs of co-morbidity need to be properly addressed and, if possible, included in future COI studies.

1. INTRODUCTION

Aeroallergens are classified into three groups: pollens (tree, weed, and grass), mold, and indoor allergens. There is evidence to support a causal relationship between each aeroallergen within these groups and one or more allergenic illnesses, including allergic rhinitis (hay fever), asthma, and atopic dermatitis (eczema). Over the last thirty years there has been a substantial increase in the prevalence of allergenic illnesses within the United States.[1] The underlying reasons behind the increased prevalence of each illness remain unclear. It has been hypothesized that global climate change could alter the concentrations, distributions, dispersion patterns, and allergenicities of aeroallergens in the environment in ways that could further increase the prevalence of allergenic illnesses in the United States.

Although climate change prediction is still considered an uncertain science, there have been many attempts to derive future climate scenarios, based on projected concentrations of greenhouse gases and models that simulate atmospheric circulation. In 2001, The United Nations Intergovernmental Panel on Climate Change (IPCC) conducted a comprehensive review of the science behind projected climate changes. The IPCC report predicted changes in average, minimum, and maximum temperature; precipitation patterns; and impacts on cyclical climate patterns, such as the El Niño-Southern Oscillation (IPCC, 2001).

The IPCC predicts that by the year 2100 the average global temperature may rise by 2.0°C, within a range of 1.4 to 5.8°C relative to 1990. Models projecting the global distribution of temperature change predict that the Northern Hemisphere will see the largest increase, with the United States experiencing an increase of 3 to 5ºC in annual mean temperature by 2100 (IPCC, 2001). Rising minimum temperatures are expected to result in fewer cold days, frost days, and cold waves globally. Change has already been detected, with global average temperature increasing by more than 0.5ºC over the past 50 years, with corresponding increases in the frequency of hot days and decreases in the frequency of cold nights.

Along with increasing temperatures, other ancillary effects of climate change, such as changes in precipitation, have also been predicted. Globally, tropical areas are predicted to receive more precipitation, with higher latitudes receiving smaller increases in both winter and summer. Present observations indicate that annual land precipitation has increased in the middle

[1] Over the last 30 years prevalence of asthma and allergenic rhinitis has increased from approximately 8 to 55 per 1,000 persons and approximately 55 to 90 per 1,000 persons, respectively.

and high latitudes of the Northern Hemisphere at a rate of about 0.5 to 1 percent per decade, along with increases in atmospheric moisture (IPCC, 2001). In some regions, total precipitation has remained the same or decreased, but the percent of precipitation from heavy and extreme events has increased, primarily in the Northern Hemisphere. The IPCC estimates that there has been a 2 to 4 percent increase in the frequency of heavy precipitation events worldwide over the second half of the 20th century, with a 5 to 10 percent increase over the Northern Hemisphere (IPCC, 2001).

Conversely, episodes of drought have occurred more frequently and intensely in recent decades in some regions, such as parts of Asia and Africa. The tendency for these droughts may be influenced by large-scale climate fluctuations such as those caused by the El Niño-Southern Oscillation, which has been shifting towards more warm events (IPCC, 2001).

Overall, the frequency of floods, extreme precipitation events, heat waves, and other extreme weather events have been predicted to increase. Much of the increase in precipitation over the Northern Hemisphere in the past century has been due to heavy or extreme precipitation events (IPCC, 2001). It is believed that some of the expected changes will be caused in part by the predicted increase in temperature, because higher temperatures can affect the hydrological cycle by increasing evaporation and allowing more water vapor to be held in the atmosphere. It remains unclear if the frequency of small-scale weather events such as thunderstorms and tornadoes will change, because there is insufficient information to include these in global models (IPCC, 2001).

The frequency and magnitude of El Niño-Southern Oscillation events are also predicted to increase. These events are cyclical changes in sea surface temperatures and air pressure, and they result in short-term episodes of increased climate variability. El Niño events generally occur in cycles of three to six years and cause very different impacts globally. They are associated with heat waves and drought in southern Africa and Southeast Asia, while causing flooding in western South America and central Africa. In the United States, results of El Niño events vary by region, with southeastern and Gulf states receiving increased rainfall, while midwestern and southwestern states may be warmer and drier. El Niño events have occurred with greater frequency over the last few decades, with the El Niño event of 1997-1998 being the strongest recorded (Sutherst, 2004). In particular, warm phase El Niño periods have occurred more frequently and have been more intense since the mid-1970's (IPCC, 2001). Other circulation patterns that affect climate have also changed recently, including the North Atlantic

Oscillation and the Antarctic Oscillation, both of which have contributed to stronger westerlies over the Atlantic and Southern Oceans in the past few decades.

The potential impacts of these climatic changes on aeroallergens and allergenic illnesses in the United States are unclear. Current research has focused on examining how specific elements of climate change – e.g., increased carbon dioxide (CO_2) levels, and increased and decreased regional precipitation – can alter the production, distribution, and allergen content of aeroallergens. A change in any of these characteristics of aeroallergens could lead to a substantial increase in the overall prevalence of allergenic illnesses in the United States, above and beyond the increase already observed.

This report provides an overview of the literature detailing the potential impacts of climate change on aeroallergens and their associated allergenic illnesses in the United States. Section 2 provides background information on the major aeroallergens in the United States and the allergenic illnesses associated with them. Section 3 discusses historical trends in levels of aeroallergens and the prevalence of their associated allergenic illnesses in the United States. Section 4 discusses the potential impacts of climate change on aeroallergens in the U.S. – their production, distribution, dispersion, and allergen content, as well as the potential indirect impacts on the allergenic illnesses associated with them. Section 5 discusses the economic impacts that these allergenic illnesses impose on the U.S. economy and the quality-of-life impacts they impose on the people who suffer from them. Finally, Section 6 addresses the current gaps in relevant research, and Section 7 provides a summary and concluding remarks.

2. AEROALLERGENS AND ASSOCIATED ALLERGENIC ILLNESSES IN THE UNITED STATES

This section of the report discusses the most prevalent aeroallergens in the United States, their distributions, their periods of production, and the primary clinical manifestations associated with exposure to each.

2.1. AEROALLERGENS

Aeroallergens are classified into three primary categories: pollens, mold, and indoor allergens. The major clinically relevant aeroallergens in North America, identified in *Practice Parameters for Allergen Immunotherapy*, the 2003 publication by the Joint Council of Allergy, Asthma and Immunology (JCAAI), are shown in Table 2-1 below.

Table 2-1. Most clinically relevant aeroallergens in the United States

Tree Pollen	
Latin Name	**Common Name**
Acer negundo	Box-elder
Acer rubra	Red maple
Alnus rubra	Alder
Betula papyrifera	Paper birch
Carya illinoensis	Pecan
Fraxinus Americana	White ash
Juglans nigra	Black walnut
Juniperus ashei	Mountain cedar
Morus alba	Mulberry
Olea europaea	Olive
Plantanus occidentalis	American sycamore
Populus deltoids	Eastern cottonwood
Quercus alba	White oak
Quercus rubra	Red oak
Ulmus Americana	American elm
Ulmus parvifolia	Chinese elm
Ulmus pumila	Siberian elm
Grass Pollen	
Latin Name	**Common Name**
Cynodon dactylon	Bermuda
Festuca elatior	Meadow fescue
Holcus halepensis	Johnson
Lolium perenne	Rye
Paspalum notatum	Bahia
Phleum pretense	Timothy
Weed Pollen	
Latin Name	**Common Name**
Amaranthus retroflexus	Red root pigweed
Ambrosia artemisiifolia	Short ragweed
Artemisia vulgaris	Mugwort
Kochia scoparia	Burning bush

Plantago lanceolata	English Plantain
Rumex acetosella	Sheep sorrel
Salsola kali	Russian thistle
Mold	
Latin Name	**Common Name**
Alternaria alternata	N/A
Aspergillus fumigatus	N/A
Cladosporium (*C. cladosporioides*; *C. herbarum*)	N/A
Drechslera or *Bipolaris* type (e.g., *Helminthosporium solani*)	N/A
Epicoccum nigrum	N/A
Penicillium (*P. chrysogenum*; *P. expansum*)	N/A
Indoor Allergens	
Latin Name	**Common Name**
Felis domesticus	Cat epithelium
Canis familiaris	Dog epithelium
Dermatophagoides farinae; Dermatophagoides pteronyssinus	Arthropods (domestic mites)
Blattella germanica	Insects (German cockroach)
Source: (Joint Task Force on Practice Parameters, 2003)	

The JCAAI identified the most common aeroallergens through consensus opinion of experts, rather than through evidence derived from clinical studies identifying a causal relationship between aeroallergen exposure and an allergenic illness (White et al., 2005). In contrast, White et al. (2005) defined major tree pollen allergens as those aeroallergens in which percutaneous reactivity to a given tree pollen extract resulted in more than 50 percent of all patients having a positive skin prick test. Using this definition, White et al. identified American sycamore, American elm, box-elder, red maple, white ash, cottonwood, and black walnut – all included in Table 2-1 above – as "major allergens," but did not recognize mulberry, also included in Table 2-1, as a major aeroallergen. As this example shows, the inconsistencies in the definitions of a "major aeroallergen" can result in the identification of clinically relevant aeroallergens not listed in Table 2-1. Other examples include the grass pollens Orchard (*Dactylis glomerata*), Kentucky blue grass (*Poa pratensis*), Red top (*Agrostis alba*), and Sweet vernal (*Anthoxanthum odoratum*) (American Academy of Allergy Asthma & Immunology, 2002). Throughout this report, Table 2-1 will be taken to represent the most common aeroallergens; however, regional differences, future changes in plant populations, and differences

in the definition of what constitutes a major aeroallergen could result in the addition of aeroallergens to this list in the future (White and Bernstein, 2003).

2.1.1. Pollens

The major pollen allergens are divided into three subcategories: tree, grass, and weed. The pollen size for all of the subcategories varies from 5 μm to greater than 200 μm (Wood, 1986). The pollen of each species has a distinct distribution, season of pollination, and level of dispersal, as discussed in detail by Kosisky and Carpenter (1997); however, within a pollen type (e.g., tree pollens), there are many similarities across species. In a study observing pollen levels during a five-year period in Washington, D.C. Kosisky and Carpenter (1997) found tree pollen accounts for approximately 90 percent of the total annual pollen produced, with weeds accounting for 6 percent and grasses 3 percent. The results reported by Kosisky and Carpenter (1997) are consistent with the results of similar studies observing yearly pollen levels. For example, in a study conducted in Philadelphia and Southern New Jersey, Dvorin et al. (2001) found that tree pollen accounts for the largest percent (approximately 75 percent) of the total annual pollen produced. Although there are clear differences in the amounts of different types of pollen produced, other factors, including prevailing winds and the pattern of land use, may also affect the level of airborne allergens in an area (Wood, 1986). The following sections discuss the defining characteristics of each pollen type, including the distributions of the relevant plant species within the U.S., the pollen seasons, and the levels of pollen dispersal.

2.1.1.1. *Tree Pollen*

Tree pollen accounts for the largest percent of pollen produced during the pollen season – approximately 75 to 90 percent (Dvorin et al., 2001; Kosisky and Carpenter, 1997). Of the total amount produced, however, only a small percentage is pollen generated from clinically relevant tree species. During a study of five-year mean tree pollen counts, for example, White et al. (2005) found that "major allergens" accounted for only 5 percent or less of the total five-year mean tree pollen count.[2] In a similar study, Kosisky and Carpenter (1997) found oak pollen represented approximately 57 percent of the pollen produced during a 6-year period in

[2] White et al. (2005) identified American sycamore, American elm, box-elder, red maple, red oak, white ash, cottonwood, and black walnut as "major allergens." They did not classify mulberry as a major allergen; therefore, it is possible the total percent contribution of "major allergens" to the 5-year mean tree pollen count could be slightly larger than 5 percent.

Washington, D.C.; however, there are 20 species of oak in the D.C. area, only two of which (white oak and red oak) produce pollens counted among the major aeroallergens. This suggests that, in the case of Washington, D.C., and possibly nationally, allergenic tree pollens may represent only a small percentage of the total tree pollen produced on a yearly basis.

Studies conducted by Weber (2003) and White and Bernstein (2003) identified regions of the major tree pollen allergens in the United States by using hardiness zones (i.e., climatic zones) defined by the United States Department of Agriculture (Weber, 2003). White and Bernstein (2003) went a step further and defined geographic locations for each pollen type through the designation of east or west, with the dividing line between east and west running from the middle of Montana diagonally to just east of the southern tip of Texas. One or more U.S. Census Bureau geographic regions (e.g., Northeast (NE), South (S), Midwest (MW), and West (W)) was assigned to each tree pollen type based on the tree growth region data provided in Weber (2003) and White and Bernstein (2003) (National Center for Health Statistics, 2004) (Table 2-2). Overall, the distribution of tree pollens spans the entire United States, but the abundance of pollen produced by certain tree species can vary within their defined geographic region(s).

Table 2-2. Geographic distribution of major clinically relevant tree pollens in the United States

Tree Pollen		
Latin Name	**Common Name**	**Geographic Region(s)[a]**
Acer negundo	Box-elder	NE, S, MW, W
Acer rubra	Red maple	NE, S, MW
Alnus rubra	Alder	W
Betula papyrifera	Paper birch	NE, MW, W
Carya illinoensis	Pecan	S, MW
Fraxinus americana	White ash	NE, S, MW
Juglans nigra	Black walnut	NE, S, MW
Juniperus ashei	Mountain cedar	NE, S, MW, W[b]
Morus alba	Mulberry	NE, S, MW
Olea europaea	Olive	W[c]
Plantanus occidentalis	American sycamore	NE, S, MW
Populus deltoids	Eastern cottonwood	NE, S
Quercus alba	White oak	NE, S, MW
Quercus rubra	Red oak	NE, S, MW
Ulmus Americana	American elm	NE, S, MW
Ulmus parvifolia	Chinese elm	NE, S, MW, W
Ulmus pumila	Siberian elm	NE, S, MW, W

Tree Pollen		
Latin Name	**Common Name**	**Geographic Region(s)[a]**
Sources: (Weber, 2003; White and Bernstein, 2003) [a] NE = Northeast; S = South; MW = Midwest; W = West [b] Mountain cedar is located throughout the U.S., but highly prevalent in central Texas and other areas of the southern Great Plains (Levetin and Van de Water, 2003). [c] Olive is most prevalent in the Southwest U.S. (White and Bernstein, 2003).		

The pollen seasons of the clinically relevant tree species are shown in Table 2-3. The overall pollen season for tree pollens tends to last from early March to mid-May, although in some cases it can run from February to June (Kosisky and Carpenter, 1997; White et al., 2005). The one exception to this is the unique pollen season of Mountain Cedar (*Juniperus ashei*), which ranges from December to January (Levetin and Van de Water, 2003).

Table 2-3. Pollen seasons of the major clinically relevant tree pollens in the United States

Tree Pollen			
Latin Name	**Common Name**	**Pollen Season**	**Reference**
Acer negundo	Box-elder	Early Spring	(Phadia, 2002)
Acer rubra	Red maple	Mid-April to Mid-May	(Dvorin et al., 2001)
Alnus rubra	Alder	February to April	(Weber, 2003)
Betula papyrifera	Paper birch	Late April to Late May	(Dvorin et al., 2001)
Carya illinoensis	Pecan	April to June	(Phadia, 2002)
Fraxinus americana	White ash	April to May	(Phadia, 2002)
Juglans nigra	Black walnut	Late Spring (May) to Early Summer	(Levetin, 2006; Phadia, 2002)
Juniperus ashei	Mountain cedar	December to January	(Levetin and Van de Water, 2003)
Morus alba	Mulberry	Spring; April to May	(Levetin, 2006; Phadia, 2002)
Olea europaea	Olive	Spring	(Phadia, 2002)
Plantanus occidentalis	American sycamore	March to April	(Levetin, 2006)
Populus deltoids	Eastern cottonwood	March to April	(Levetin, 2006)
Quercus alba	White oak	March to May	(Dvorin et al., 2001; Levetin, 2006)
Quercus rubra	Red oak	March to April	(Levetin, 2006)
Ulmus Americana	American elm	February to March[a]	(Levetin, 2006)
Ulmus parvifolia	Chinese elm	Fall	(Tidwell, 2006)
Ulmus pumila	Siberian elm	February to March[a]	(Tidwell, 2006)
[a] Pollen season can possibly extend to April (Saint Louis County, 2006).			

The period from late April to early May is of particular importance because this is the period with the highest pollen prevalence due to considerable overlap of the pollen seasons of multiple tree species (Dvorin et al., 2001). April in particular has been found to have the highest weekly average pollen concentrations (Kosisky and Carpenter, 1997). During the pollen season,

multiple tree species will release pollen at the same time, resulting in a significant amount of pollen being dispersed. The release of pollen from these tree species, and subsequently all tree species during the pollen season can result in the weekly pollen average per tree exceeding 100 grains/m^3, with the cumulative pollen abundance over the pollen season for each tree ranging upwards of 1,800 grains/m^3 (Dvorin et al., 2001; Gonzalez Minero et al., 1998).

2.1.1.2. *Grass Pollen*

Grass pollen accounts for the smallest percent of pollen produced during the pollen season – approximately 3 to 10 percent (Dvorin et al., 2001; Kosisky and Carpenter, 1997). The literature does not address what percentage of the total grass pollen count is comprised of the clinically relevant grass pollens, however, as it does for tree pollens; therefore, the total amount of clinically relevant grass pollen produced on a yearly basis is not clearly defined.

As for tree pollens, the distributions of grass pollens within the U.S. were determined using data detailed in Weber (2003) and White and Bernstein (2003), and then extrapolated to the U.S. regions defined by the U.S. Census Bureau. Table 2-4 shows the geographic regions of the most common clinically relevant grass pollens in the U.S. Consistent with what has been reported for tree pollens, the distribution of grass pollens can vary considerably within their defined geographic region(s). Grass pollen is usually deposited within 50 miles of its release, and although the exact distance can vary, it will mostly be confined to the relative vicinity in which it grows (Wood, 1986).

Table 2-4. Distribution of major clinically relevant grass pollens in the United States

Grass Pollen		
Latin Name	**Common Name**	**Geographic Region(s)[a]**
Cynodon dactylon	Bermuda	S, MW, W[c]
Festuca elatior	Meadow fescue	NE, S, MW, W[b]
Holcus halepensis	Johnson	S, MW, W[c,d]
Lolium perenne	Rye	NE, S, MW, W[b]
Paspalum notatum	Bahia	S, MW, W[c]
Phleum pretense	Timothy	NE, S, MW, W[b]

Sources: (Weber, 2003; White and Bernstein, 2003)
[a] NE = Northeast; S = South; MW = Midwest; W = West
[b] Meadow fescue, Rye, and Timothy are all located in the northern part of each region from the East to the West coast of the U.S. (White and Bernstein, 2003).
[c] Bermuda, Johnson, and bahia are all located in the southern part of each region from the East to the West coast of the U.S. and are becoming increasingly more important in the south (Phipatanakul, 2005; White and Bernstein, 2003).
[d] The growing region of Johnson extends slightly further north then that of Bermuda and bahia (White and Bernstein, 2003).

Unlike tree pollens, some grass pollens, including Bermuda, Johnson, and bahia, are produced all year (Weber, 2003). This is not the case for all grasses. Dvorin et al. (2001) found that for the majority of grasses the pollen season tends to last from late April to mid-June, with a secondary peak in early September. These findings are consistent with what has been defined as the peak grass pollen season, from May through June (Gonzalez Minero et al., 1998). Table 2-5 shows the pollen season for each of the clinically relevant grass pollens.

Table 2-5. Pollen season of the major clinically relevant grass pollens in the United States

Grass Pollen		
Latin Name	**Common Name**	**Pollen Season[a]**
Cynodon dactylon	Bermuda	Late April to mid-June, early September[b]
Festuca elatior	Meadow fescue	Late April to mid-June, early September
Holcus halepensis	Johnson	Late April to mid-June, early September[b]
Lolium perenne	Rye	Late April to mid-June, early September
Paspalum notatum	Bahia	Late April to mid-June, early September[b]
Phleum pretense	Timothy	Late April to mid-June, early September

[a] Dvorin et al. (2001) found the grass pollen season lasts from late April to mid-June with a secondary peak in early September.
[b] Weber found the pollen season lasts all year for Bermuda, Johnson, and bahia grasses.

During the peak months of the grass pollen season, the cumulative weekly average concentration of pollen is typically >100 grains/m^3, with the cumulative amount of pollen produced in a single year not exceeding 2,500 grains/m^3 (Gonzalez Minero et al., 1998). During the pollen season, grass pollen levels can oscillate both during the season and throughout a region due to anthropogenic factors. The levels can vary depending on the land under grass; the seed mix of sown pastures, and the replacement of haymaking by silage production, when grasses are cut before they flower (Nielsen et al., 2002).

2.1.1.3. *Weed Pollen*

Weed pollen accounts for the second greatest percentage of pollen produced during the pollen season – approximately 6 to 17 percent. However, the amount produced is significantly less than the total amount of tree pollen produced in a single year (Dvorin et al., 2001; Kosisky and Carpenter, 1997). Similar to grass pollens, the literature for weed pollens does not address what percentage of the total weed pollen count is composed of the clinically relevant weed pollens; therefore, the total amount of clinically relevant weed pollen produced on a yearly basis is not clearly defined.

As for both tree and grass pollen, the distribution of weed pollens within the U.S. was determined using data detailed in Weber (2003) and White and Bernstein (2003), and then extrapolated to the U.S. regions defined by the U.S. Census Bureau. Table 2-6 details the geographic regions of the most common weed pollens in the U.S. Although all of the major weeds are located throughout the U.S., some are more highly prevalent in specific regions of the country.

Table 2-6. Distribution of major clinically relevant weed pollens in the United States

Weed Pollen		
Latin Name	**Common Name**	**Geographic Region(s)[a]**
Amaranthus retroflexus	Red root pigweed	NE, S, MW, W[b]
Ambrosia artemisiifolia	Short ragweed[c]	NE, S, MW, W[e]
Artemisia vulgaris	Mugwort	NE, S, MW, W[d]
Kochia scoparia	Burning bush	NE, S, MW, W
Plantago lanceolata	English Plantain	NE, S, MW, W
Rumex acetosella	Sheep sorrel	NE, S, MW, W[b]
Salsola kali	Russian thistle	NE, S, MW, W[b]

Sources: (Weber, 2003; White and Bernstein, 2003)
[a] NE = Northeast; S = South; MW = Midwest; W = West
[b] Found throughout the U.S., but especially in the western half of the United States (Powell and Smith, 1978; White and Bernstein, 2003).
[c] Not found in the Pacific Northwest (Phipatanakul, 2005).
[d] Highly localized to the eastern U.S. and Pacific Northwest (White and Bernstein, 2003).
[e] Not found in Utah, Nevada, and California (White and Bernstein, 2003).

Unlike the tree and grass pollen seasons, which are relatively consistent across all species, the pollen season for weeds has been shown in multiple studies to vary across species (Table 2-7). In some cases, the region of the country in which the weed species is located can influence the pollen season. For example, in most areas of North America ragweed pollinates from August through October, but the pollen season tends to be earlier in northern areas and progressively later in southern states (Levetin and Van de Water, 2003). Overall, the weed pollen season is typically defined as mid-August through late-September (Dvorin et al., 2001).

Table 2-7. Pollen season of clinically relevant weed pollens in the United States

Weed Pollen			
Latin Name	**Common Name**	**Pollen Season**	**Reference**
Amaranthus retroflexus	Red root pigweed	High Summer and Fall	(Phadia, 2002)
Ambrosia artemisiifolia	Short ragweed	March to November[a]	(Weber, 2003)
Artemisia vulgaris	Mugwort	August to October	(White and Bernstein,

			2003)
Kochia scoparia	Burning bush	Mid-Summer	(Phadia, 2002)
Plantago lanceolata	English Plantain	July to August[b]	(Weber, 2003)
Rumex acetosella	Sheep sorrel	April to May[c]; Mid-August to Late September	(Dvorin et al., 2001; Weber, 2003)
Salsola kali	Russian thistle	Late Summer and Autumn	(Phadia, 2002; Powell and Smith, 1978)
a Pollen season August to October in northern regions of the U.S. (Dvorin et al., 2001; White and Bernstein, 2003). b Pollen season may extend slightly longer, May to October, with the peak being May to July (White and Bernstein, 2003). c Specific to western U.S.			

During the peak pollen season, from mid-August through late-September, weed pollen levels may exceed 250 grains/m^3 weekly (Dvorin et al., 2001). The total amount of pollen released during the pollen season can vary from region to region with the total amount of pollen released being determined by the prevalence of each weed species in each geographic region of the U.S. For example, although it is found throughout the U.S., ragweed has the highest pollen counts in the Omaha region of the Midwest, which will highly influence the overall weed pollen count in that region of the country (Weber, 2003).

2.1.2. Mold

The second major class of clinically relevant aeroallergens is mold. Mold spores are substantially smaller than pollen spores, ranging in size from 2μm to 10μm, and are more abundant (Burge, 2002). Mold spore counts are often 1000-fold greater than pollen counts (Bush and Prochnau, 2004).[3] Unlike pollens, mold is not localized to specific regions of the country; it can be found throughout the U.S., except in the coldest regions, but it can be found in higher concentrations in some regions due to specific environmental conditions, most notably humidity ((Phipatanakul, 2005), (Table 2-8)). Mold requires a consistently high relative humidity, ranging between 70 and 85 percent (Burge, 2002; Hamilton and Eggleston, 1997).

Table 2-8. Distribution of major clinically relevant mold in the United States

Mold	Geographic Region[a]	Reference
Alternaria alternate	Grain-growing areas	(Corden and Millington, 2001; Targonski et al., 1995)
Aspergillus fumigatus	Warm Climates (>40º C)	(Hamilton and Eggleston, 1997)

[3] Hamilton and Eggleston (1997) state, although fungal counts are substantially larger than those observed for pollens it is currently unclear if the viable spore colony count or the total (viable and non-viable) spore count is a better indicator for clinically relevant mold allergens in the environment.

Cladosporium (C. cladosporioides; C. herbarum)	Temperate Zones	(Hamilton and Eggleston, 1997)
Drechslera or *Bipolaris type* (e.g., *Helminthosporium solani*)	N/A	N/A
Epicoccum nigrum	N/A	N/A
Penicillium (*P. chrysogenum; P. expansum*)	N/A	N/A
[a] Studies detailing common mold aeroallergens do not address their distribution within the United States. The literature has hinted at mold being found ubiquitously in the U.S. Areas or regions of the U.S. are included for those types of mold where information was available.		

Mold is primarily located outdoors, but unlike pollen can colonize indoor materials (Burge, 2002). *Alternaria* and *Cladosporium* are universally dominant outdoor fungal species that are detected indoors, while *Penicillium* and *Aspergillus* are universally dominant indoors (Hamilton, 2005). Burge et al. (2002) found that the concentrations of outdoor fungal species in indoor environments are driven by outdoor concentrations. Indoors, the distribution of fungal concentrations throughout the aboveground living space of a home is fairly consistent with the highest concentrations being found in basements due to ideal growing conditions, but the types found in basements are usually not related to those found outdoors (Burge, 2002).

The literature focuses primarily on *Alternaria*, the most common atmospheric mold spore in the U.S. (Corden and Millington, 2001). *Alternaria* flourishes in warm, humid environments (Hamilton and Eggleston, 1997). It grows well on fruits and tomatoes, as well as textiles, allowing it to flourish in indoor environments; however, it is usually not found indoors (Corden and Millington, 2001; Hamilton and Eggleston, 1997). *Alternaria* is found in highest concentrations in cultivated areas, such as the Midwest, in which grasslands and grain fields predominate (Bush and Prochnau, 2004). In studies conducted in Derby, UK by Corden and Millington (2001), and in Chicago by Targonski et al. (1995), seasonal *Alternaria* concentrations were observed primarily from June to October, and July to October, respectively, periods which coincide with harvest time, although spores were occasionally found at other times throughout the year.

Unfortunately, information for the other clinically relevant mold is limited. Specific regions of growth and periods of highest concentration have been identified for only a few mold types, as shown in Table 2-8. *Cladosporium* thrives in temperate zones and *Aspergillus* thrives in warm climates (>40º C), while Pencillum grows on stale bread, citrus fruits, and apples (Hamilton and Eggleston, 1997). It is unclear if a specific time of year is associated with increased concentrations of *Cladosporium* and *Pencillum*, but *Aspergillus* concentrations do have

seasonal peaks, if they are able to penetrate indoor environments, when heating is the highest, during autumn and winter (Hamilton and Eggleston, 1997).

2.1.3. Indoor Allergens

Similar to mold, indoor allergens are not particularly associated with specific regions of the U.S. Indoor environments have been found to be the main determinant influencing the level of indoor allergens. It has been postulated that an increase in the price of energy has resulted in an increase in insulation and a decrease in ventilation in buildings, providing ideal growth conditions for the most prevalent indoor allergen, house dust mites (Nielsen et al., 2002). House dust mites are ubiquitous throughout the U.S. except in very dry climates and at higher elevations (Phipatanakul, 2005). They have also been found to thrive in warm conditions where the relative humidity is approximately 70 percent (Hamilton, 2005). Cockroaches, on the other hand, are found more predominantly in urban areas, particularly in inner city, low-income environments, but are also more common than previously thought in suburban middle-class homes (Hamilton, 2005; Phipatanakul, 2005). The concentrations of all indoor allergens do not vary with season as is observed for pollens and some mold, but are instead found perennially. The distribution of major clinically relevant indoor allergens appears in Table 2-9.

Table 2-9. Distribution of major clinically relevant indoor allergens

Indoor Allergens		
Latin Name	**Common Name**	**Geographic Region(s)[a]**
Felis domesticus	Cat epithelium	N/A
Canis familiaris	Dog epithelium	N/A
Dermatophagoides farinae; Dermatophagoides pteronyssinus	Arthropods (domestic mites)	N/A
Blattella germanica	Insects (German cockroach)	N/A
[a] Indoor allergens are not confined to specific regions of the U.S., but factors have been identified, which influence the levels of allergens found in indoors.		

2.2. ASSOCIATED ALLERGENIC ILLNESSES

Exposure to allergens results in allergenic illnesses in approximately 20 percent of the U.S. population (American Academy of Allergy Asthma & Immunology, 1996-2006). The development of allergenic illnesses occurs through a two-step process. In the first stage an immunologically naïve individual is sensitized to an allergen, resulting in the production of IgE antibodies; in the second stage, renewed exposure to the allergen elicits a disease response due to

the presence of IgE antibodies and the associated cellular response (Nielsen et al., 2002). Currently, three main allergenic illnesses have been associated with exposure to aeroallergens: allergic rhinitis (hay fever), asthma, and atopic dermatitis (eczema).

The initial sensitization to an aeroallergen can occur during any period of an individual's life. Wood (1986) cites a study by Ziering and Klein (1982), which found that respiratory allergy develops by two years of age in 40 percent of those affected and by six years of age in the remaining 60 percent. Wood (1986) also cites a study by Kemp (1979), which found that the sensitivity to grass pollens of children who reached the age of three months during a time of high environmental exposure to grass pollen was significantly greater than the sensitivity to grass pollens of children born at other times of the year. Although sensitization and the subsequent development of allergenic illnesses can occur during childhood, sensitization to common aeroallergens increases with age and with the length of the exposure period (Nielsen et al., 2002). The German Multicenter Allergy birth cohort study, for example, observed rates of sensitization to grass pollen and dust mites of 6.2 percent and 3.0 percent, respectively, before the age of 2, but as the children grew older the rates of sensitization to both outdoor and indoor allergens increased (Phipatanakul, 2005). The incidence of allergic rhinitis was observed in the study to increase by as much as 3 to 4 percent each year after the age of three (Phipatanakul, 2005).

Underlying genetic factors have been found to have a strong influence on the process of sensitization and the subsequent development of allergenic illnesses during the course of an individual's life. Individuals classified as atopic are inheritably predisposed to produce elevated amounts of IgE antibodies upon exposure to allergens, and as a result are more easily sensitized to allergens than are non-atopic individuals (Nielsen et al., 2002). The hereditary association between aeroallergen exposure and allergenic illness development has been identified as a primary risk factor for the development of allergic rhinitis in children, especially if both parents are affected by the illness (Phipatanakul, 2005). Although there is a major hereditary contribution to the development of these allergenic illnesses, environmental factors, specifically exposure to aeroallergens, play a significant role in their manifestation (Nielsen et al., 2002).

The degree to which an aeroallergen causes an allergenic illness in a sensitized individual depends on multiple factors, one of the primary factors being the aeroallergen to which the individual is exposed. Galant et al. (1998) performed skin prick tests for different allergens on individuals in California with allergic rhinitis and asthma and found that some allergens are more prone to result in the development of allergenic illnesses than others. The study showed the following rank order of positive responses: pollen (grasses > weeds ≈ trees) and house dust

mites > pets (cat > dog) > cockroach and mold (Galant et al., 1998). These findings are consistent with the findings in other studies that have examined the association between aeroallergen exposure and the development of allergenic illnesses. For example, Nielsen et al. (2002) reported that allergy to mold alone has low predictive value for the development of asthma and allergic rhinitis. In one study, 15 percent of subjects sensitized exclusively to mold had allergic symptoms, but subjects sensitized to mold and pollen and/or house dust mites had a prevalence of allergic symptoms of about 50 percent, suggesting that sensitization to mold alone is not as important in causing allergic symptoms as sensitization to the other aeroallergens (Nielsen et al., 2002). In addition, a study conducted in central Indiana found the sensitization rate to mold was only about half the sensitization rate for pollens (Nielsen et al., 2002).

Not only the type, but also the amount of aeroallergen to which an individual is exposed is influential in the development of an allergenic illness. Similar to what is observed in most disease causation scenarios, a dose-response relationship between aeroallergen exposure and sensitization and exacerbation of disease has been observed – i.e., sensitized patients are more likely to have more severe disease if exposure to allergens is high (Nielsen et al., 2002). This relationship was observed in a study conducted in France, which looked at hay fever and grass pollen sensitivity. The study found the prevalence of allergy to a given allergen is higher in communities that are heavily exposed to allergens than those that are not (Burr, 1999). Although the probability of an allergic response increases with increasing levels of exposure to aeroallergens, a large exposure is not required to initiate allergic symptoms. Comtois and Gagnon (1988) (cited in (Kosisky and Carpenter, 1997)) found that it only takes a small amount, 9 to 23 grains/m^3, of tree pollen and 4 to 12 grains/m^3 of grass pollen, to cause allergic symptoms in a sensitized individual.

The observation of a dose-response relationship between aeroallergen exposure and the development of allergenic illness is not specific to pollen exposure; such dose-response relationships have also been observed for individuals sensitized to indoor allergens, specifically house dust mites. Nielsen et al. (2002) cites Custovic et al. (1996), who found the level of indoor allergen exposure highly influenced the severity of asthma. Because of this, exposure reduction is one of the main methods used to control the development of allergenic illness in sensitized individuals (Nielsen et al., 2002).

Although there may be a dose-response relationship between aeroallergen exposure and the development of allergenic illness, other confounding factors may make this relationship difficult to observe. If, for example, the proportion of the population that is genetically

predisposed to develop allergenic illnesses happens to decrease as the level of the aeroallergen increases, a dose-response relationship could be masked. Although multiple studies have shown a direct correlation between aeroallergen levels and disease development, this is not the case for all such studies. White et al. (2005) found no association between regional pollen levels and the frequency of skin test reactivity to specific tree pollen allergens in a study conducted in Southwestern Ohio. These researchers noted that their findings might be specific to Southwestern Ohio; however, these findings call into question whether increased exposure to aeroallergens elicits the same disease response throughout the U.S.

All of the factors discussed above influence the development of allergenic illnesses in individuals exposed to aeroallergens. Table 2-10 shows the allergenic illnesses associated with exposure to each of the clinically relevant aeroallergens listed in Table 2-1.[4] The allergenic illnesses associated with exposure to aeroallergens are discussed more fully below, including the evidence supporting causal relationships between aeroallergen exposure and disease development.

Table 2-10. Allergenic illnesses associated with the major clinically relevant aeroallergens

Tree Pollen			
Latin Name	**Common Name**	**Allergenic Illness**	**Reference**
Acer negundo	Box-elder	Asthma, Allergic rhinitis	(Phadia, 2002; White et al., 2005)
Acer rubra	Red maple	Allergic rhinitis	(White et al., 2005)
Alnus rubra	Alder	Allergic rhinitis[a]	(Nielsen et al., 2002)
Betula papyrifera	Paper birch	Asthma, Allergic rhinitis	(White et al., 2005; White and Bernstein, 2003; Emberlin et al., 2002)
Carya illinoensis	Pecan	Allergic rhinitis[a, d]	(White et al., 2005)
Fraxinus americana	White ash	Asthma, Allergic rhinitis	(Phadia, 2002; White et al., 2005)
Juglans nigra	Black walnut	Allergic rhinitis	(White et al., 2005)
Juniperus ashei	Mountain cedar	Asthma, Allergic rhinitis	(Phadia, 2002)
Morus alba	Mulberry	Asthma, Allergic rhinitis	(Phadia, 2002)
Olea europaea	Olive	Asthma, Allergic rhinitis	(Phadia, 2002)
Plantanus occidentalis	American sycamore	Asthma, Allergic rhinitis	(White et al., 2005; White and Bernstein, 2003)
Populus deltoids	Eastern cottonwood	Asthma, Allergic rhinitis	(Phadia, 2002; White et al., 2005)
Quercus alba	White oak	Allergic rhinitis	(White et al., 2005; White and Bernstein, 2003)
Quercus rubra	Red oak	Allergic rhinitis	(White et al., 2005; White and Bernstein, 2003)

[4] Table 2-10 does not include atopic dermatitis (eczema) because the literature to date has not definitively concluded that there is a casual association between aeroallergen exposure and atopic dermatitis development (Whitmore, 1996).

Ulmus Americana	American elm	Asthma, Allergic rhinitis	(Phadia, 2002)
Ulmus parvifolia	Chinese elm	Allergic rhinitis[a]	(Nielsen et al., 2002)
Ulmus pumila	Siberian elm	Allergic rhinitis[a]	(Nielsen et al., 2002)
Grass Pollen[a]			
Latin Name	**Common Name**	**Allergenic Illness**	**Reference**
Cynodon dactylon	Bermuda	Asthma, Allergic rhinitis	(Nielsen et al., 2002)
Festuca elatior	Meadow fescue	Asthma, Allergic rhinitis	(Nielsen et al., 2002)
Holcus halepensis	Johnson	Asthma, Allergic rhinitis	(Nielsen et al., 2002)
Lolium perenne	Rye	Asthma, Allergic rhinitis	(Nielsen et al., 2002)
Paspalum notatum	Bahia	Asthma, Allergic rhinitis	(Nielsen et al., 2002)
Phleum pretense	Timothy	Asthma, Allergic rhinitis	(Nielsen et al., 2002)
Weed Pollen			
Latin Name	**Common Name**	**Allergenic Illness**	**Reference**
Amaranthus retroflexus	Red root pigweed	Asthma, Allergic rhinitis	(Phadia, 2002)
Ambrosia artemisiifolia	Short ragweed	Allergic rhinitis	(White and Bernstein, 2003)
Artemisia vulgaris	Mugwort	Asthma, Allergic rhinitis	(Phadia, 2002)
Kochia scoparia	Burning bush	Asthma, Allergic rhinitis	(Phadia, 2002)
Plantago lanceolata	English Plantain	Asthma, Allergic rhinitis	(Phadia, 2002)
Rumex acetosella	Sheep sorrel	Allergic rhinitis[a]	(Nielsen et al., 2002)
Salsola kali	Russian thistle	Allergic rhinitis[a]	(Nielsen et al., 2002)
Mold			
Latin Name	**Common Name**	**Allergenic Illness**	**Reference**
Alternaria alternate	N/A	Asthma, Allergic	(Halonen et al., 1997; Corden and Millington, 2001; Andersson et al., 2003)
Aspergillus fumigatus	N/A	Asthma	(Nielsen et al., 2002)
Cladosporium (*C. cladosporioides*; *C. herbarum*)	N/A	Asthma	(Nielsen et al., 2002)
Drechslera or *Bipolaris* type (e.g., *Helminthosporium solani*)	N/A	Asthma[b]	(Nielsen et al., 2002)
Epicoccum nigrum	N/A	Asthma[b]	(Nielsen et al., 2002)
Penicillium (*P. chrysogenum*; *P. expansum*)	N/A	Asthma[b]	(Nielsen et al., 2002)
Indoor Allergens			
Latin Name	**Common Name**	**Allergenic Illness**	**Reference**
Felis domesticus	Cat epithelium	Asthma, Allergic rhinitis	(Phadia, 2002; Phipatanakul, 2005; Halonen et al., 1997)
Canis familiaris	Dog epithelium	Asthma, Allergic rhinitis	(Nielsen et al., 2002; Halonen et al., 1997; (Phipatanakul, 2005)
Dermatophagoides farinae; Dermatophagoides pteronyssinus	Arthropods (domestic mites)	Asthma, Allergic rhinitis	(Nielsen et al., 2002; Phipatanakul, 2005)
Blattella germanica	Insects (German cockroach)	Asthma, Allergic rhinitis	(Phipatanakul, 2005; Hamilton and Eggleston, 1997)

[a] The literature did not detail a specific allergenic illness or illnesses associated with exposure to these pollen types. Exposure to all pollen types is known to cause pollinosis (i.e. allergic rhinitis); therefore, allergic rhinitis was listed as the associated allergenic illness for these pollen types (Nielsen et al., 2002).
[b] The literature did not detail a specific allergenic illness(es) associated with exposure to these types of mold. Nielson et al. (2002) states exposure to mold is a primary risk factor for the development of asthma; as a result, asthma was defined as the associated allergenic illness for these types of mold.
[c] Mold can cause both asthma and allergic rhinitis (Nielsen et al., 2002). Allergic rhinitis is only associated with exposure to *Alternaria* in this table because the literature did not provide definitive evidence that the other types of mold detailed in the table can also cause allergic rhinitis.
[d] The literature does not associate a specific allergenic illness with exposure to pecan. It only states pecan is highly allergenic (White et al., 2005).

2.2.1. Allergic Rhinitis

The most common allergenic illness associated with exposure to aeroallergens is allergic rhinitis (hay fever). Allergic rhinitis is also commonly referred to as rhinoconjunctivitis – because the clinical manifestations associated with the condition may include not only sneezing, itching rhinorrhea, or nasal congestion, but also itchy, red and watery eyes (conjunctivitis) (Phipatanakul, 2005). It is also sometimes called pollinosis, because seasonal allergic rhinitis is primarily caused by airborne pollen (Nielsen et al., 2002). In some cases the symptoms of allergic rhinitis may also affect the ears and throat and include postnasal dripage (Phipatanakul, 2005). All of these symptoms result from exposure to aeroallergens after an initial sensitization; hence allergic rhinitis is termed a type 1 or immediate hypersensitivity reaction (Wood, 1986).

Allergic rhinitis annually affects approximately 20 to 40 million people in the U.S., including 10 to 30 percent of adults and up to 40 percent of children (Gilmour et al., 2006; O'Connell, 2004). Although exposure to the majority of aeroallergens can result in the development of allergic rhinitis (Table 2-10), sensitization to pollen is a primary risk factor for its development (Nielsen et al., 2002). Pollens from wind-pollinated plants are of particular concern because they are lighter and can become airborne without difficulty, allowing for individuals to be easily exposed (Wood, 1986; White et al., 2005). The significance of pollen exposure in the development of allergic rhinitis was highlighted in a study conducted by the Spanish Society of Clinical Allergy and Immunology. The study found that 65 percent of pollinosis cases reported in city hospitals were caused by grass pollen (Gonzalez Minero et al., 1998).

Numerous studies have found that exposure to specific pollens increases the risk of developing allergic rhinitis, but it remains unclear which pollens are more highly associated with the development of allergic rhinitis. It has been estimated that ragweed pollen is responsible for 50 to 75 percent of all allergic rhinitis cases in the U.S. (American College of Allergy, 2006;

Nielsen et al., 2002), while 20 to 25 percent of hay fever sufferers are allergic to birch (Emberlin et al., 2002). A study conducted in Tucson, Arizona, however, found that children who had immediate skin test responses to Bermuda grass were more prone to develop allergic rhinitis (Halonen et al., 1997). These findings are consistent with those of Levetin and Van de Water (2003), who classify Bermuda, Johnson, and bahia as important allergenic grasses, but they also contribute to the overall confusion about which plant species has the largest influence on the development of allergic rhinitis.

The literature on the development of allergic rhinitis in response to aeroallergen exposure focuses primarily on pollens, but studies have found that exposure to both indoor allergens and mold can also contribute to the development of allergic rhinitis in sensitized individuals. Multiple studies have shown a causal relationship between sensitization for hay fever and exposure to indoor allergens, such as dust mites and cockroaches, as well as exposure to mold (Phipatanakul, 2005). Although exposures to indoor allergens and pollens both result in the development of allergic rhinitis, a difference has been observed in the symptom pattern. Unlike allergic rhinitis symptoms associated with exposure to pollens, which follow the months of the pollen season, the symptoms associated with exposure to indoor allergens are perennial (Phipatanakul, 2005).

The (minimal) literature on the development of allergic rhinitis associated with exposure to mold focuses specifically on *Alternaria*. It has been hypothesized that the smaller spores of *Alternaria* (2 μm to 8 μm) could allow it to be a more potent cause of allergic rhinitis than other types of mold, such as *Cladosporium*, which has much larger spores (Andersson et al., 2003). In a study examining the association between exposure to *Alternaria* in sensitized children and the development of allergic rhinitis, Andersson et al. (2003) concluded that sensitized individuals in regions of the U.S. with high concentrations of fungal spores are at risk of developing allergic rhinitis.

2.2.2. Asthma

Second only to allergic rhinitis in prevalence, asthma is one of the primary allergenic illnesses associated with exposure to aeroallergens. Unlike allergic rhinitis, which is primarily associated with exposure to pollens, asthma has been found to be more strongly associated with exposure to indoor allergens and mold. The Centers for Disease Control and Prevention (CDC) estimated the prevalence of asthma in the U.S. adult population as of 2004 to be 7.5 percent, or 16 million people, with the overall prevalence in the entire population ranging from 5 to 8

percent (Gilmour et al., 2006; O'Connell, 2004). It is unclear, however, what percent of the asthma cases identified each year can be attributed solely to exposure to aeroallergens. In epidemiological studies, the proportion of asthmatics who showed an allergic reaction to skin prick test to one or more common aeroallergens was usually less than one half (Nielsen et al., 2002). Therefore, the estimated prevalence of asthma within the U.S. may not accurately reflect the prevalence of asthma attributed specifically to exposure to aeroallergens.

Although there is a perceived association between exposure to pollens and asthma development (Table 2-10), pollen exposure has been historically considered to lead primarily to hay fever (Burge, 2002). However, recent data suggests a supporting role for exposure to pollen in the development of asthma (Burge, 2002). In a prospective study conducted in England, detailed by Burr (1999), most patients with grass pollen sensitivity and a history of seasonal exacerbations experienced an asthma attack following a rise in pollen count. White and Bernstein (2003) also found that sensitization to plant aeroallergens is associated with significant morbidity caused by symptoms of seasonal asthma. Although there is mounting evidence suggesting that exposure to pollen can lead to asthma, overall sensitization to pollen remains a low risk factor for asthma development (Nielsen et al., 2002).

The majority of studies examining the development of asthma in response to aeroallergen exposure have focused on the role of indoor allergens and mold. This is primarily because mold, allergens from pets, and cockroaches have shown strong associations with asthma development, unlike common tree, weed, and grass pollens, which have not shown strong independent associations (Halonen et al., 1997; Nielsen et al., 2002; Hamilton, 2005; Henderson et al., 2000). As with exposure to all aeroallergens, including indoor allergens, sensitization influences the allergenic illness an individual will develop. For example, an increased risk of asthma sensitization in atopic individuals has been associated with house dust mite levels higher than 2000 ng/G of fine dust (Hamilton, 2005). After sensitization, exposure to house dust mite levels higher than 10,000 ng/G has been associated with an increased risk of asthma symptoms (Hamilton, 2005). The association between high indoor allergen levels and an increase in asthma severity suggests a dose-response relationship (Nielsen et al., 2002). The National Co-operative Inner City Asthma Study clearly implied such a dose-response relationship between indoor allergen levels and asthma severity when it concluded that children allergic to cockroach allergens and exposed to high levels had a greater severity of asthma (Custovic et al., 2002).

Multiple studies have found that exposures to mold, including *Alternaria*, *A. fumigatus*, and *Cladosporim*, are also risk factors for the development of asthma (Halonen et al., 1997;

Nielsen et al., 2002; Lin and Williams, 2003). In a study conducted in Tucson, Arizona, Halonen et al. (1997) found that children who had an immediate skin test response to *Alternaria* were more prone to develop asthma. Bush and Prochnau (2004) noted that in the U.S. up to 80 percent of individuals with confirmed asthma have demonstrated positive reactivity to one or more species of mold. Although there is evidence of associations between asthma development and exposure to all mold (Table 2-10), the literature focuses primarily on the development of asthma in response to *Alternaria* exposure.

Exposure to *Alternaria*, and subsequently sensitization, has been increasingly recognized as a risk factor for the development and persistence of asthma, increased asthma severity, and potentially fatal asthma exacerbations (Nielsen et al., 2002; Bush and Prochnau, 2004). Similarly, a study conducted in Chicago by Targonski et al. (1995) found that mean mold spores, rather than tree, grass, or ragweed pollen, was associated with asthma-related deaths. Targonski et al. (1995) also found the risk of asthma-related deaths increased 2.16 times when the total *Alternaria* spore count was about 1,000 spores/m^3. Overall, individuals sensitized to *Alternaria* appear to be more at risk for developing severe asthma compared to individuals with sensitivities to other aeroallergens (Bush and Prochnau, 2004).

Although there is evidence to support causal relationships between asthma development and exposure to both indoor allergens and mold, it is still unclear which class of aeroallergens is the greater risk factor for asthma development. Some data, such as that provided by Halonen et al. and Targonski et al., suggest that mold may have a larger impact on asthma development. However, a study conducted on children in Virginia and New Mexico found that hypersensitivity to indoor allergens (e.g., cat and house dust mites) has a stronger association with asthma than hypersensitivity to mold (Lin and Williams, 2003).

Although these studies suggest that exposure to either indoor allergens or mold can cause asthma, other researchers have found the evidence for such associations inconclusive (Tortolero et al., 2002). As a result, some members of the scientific community feel they cannot definitively state that a direct relationship exists between indoor allergen or mold exposure and asthma development. Overall, however, most of the literature suggests that exposure to indoor allergens and mold in sensitized individuals can result in a strong disposition to both the development of asthma and subsequent asthma exacerbations.

2.2.3. Atopic Dermatitis

Exposure to aeroallergens has also been implicated in the development of atopic dermatitis (eczema), and its development has commonly been found to predate the development of the more prevalent allergenic illnesses, allergic rhinitis and asthma (O'Connell, 2004). It has been estimated that atopic dermatitis affects 15 to 20 percent of the population of children worldwide (O'Connell, 2004).[5] Studies examining the association between aeroallergen exposure and the development of atopic dermatitis have focused on individual responses to allergens by way of skin patch or skin prick tests. Most studies have found that 30 to 40 percent of patients with atopic dermatitis have positive skin patch tests to allergens (Whitmore et al., 1996). Whitmore et al. (1996) cite Clark and Adinoff (1989), which found that the most common responses in skin patch tests on individuals with atopic dermatitis were for animal danders (53 percent), mites or dust (37 percent), mold (32 percent), and tree, grass, and weed pollens (14 to 35 percent). Adinoff et al. (1988) also observed positive skin prick tests for aeroallergens: 30 percent positive for pollens, 20 percent for mold, and 75 percent for dust, mites, and animals.[6]

Although these studies hint at an association between exposure to aeroallergens and the development of atopic dermatitis, there is conflicting evidence. Studying patients presenting with contact dermatitis, Whitmore et al. (1996) found that regardless of whether or not they were atopic, those suspected of having allergic contact dermatitis had a low incidence of presently relevant allergic dermatitis when exposed to aeroallergens (Whitmore et al., 1996). Powell and Smith (1978), studying individuals sensitized to Russian thistle, observed dermatitis only in individuals who came into direct contact with the plant, rather than by way of exposure to its pollen.

Because of this contradictory evidence, the role of aeroallergens in the development of atopic dermatitis remains controversial (Whitmore et al., 1996). Whitmore et al. (1996) explains that the uncertainty surrounding the association is due partly to the fact that most of the studies do not include nonatopic control subjects. As a result, it is unclear if aeroallergens are the primary culprit in atopic dermatitis (Whitmore et al., 1996).

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[5] O'Connell (2004) was the only study that provided a prevalence rate for atopic dermatitis. Unfortunately, the rate provided is worldwide, although the rest of the paper focuses on U.S. allergenic illness rates.

[6] This study was not an epidemiological study. It was conducted to examine the possibility that atopic dermatitis may be triggered by aeroallergens in some individuals; therefore, the findings cannot be used to infer a causal association.

2.2.4. Cross-Reactivity

There is substantial evidence suggesting a causal relationship between aeroallergens and allergenic illnesses, but it remains unclear which aeroallergens are more highly associated with causing sensitization and subsequent disease development. The inability to develop a hierarchy of specific aeroallergens and their role in initiating an allergic response is primarily due to the cross-reactivity of aeroallergens – the ability of two or more aeroallergens, due to biochemical similarities, to elicit an allergic response in an individual who may be sensitized to only one of them. Multiple studies have found cross-reactivity among the aeroallergens implicated in causing allergenic illnesses (Table 2-11). Some aeroallergens not identified as being clinically relevant have shown cross-reactivity with those that are, which further complicates the ability to identify allergens associated with causing allergenic illnesses. For example, short ragweed is identified as a major cause of allergic rhinitis, but giant, false, and western ragweed all cross-react with short ragweed, which could result in an allergic response in a sensitized individual exposed to any of the giant ragweeds (White and Bernstein, 2003). Cross-reactivity is not specific to pollens; it has also been observed in mold and among asthma-related indoor allergens as well (Andersson et al., 2003; Halonen et al., 1997).

Table 2-11. Cross-reactivity of major clinically relevant aeroallergens

Tree Pollen			
Latin Name	**Common Name**	**Cross Reactive Aeroallergen(s)**	**Reference**
Acer negundo	Box-elder	Red maple	(Phipatanakul, 2005)
Acer rubra	Red maple	Box-elder	(Phipatanakul, 2005)
Alnus rubra	Alder	Paper birch, White Oak, Red Oak	(White and Bernstein, 2003)
Betula papyrifera	Paper birch	Alder, White Oak, Red Oak	(White and Bernstein, 2003)
Carya illinoensis	Pecan	Black walnut	(White and Bernstein, 2003)
Fraxinus americana	White ash	Olive	(White and Bernstein, 2003)
Juglans nigra	Black walnut	Pecan	(White and Bernstein, 2003)
Olea europaea	Olive	White ash	(White and Bernstein, 2003)
Quercus alba	White oak	Paper birch, Alder, Red oak	(White and Bernstein, 2003)
Quercus rubra	Red oak	Paper birch, Alder, White oak	(White and Bernstein, 2003)
Ulmus americana	American elm	Chinese elm, Siberian elm	(Phipatanakul, 2005)
Ulmus parvifolia	Chinese elm	American elm, Siberian elm	(Phipatanakul, 2005)
Ulmus pumila	Siberian elm	American elm, Chinese elm	(Phipatanakul, 2005)
Grass Pollen			
Latin Name	**Common Name**	**Cross Reactive Aeroallergen**	**Reference**
Cynodon dactylon	Bermuda	Johnson	(White and Bernstein, 2003)
Festuca elatior	Meadow fescue	Bahia	(White and Bernstein, 2003)
Holcus halepensis	Johnson	Bermuda	(White and Bernstein, 2003)
Lolium perenne	Rye	Bahia	(White and Bernstein, 2003)
Paspalum notatum	Bahia	Timothy, Meadow Fescue, Rye	(White and Bernstein, 2003)
Phleum pretense	Timothy	Bahia	(White and Bernstein, 2003)
Weed Pollen			
Latin Name	**Common Name**	**Cross Reactive Aeroallergen**	**Reference**

Amaranthus retroflexus	Red root pigweed	Russian thistle	(Phadia, 2002)
Ambrosia artemisiifolia	Short ragweed	Mugwort	(White and Bernstein, 2003)
Artemisia vulgaris	Mugwort	Ragweed	(White and Bernstein, 2003)
Salsola kali	Russian thistle	Red root pigweed	(Phadia, 2002)
Mold			
Latin Name	**Common Name**	**Cross Reactive Aeroallergen**	**Reference**
Alternaria alternata	N/A	*Epicoccum nigrum*	(Levetin, 2006)
Epicoccum nigrum	N/A	*Alternaria alternate*	(Levetin, 2006)
Indoor Allergens			
Latin Name	**Common Name**	**Cross Reactive Aeroallergen**	**Reference**
Dermatophagoides farinae; Dermatophagoides pteronyssinus	Arthropods (domestic mites)	Cross reactive with one another	(Phipatanakul, 2005)
Note: This table includes only those aeroallergens that have been implicated as being cross-reactive with another aeroallergen.			

3. HISTORICAL TRENDS IN AEROALLERGENS AND ALLERGENIC ILLNESSES IN THE UNITED STATES

The amount and distribution of aeroallergens, as well as the prevalence of allergenic illnesses in the U.S. is likely to change over time. This section examines past trends and current levels of both aeroallergens and allergenic illnesses.[7]

3.1. AEROALLERGENS

During approximately the last thirty years, numerous studies have examined historical trends in aeroallergen production and distribution, most notably for pollens and some types of mold. Most studies observing pollen levels over time have found year-to-year fluctuations but no major trends. Observing pollen trends in Philadelphia and Southern New Jersey, Dvorin et al. (2001) found that although all pollen levels fluctuate yearly, tree pollen demonstrates a larger fluctuation than either grass or weed pollen. In a 21-year study of airborne pollen levels in Switzerland, Clot (2003) observed no major change in the yearly pollen abundance for the majority of pollen species studied.[8]

In some studies the overall abundance of pollen in an area did change dramatically over time, but this was due to specific non-climatic factors. For example, Burr (1999) cites a study observing pollen trends conducted at three sites within the UK – London, Cardiff, and Derby – by Emberlin et al. (1999), which found pollen levels decreased in Derby and London while they significantly increased in Cardiff. The substantial changes in pollen levels at each site were attributed to changes in land use that occurred during the study period (Burr, 1999). Similarly, Sneller et al. (1993) found a dramatic increase in pollen levels over five decades in Tucson, Arizona as a result of the importation of certain tree species to the city due to changing architectural and landscape preferences. With the exception of cases of anthropogenic changes, which altered the abundance of aeroallergen levels observed in Emberlin (1994) and Sneller et al. (1993), however, pollen levels have tended to remain fairly consistent on a year-to-year basis.

Some studies have shown that the duration of the pollen season has remained fairly stable over time. In their six-year study of pollen levels in Philadelphia and Southern New Jersey,

[7] This section of the report does not address other factors that have been implicated in affecting the overall trends of aeroallergens, specifically climate change.

[8] Clot (2003) found that *Alnus*, *Taxus/Cupressaceae*, and *Artemisia* pollen were significantly higher at the end of the 20-year study then at the beginning, but it is unclear why the pollen levels for these four species increased over time.

Dvorin et al. (2001) observed that the pollen season did not change significantly. They found late April to early May and early September consistently represented the significant spring and fall periods, respectively, of airborne pollen prevalence (Dvorin et al., 2001). These findings agree with those of Kosisky and Carpenter (1997), who found in a study observing tree pollens over a five-year period in Washington, D.C. that April remained the month with the highest weekly average concentrations over the study period (Kosisky and Carpenter, 1997).

Although these studies suggest that the duration of the pollen season has been relatively stable, other studies suggest a trend towards an earlier initiation of the pollen season. Emberlin et al. (2002) and Clot (2003) both observed a shift in the timing of the pollen season during long-term pollen observation studies. Clot (2003) observed strong trends towards an earlier pollen season for tree pollens and a less remarkable shift for grass and weed pollens. Emberlin et al. (2002) observed a trend towards an earlier start date for the *Betula* (Birch) pollen season by about 6 days, but ranging up to 30 days. Preliminary data suggest that a change in the initiation of the pollen season may not influence its overall duration (Clot, 2003).[9]

While pollen levels have remained fairly consistent over time, this is not the case for mold. The evidence suggests a possible increase in the concentration of some types of mold. *Epicoccum nigrum* has recently been sprayed onto sunflowers to control sunflower head rot (Burge, 2002). A continued increase in the use of *Epicoccum nigrum* and other types of mold as biocontrol agents might increase the proportion of those outdoor mold that are associated with allergenic illnesses in the environment (Burge, 2002). Although the increased use of mold commercially could result in an increase in mold in the environment, an increase in the abundance of *Alternaria* has already been observed. In a study conducted in Derby, UK from 1991-1998, Corden and Millington (2001) found a dramatic increase in the number of days with *Alternaria* spore counts above 50 spores/m^3.

The literature does not directly address historical trends for indoor allergens and indoor mold, but some studies, particularly those involving indoor allergens, provide ancillary evidence that the levels of both may have increased. One hypothesis is that high-energy prices have resulted in increased insulation and decreased ventilation in buildings, causing optimal conditions for house dust mite growth (Nielsen et al., 2002). A study by Hirsch et al. (2000) supports this hypothesis, finding that insulated windows and central heating increased house dust mite concentrations in carpets and mattresses and *A. fumigatus* in carpet dust in apartment

[9] Emberlin et al. (2002) did not study the duration of the pollen season.

bedrooms. This evidence, however, is only ancillary. Although there could be a trend towards increased levels of indoor allergens and indoor mold, the evidence is as yet insufficient to support that conclusion.

3.2. ALLERGENIC ILLNESSES

With aeroallergen levels remaining fairly stable, the prevalence of allergenic illness would be expected to remain stable as well. The evidence suggests, however, that this is not the case. The prevalence of allergenic illnesses in the U.S. has increased over the last 30 years (Figure 3-1 and Figure 3-3). This upward trend in the U.S. appears to be mirrored in other countries too. In The Copenhagen Allergy Study, Linneberg et al. (2000) found the prevalence of specific IgE antibodies to at least one allergen in the cohort increased significantly from 1990 to 1998, which coincided with an increase in the prevalence of allergic rhinitis. Linneberg et al. (2000) also cite Nakagomi et al. (1994), which found an increase in IgE positivity from 21.4 percent in 1978 to 39.4 percent in 1991 to one or more of 16 allergens in schoolgirls in Japan.

Although these findings and data collected via surveys by the U.S. Centers for Disease Control and Prevention (CDC) suggest the prevalence of allergenic illnesses has increased over time, Phipatanakul (2005) notes that epidemiological studies examining the prevalence of allergenic illness lack objective allergen skin testing data; therefore, the actual prevalence of allergenic illnesses may not be accurately depicted, and the allergenic illness trends described here should be viewed with caution.

The perceived increase in allergenic illnesses over time has not been adequately explained. It might be expected that an increase in the prevalence of allergenic illnesses would imply a corresponding increase in the levels of their associated aeroallergens, but as noted above, this has not occurred. Therefore, there must be other factors to explain the increase in the prevalence of allergenic illnesses. The rate at which the prevalence of respiratory allergies have been increasing argues against the trend being solely attributed to genetic factors. One theory, known as the "hygiene hypothesis," suggests that larger family size, exposure to respiratory infections, microbial exposure, and exposure to other bacterial components such as endotoxin have a protective effect against the development of hay fever and other allergic diseases (Phipatanakul, 2005). The smaller family sizes now observed in Western countries have reduced children's exposure to cross infections, which may prevent the development of hay fever (Von Hertzen, 1998). Evidence supporting this hypothesis comes from studies that have found a correlation between the prevalence of allergic rhinitis and the number of older siblings, implying

that increased family size reduces a child's risk of developing allergic rhinitis (Phipatanakul, 2005). A similar protective effect has also been observed for children who have early exposure to day care after one year of age (Phipatanakul, 2005). Unfortunately, recent studies have been unable to identify single or multiple determinants in lifestyle or home environment that could significantly affect disease development (Linneberg et al., 2000).

3.2.1. Asthma

Over the last thirty years there has been a significant increase in the prevalence of asthma (Figure 3-1). It is unclear what is driving the observed increase in asthma prevalence, because many factors may influence its development. As noted above, aeroallergens have a significant impact on asthma development, but it is unclear what percentage of asthma cases each year can be attributed to exposure to aeroallergens and aeroallergens have also not shown a corresponding increase that could potentially account for some of the increase in asthma prevalence (Nielsen et al., 2002).

The increase in the prevalence of asthma has been particularly acute among individuals of low socioeconomic status (Phipatanakul, 2005; Hamilton and Eggleston, 1997). This has been believed to be primarily the result of higher levels of exposure to indoor allergens, especially cockroach, in this population (Phipatanakul, 2005; Hamilton and Eggleston, 1997). This trend may extend beyond the inner city; recently cockroach allergen has been found to be more common in suburban middle class homes with asthmatic children than previously thought (Hamilton and Eggleston, 1997; Hamilton, 2005).

Figure 3-2 shows that asthma prevalence has increased in all regions of the U.S., with the most significant increase occurring in the Northeast. Some recent studies have shown a possible stabilizing of asthma prevalence, but it is unclear if this is a true effect or a result of multiple definitions being used to identify asthma ((Lawson and Senthilselvan, 2005)). These studies have not shown consistent results across geographic regions or demographic characteristics, but instead have shown a heterogeneity of patterns of asthma diagnosis, symptoms, and allergic sensitization ((Lawson and Senthilselvan, 2005)). An overall assessment of the trends observed in asthma prevalence is thus difficult because of the heterogeneity of the disease and the fact that there is no recognized standard used to make a diagnosis ((Lawson and Senthilselvan, 2005)).

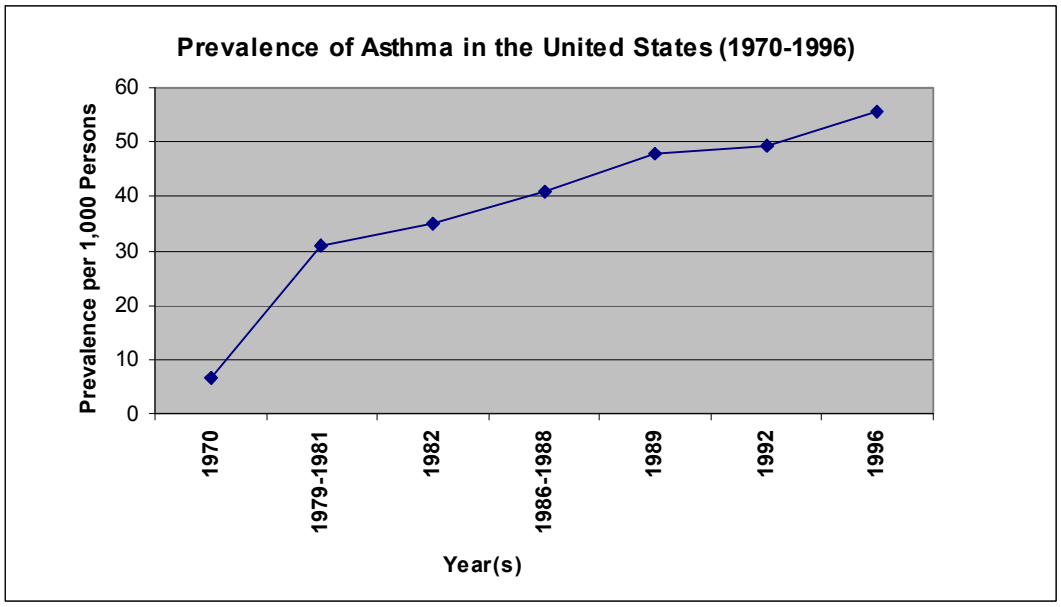

Figure 3-1. Prevalence of asthma in the United States 1970 through 1996.[10]

3.2.2. Allergic Rhinitis

Consistent with the findings for asthma, there has also been an increase in the prevalence of allergic rhinitis (hay fever) in industrialized countries over the last thirty years (Figure 3-3). Similarly, because this increase is not accompanied by a corresponding increase in pollen abundance, its origins remain unclear (Clot, 2003).

[10] *Sources:*

National Center for Health Statistics (NCHS) and C. S. Wilder. *Prevalence of Selected Chronic Respiratory Conditions, United States-1970.* Vital and Health Statistics, 1973. 10(84, DHEW Publication No. (HRA) 74-1511).,

National Center for Health Statistics (NCHS) and J. G. Collins. *Prevalence of selected chronic condtions, United States, 1979-81.* Vital and Health Statistics, 1986. 10(155, DHHS Pub. No. (PHS) 86-1583.).,

National Center for Health Statistics (NCHS). *Current Estimates from the National Health Interview Survey, United States, 1982.* Vital and Health Statistics, 1985. 10(150, DHHS Pub No. (PHS) 85-1578).,

National Center for Health Statistics (NCHS) and J. G. Collins. *Prevalence of Selected Chronic Conditions, United States, 1986-88.* Vital and Health Statistics, 1993. 10(182, DHHS Publication No, (PHS) 93-1510).,

National Center for Health Statistics (NCHS), P. F. Adams, and V. Benson. *Current Estimates from the National Health Interview Survey, 1989.* Vital and Health Statistics, 1990. 10(176, DHHS Publication No. (PHS) 90-1504).,

National Center for Health Statistics (NCHS), C. S. W., V. Benson, and M. A. Marano. *Current Estimates from the National Health Interview Survey, 1992.* Vital and Health Statistics, 1994. 10(189, DHHS Publication No, (PHS) 94-1517).,

National Center for Health Statistics (NCHS), et al. *Current Estimates of the National Health Interview Survey, 1996.* Vital and Health Statistics, 1999. 10(200, DHHS Publication No. (PHS) 99-1528).

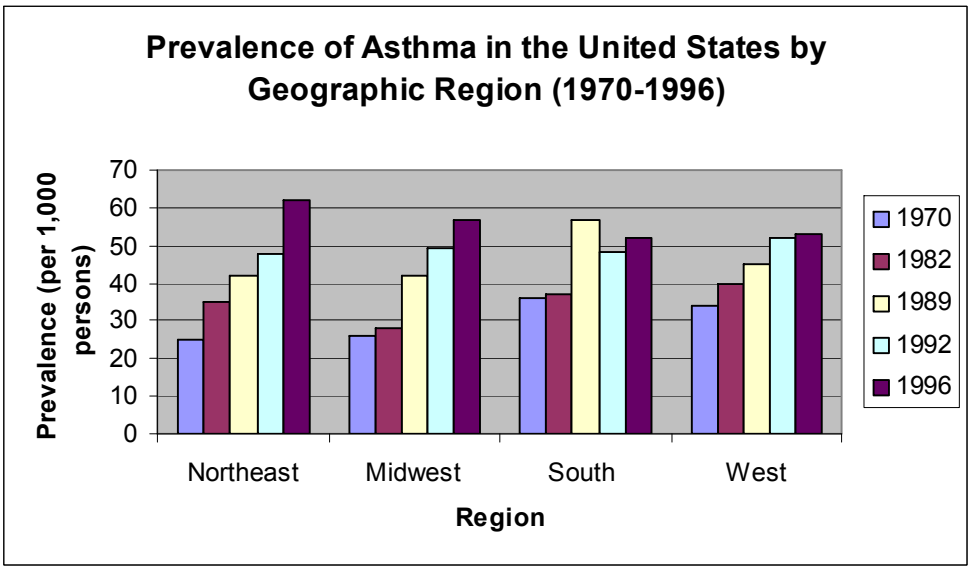

Figure 3-2. Prevalence of asthma in the United States by geographic region 1970 through 1996.[11]

Numerous studies have shown that, unlike asthma, allergic rhinitis has a higher prevalence in individuals of higher socioeconomic status (Phipatanakul, 2005). It is unclear why this might be the case, but according to the hygiene hypothesis, a decrease in exposure to certain infections may account for this observation.

As shown in Figure 3-4, there have been significant increases in the prevalence of allergic rhinitis in all regions of the United States, with the greatest number of cases consistently occurring in the West. The sampling protocols used to obtain prevalence rates, however, may not accurately reflect the true prevalence. Studies have observed the prevalence primarily

[11] *Sources:*
National Center for Health Statistics (NCHS) and C. S. Wilder. *Prevalence of Selected Chronic Respiratory Conditions, United States-1970.* Vital and Health Statistics, 1973. 10(84, DHEW Publication No. (HRA) 74-1511).,
National Center for Health Statistics (NCHS). *Current Estimates from the National Health Interview Survey, United States, 1982.* Vital and Health Statistics, 1985. 10(150, DHHS Pub No. (PHS) 85-1578).,
National Center for Health Statistics (NCHS), P. F. Adams, and V. Benson. *Current Estimates from the National Health Interview Survey, 1989.* Vital and Health Statistics, 1990. 10(176, DHHS Publication No. (PHS) 90-1504).,
National Center for Health Statistics (NCHS), C. S. W., V. Benson, and M. A. Marano. *Current Estimates from the National Health Interview Survey, 1992.* Vital and Health Statistics, 1994. 10(189, DHHS Publication No, (PHS) 94-1517).,
National Center for Health Statistics (NCHS), et al. *Current Estimates of the National Health Interview Survey, 1996.* Vital and Health Statistics, 1999. 10(200, DHHS Publication No. (PHS) 99-1528).

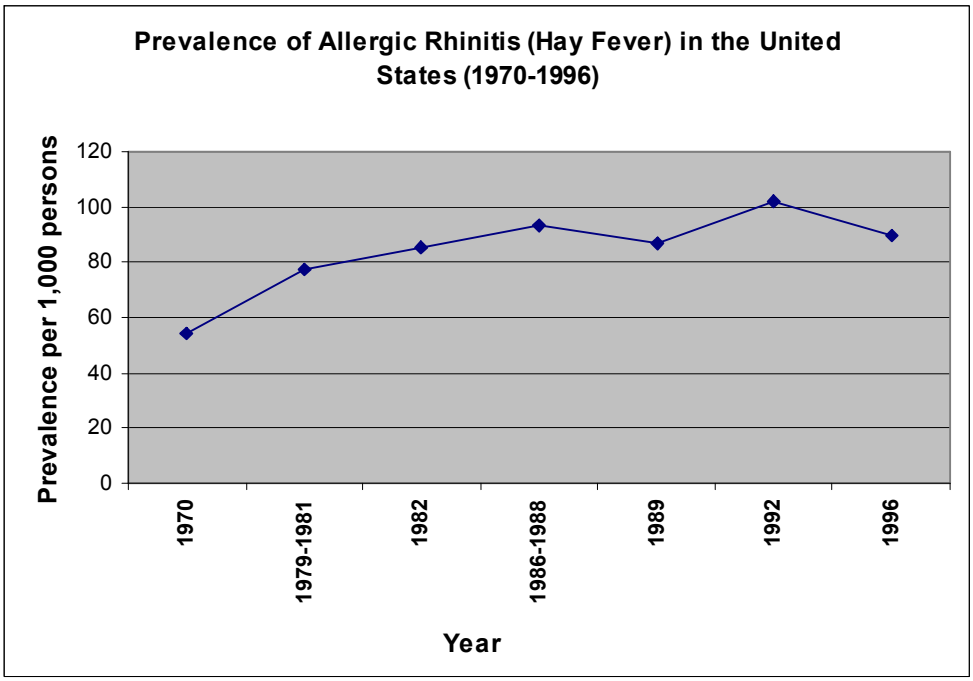

Figure 3-3. Prevalence of allergic rhinitis (hay fever) in the United States 1970 through 1996.[12]

through two avenues: questionnaires/interviews and physician diagnosis, both of which tend to underestimate the actual prevalence of the disease (Phipatanakul, 2005).

[12] *Sources:*

National Center for Health Statistics (NCHS) and C. S. Wilder. *Prevalence of Selected Chronic Respiratory Conditions, United States-1970.* Vital and Health Statistics, 1973. 10(84, DHEW Publication No. (HRA) 74-1511).,

National Center for Health Statistics (NCHS) and J. G. Collins. *Prevalence of selected chronic condtions, United States, 1979-81.* Vital and Health Statistics, 1986. 10(155, DHHS Pub. No. (PHS) 86-1583.).,

National Center for Health Statistics (NCHS). *Current Estimates from the National Health Interview Survey, United States, 1982.* Vital and Health Statistics, 1985. 10(150, DHHS Pub No. (PHS) 85-1578).,

National Center for Health Statistics (NCHS) and J. G. Collins. *Prevalence of Selected Chronic Conditions, United States, 1986-88.* Vital and Health Statistics, 1993. 10(182, DHHS Publication No, (PHS) 93-1510).,

National Center for Health Statistics (NCHS), P. F. Adams, and V. Benson. *Current Estimates from the National Health Interview Survey, 1989.* Vital and Health Statistics, 1990. 10(176, DHHS Publication No. (PHS) 90-1504).,

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National Center for Health Statistics (NCHS), et al. *Current Estimates of the National Health Interview Survey, 1996.* Vital and Health Statistics, 1999. 10(200, DHHS Publication No. (PHS) 99-1528).

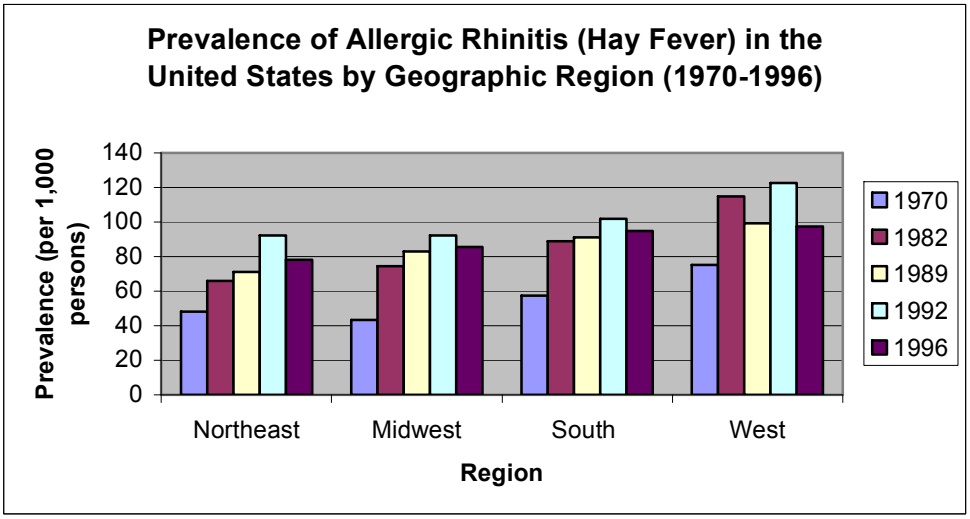

Figure 3-4. Prevalence of allergic rhinitis (hay fever) in the United States by geographic region 1970 through 1996.[13]

3.2.3. Atopic Dermatitis

There is only limited information on the historical trends of atopic dermatitis. Approximately 15 to 20 percent of the worldwide childhood population is currently afflicted with the illness, but considerable evidence suggests the prevalence of atopic dermatitis may be increasing above the 15 to 20 percent now observed (O'Connell, 2004). Because of the controversy surrounding the diagnosis of atopic dermatitis, as discussed by Whitmore et al. (1996), it will be possible to accurately reflect the prevalence of atopic dermatitis over time only when studies are conducted with adequate controls.

[13] *Sources:*

National Center for Health Statistics (NCHS) and C. S. Wilder. *Prevalence of Selected Chronic Respiratory Conditions, United States-1970.* Vital and Health Statistics, 1973. 10(84, DHEW Publication No. (HRA) 74-1511).,

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4. IMPACTS OF CLIMATE CHANGE ON AEROALLERGENS

Climate change, caused in part by increased atmospheric CO_2 concentrations, may result in alterations or increases in temperature, precipitation, humidity, and extreme weather events. These factors, including CO_2 concentration, can impact the production, distribution, dispersion and allergen content of aeroallergens and the growth and distribution of organisms that produce them (i.e., weeds, grasses, trees, and fungus). Shifts in aeroallergen production and, subsequently, human exposures may result in changes in the prevalence and severity of symptoms in individuals with allergenic illnesses. This section reviews the potential and observed impacts of climate change on aeroallergen production, distribution, dispersion, and allergen content, and discusses how climate-related changes in aeroallergen production may lead to indirect impacts on allergenic illnesses.

4.1. PRODUCTION OF AEROALLERGENS

It has generally been observed that the presence of elevated CO_2 concentrations and temperatures stimulates plants to increase photosynthesis, biomass, water use efficiency, and reproductive effort (The Center for Health and the Global Environment, 2005; Jablonski et al., 2002). However, these relationships are complex and likely differ among taxa and species. Short-term responses to climate change (i.e., over 10 to 20 years) might involve changes in plant phenology and biochemistry. This is consistent with a recent meta-analysis that indicates the current rate of phenologic advance is 5 days per decade for numerous species of plants (Root et al., 2003). A key finding of the National Assessment Synthesis Team (Mellilo et al., 2001) was that over the next few decades climate change is very likely to lead to increased plant productivity and carbon storage for many parts of the country, especially those areas that become warmer and wetter (Melillo et al., 2001; Joyce et al., 2001). We might infer, then, that pollen production in these areas, on average, would be expected to increase. The NAST also found that areas where soils dry out during the growing season, such as the Southeast under certain scenarios, are likely to see reduced productivity and carbon storage, and hence, less pollen production. The following subsections review specific studies on how climate change may alter plant and fungal reproductive responses in the United States.

4.1.1. Pollens

4.1.1.1. *Tree Pollens*

Research on the potential effects of climate change on tree pollen production in the United States is limited. Researchers have tried to identify important climatic variables for seasonal forecasting of tree pollen seasons, but often these models do not directly take into account climate change and are specific to species and geographic locales outside of the United States. However, to the extent that this research successfully identifies strong predictors of pollen season severity, one can infer that changes in those predictors may directly impact pollen production. Overall, research shows pre-season temperature and precipitation to be the most consistent predictors of tree pollen seasons. The relevant details of studies on tree pollen production are presented below using the framework of start date and pollen season severity.

Levetin (2001) reported that cumulative season total pollen for *Juniperus* (cedar), *Quercus* (oak), *Carya* (hickory and pecan) and *Betula* (birch) increased significantly during a 14-year period beginning in 1987 in Oklahoma. Meteorological data also showed a significant increase in average winter temperatures. Correlations between winter temperatures and pollen totals were not significant. The authors note that the cause of the increasing trend is unknown and could include climate change, urbanization, or evolving landscaping patterns. U.S. researchers examined pollen counts in New England before and after the occurrence of an El-Niño event that started in mid-1997 and continued until the summer of 1998 (Freye, 2001). While El-Niño is a cyclical climatic event not associated with climate change, it can serve as an example of the impact of short-term variability on pollen production. This El-Niño was similar to projected climate change in that precipitation was 2 to 8 inches higher than normal during the winter and spring of 1998 and temperature was 4 to 6 degrees (F) higher than normal during winter of 1998. The authors observed that, relative to 1997 and 1999, maximum pollen counts were higher and occurred about two to four weeks earlier for most tree types during 1998, but a statistical analysis of the difference is not provided. Similarly, Reiss and Kostic (1976) found strong correlations (r^2 range 0.85 to 0.94) between pollen season severity and spring and summer minimum temperatures and mid-spring precipitation amounts in New Jersey, but they did not specify pollen types. Oak pollen counts in the San Francisco Bay Area were strongly correlated with total rainfall during the previous year (Weber, 2003).

In Cordoba, Spain, researchers studied the influence of meterological parameters on *O. europaea* L pollen and found that cumulative variables for temperature and sunlight hours were the most common significant (Students $t < 0.05$) predictors of pollen concentration in regression

analysis (Vazquez et al., 2003). In Poland, researchers found positive significant ($p<0.05$) correlations between air temperature and birch pollen concentration but negative non-significant correlations with poplar pollen, indicating the need for species-specific analysis (Puc and Wolski, 2002).

International research to identify trends in pollen season start dates, using databases including species relevant to the United States, such as birch (*Betula*) and olive (*Olea europaea* L.), is also informative. Even in this case, however, there is limited assessment of changes in pollen production. Long-term pollen monitoring data are available for several locations in Europe, and researchers have analyzed these data for changes in pollen season start dates. Overall, while several analyses show earlier start dates, there is a clear indication that the effect may be specific to species and geography. Clot (2003) analyzed time series of 21 years of data in Switzerland. Using the Seasonal Pollen Index (SPI), Clot (2003) found that there was no major change in the abundance of pollen among most of the 25 taxa studied. There were a few exceptions to this; linear trend analysis showed increases ($P<0.05$) of pollen quantities were observed for *Alnus* (alder), *Ambrosia* (ragweed), *Artemisia* (mugwort), and *Taxus/Cupressacaea* (yew/cypress) and decreases were seen in *Ulmus* (Elm). Clot (2003) also observed that the duration of the pollen season did not appear to change but that 71 percent of the start or end dates of the pollen season occurred significantly earlier in the year. The average observed advance was 0.84 days/year and was stronger in trees than in weeds and grasses (Clot, 2003).

Frenguelli (2002) reviewed 20 years of data, from 1982 to 2001, on airborne pollen and mean air temperature in Perugia (central Italy) and reported an increase in annual mean temperature of 0.7 Celsius, with the months of February, May, June, and August experiencing the greatest increases. Results show the pollen seasons of most taxa starting earlier, and for several taxa the duration is shorter as well. An exception is *Urticaceae* (Nettle), which experienced an increased duration.

Emberlin et al. (2002) investigated relationships between changes in start dates of birch pollen seasons and changes in spring temperatures, using daily birch pollen counts from six metropolitan cities in Europe from 1982-1999. London, Brussels, Zurich, and Vienna showed trends towards earlier start dates, and a regression analysis indicated the mean start dates at these sites would advance by about 6 days over the next 10 years (Emberlin et al., 2002). In Kevo, Finland the opposite effect was observed, with cooler springs and therefore later starts of 6 days on average per decade. While the data are suggestive of changes in the timing of pollen season

starts, there was no assessment of whether or not this would lead to greater pollen production or allergen content.

In Andalusia, Spain, researchers Galan et al. (2005) compared the start of *O. europaea* L. pollen season and heat accumulation over a selected temperature threshold while investigating the influence of topography on the results. The authors used pollen and meterological data from 1982-2001 for five sites in central and eastern Andalusia. An incidental finding was that all of the study sites had increasingly earlier start dates during the study period. The authors used the Regional Climate Model (Hadley Meteorological Centre, UK) to estimate the impact of predicted climate change on the olive tree's flowering phenology. Their results indicated an advance of 1-3 weeks by the end of the century. As with previous research, however, it is not clear how a shift in pollen season start may affect production. Researchers have also found advances in start dates in Japanese cedar (*Cryptomeria japonica*) as well as an increased pollen count and an extended pollen season (Teranishi et al., 2000).

Glassheim et al. (1995) examined the short-term (i.e., 1-day lag) relationship between observed tree pollen counts from elm, juniper, maple, cottonwood, and pine in Denver, Colorado and a selection of independent meterologic variables. With the exception of pine, none of the tree pollens studied for the five-year period appeared affected by temperature. However, this short-term type of analysis may have limited relevance to seasonal pollen production and climate change. The authors did observe modest negative correlations with both precipitation and relative humidity, which is likely due to 'scrubbing' or particle adsorption (to raindrops), which removes pollen from the air.

In summary, preseason temperature and precipitation are important predictors of tree pollen production. To the extent that climate change results in changes in these two meterological variables, then, we would expect corresponding changes in tree pollen production, all else equal, although the evidence to date suggests that the nature of the changes may be region and species-specific. One U.S. study observed a trend of increasing pollen production in Oklahoma (Levetin, 2001). Changes in phenology (start date) appear to be a relatively consistent finding, especially for European species. However, in most studies, the change in start date did not correspond to a lengthening of the pollen season. Additionally, it is unclear whether the phenologic changes have an effect on total pollen production or allergen content. The literature does not provide clear evidence of changes in phenology in U.S. species; however, this may be due to the unavailability of data.

4.1.1.2. *Grass Pollens*

As with tree pollens, research on the potential effects of climate change on grass pollen production in the United States appears to be limited. Overall, forecast models show temperature and precipitation to be the most consistent predictors of grass pollen seasons, but these models do not directly take into account climate change and are again specific to geographic locales most of which are non-U.S.

As described above, U.S. researchers Freye et al. (2001) examined pollen counts in New England before and after the occurrence of an El-Niño event. With the exception of an earlier peak in 1998, overall grass pollen concentrations did not appear to be affected. The details of selected research are reviewed below.

Contrary to general predictions of increased production, one of the longest data series for grass pollen suggests earlier starts but declining annual counts and severity in England. These changes are most likely due to land use trends such as declining agriculture and pasture areas (Emberlin, 1994). In England, Emberlin et al. (1999) used data from 1961-1993 at Cardiff, Derby, and London to predict total seasonal catches, the severity of seasons in terms of the number of days with high counts, and the start dates of seasons. The authors found that at two of the sites (Derby and London) the annual counts and severity declined but at different rates, while at the third site (Cardiff) annual counts and severity increased in the 1960s, declined in the 1970s, and rose again in the 1980s. There was a trend towards earlier start dates at the Derby site, a less pronounced trend at Cardiff, and a trend towards later starts in London. In models, the most important climatic variables influencing the broad features of grass pollen seasons (e.g., seasonal cumulative pollen counts and peaks) were cumulative rain and temperature, but the importance of these variables differed by site and was overshadowed by the influence of land use. The authors conclude that the contrasting patterns both in pollen records and land use changes among the three sites underscore the need for regional data. In a prior analysis, they reached similar conclusions, suggesting that changes in pollen production will vary by region such that many central areas north of the Alps could have longer grass pollen seasons while grass pollen concentrations are likely to decrease in the southern Mediterranean area during summer months (Emberlin, 1994). The regional differences reflect the interaction of climate change at different latitudes and topography, i.e., reduced snow cover in the Alps and increasing drought in the Mediterranean; both of which much be evaluated against land use trends as well. In contrast, Clot (2003) reviewed 21 years of grass pollen data from a single trap in Switzerland and found

an earlier start date (-14 days) but no significant change in the duration or intensity of the pollen season.

Puc and Puc (2004) analyzed grass pollen seasons in western Poland from 2000 to 2003 to evaluate relationships between metrological parameters and *Poaceae* (Grass) pollen counts. The authors found that air temperature and relative humidity were most consistently correlated with pollen counts.

In Australia, grass pollen accounts for 71 percent of the total atmospheric pollen count (Green et al., 2004). Green et al. (2004) evaluated grass pollen counts and associations with meterological parameters in Brisbane, Australia from 1994 to 1999. The authors found that daily grass pollen counts were positively associated ($p<0.0001$) with maximum and minimum temperature each sampling year. Precipitation was observed to "scrub" or remove pollen grains from the atmosphere during significant periods of rainfall.

Glassheim et al. (1995) examined the short-term (i.e., 1-day lag) relationship between meteorologic variables and grass pollen in Denver, Colorado. The authors found that grass pollen counts during the period 1987-1991 were correlated with high temperature ($r = 0.305$, $p<0.001$) and less so with percent daily sunshine ($r =0.149$, $p<0.006$) and were negatively associated with precipitation ($r=-0.227$, $p<0.001$) and relative humidity ($r = -0.430$, $p<0.006$). Glassheim et al. (1995) also found that correlations were not consistent from year to year, suggesting the intra-seasonal meteorologic conditions that determine pollen counts may vary from year to year or that pre-season conditions are more important.

Research in Spain also indicates that pre-season meteorological variables are more important and consistent determinants of seasonal pollen load than are day-to-day weather conditions (Gonzalez Minero et al., 1998). Declines in grass pollen were observed for the period 1987-1996. This was attributed to several years of drought, a potentially important but less predictable feature of climate change. Pre-seasonal rainfall, temperature, and average monthly humidity in Spain were strong predictors of total grass pollen count (Burr, 1999; Gonzalez Minero et al., 1998).

In summary, temperature and precipitation are important predictors of grass pollen production, but more so in terms of pre-season conditions than day-to-day meteorological conditions during the pollen season. The correlation with precipitation is not straightforward as pre-season precipitation may increase pollen counts but in-season precipitation tends to "scrub" or remove pollen from the air. To the extent that climate change results in changes in these two meteorological variables we would expect some changes in grass pollen production. In Europe,

earlier start dates have been observed as well as declines in production but this is attributed to changes in land use. The literature does not provide clear evidence of changes in start dates or production in U.S. species.

4.1.1.3. *Weed Pollens*

Common ragweed (*Ambrosia artemisiifolia* L.) is recognized as a significant cause of allergic rhinitis in the U.S. and there is relatively more research on the response of this weed to climatic variables, especially in the context of climate change. Specifically, several researchers have used controlled environments to examine ragweed response to carbon dioxide levels and temperature, the two covariates for which climate models reliably predict increased levels in the future. The following section details the studies that observed the association between climatic variables and ragweed production.

Ziska and Caufield (2000) tested whether the increase in atmospheric CO_2 concentrations since the Industrial Revolution and projected future increases may alter growth and pollen production of common ragweed. Experiments were conducted using a controlled environmental chamber to measure the growth and pollen production of common ragweed from preindustrial levels of CO_2 (280 umol/mol) to current concentrations (370 umol/mol) to a projected 21st century concentration of 600 umol/mol. The experiments showed that pollen production increased approximately 90 percent from pre-industrial levels to projected levels of carbon dioxide. The observed increase of pollen production from the pre-industrial CO_2 concentrations was due to an increase in the pollen per floral spike (at 370 umol/mol) and number of floral spikes (at 600 umol/mol).

Wayne et al. (2002) found similar results using environmentally controlled greenhouses to grow stands of ragweed plants from seed through flowering stages at CO_2 concentrations of 350 vs. 700 uL/L. The authors found that stand level pollen production was 61 percent higher in elevated versus ambient CO_2 environments ($F=15.16$, $p=0.005$). The authors comment that previous studies with ragweed have shown that adding essential resources to stands (e.g., nitrogen) results in plants investing in proportionally more male pollen-generating reproductive structures versus female pollen-accepting reproductive structures, consistent with the observations of Ziska and Caufield (2000).

Ziska et al. (2003) followed up on the chamber studies conducted by Ziska and Caufield (2000) and Wayne et al. (2002) with field studies. The authors used existing temperature/CO_2 concentration gradients between urban and rural areas in Maryland to examine the quantitative

and qualitative aspects of ragweed growth and pollen production. In addition, pollen was subjected to immunochemical analysis to quantify content of the allergen protein Amb a 1. Average daily (24-hour) values of CO_2 were 30 and 31 percent higher in 2000 and 2001, respectively, within an urban environment vs. at a rural site; air temperature was 1.8 and 2.0 degrees (Celsius) higher in 2000 and 2001, respectively, within an urban environment. Overall, the results demonstrated small but measurable phenologic differences as a function of both temperature and CO_2 concentration. Ragweed grew faster, flowered earlier, and produced significantly greater aboveground biomass and ragweed pollen at urban locations, which have a higher CO_2 concentration and temperature than at rural locations (see Figures 4-1 and 4-2 below). However, a significantly ($p<0.01$) higher quantity of antigenic protein was extracted from pollen at the rural site relative to other sites, suggesting the potential complexity of understanding the public health implications of climate change.

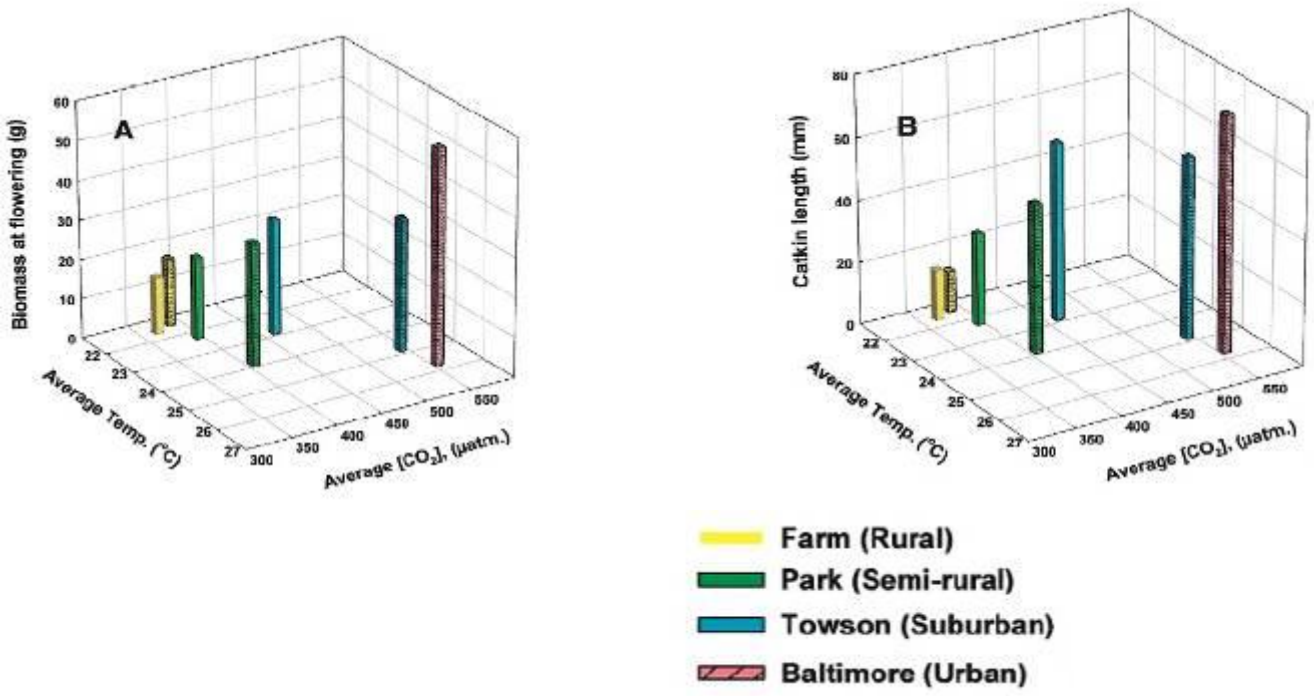
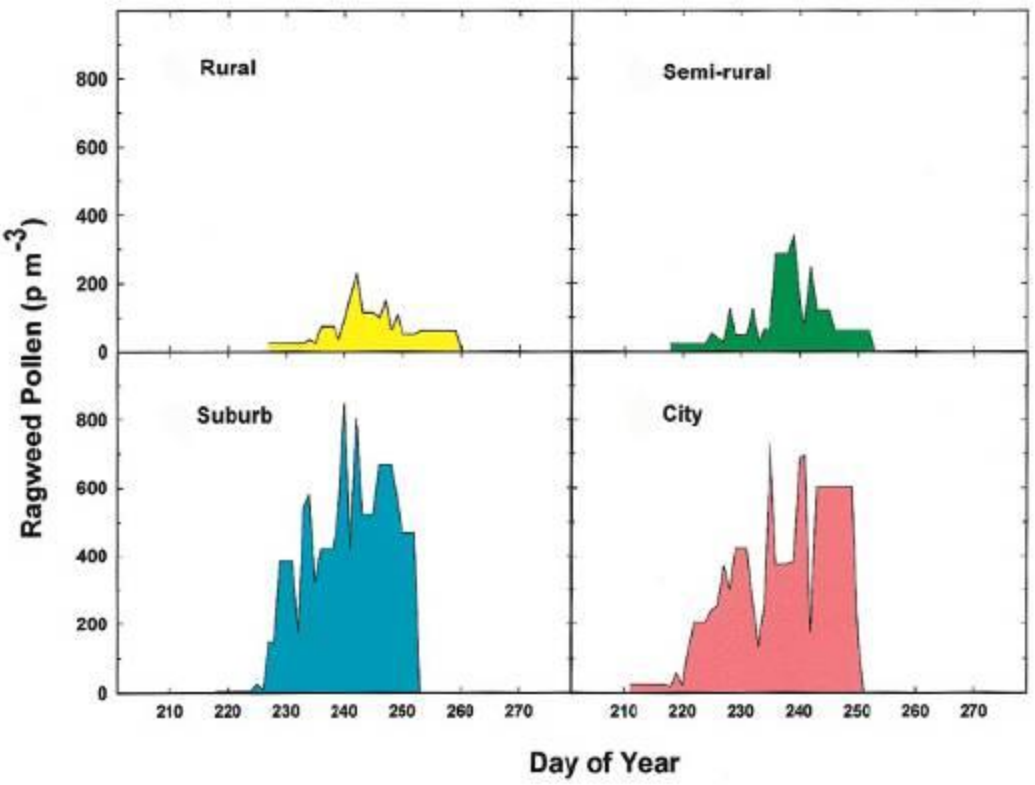


Figure 4-1. Biomass (A) and average catkin length (B) during anthesis for ragweed (per plant) as a function of CO_2 concentration and air temperature during the pollen release period.

Notes: Open bars and *hatched bars* are for 2000 and 2001, respectively. Catkin length is the average for the first 3 weeks after anthesis.
Source: (Ziska et al., 2003), Figure 1.



Notes: Values are numbers of pollen grains per cubic meter of air.
Source: (Ziska et al., 2003), Figure 2.

Figure 4-2. Time course of ragweed pollen production for 4 sites along an urban transect for 2001 as a function of day of year.

Rogers et al. (2006) designed a study to examine the potential impact of earlier arrival of spring and the interaction with CO_2 concentrations on pollen productively in ragweed. The authors used climate controlled greenhouses to test 1) whether variability in the onset of spring alters the rate and magnitude of ragweed development, flowering phenology, and seasonal pollen production; and 2) whether atmospheric CO_2 concentrations directly alter ragweed development and productivity, and influence plant responses to climatic variability. Cohorts of ragweed seeds were released from dormancy at three 15-day intervals and grown at ambient concentration or 700 ppm CO_2 concentration. Carbon dioxide treatment did not significantly affect days to anthesis or anthesis date (see Table 4-1 below).

The authors found the timing of spring onset was the primary factor in a model fit for indicators of plant growth and thus pollen production. At ambient CO_2 concentration the earlier cohort had 54.8 percent greater pollen production than the latest cohort. However, in the early cohort, pollen production was similar under ambient and high CO_2 concentrations but in the middle and late cohorts, high CO_2 concentration increased pollen production by 32 percent and 55 percent respectively compared to ambient CO_2 levels (See Figure 4-3 below). Thus, at elevated CO_2 concentrations pollen productivity appears less sensitive to variability in season onset. The authors predict that in future climates with elevated CO_2 concentrations, pollen production will be just as robust in years with late springs as those with early springs.

Table 4-1. Effects of time of release, CO_2 concentration, and the interaction of time and CO_2 modeled on measures of biomass, reproduction, phenology, and pollen production.

Response	Term	*F*-value[a]	*p*-Value
Pollen count (estimated)	Time	8.49	0.0003
	CO_2	2.54	0.2519
	Time × CO_2	4.39	0.0143
Inflorescence number	Time	2.91	0.0579
	CO_2	13.12	0.0685
	Time × CO_2	3.58	0.0306
Inflorescence weight	Time	40.24	< 0.0001
	CO_2	3.61	0.1979
	Time × CO_2	8.66	0.0003
Aboveground biomass	Time	42.78	< 0.0001
	CO_2	5.06	0.1534
	Time × CO_2	4.13	0.0181
Plant height	Time	23.80	< 0.0001
	CO_2	0.07	0.8125
	Time × CO_2	2.97	0.0546
Days to anthesis	Time	62.40	< 0.0001
	CO_2	1.63	0.3299
	Time × CO_2	1.25	0.2890
Anthesis date	Time	49.42	< 0.0001
	CO_2	1.63	0.3299
	Time × CO_2	1.25	0.2890

[a]For the *F*-statistic, numerator degrees of freedom: time = 2, CO_2 = 1, time × CO_2 = 2; denominator degrees of freedom: time = 134, CO_2 = 2, time × CO_2 = 134 (except for plant height, where denominator degrees of freedom for time and time × CO_2 are 133).

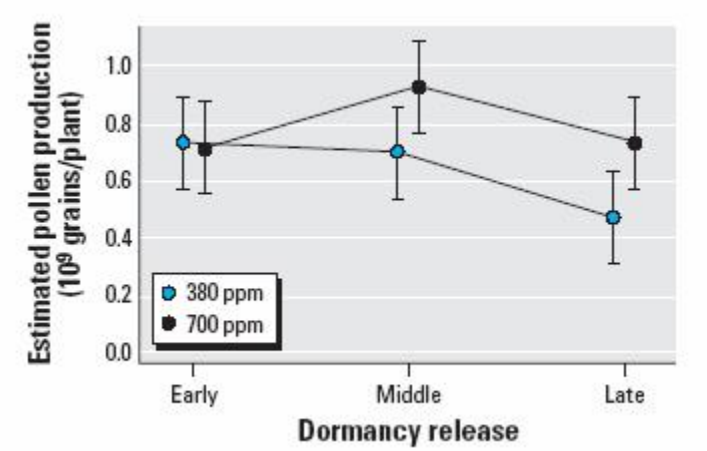
Source: (Rogers et al., 2006), Table 2.

Glassheim et al. (1995) calculated correlation coefficients between observed pollen counts in Denver, Colorado and a selection of independent meteorologic variables. The prevalent weeds analyzed were ragweed, sage, and the chenopod/amaranth group (pigweed). High and low temperature were most strongly correlated with total weed pollen counts during 1987-1991 ($r= 0.603$, $p<0.001$). This is consistent with the work by Rogers et al. (2006), which indicates that an early start to the growing season, as indicated by minimum temperature, results in larger, more productive plants. Similar observations of increased biomass have been observed in CO_2 enrichment experiments with poison ivy (Mohan et al., 2006). While poison ivy does not produce aeroallergens per se, the smoke generated from burning poison ivy can be highly

allergenic.[14] Stefanic et al. (2005) found similar results in the Republic of Croatia, reporting that mean and minimum annual air temperatures were significantly correlated with the amount of ragweed pollen in the air during 2001-2003. Similar to Glassheim et al. (1995), however, the authors found inconsistency in relationships from year to year.

Overall, studies of ragweed in controlled environments and in field studies clearly show that pollen production can be expected to increase with increased temperature and carbon dioxide levels. The experimental results have consistently demonstrated that doubling carbon dioxide levels from current (350 umol/mol) to predicted future levels (i.e., 700 umol/mol) would result in a 60 to 90 percent increase in ragweed pollen production (Ziska and Caufield, 2000; Wayne et al., 2002). Field studies of differences between rural and urban growth patterns also clearly show that ragweed flowers earlier and produces greater amounts of pollen at urban locations compared to rural locations (Ziska et al., 2003). Rogers et al. (2006) confirmed this effect by showing that the timing of spring onset (i.e., early start) was the primary factor in a model fit for indicators of ragweed growth and thus pollen production. The higher allergen concentration in pollen at the rural site, however, highlights the need for caution in making inferences about public health implications.

Figure 4-3. Pollen production in A. artemisiifolia for three springtime dormancy release cohorts grown at two CO_2 concentrations (380 ppm and 700 ppm).



Notes: Error bars indicate 95 percent confidence intervals.
Source: (Rogers et al., 2006), Figure 4.

4.1.2. Mold

Assessment of mold production in response to climate change is mainly derived from observational analyses of long-term data sets. Other assessments of mold production are essentially short-term forecasts of intra-seasonal spore counts and are strongly dependent on whether the mold is a wet- or dry-weather type. Details of these studies are presented below.

[14] Personal communication with J. Patz, June 9, 2006.

Katial et al. (1997) analyzed 8 years of spore count data for *Cladosporium*, *Alternaria*, and *Epicoccum* in Denver, Colorado. The authors found a statistically significant year effect ($p<0.01$), indicating a positive linear trend in *Cladosporium* spore counts over time. No trends were observed for *Alternaria* or *Epicoccum*. In addition, there were no trends in annual temperature, precipitation, or humidity to account for the trend in *Cladosporium* spore counts. The authors suggest urbanization of Denver as a potential explanation for the increase in *Cladosporium* but the mechanism for the increase (e.g., soil disturbance, changing land use, etc) is not clear. They found that for *Cladosporium*, average temperature ($p<0.02$) and humidity ($p<0.01$) were positively associated with spore counts while precipitation was negatively associated with spore counts ($p<0.01$). Neither *Alternaria* nor *Epicoccum* showed correlations with meteorological parameters.

Corden and Millington (2001) examined *Alternaria* concentrations during 1970-1998 in Derby, UK and found an upward trend, which increased markedly after 1992. Their analysis also showed an earlier start date and a longer season over time. This is in contrast to the analysis of grass pollen by Emberlin et al. (1999), which demonstrated earlier start dates but declining annual counts and severity, an effect that was attributed to changes in land use patterns such as declining agriculture and pasturelands. However, it isn't clear if this explanation is also consistent with increasing trends in mold counts observed by Cordon and Millington (2001), who note that bursts of *Alternaria* follow grass mowing and harvest time. Hollins et al. (2004) found that summer temperature was the strongest predictor of the number of days that *Cladosporium* spore concentrations exceeded 4,000 spores/m^3, while there was a negative relationship between precipitation and spore counts.

In Tulsa, Oklahoma Troutt and Levetin (2001) attempted to correlate fungal spore concentrations with meteorological data during May 1998 and May 1999. These two months were selected because they represented climatic extremes – May 1998 was exceptionally dry and May 1999 had unusually high precipitation. The spore types studied were *Cladosporium, Alternaria, Epicoccum, Curvularia, Pithomyces, Drechslera, smut spores, ascospores*, and *basidiospores*. Dry air spora (i.e., *Cladosporium*) were much more prevalent during May 1998 (the dry year). No single multiple regression model successfully predicted all spore concentrations but temperature and dew point were important indicators.

Recent cyclic and extreme weather events have also been implicated in increased mold production. Research in New England found maximum mold counts to be higher and two to four weeks earlier after the occurrence of an El Niño event (Freye, 2001). An examination of New

Orleans housing stock after Hurricane Katrina revealed extensive mold growth (Ratard et al., 2006). The CDC assessed the extent of mold growth in a sample (N=112) of households in the area. Almost half the homes had "visible mold growth" and 17 percent had "heavy mold coverage," defined as ">50 percent coverage on [the] interior wall of most-affected room." Indoor and outdoor air sampling indicated *Aspergillus* spp. and *Penicillium* spp. were the predominant populations (Ratard et al., 2006).

In summary, there is limited, but inconsistent evidence of increasing trends in mold production. Short-term forecasts indicate that while temperature can be a strong predictor of mold concentrations, the effect varies by mold species and geography. At least one U.S. study observed an upward trend in *Cladosporium* but not for co-occurring mold such as *Alternaria* or *Epicoccum*. Another U.S. study observed increases in mold counts after an El Niño event, while in the U.K., an analysis showed increasing trends in *Alternaria.* After Hurricane Katrina, large portions of the housing stock were shown to have extensive mold growth (Ratard et al., 2006). Overall, it is unclear whether climatic factors have any impact on mold production or what other mechanisms may be responsible for variations observed locally.

4.1.3. Indoor Allergens

The indoor environment is the main determinant of variation in indoor allergens. It has been postulated that an increase in the price of energy has resulted in an increase in insulation and a decrease in ventilation in buildings, providing ideal growth conditions for the most prevalent indoor allergen, house dust mites (Nielsen et al., 2002). House dust mites are ubiquitous throughout the U.S. except in very dry climates and at higher altitudes (Phipatanakul, 2005). They have also been found to thrive in warm conditions where the relative humidity is approximately 70 percent (Hamilton, 2005). Cockroaches, on the other hand, are found more predominantly in inner city, urban, and low-income environments, but are also found more commonly than previously thought in suburban middle-class homes (Hamilton, 2005; Phipatanakul, 2005). The concentrations of indoor allergens do not vary with season, in contrast to what is observed for pollens and some mold; instead, they are found perennially. It remains unclear whether indoor allergens will be affected by future climatic changes.

4.2. DISTRIBUTION OF AEROALLERGENS

Long-term responses to climate change (over 50 to 100 years) are likely to include changes in species' ranges or distributions. In some cases extinction may occur. The National Assessment Synthesis Team (NAST, 2001) evaluated continental level shifts in forest and vegetation distribution in the U.S. using various models and scenarios. Climate change scenarios were based on two atmospheric general circulation models (GCM) – the Hadley model and the Canadian model. These models were selected because they represented the higher and lower halves of the range of temperature sensitivity among the GCMs available when the analysis was conducted. For both models, shifts in the distribution of vegetation types were projected with significant variation across geographic regions (Melillo et al., 2001). Other researchers, Davis and Shaw (2001), predict distribution shifts and extinctions based on extensive range shifts seen in studies of fossil records in the U.S. In Europe, Emberlin (1994) also used computer models of future climatic changes resulting from increased CO_2 emissions and discussed the potential impact on the distribution of major allergenic pollen types.

Joyce et al. (2001) conducted a continental-scale analysis, for forest vegetation, of climate-induced changes in the distributions of biomes, community types, species richness, and individual tree and shrub species. Species interactions and the physiological response of species to carbon dioxide are not included in these models. The baseline scenario was the average climate for the 1961-1990 period. Comparisons were made to the transient Canadian and Hadley scenarios for the period 2070 to 2100.

The results of these ecological models suggest that the potential habitats (i.e., distribution) for many tree species in the U.S. are likely to change, in some cases dramatically, by the end of the 21st century. Potential habitats for trees favored by cool environments are likely to shift northward. The habitats of alpine, subalpine spruce/fir, and aspen communities are likely to contract dramatically in the U.S. and largely shift into Canada. Potential habitats are likely to increase in the U.S. for oak/hickory, oak/pine, ponderosa pine, and arid woodland communities.

In a related review and analysis, Melillo et al. (2001) used biogeography model outputs to simulate shifts in the geographic distributions of major plant species by 2090-2099. The authors assume biogeochemical (i.e., production) changes will dominate ecological response to climate change in the next few decades, while species shifts will dominate by the end of the 21st century. Unlike the models used for tree distribution, these models include CO_2 effects. Some of the

major regional changes predicted by the biogeography models for both Hadley and Canadian scenarios are as follows:

- *Northeast*: Forest will remain the dominant natural vegetation but winter deciduous forest may expand at the expense of mixed conifer-broadleaf forest (Hadley). There could be a modest increase in savannas and woodlands (Canadian).

- *Southeast*: Forest remains the dominant natural vegetation but the forest mix changes (Hadley). Alternatively there could be significant expansion of savannas and grasslands at the expense of forest (Canadian).

- *Midwest*: Under both simulated climates (Hadley and Canadian) forest remains the natural vegetation, but the mix of forest types changes.

- *Great Plains*: Two of three models project an increase in woodiness while one (Hadley) does not. Canadian model suggests no change or a slight decrease in woodiness.

- *West*: Forest ecosystems grow at the expense of desert ecosystems (Hadley and Canadian)

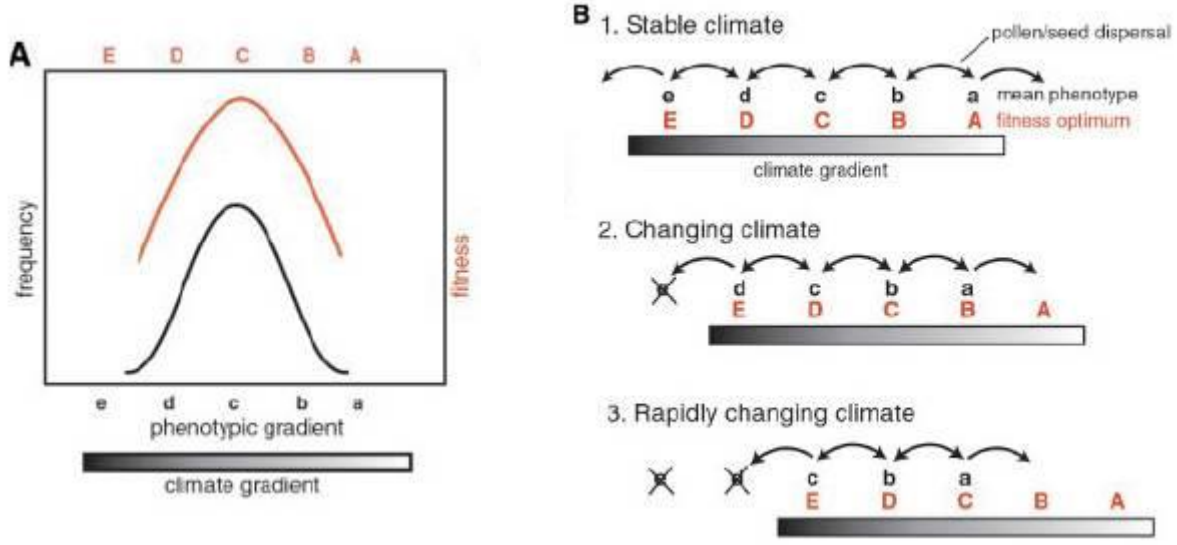
- *Northwest*: Forest area grows slightly (Hadley and Canadian).

How well plants and trees actually track changes in potential habitats will be influenced by their dispersal abilities and disturbances in their environments. Davis and Shaw (2001) note that changes in geographic distribution are so frequently documented in the fossil record that range shifts are seen as the expected plant response to future climate change. These authors use fossil records of trees and cite evidence of genetic adaptation to climate to argue that the interplay of adaptation and migration has been central to the biotic response to climate change. The authors conclude that unprecedented rates of climate change anticipated to occur in the future, coupled with land use changes that impede gene flow could result in extinctions of many taxa (See Figure 4-4 below).

Other research has relied on computer models of future climatic changes resulting from increased CO_2 emissions to gauge the potential impact on the distribution and abundance of major allergenic pollen types in Europe (Emberlin, 1994). The results suggest an extension of the northern limit of birch by several hundred kilometers and a corresponding increase in height

of the altitudinal tree line and contraction of the range in the south. Emberlin indicates that olive trees and ragweed could also experience a northward expansion.

Figure 4-4. (A) Schematic depiction of phenotypic frequencies (mean phenotype 5 c) for a population at a location along a climate gradient where fitness maximum is C. (B) Schematic depiction of fitness optima (red) for a species that ranges across a climate gradient.



Notes: Adaptive differentiation of population phenotypes is shown in black; arrows indicate gene flow through pollen and seed dispersal. Spatial distributions of the climate gradient, fitness optima, and phenotypic frequencies are shown for three conditions: 1, stable climate; 2, slowly changing climate; and 3, rapidly changing climate. *Source:* (Davis and Shaw, 2001), Figure 5.

In summary, long-term responses to climate change (over 50 to 100 years or more) are likely to involve range or distribution shifts in species, with possible extinction in some cases. Trees favoring cool environments, such as maple and birch, are likely to shift northward out of the U.S. entirely, thus dramatically altering the pollen distribution associated with them. Under certain scenarios, the Southeast will experience significant warming trends leading to an expansion of savannas and grasslands at the expense of forest, again altering the presence of major aeroallergens in large regions of the country.

4.3. DISPERSION

There has been only limited research on how climate change could effect the dispersal of pollen and mold. However, there are cases of both pollen and dust being dispersed long distances from its release sites. For example, long distance dispersion of *Juniperus ashei* pollen

has been routinely observed in Tulsa, Oklahoma (Van de Water et al., 2003). The nearest upwind sources of *J. ashei* pollen are 200 to 600 km from their deposition site (Tulsa). Emberlin (1994) suggests that in Europe increased strength of westerly winds due to climate change will enhance the long-range transport of birch pollen already observed to take place from north and central Europe to Scandinavia. Transcontinental transport of dust particulates has also been observed (Husar et al., 2001). During April 1998, two large dust storms occurred over the Gobi desert (Mongolia and north central China). The dust plume crossed the Pacific Ocean and resulted in strong spikes in particulate matter concentrations 10 days later (April 29) along the west coast of the United States (Husar et al., 2001).

To the extent that climate change results in altered wind patterns and increased extreme weather events, one might expect corresponding changes in dispersion patterns of pollen and mold.

4.4. Allergen Concentration

Allergic symptoms are related to pollen in a dose-response manner (Singer et al., 2005). While pollen concentration has been taken as the indicator of potential dose, the underlying mechanism for allergic symptoms comes in part from the protein allergens (antigen) in the pollen (Singer et al., 2005; Ahlholm et al., 1998). Recent research has examined the influence of meteorological variables such as temperature and carbon dioxide on the concentration of allergen protein, or the allergenicity[15], of pollen produced by ragweed and birch. The major allergen proteins in ragweed and birch are Amb a 1 (Antigen E) and Bet v 1, respectively.

Using controlled environmental chambers, Singer et al. (2005) evaluated how Amb a 1 allergen concentrations changed in response to rising carbon dioxide concentrations. The authors used an enzyme-linked immunoabsorbent assay (ELISA) to quantify Amb a 1 in protein extracted from pollen of *A. artemisiifolia* grown at different CO_2 concentrations in a previous experiment. The CO_2 concentrations were 280, 370, and 600 umol/mol. A key finding was that, while total pollen protein remained unchanged, Amb a 1 concentrations increased as a function of CO_2 concentrations. Relative to pollen grown at current CO_2 concentrations (i.e., 370 umol/mol), pollen grown at 700 umol/mol contained 1.6 times more Amb a 1 allergen ($p<0.01$) (see Table 4-2 below). The authors note that recent and projected increases in CO_2

[15] Allergenicity refers to the degree to which a protein is likely to elicit an allergic response. However, the term is periodically used in the literature in reference to pollen protein concentrations.

concentrations could directly increase the allergen concentrations in ragweed pollen and consequently the prevalence and/or severity of seasonal allergic disease. They also point out, however, that genetic and abiotic factors governing allergen expression will need to be better established to fully understand these data and their public health implications.

Ahlholm et al. (1998) investigated the impact of genetics and temperature on the allergen content of birch (*B. pubescens*) pollen by studying trees of 10 half-sib families. Pollen samples were collected from two tree line gardens where the daily mean temperatures were different during the growing season due to altitude differences between the gardens. The temperature difference was approximately 1.0 to 2.5 degrees Celsius. After controlling for descendant group, the authors found that IgE-immunoblotting responses were stronger in sera exposed to pollen grown at the higher temperature. It is unclear whether the effect originated during the previous or the current growing season. Differences in allergen concentration were also seen between different progenies of trees. The authors suggest the lower soil temperature, which limits nutrient (i.e., nitrogen) uptake and thus the rate of allergen synthesis, as a possible mechanism.

Table 4-2. Protein and Amb a 1 in extracts of ragweed pollen obtained from plants grown under controlled conditions of CO2 concentration.

[CO_2] (µmol mol−1)	Protein concentration (µgmg−1 pollen)	Amb a 1 concentration (ELISA mg−1 protein)	Amb a 1 concentration (ELISA mg−1 pollen)
280	21 ± 2	4490 ± 960[a]	93 ± 20[a]
370	20 ± 2	5290 ± 560[b]	103 ± 11[b]
600	22 ± 2	8180 ± 900	178 ± 20

[a] $P<0.005$ when compared with projected 21st century CO_2 concentrations, *t*-test using unequal variances.
[b] $P<0.01$ when compared with projected 21st century CO_2 concentrations, *t*-test using unequal variances.

Notes: The CO_2 concentration used corresponds approximately to the pre-industrial concentration, the current concentration and that projected for 2050. Samples of pollen pooled from plants grown under the different CO_2 concentrations were extracted as described in the methods. ELISA was performed in triplicate with each sample; results aremean±standard deviation.
Source: (Singer et al., 2005), Table 2.

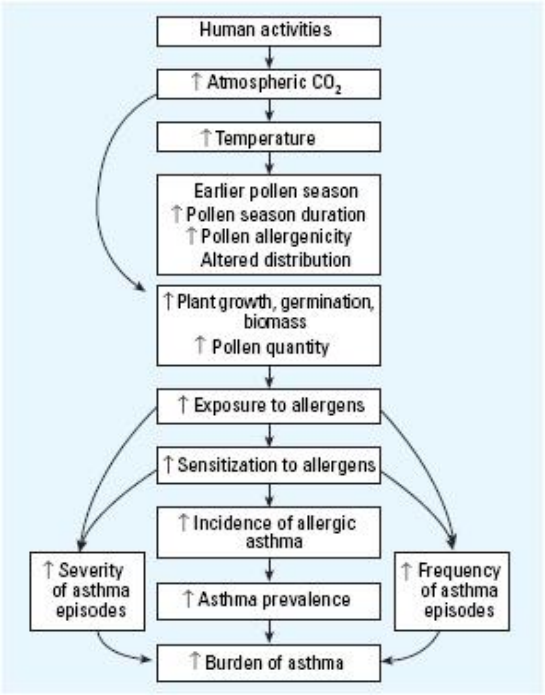
The research on allergen content of pollens/mold is limited but provocative in suggesting that even if pollen production remained unchanged, allergenic illness could increase due to increasing levels of allergenic protein.

4.5. Potential Indirect Impacts on Allergenic Illnesses

Climate change caused by elevated greenhouse gases, including carbon dioxide, is expected to lead to increases in global mean temperature, a stronger hydrologic cycle, and an increase in the number and severity of extreme weather events. These changes may lead to alterations in the production, distribution, and dispersion of aeroallergens as well as changes in allergen protein concentration. It is possible that production (both timing and amount) and protein content of aeroallergens will increase, and with time, plant distributions will shift as well. If changes in aeroallergen production occur as a result of climate change then the patterns of seasonal allergic disorders, such as allergic rhinitis (hayfever), asthma, and possibly atopic dermatitis could be affected as well.

The development of allergenic illness is a multistage process in which a genetically predisposed and immunologically naïve individual is first sensitized to an allergen, resulting in the production of IgE antibodies (Nielsen et al., 2002), and then subsequent exposures elicit a disease response due to the presence of IgE antibodies and the associated cellular response. Furthermore, there appears to be a dose-response relationship between allergen exposure and sensitization and exacerbation of disease (Neilsen et al., 2002). Thus, there are at least three causal pathways for climate change-induced impacts on aeroallergens to alter the severity and possibly the prevalence and of allergic diseases. First, a longer exposure during sensitization may lead to greater likelihood of the development of allergy (increased prevalence). Second, a higher dose during sensitization may lead to a greater likelihood of development of an allergy (increased prevalence). Third, a higher dose during subsequent exposures (post-sensitization) may lead to a more severe allergic response (Nielsen et al. 2002). Figure 4-5 outlines this process using asthma as an example (Beggs and Bambrick, 2005).

Figure 4-5. Schematic diagram of the relationship between global climate change and the rise in asthma prevalence and severity, via impacts of climate change on plant and pollen attributes.



Source: (Beggs and Bambrick, 2005), Figure 4.

Definitive statements on the impact of climate change on aeroallergens and subsequent allergenic illness, however, are rarely found in the literature. This is in part because studies are of necessity often narrowly defined, and a single study is unlikely to encompass the broad subject of weather, aeroallergens, and allergenic illness. There is also an inherent uncertainty as to how the climate will change, especially at a regional level. The etiology of allergic diseases, especially asthma, is complex and has a gene-environment interaction that is poorly understood. In addition, there are numerous other factors that come into play, such as changes in land use, air pollution, adaptive responses, and modifying factors, that are difficult to assess (See Figure 4-6 below).

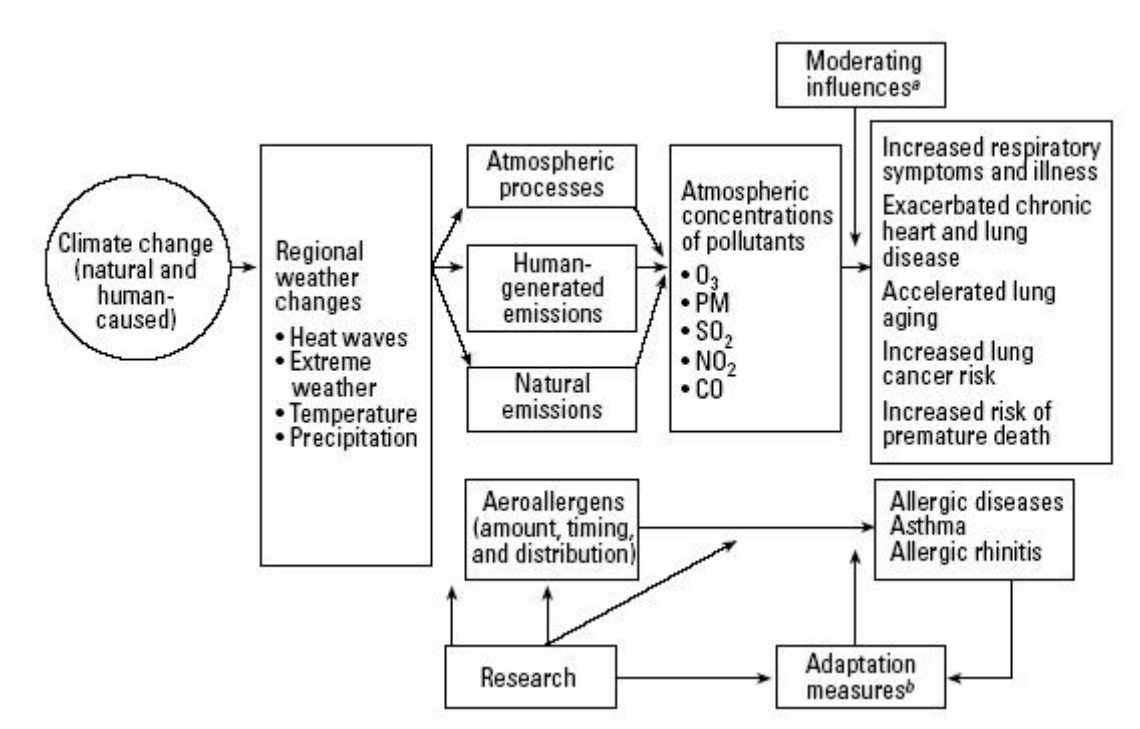


Figure 4-6. Potential air pollution-related health effects of climate change.

Notes: a. Moderating influences include non-climate factors that affect climate-related health outcomes, such as population growth and demographic change, standards of living, access to health care, improvements in health care, and public health infrastructure. *b.* Adaptation measures include actions to reduce risks of adverse health outcomes, such as emission control programs, use of weather forecasts to predict air quality levels, development of air quality advisory systems, and public education.
Source: (Bernard et al., 2001), Figure 1.

This section reviews the evidence described within this document and provides a qualitative assessment of the likely impact of climate change on allergenic illnesses based on the expected changes in production, distribution, dispersion of aeroallergens and allergen content of

aeroallergens in response to climate change. It then reviews a limited number of studies on weather, aeroallergens, and allergic disease.

4.5.1. Timing of Aeroallergen Production and Subsequent Illness

Shifts in phenology are one of the most consistent findings in studies of plant pollen production (Root et al., 2003). Alterations in the timing of aeroallergen production in response to weather variables have been clearly demonstrated for certain tree species, but less so for grass and weed pollens and mold (Clot, 2003; Emberlin et al., 2002; Katial et al., 1997). This is consistent with the observation that the flowering of many trees is regulated by temperature whereas photoperiod determines the flowering of many weeds in late summer. Evidence is mixed for grass pollens, with trend studies showing substantial differences by region in England (Emberlin, 1994), earlier start dates in Switzerland (Clot, 2003), but no apparent effect after an El Niño event in New England (Freye, 2001).

Ragweed has been shown to flower earlier in urban environments where temperature and CO_2 concentrations were higher compared to rural areas (Ziska et al., 2003). There was limited evidence on the start dates for the emergence of mold, although the El Niño event in New England indicated an earlier start (Freye, 2001). Some mold such as *Alternaria* is associated with agriculture and therefore the timing of production will be associated with the harvest (Corden and Millington, 2001). The concentrations of indoor allergens (e.g., dust mites, cockroaches) do not vary seasonally.

Analyses of trends in allergenic illness, however, are based on annual prevalence and generally do not document the seasonal timing of these illnesses within the year. Nevertheless, in sensitized individuals, exposure clearly leads to allergic response; thus it is reasonable to expect that changes in the timing of production of seasonal aeroallergens would result in corresponding changes in the timing of the associated seasonal allergenic illness (i.e., rhinitis). This assessment is concurrent with the NAST (Mellilo et al., 2001), which notes that climate change may affect the timing or duration of seasonal allergies such as hay fever. There is not clear evidence that the timing of mold emergence has shifted, and indoor allergens are generally not seasonal. In addition, the relationship between indoor allergens and climate change is unclear. Shifts in the timing of asthma and atopic dermatitis in response to changes in phenology are not as predictable.

4.5.2. Aeroallergen Production, Allergen Content, and Subsequent Illness

Increases in aeroallergen production and/or protein concentration could impact the prevalence or severity of allergenic illness via sensitivity and response pathways. A key conclusion of the National Assessment Synthesis Team (Mellilo et al., 2001)) was that over the next few decades climate change is likely to lead to increased plant productivity and carbon storage for many parts of the country, especially those areas that become warmer and wetter. Therefore, pollen production and possibly mold (e.g., *Cladosporidium*) in these areas would be expected to increase, on average. The NAST also concluded that areas where soils dry out during the growing season, such as the Southeast under certain scenarios, are likely to see reduced productivity and carbon storage, and hence, less pollen production.

These conclusions are supported by experimental and field studies that have demonstrated increased pollen production in ragweed and other species in conditions similar to those expected with climate change (Ziska et al., 2003, Jablonski et al., 2002; The Center for Health and the Global Environment, 2005). There are several examples where regional weather patterns, i.e., increased precipitation and temperature, lead to stronger pollen production (Freye, 2001; Reiss and Kostic, 1976; Weber, 2003). One study conducted in the U.S. showed increasing trends of total pollen production in cedar, oak, hickory, pecan, and birch in Oklahoma that may have been attributable to warmer winters (Levetin, 2001). In addition, studies of birch and ragweed provide evidence of increasing allergen content under similar conditions.

However, while the prevalence of both hay fever and asthma have increased in recent years (see Section 3.2), the limited observational data on aeroallergen trends in the U.S. present some difficulty in making an association to the observed increases in these allergic illnesses. While there is at least one regional example of increasing trends in mold (Katial et al., 1997) and tree pollen (Lapidus, 2001) the observational studies of U.S. pollen levels do not appear to have sufficient data (i.e., >10 years) to conduct trend analyses. The increases in allergen content observed in experiments, however, may provide an alternative explanation for increasing allergenic illness prevalence in the absence of documented increases in pollen levels.

On the basis of model projections by the NAST, pollen production in many areas of the country will increase until mid-21st century. It is also possible but less clear if allergen content and mold production will increase as well. Exposure to elevated pollen and mold concentrations during sensitization may lead to a greater likelihood of development of an allergy such as rhinitis or asthma – i.e., the prevalence of allergic disease might increase. In addition, exposures to higher concentrations aeroallergens or allergen proteins may lead to more severe allergic

responses (Nielsen et al., 2002) (Singer et al., 2005). It is unclear how indoor allergen concentrations might change, but there may be changes in exposure patterns. For example, more time could be spent indoors during summer heat waves but less time could be spend indoors during the winter as minimum temperatures rise (Patz et al., 2000).

These inferences are similar to the findings of a recently published report, *Climate Change Futures*, sponsored by Swiss Re and the United Nations Development Programme and conducted by The Center for Health and the Global Environment at Harvard Medical School. The CCF project relied on two scenarios of gradual warming with growing variability and more weather extremes. These scenarios were then applied to case studies, one of which included asthma. Both scenarios are based on business-as-usual, which, if unabated, would lead to a doubling of atmospheric CO_2 concentrations by mid 21st century. The first impact scenario (CCF-1) is based on gradual warming with increasing variability and escalating impacts. The second impact scenario (CCF-2) is also based on gradual warming with increasing variability but includes surprise impacts due to abrupt climate change.

The CCF-1 envisions a perceptible impairment of public health as a result of higher concentrations of aeroallergens whether measured by morbidity and mortality, disability adjusted life years (DALY)[16] lost, or the value of the incremental medical resources devoted to the emerging medical problems. The CCF-2 projects that the combination of more aeroallergens, more heat waves, photochemical smog, greater humidity, more wildfires, and more dust and particulates could considerably compromise respiratory and cardiovascular health in the near term. Widespread respiratory distress is a plausible projection for large parts of the world, bringing with it increasing disability, productivity losses, school absences, and rising costs for health care and medications.

Ecological models indicate climate change will likely lead to increased plant productivity and carbon storage in many parts of the country. Experimental and observational analyses support model assessments but production changes may be species- and region-specific, and data gaps limit assessment of trends in U.S. pollens and mold. Increases in aeroallergen production and/or allergen content could lead to increased prevalence and severity of allergic illnesses. A recent report by Harvard Medical School envisions perceptible impairments in public health as a

[16] DALY = The sum of years of potential life lost due to premature mortality and the years of productive life lost due to disability.

result of higher concentrations of allergens due to climate change (The Center for Health and the Global Environment, 2005).

4.5.3. Distribution and Dispersion of Aeroallergens and Subsequent Illness

Changes in the geographic distribution of plants and mold may alter the distribution of allergic illness. Long-term responses to climate change (over 50 to 100 years) are likely to involve range or distribution shifts in species and, in some cases, extinction of species (Joyce et al., 2001; Melillo et al., 2001; Davis and Shaw, 2001). The results of ecological models indicate that the potential habitats (i.e., distribution) for many tree species in the U.S. are likely to change, in some cases dramatically, by the end of the 21st century. Potential habitats for trees favored by cool environments are likely to shift northward (Joyce et al., 2001). The habitats of alpine, subalpine spruce/fir, and aspen communities are likely to contract dramatically in the U.S. and largely shift into Canada. Potential habitats are likely to increase in the U.S. for oak/hickory, oak/pine, ponderosa pine, and arid woodland communities. Projections for (non-forest) vegetation redistribution suggest that savannahs and grasslands are likely to expand, especially in the Southeast, where hot and dry climate conditions are predicted in response to climate change.

The models developed for the NAST are supported by fossil record evidence. Davis and Shaw (2001) note that changes in geographic distribution are so frequently documented in the fossil record that range shifts are seen as the expected plant response to future climate change. These authors cite evidence of genetic adaptation to climate and argue that the interplay of genetic adaptation and migration has been central to the biotic response to climate change.

Assessing the potential impact of vegetation range shifts on allergenic illness is difficult. Shifts in vegetation distribution are likely to occur over relatively long periods of time, i.e., decades. Furthermore, cross-reactivity between species implies that the range of a species (e.g., birch) could contract or move northward and another (e.g., white oak) could take its place without any appreciable difference in allergenic illness. However, one can look to examples of invasive and cultivated species to assess the potential impacts on allergenic illness. Ragweed, for example, has spread through out Europe in recent decades and is now regarded as a major allergen in France, north Italy, Hungary, and Croatia (Stefanic et al., 2005). In desert regions such as the southwestern United States, the natural vegetation is primarily animal or insect-pollinated (Sneller et al., 1993). However, urban development and landscape preferences for grasses and shade trees (i.e., wind-pollinated plants) in areas such as Tuscon, Arizona have led to dramatic changes and increases in the pollen burden (Sneller et al., 1993).

There has been only limited research on how climate change could effect the dispersal of pollen and mold. Dispersion has the potential via shifts in long-term weather patterns and extreme weather events to expose populations (sensitize) to novel allergens and to create severe and possibly life threatening exposures. There are cases of both pollen and dust being dispersed long distances from its release sites. For example, long distance (200-600 km) dispersion of *Juniperus ashei* pollen has been routinely observed in Tulsa, Oklahoma and is associated with allergic illness in that community (Van de Water et al., 2003). Transcontinental transport of dust particulates has also been observed (Husar et al., 2001). During April 1998, two large dust storms occurred over the Gobi desert (Mongolia and north central China). The dust plume crossed the Pacific Ocean and resulted in strong spikes in particulate matter concentrations 10 days later (April 29) along the west coast of the United States (Husar et al., 2001). It is unclear if there were any health impacts associated with the dust in the United States, but state health agencies issued air pollution advisory warnings to the general public (Husar et al., 2001).

In summary, shifts in vegetative distribution are expected to occur but over relatively long periods of time. There does not appear to be any literature estimating the impact of climate change on the distribution of aeroallergens and subsequent illness. The impact of climate change on aeroallergen dispersion and subsequent illness does not appear to be well studied either. There are specific examples of dispersion, indicating that exposure to novel aeroallergens or unusually high concentrations of allergens are distinct possibilities. Overall, however, it is difficult to predict how changes in dispersal patterns and geographic distribution of plants and mold may impact allergenic illness.

4.5.4. Observational Studies of Weather, Aeroallergens, and Illness

There are several examples of observational studies that provide a linkage between weather, aeroallergens, and health outcomes, including asthma. These studies provide limited evidence of the seemingly obvious but difficult to demonstrate link between weather, aeroallergen production, and subsequent illness. A study by Epton et al. (1997) is one of the few examples of a prospective design that integrates the three variable categories (i.e., weather, aeroallergens, illness) and can serve as a model for future studies.

Epton et al. (1997) conducted a one-year prospective study to explore relationships between weather, fungal spore counts, pollen counts, and peak expiratory flow rates (PEFR) and asthma in a group of asthmatic subjects. A small positive association was found between PEFR and mean temperature. The study also found an association between days with high basidiospore

counts and nocturnal wakening and medication use to relieve asthma. The authors concluded that the effects of weather and aeroallergens on PEFR and asthma symptoms in the studied population were small and that other causes needed to be sought out to explain variations in asthma severity and exacerbations. However, there were no control subjects and 75 percent of the cases were users of prescribed inhaled anti-inflammatory medications—usually corticosteroids. Steroid use combined with the low to moderate pollen levels during the study may explain why the authors did not find a more substantial role of aeroallergen influence on asthma.

Lewis et al. (2000) investigated the joint effects of aeroallergens, rainfall, thunderstorms and outdoor air pollutants on daily asthma admissions and Accident and Emergency (A&E) attendance using routinely collected data between 1993 and 1996 in Derby, England. The authors found a significant interaction between the effects of grass pollen and weather conditions on A&E attendance, such that the increase in attendance with grass pollen count was most marked on days of light rainfall. Asthma admissions also increased significantly with *Cladosporium* count.

Severe weather events also provide intriguing evidence of an association between weather, aeroallergens, and allergenic illness. Dales et al. (2003) explored the hypothesis that thunderstorms, by increasing aeroallergen levels, cause exacerbations in asthma. The analysis was done using six years of emergency department visit data with approximately 4,000 asthma hospital admissions yearly. Air pollution, meteorologic factors, and aeroallergen levels were accounted for simultaneously. The authors found an average daily rate of 8.6 asthma visits on days without thunderstorms and a 15 percent increase to 10 visits ($p<0.05$) on days with thunderstorms. The concentrations of total fungal spores almost doubled during thunderstorms (from 1,512 m^3 to 2,419 m^3). A time series analysis was used to test the association between changes in daily concentrations of aeroallergens and changes in the daily number of emergency visits irrespective of thunderstorms; there was a significant association with fungal spores but not pollens. Air pollution was also higher on days with thunderstorms compared to days without, but the time series analysis detected no significant affect of these pollutants (O_3, SOx, NOx, haze) on asthma.

Hurricane Katrina provides a recent example of extreme weather in the United States and the potential impact on aeroallergens and allergenic illness. Large sections of New Orleans were flooded for weeks, resulting in extensive mold growth in buildings. The CDC assessed the extent of mold growth in a sample (N=112) of households in the area (Orleans, Jefferson,

Plaquemines, and St. Bernard Parishes) and collected indoor (N= 20) and outdoor (N=11) air samples. Almost half the homes had "visible mold growth" and 17 percent had "heavy mold coverage," defined as ">50 percent coverage on [the] interior wall of most-affected room." Indoor and outdoor air sampling indicated *Aspergillus* spp. and *Penicillium* spp. were the predominant populations (Ratard et al., 2006). Geometric mean glucan levels were 1.6 ug/m^3 inside homes and 0.9 ug/m^3 outside. Geometric mean endotoxin levels were 23.3 EU/m^3 inside and 10.5 EU/ m^3 outside (Endotoxin units per cubic meter).

Hospitals in the area have reported seeing an increased number of patients with allergy and cold symptoms, and doctors have suggested that allergy to the mold and dust circulating in New Orleans is making residents susceptible to respiratory illness (Wilson, 2006). There are also reports of a nagging cough throughout New Orleans that has been nicknamed "Katrina cough," believed to be caused by high levels of 'dust' in the air—particles from construction debris and dried mud, coupled with high spore counts from mold and mites that feed on mold spores (Bennett, 2006). This a particular concern for workers removing debris (Wilson, 2006). Overall rates of asthma in Louisiana children have also increased post-Katrina from 14 percent (2003) to 18 percent (2006) according to results from the Louisiana Child & Family Health Study, and may be even higher for minority and underprivileged children or children residing in certain geographical areas that were affected by post-Katrina flooding (The Center for Health and the Global Environment, 2005).

Studies examining the relationship between weather, aeroallergens, and health outcomes, provide intriguing evidence of potentially serious impacts on health. For example, asthma prevalence is reportedly higher in post-Katrina Louisiana; spikes in mold spore concentrations and asthma have been observed on days with thunderstorms; light rain and grass pollen counts were associated with asthma admissions in the United Kingdom. However, for diseases with complicated etiologies, such as asthma, more rigorous prospective designs as conducted by Epton et al. (1997) may be required to better understand the relationship between weather, aeroallergens, and illness.

5. ECONOMIC AND QUALITY-OF-LIFE IMPACTS OF ALLERGENIC ILLNESSES

This section of the report focuses on the costs, both monetized and non-monetized, of allergenic illnesses. Unless stated otherwise, all costs are in 2005 dollars.[17] The incidence of allergic disease has grown substantially in recent years, affecting millions of people annually. Allergic reactions can involve several organ systems, including the respiratory tract, skin, cardiovascular system, and the gastrointestinal tract. A recent nationwide survey reported that 54.6 percent of people in the U.S. test positive for one or more allergens (American Academy of Allergy Asthma and Immunology (AAAAI), 1996-2005); among specific allergens, dust mite, rye, ragweed, and cockroach caused sensitization in approximately 25 percent of the population (Arbes et al., 2005). Allergies are the sixth most costly chronic disease category in the United States, costing the health care system approximately $21 billion annually (American Academy of Allergy Asthma and Immunology (AAAAI), 1996-2005).

Although there are several different types of allergic disease affecting the respiratory tract, skin, and other organ systems, this section discusses the costs of those allergic illnesses that have been associated with aeroallergens in the U.S. – primarily, allergic rhinitis/ rhinoconjunctivitis (hereafter referred to as "allergic rhinitis"), asthma, and atopic dermatitis/ eczema (hereafter referred to as "atopic dermatitis"). Table 5-1shows nationwide hospital statistics for the conditions of interest.

The AAAAI reports that allergic rhinitis affects approximately 40 million people in the United States each year, 40 percent of whom are children. Estimated total direct costs of treatment are $6.2 billion per year. Indirect costs include 3.8 million missed days of school and work per year. Allergic rhinitis seldom results in hospitalization. In 2003, the total number of hospital discharges with allergic rhinitis listed as the principal diagnosis was 293; the total number including those with allergic conjunctivitis in addition was 368. The aggregate charges totaled $2.1-$2.5 million (see Table 5-2 and Table 5-3). For the most part, direct medical costs of allergic rhinitis treatment can be attributed to outpatient services and medications (Schoenwetter et al., 2004).

[17] Medical costs were inflated to 2005 dollars using BLS CPI for Medical Care. All other costs were inflated to 2005 dollars using BLS CPI

Table 5-1. National statistics, 2003 – principal diagnosis only (all conditions)

	Total number of discharges	LOS (length of stay), days (mean)	Mean Hospital Charge (2005$)	Aggregate charges, (the "national bill") (2005$)	Admitted from emergency department	In-hospital deaths
Asthma (ICD-9: 493)	469,738	3.4	12,623	5,931,347,575	338,659 (72.10%)	1,669 (0.36%)
Allergic Rhinitis[a] (ICD-9: 477)	293	1.9	7,192	2,109,848	178 (60.90%)	0 (0.00%)
Allergic Conjunctivitis[b] (ICD-9: 372.05, 372.13, 372.14)	75	2.1	5,629	420,298	45 (60.56%)	0 (0.00%)
Allergic Rhinoconjunctivitis AR+AC	368	1.9	6,870	2,530,146	224 (60.83%)	0 (0.00%)
Atopic Dermaitits/ Eczema[c] (ICD-9: 691.8 692.9 373.3)	2,582	3.2	9,163	23,801,038	1,550 (60.03%)	0 (0.00%)

Source: Weighted national estimates from HCUP Nationwide Inpatient Sample (NIS), 2003, AHRQ, based on data collected by individual States and provided to AHRQ by the States. Total number of weighted discharges in the U.S. based on HCUP NIS = 38,220,659. (http://hcup.ahrq.gov/HCUPnet.asp).

Notes: 2003 dollar values were inflated to 2005 dollars using BLS CPI for Medical Care;
a. AR
b. AC (defining ICD codes adopted from (Ray et al., 1999));
c. Defining ICD codes adopted from (Ellis et al., 2002).

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Table 5-2. Allergic rhinitis national statistics, 2003 – principal diagnosis only

		Total number of discharges	LOS (length of stay), days (mean)	Mean Hospital Charge, (2005$)	Aggregate charges, (the "national bill") (2005$)	Admitted from emergency department	In-hospital deaths
All discharges		293 (100.00%)	1.9	7,192	2,109,848	178 (60.90%)	0 (0.00%)
Age group	<1	*	*	*	*	*	*
	1-17	71 (24.17%)	1.6	5,948	420,884	41 (57.76%)	0 (0.00%)
	18-44	100 (34.29%)	1.8	7,372	740,138	58 (57.51%)	0 (0.00%)
	45-64	52 (17.93%)	2.8	*	*	24 (46.62%)	0 (0.00%)
	65-84	55 (18.90%)	1.6	6,855	379,407	46 (83.33%)	0 (0.00%)
	85+	*	*	*	*	*	*
Region	Northeast	89 (30.54%)	1.7	4,809	429,975	65 (73.04%)	0 (0.00%)
	Midwest	*	*	*	*	*	*
	South	133 (45.27%)	2.2	9,224	1,222,748	82 (61.64%)	0 (0.00%)
	West	*	*	*	*	*	*

Source: Weighted national estimates from HCUP Nationwide Inpatient Sample (NIS), 2003, Agency for Healthcare Research and Quality (AHRQ), based on data collected by individual States and provided to AHRQ by the States. Total number of weighted discharges in the U.S. based on HCUP NIS = 38,220,659. (http://hcup.ahrq.gov/HCUPnet.asp)

Notes: 2003 dollar values were inflated to 2005 dollars using BLS CPI for Medical Care; ICD-9 code 477; Statistics based on 70 or fewer unweighted cases in the nationwide statistics (NIS and KID) are not reliable. These statistics are suppressed and are designated with an asterisk (*).

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Table 5-3. Allergic rhinoconjunctivitis national statistics, 2003 – principal diagnosis only

		Total number of discharges	LOS (length of stay), days (mean)	Mean Hospital Charge, (2005$)	Aggregate charges, (the "national bill") (2005$)	Admitted from emergency department	In-hospital deaths
All discharges		368 (100.00%)	1.9	6,870	2,530,146	224 (60.83%)	0 (0.00%)
Age group	<1	*	*	*	*	*	*
	1-17	95 (25.71%)	1.6	5,311	501,866	45 (47.84%)	0 (0.00%)
	18-44	121 (32.80%)	1.8	6,894	831,111	78 (64.61%)	0 (0.00%)
	45-64	58 (15.87%)	2.7	9,225	530,748	30 (51.94%)	0 (0.00%)
	65-84	75 (20.52%)	2.1	7,688	579,817	56 (74.44%)	0 (0.00%)
	85+	*	*	*	*	*	*
Region	Northeast	114 (31.04%)	1.7	5,214	594,857	85 (74.51%)	0 (0.00%)
	Midwest	61 (16.72%)	1.4	4,231	260,040	31 (50.26%)	0 (0.00%)
	South	142 (38.56%)	2.3	9,142	1,295,354	86 (60.96%)	0 (0.00%)
	West	*	*	*	*	*	*

Source: Weighted national estimates from HCUP Nationwide Inpatient Sample (NIS), 2003, Agency for Healthcare Research and Quality (AHRQ), based on data collected by individual States and provided to AHRQ by the States. Total number of weighted discharges in the U.S. based on HCUP NIS = 38,220,659. (http://hcup.ahrq.gov/HCUPnet.asp)

Notes: 2003 dollar values were inflated to 2005 dollars using BLS CPI for Medical Care; ICD-9 codes 477 (AR), and 372.05, 372.13, 372.14 (AC, see (Ray et al., 1999)); Statistics based on 70 or fewer unweighted cases in the nationwide statistics (NIS and KID) are not reliable. These statistics are suppressed and are designated with an asterisk (*).

Asthma is estimated to affect approximately 15 million Americans (American Academy of Allergy Asthma and Immunology (AAAAI), 1996-2005). The condition often begins in childhood, and it has been estimated that 30 percent of all patients are children. There were 1,669 deaths due to asthma in 2003 (see Table 5-4). The age-adjusted death rate for asthma has been in the neighborhood of 5 deaths per 100,000 during the past decade (see Figure 5-1). In addition, asthma is indicated as a "contributing factor" for nearly 7,000 other deaths in the U.S. each year (NCHS/CDC, 2001). Asthma was given as the primary diagnosis in about 500,000 hospitalizations in 2000 and was listed as a secondary diagnosis in over 1 million hospitalizations (see Table 5-2).

According to a 2000 study (American Academy of Allergy Asthma and Immunology (AAAAI), 1996-2005), the direct costs of asthma totaled nearly $12.5 billion (with hospitalizations the single largest portion of direct cost) and indirect costs (lost earnings due to illness or death) totaled $9.1 billion. In 2003, the national hospital bill for asthma was $5.9 billion (see Table 5-4). For the past decade the number of physician office visits has fluctuated around 10 million per year (see Table 5-3). For adults, asthma is the fourth leading cause of

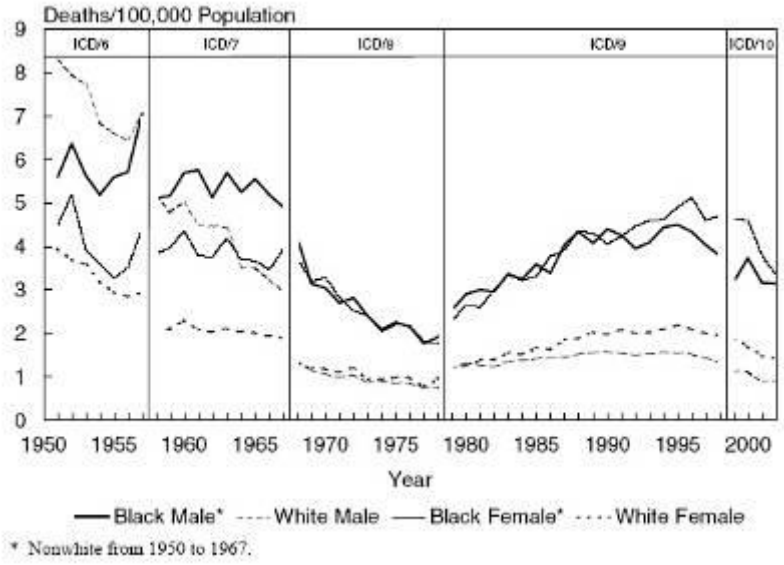
work absenteeism and "presenteeism" (significant lowering of on-the-job productivity) resulting in nearly 15 million missed or "reduced productivity" workdays each year (Mannino et al., 2002). Among children ages 5 to 17, asthma is the leading cause of school absences from a chronic illness. It accounts for an annual loss of more than 14 million school days per year (approximately 8 days for each student with asthma) and more hospitalizations than any other childhood disease. It is estimated that children with asthma spend nearly 8 million days per year restricted to bed (Asthma and Allergy Foundation of America, 2000).

Table 5-4. Asthma national statistics, 2003 – principal diagnosis only

		Total number of discharges	LOS (length of stay), days (mean)	Mean Hospital Charge (2005$)	Aggregate charges, (the "national bill") (2005$)	Admitted from emergency department	In-hospital deaths
All discharges		469,738 (100.00%)	3.4	12,623	5,931,347,575	338,659 (72.10%)	1,669 (0.36%)
Age group	<1	16,631 (3.54%)	2.5	8,655	143,854,405	9,528 (57.29%)	5 (0.03%)
	1-17	148,170 (31.54%)	2.2	8,201	1,216,728,121	97,712 (65.95%)	34 (0.02%)
	18-44	104,400 (22.23%)	3	11,748	1,228,750,528	83,191 (79.68%)	130 (0.12%)
	45-64	111,670 (23.77%)	4	15,626	1,744,778,735	83,997 (75.22%)	404 (0.36%)
	65-84	74,650 (15.89%)	4.9	18,099	1,348,215,082	53,867 (72.16%)	829 (1.11%)
	85+	13,007 (2.77%)	5.3	17,949	233,476,765	9,645 (74.16%)	268 (2.06%)
	Missing	1,211 (0.26%)	2.1	13,197	15,543,940	719 (59.36%)	0 (0.00%)
Region	Northeast	128,928 (27.45%)	3.4	14,979	1,931,237,122	108,523 (84.17%)	429 (0.33%)
	Midwest	98,392 (20.95%)	3.2	9,188	905,320,891	65,535 (66.61%)	330 (0.34%)
	South	171,441 (36.50%)	3.5	11,250	1,928,278,846	114,966 (67.06%)	558 (0.33%)
	West	70,976 (15.11%)	3.3	16,777	1,166,510,716	49,635 (69.93%)	352 (0.50%)

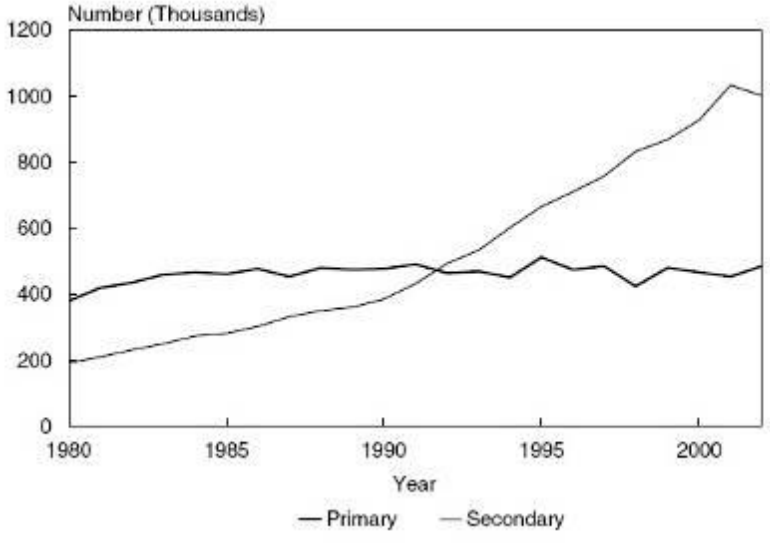
Source: Weighted national estimates from HCUP Nationwide Inpatient Sample (NIS), 2003, Agency for Healthcare Research and Quality (AHRQ), based on data collected by individual States and provided to AHRQ by the States. Total number of weighted discharges in the U.S. based on HCUP NIS = 38,220,659. (http://hcup.ahrq.gov/HCUPnet.asp)
Notes: 2003 dollar values were inflated to 2005 dollars using BLS CPI for Medical Care; ICD-9 code 493; Statistics based on 70 or fewer unweighted cases in the nationwide statistics (NIS and KID) are not reliable. These statistics are suppressed and are designated with an asterisk (*).

Figure 5-1. Age-adjusted death rates for asthma by race and sex, U.S. 1951-2002.



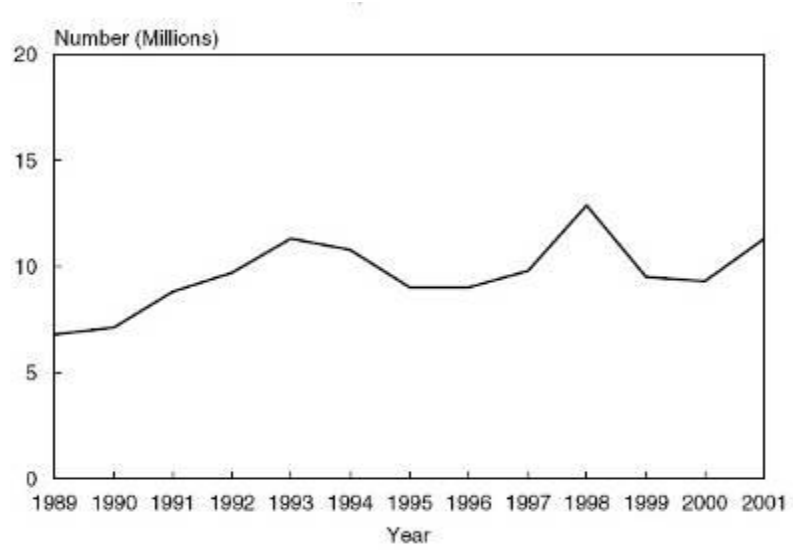
Source: (National Heart Lung and Blood Institute (NHLBI/NIH), 2004) Chartbook on Cardiovascular, Lung, and Blood Diseases (p. 70)

Figure 5-2. Hospitalizations for asthma, U.S. 1980-2002.



Source: (National Heart Lung and Blood Institute (NHLBI/NIH), 2004) Chartbook on Cardiovascular, Lung, and Blood Diseases (p. 66)

Figure 5-3. Physician office visits for asthma, U.S. 1989-2001.



Source: (National Heart Lung and Blood Institute (NHLBI/NIH), 2004) Chartbook on Cardiovascular, Lung, and Blood Diseases (p. 65)

As noted previously, atopic dermatitis is one of the most common skin diseases, particularly in infants and children. According to the (American Academy of Allergy Asthma and Immunology (AAAAI), 1996-2005), 10-15 percent of the population is affected during childhood, and there is considerable evidence that the prevalence is increasing. It often precedes other allergic disorders – up to 50 percent of patients with atopic dermatitis develop asthma. A recent estimate of the direct medical costs associated with atopic dermatitis is $1.2-$5.9 billion per annum (Ellis et al., 2002). As in the case of allergic rhinitis, atopic dermatitis seldom results in hospitalization. The total number of hospital discharges with atopic dermatitis listed as the primary diagnosis was 2,582 in 2003, while the aggregate hospital charges totaled $23 million (see Table 5-5).

The impacts these allergenic illnesses impose on the U.S. economy and the non-monetized quality-of-life impacts they impose on the individuals who suffer from them are discussed more fully below. Because cost-of-illness (COI) studies are the primary means by which the direct (medical) and indirect (opportunity) costs of illnesses are assessed, an introduction to COI methodology is provided in subsection 5.1. Recent COI estimates available for asthma, allergic rhinitis, and atopic dermatitis are given in subsection 5.4.

Table 5-5. Atopic dermatitis national statistics, 2003 – principal diagnosis only

		Total number of discharges	LOS (length of stay), days (mean)	Mean Hospital Charge (2005$)	Aggregate charges, (the "national bill") (2005$)	Admitted from emergency department	In-hospital deaths
All discharges		2,582 (100.00%)	3.2	9,163	23,801,038	1,550 (60.03%)	0 (0.00%)
Age group	<1	212 (8.20%)	3	10,797	2,285,682	109 (51.28%)	0 (0.00%)
	1-17	755 (29.24%)	2.9	8,086	6,134,619	366 (48.48%)	0 (0.00%)
	18-44	465 (17.99%)	2.9	8,379	3,892,126	354 (76.31%)	0 (0.00%)
	45-64	594 (23.01%)	3	8,147	4,840,298	392 (66.06%)	0 (0.00%)
	65-84	474 (18.36%)	3.9	12,009	5,689,869	274 (57.72%)	0 (0.00%)
	85+	67 (2.60%)	4.9	10,877	845,183	44 (65.52%)	0 (0.00%)
	Missing	*	*	*	*	*	*
Region	Northeast	651 (25.20%)	3.2	12,268	7,982,066	508 (78.05%)	0 (0.00%)
	Midwest	551 (21.35%)	3.1	6,864	3,783,047	333 (60.50%)	0 (0.00%)
	South	964 (37.35%)	3.3	8,057	7,769,804	549 (56.95%)	0 (0.00%)
	West	415 (16.09%)	2.8	9,983	4,266,119	159 (38.36%)	0 (0.00%)

Source: Weighted national estimates from HCUP Nationwide Inpatient Sample (NIS), 2003, Agency for Healthcare Research and Quality (AHRQ), based on data collected by individual States and provided to AHRQ by the States. Total number of weighted discharges in the U.S. based on HCUP NIS = 38,220,659. (http://hcup.ahrq.gov/HCUPnet.asp)
Notes: 2003 dollar values were inflated to r2005 dollars using BLS CPI for Medical Care; ICD-9 codes 691.8, 692.9, 373.3 ((Ellis et al., 2002)); Statistics based on 70 or fewer unweighted cases in the nationwide statistics (NIS and KID) are not reliable. These statistics are suppressed and are designated with an asterisk (*).

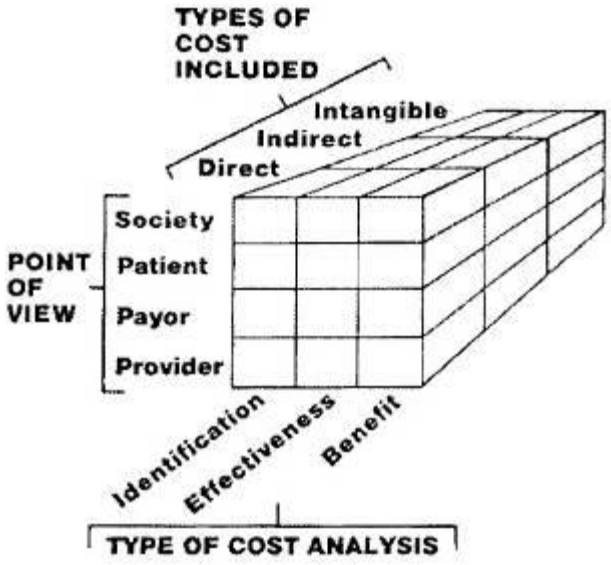
5.1. COST OF ILLNESS—METHODOLOGY

Cost-of-illness (COI) studies are a type of economic study common in the medical literature, particularly in specialist clinical journals. COI studies were pioneered in the late 1950s and early 1960s and have proliferated over the past 30 years. The aim of a COI study is to identify and measure the costs of a particular disease, including the direct (medical) costs, the indirect (opportunity) costs, and the intangible costs (e.g., pain and suffering). A COI study thus attempts to estimate the total cost to society of a particular disease and by implication the amount that would be saved if the disease were abolished. It also identifies the different components of cost and the size of the contribution of each.

The COI study is one of several types of economic evaluation of clinical care, as shown in Figure 5-4. While the COI study focuses on the identification of costs, cost-effectiveness analysis (CEA) focuses on the relative cost-effectiveness of different treatments, and cost-benefit analysis (CBA) compares the costs of treatment with the benefits. Economic studies also vary with respect to the perspective ("points of view") for cost evaluation: society, patient, payor, or provider. Finally, the studies may include different cost components. Thus, even if the studies

belong to the same type (e.g., COI), there still may be substantial variability along the other two dimensions (perspective and cost components), which may potentially affect comparability of the estimates. The key distinctions are summarized below.

Figure 5-4. Three dimensions of economic evaluation of clinical care.



Source: (Bombardier and Eisenberg, 1985)

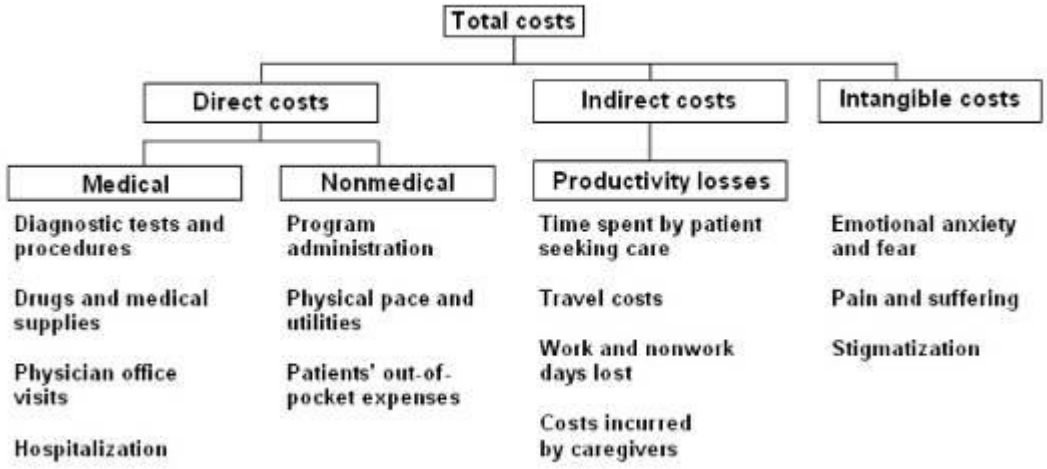
5.2. COST COMPONENTS

Figure 5-5 summarizes the types of costs that may be subject to evaluation by a given study. COI studies measure the economic burden resulting from disease and illness across a defined population, including both direct and indirect costs. Direct costs are the value of resources used in the treatment, care, and rehabilitation of persons with the condition under study and are, therefore, unavailable to produce other goods and services. Indirect costs represent the value of economic resources lost because of disease-related work disability or premature mortality. In addition, a disease typically involves deterioration in the quality of life of the patient (and his or her family) through its impacts on physical, social and emotional health – i.e., intangible costs (Kirschstein, 2000).

5.2.1. Direct Medical Costs

Direct medical costs are the costs connected with the use of medical care in the prevention, diagnosis, and treatment of disease and in the continuing care, rehabilitation, or terminal care of patients. Examples include expenditures for hospitalization, outpatient clinical care, nursing home care, and home health care; services of primary physicians and specialists, dentists, and other health practitioners; drugs and drug sundries; and rehabilitation counseling and other rehabilitation costs, such as for prostheses, appliances, eyeglasses, hearing aids, and other devices to overcome impairments resulting from illness or disease. Collectively, these expenditures represent the personal health care component of the United States National Health Accounts (Kirschstein, 2000).

Figure 5-5. Cost inventory diagram.



Source: CDC Economic Evaluation of Public Health Preparedness and Response Efforts http://www.cdc.gov/owcd/EET/Cost/Fixed/2.html

5.2.2. Direct Non-medical Costs

Direct non-medical costs are the costs borne by patients or other payers that are not included in the National Health Expenditures Accounts. Examples of such costs are expenditures for transportation to hospitals, to physicians' offices or to other health providers; certain household expenditures (e.g., help for cleaning, laundering, and cooking); special diets and clothing, and relocation and moving expenses (Kirschstein, 2000).

5.2.3. Indirect Costs

Indirect costs are the value of time that patients lose from employment or other productive activity due to mortality or morbidity. These costs also include reduced productivity once the patient returns to work, including unwanted job changes and loss of opportunities for promotion or education, and the value of time lost from work, housekeeping, etc., by family members or friends who transport, visit, and care for patients (Kirschstein, 2000).

5.2.4. Intangible Costs

COI studies rarely attempt to evaluate the intangible costs of disease – the associated pain, suffering, and changes in the quality of life. This issue is of particular importance in the

case of chronic diseases (such as those considered here), where there can be a substantial impact on the quality of life over a long period of time (Kirschstein, 2000).

5.2.5. Hidden Costs

There are often, in addition, some "hidden costs" associated with illnesses, which are usually neglected by COI studies (Schoenwetter et al., 2004). A disease or condition may contribute to increased costs as a secondary diagnosis, or as a risk factor for other diseases and conditions. For instance, inadequately treated or untreated allergic rhinitis can be associated with a dramatic increase in the cost of caring for co-morbid conditions such as asthma, recurrent nasal polyps, sinusitis, and chronic otitis media (Halpern et al., 2004).

5.3. SOURCES OF VARIABILITY IN COST ESTIMATES FROM COI STUDIES

The literature on COI studies documents substantial variation in the methods and data used to estimate the overall costs of illness. Attempts to compare cost data across disease categories should consider the conceptual and methodological issues that may lead to variations in cost estimates. The following are the issues that should be taken into account when considering the COI estimates within and across conditions (see (Kirschstein, 2000)).

5.3.1. Reference Year

COI estimates are expressed in dollars for a particular reference year. To express all estimates in a common reference year, it is necessary to adjust for changes in the disease burden over time, patterns of treatment and care, and the purchasing power of the dollar for health care services (Kirschstein, 2000).

5.3.2. Cost Components

The comprehensiveness of the estimates of direct and indirect costs differs across studies because of the difficulty and cost required to estimate the non-medical costs, and the indirect costs related to reduced productivity after returning to the job and the value of services of unpaid care providers. Studies often make a number of specialized assumptions that may drive their results (Kirschstein, 2000).

5.3.3. Discount Rate

In some cases, the present discounted value of the expected stream of lost earnings or medical expenditures incurred over future years is calculated for a base or reference year using a discount rate intended to reflect people's rate of time preference – i.e., the tradeoff between the value of a dollar received today versus one received next year. The choice of an appropriate discount rate remains controversial and may vary considerably between studies (Kirschstein, 2000).

5.3.4. Definition of Disease

Because the interrelationships among disease categories or causal agents are complex and patients often present more than one disease or condition, it is not always feasible or appropriate to construct mutually exclusive disease categories and associated cost estimates. Cost estimates depend on how narrowly or broadly the disease is defined, whether it includes related conditions beyond its narrowly defined or primary ICD-9-CM code; whether the estimate includes identifiable extra costs attributable when the disease is listed as a secondary diagnosis or co-morbidity; and whether the estimate includes costs attributable to the disease or condition as an underlying cause or risk factor for other diseases (Kirschstein, 2000).

5.3.5. Prevalence vs. Incidence Approach

COI studies approach cost estimation from either of two perspectives. Most COI studies use the prevalence-based (or annual cost) approach that measures the costs that accrue during a base year due to all existing (or prevalent) cases of disease in that year. In estimating the economic burden resulting from the prevalence of disease, the present discounted value of future losses due to mortality occurring in the base year is calculated. The conventional methodology attributes the future losses to the year in which the death occurs (Kirschstein, 2000).

The incidence-based (or lifetime cost) approach measures the present value of the lifetime costs of the disease for all new (incident) cases with onset of disease during the given base year (Weiss and Sullivan, 1993). Estimation of incidence-based costs requires knowledge of the likely course of a disease and its duration, survival rates, onset and patterns of medical care, and the impact of disease on employment, so it is generally more difficult than estimation of prevalence-based costs. However, the incidence-based approach is sometimes more useful for comparing the effects of alternative interventions to prevent, treat, or manage a particular disease.

5.3.6. Scope and Perspective of Estimation

COI estimates may focus on the total U.S. resident population, or they may be specific to particular geographic areas or ethnic groups. They may cover all ages or they may be limited to certain age groups. Similarly, COI studies may estimate costs to the total society, regardless of who bears the costs, or they may estimate the costs to patients, payors, or providers (Kirschstein, 2000).

5.4. COST OF ILLNESS—ESTIMATES

The COI studies discussed below were based on U.S. data, but varied with respect to scope, perspective, reference year, cost components, and, in some cases, the definition of disease. None of the studies used the incidence approach or applied discount rates to the stream of lost earnings over future years. The majority of COI studies were for asthma, followed by allergic rhinitis and atopic dermatitis. For convenience, the findings of the original COI studies are summarized in Table, 5-6, Table 5-7, and Table 5-8.

5.4.1. Allergic Rhinitis

Reed et al. (2004) and Schoenwetter et al. (2004) are two recent comprehensive allergic rhinitis burden-of-disease literature reviews. Two older review papers by Kozma et al. (1996) and Blaiss (2000) discuss the economic and quality-of-life consequences of allergic rhinitis. Finally, O'Connell (2004) and Weiss and Sullivan (2001) discuss allergic rhinitis in the context of atopic diseases in general.

The key features and findings of the original research papers on allergic rhinitis are summarized in Table 5-6. Direct medical costs and/or indirect costs were estimated by this body of research. However, no attempt was made to monetize the intangible costs of allergic rhinitis. In addition, studies vary in the way they define the condition. Some create estimates for allergic rhinitis only, while others define the disease as “allergic rhinoconjunctivitis” by combining ICD-9 codes for allergic rhinitis and a set of conjunctivitis-related codes (Ray et al., 1999). The direct medical costs of allergic rhinitis range from $1.7 billion to $6.2 billion, while indirect costs are estimated to range from $0.1 billion to $6.6 billion. Variation in estimates comes largely from different assumptions about prevalence, inclusion of over-the-counter drugs, and partial productivity losses.

Table 5-6. Annual cost of allergic rhinitis/ rhinoconjunctivitis estimates, in 2005$ by cost category

Study Name Period Data Sources Methodology	Direct Medical Costs	Direct Non-Medical Costs	Hidden Costs	Indirect Costs		Intangible Costs
				Lost School Days	Loss of Work	
(Malone et al., 1997) 1987 Various US national, 1987 NMES S, preval. 39 mill	**1,741 mill**	NA	NA	**126 mill**		NA
(McMenamin, 1994) 1985-1990 Various US national S, preval. 22 mill	**2,285 mill**	NA	NA	**1,168 mill**		NA
(Baraniuk et al., 1996) 1990 Various US national S, Meta-study	**2,393 mill**	NA	NA	**2,335 mill**		NA
(Mackowiak, 1997) Various Yrs, *used 1997 for inflation adjustments* Various US national S, preval. 12 mill	**6,199 mill**	NA	NA	**4,137 mill**		NA
(Law et al., 2003) 1996 MEPS S, SR, preval. 12 mill	**4,787 mill**	NA	NA	NA		NA
(Ray et al., 1999) 1994 Various US national, NCHS D, S, SR, preval. 27 mill	**2,611 mill**	NA	**5,665 mill**	NA		NA
(Storms et al., 1997) 1993 Population-based survey Incl. OTC, preval. 36 mill	**5,331 mill**	NA	NA	NA		NA
(Kessler et al., 2001) 1996-1997 Repr. diary survey of 739 Partial productivity, preval. 13 mill	NA	NA	NA	**10,296 mill**		NA
(Crystal-Peters et al., 2000) 1995 Various US national, NHIS/BLS S, preval. 26 mill	NA	NA	NA	**6,687 mill**		NA
				INC	INC	
(Ross, 1996) 1983-1994 Various US national S, preval. 13 mill	NA	NA	NA	**5,838 mill**		NA

Notes: Bold type indicates a national estimate. Medical costs were inflated to 2005 dollars using BLS CPI for Medical Care; All other costs were inflated to 2005 dollars using BLS CPI; Methodology abbreviations: S – society perspective, SR – self-reported data, OTC – over-the-counter drugs, D – Delphi method used.

There are several methodological issues specific to allergic rhinitis COI studies. First, inadequately treated or untreated allergic rhinitis can be associated with a dramatic increase in the cost of caring for co-morbid conditions such as asthma, recurrent nasal polyps, sinusitis, and chronic otitis media (Schoenwetter et al., 2004). These are among the hidden costs of allergic rhinitis. A survey by Halpern et al. (2004) of over 27,398 patients with asthma demonstrated that costs for those with allergic rhinitis and asthma were roughly twice those for patients with asthma alone. Ray et al. (1999) estimate these hidden costs were $5.7 billion. Blaiss (2000)

reports that 58 percent of patients with asthma, 25 percent of patients with sinusitis, and 35 percent of children with otitis media have allergic rhinitis. Second, very few allergic rhinitis COI studies consider the cost of over-the-counter medications. Reed et al. (2004) estimate that 69 percent of individuals with symptoms of allergic rhinitis used over-the-counter medications in 1993, compared with 45 percent who used prescription medications. Storms et al. (1997) estimate that the cost of over-the-counter medications was $90 per patient per year. Thus, excluding the cost of over-the-counter medications will result in a substantial underestimate of the direct medical costs of allergic rhinitis.

Third, the symptoms of allergic rhinitis and sedating side effects of some allergic rhinitis medications are typically not severe enough to cause work absence. However, the symptoms may significantly lower on-the-job productivity ("presenteeism"). Thus, the studies that rely only on estimates of days lost from work are likely to significantly underestimate the indirect costs of allergic rhinitis. In addition, assigning monetary values to decreased work productivity and performance at school is difficult.

Finally, studies by Tripathi and Patterson (2001) and Meltzer (2001) discuss the impact of allergic rhinitis on the quality of life. They point out that poorly controlled symptoms of allergic rhinitis may contribute to loss of sleep, secondary daytime fatigue, learning impairment, decreased cognitive functioning, and decreased long-term productivity. Pharmacological therapies in some cases have considerable adverse side effects, affecting attention, working memory, vigilance, and speed (via sedation mechanism). However, to date no studies have attempted to assign monetary value to the deterioration of quality of life resulting from allergic rhinitis.

5.4.2. Asthma

There is international concern about growing asthma morbidity, and the literature on asthma is very extensive. The review papers that discuss the burden of asthma are Bousquet et al. (2005), Milton et al. (2004), O'Connell (2004), Gergen (2001), Weiss and Sullivan (2001), and Weiss and Sullivan (1993). In addition, there are a number of comprehensive COI studies (Weiss et al., 1992; Weiss et al., 2000; Smith et al., 1997; Farquhar et al., 1998; Birnbaum et al., 2002; Cisternas et al., 2003), including a recent analysis of willingness to pay (WTP) to avoid asthma (Zillich et al., 2002).

Table 5-7 provides a summary of the available asthma COI studies conducted in the U.S. As with allergic rhinitis, the studies differ substantially in cost estimates and methods employed; however, importantly, efforts have been made to estimate all known cost components. Direct

Table 5-7. Annual cost of asthma estimates, in 2005$ by cost category.

Study Name Period Data Sources Methodology	Direct Medical Costs	Direct Non-Medical Costs	Hidden Costs	Indirect Costs			Intangible Costs
				Lost School Days	Loss of Work	Loss of Life	
(Vance and Taylor, 1971) 1967-1969 3 year panel of 21 families with active asthmatics F	2,903/ family	NA	NA	NA			NA
(US NHLI, 1972) 1967 Various US National data sources S	**2,784 mill**	NA	NA	**1,591 mill**			NA
(Marion et al., 1985) 1977-1980 *used 1980 for inflation adjustments* 1-year panel of 30 families with an asthmatic child F	4,057/ family	NA	NA	348/ family			NA
(Weiss et al., 1992) 1985 Various US National data sources S, CHG, SR	**7,633 mill**	NA	NA	**2,624 mill**			NA
				911 mill	**866 mill**	**847 mill**	
(Smith et al., 1997) 1987 NMES S, SR	**7,883 mill**	NA	NA	**890 mill**[a]			NA
				257 mill	**555 mill**	NA	
(Farquhar et al., 1998) 1996 1987 NMES, other S	**16,995 mill**	NA	NA	**2,489 mill**			NA
				INC	INC	INC	
(Weiss et al., 2000) 1994 Various US National data sources S, CHG, SR	**9,357 mill**	NA	NA	**6,116 mill**			NA
				1,261 mill	**2,725 mill**	**2,130 mill**	
(Birnbaum et al., 2002) 1996-1998 *used 1998 for inflation adjustments* Claims data for Fortune 100 national company E, Case-control	1,340/ patient	NA	2,450[b]/ 373[c]/ patient	NA	138/ patient	NA	NA
(Zillich et al., 2002) 2002(?) *used 2002 for inflation adjustments* Survey of 100 asthmatics from community pharmacies in KY P, WTP	NA	NA	NA	NA			2,102[d]/ 1,599[e]/ patient
(Cisternas et al., 2003) 1998-1999 MEPS, NCS, panel of 401 adults from a sample of CA providers S	3,600/ patient	579/ patient	NA	NA	2,074/ patient	NA	NA

Notes: Bold type indicates a national estimate. Medical costs were inflated to 2005 dollars using BLS CPI for Medical Care; All other costs were inflated to 2005 dollars using BLS CPI; Methodology abbreviations: F – family perspective, S – society perspective, E – employer perspective, P – patient perspective, CHG – includes hospital charges and not costs, WTP – willingness to pay, SR – self-reported data; a – components may not add up to the total because other categories of indirect costs included bed days for children under 4; b – extra direct medical costs for other asthma-related conditions; c – extra loss of work costs for other asthma-related conditions; d – objective Willingness To Pay; e – subjective Willingness To Pay.

medical costs range from $2.7 billion to $16.9 billion in total (and from $1,340 to $3,600 per patient) per annum. Cisternas et al. (2003) estimated $579 per patient in direct non-medical costs. Hidden costs were estimated to be $2,450 per patient in extra direct medical costs for asthma co-morbidities and $373 per patient in work loss costs due to exacerbating effects of asthma on related conditions (Birnbaum et al., 2002).

Total indirect costs are not always comparable due to differences in components included. Estimates that include loss of life are substantially higher ($2.6 billion to $6.1 billion as compared to $0.9 billion). In addition to these estimates, a recent comprehensive study of productivity loss by Ward et al. (2002) reports that 25.2 percent of asthma patients in their sample were unable to work, 17.5 percent were limited in kind or amount of work, and 47.2 percent attributed the limitation in their ability to work to asthma.

Weiss and Sullivan (2001) noted that (i) asthma imposes a considerable financial burden on the family, which may adversely affect access to care by poorer individuals; and (ii) emergency department visits and hospitalizations are the key components of asthma care, with estimated costs per family of $2,784-$4,057 per annum. Hospitalization and medication represent two thirds to three quarters of total direct asthma-related costs (Gergen, 2001). Stanford et al. (1999) concludes that nursing accounts for the largest portion of hospital costs (43.6 percent), followed by respiratory therapy (13.6 percent), and medications (10.4 percent). Based on international comparisons, the percent of direct costs associated with hospitalization appears to be inversely correlated with the percent associated with medications (Gergen, 2001). This relationship may reflect the well-known fact that adequately managed asthma can reduce hospitalizations. The cost of asthma can be substantially non-uniform across asthmatics. Smith et al. (1997) noted that less than 20 percent of the individuals with asthma in their sample accounted for more than 80 percent of the total direct costs.

Finally, Zillich et al. (2002) estimated willingness to pay (WTP) to avoid asthma, the only measure that would include the intangible costs of the illness. Their survey of one hundred patients with asthma (recruited from Kentucky pharmacies) suggested that WTP was significantly related to both objective disease severity (as defined by a physician) and disease severity subjectively assessed by the patient. For objective disease severity the mean monthly WTP was $97 for mild asthma, $142 for moderate asthma, and $359 for severe asthma. For subjective disease severity, the mean monthly WTP was $52 for mild asthma, $180 for moderate asthma, and $262 for severe asthma. A weighted annual average is $2,102 for objective WTP and $1,599 for subjective WTP per patient.

5.4.3. Atopic Dermatitis

A recent review paper by Carroll et al. (2005) on the burden of atopic dermatitis on patients, family and society indicates that COI estimates for atopic dermatitis are very limited in the U.S. This is despite the fact that atopic dermatitis is widespread and is generally considered to be associated with substantial deteriorations in quality of life for patients and their families. In addition, O'Connell (2004) notes that atopic dermatitis can have a large social/emotional and financial effect on the family and often predates the development of allergic rhinitis and asthma.

Table 5-8 summarizes the available U.S. evidence. Lapidus et al. (1993) studied emergency room visits and ambulatory care billing records of an urban hospital in Philadelphia and extrapolated the direct costs to the United States to be $665 million annually. However, this study, published in 1993, was thought to underestimate the true cost of atopic dermatitis because it included only ER and physician visits (Carroll et al., 2005).

Table 5-8. Annual cost of atopic dermatitis estimates, in 2005$ by cost category.

Study Name Period Data Sources Methodology	Direct Medical Costs	Direct Non-Medical Costs	Hidden Costs	Indirect Costs		Intangible Costs
				Lost School Days	Loss of Work	
(Lapidus et al., 1993) 1991 Phila Children Hospital S, Natl. estimate	**665 mill**[a]	NA	NA	NA		NA
(Ellis et al., 2002) 1997 Claims Data (private provider & a state Medicaid program) PAY, D, case control	**1,239 mill-5,234 mill** or 1,460/person[b]	NA	NA	NA		NA
(Fivenson et al., 2002) 1997 Survey of 248 individuals in a managed care population P, OTC	427/person	NA	NA	411/person		NA
				INC	INC	

Notes: Bold type indicates a national estimate. Medical costs were inflated to 2005 dollars using BLS CPI for Medical Care; All other costs were inflated to 2005 dollars using BLS CPI; Methodology abbreviations: S – society perspective, PAY – payer perspective, P – patient perspective, OTC – over-the-counter drugs, D – Delphi method; a – likely to underestimate direct medical costs because includes only ER and physician's office visits; b – estimate for privately insured individuals was $799/person.

In a systematic review of third party claims data, Ellis et al. (2002) estimated the direct cost of atopic dermatitis in the United States to be $1.2-$5.2 billion. This analysis used claims from a managed care payer and state Medicaid program, with atopic dermatitis diagnoses based on International Classification of Diseases (ICD-9-CM) codes. Claims were reviewed by a panel, and co-morbidities were classified as most likely related to atopic dermatitis and possibly related to atopic dermatitis (using the Delphi method to create consensus, as explained in (Powell, 2003). The cost quoted included all atopic dermatitis claims for visits, prescription drugs, and

"likely" atopic dermatitis-related co-morbidities. The estimate, however, did not include the costs of over-the-counter medications or any indirect costs of lifestyle changes.

Fivenson et al. (2002) estimated the direct and indirect costs of atopic dermatitis at $838 per patient annually, using a patient survey to determine the indirect costs (including time lost from work) and managed care claims data to assess the direct costs. The direct medical costs (not including over-the-counter medications) were found to be only 27 percent of the total, suggesting the significant underestimation that occurs if only direct costs are used to estimate the economic burden of atopic dermatitis. Additionally, as discussed in an editorial by Ellis et al. (2003), there may have been an unrepresentatively small number of severely affected patients in Fivenson's study sample, which would lead to lower cost estimates (Carroll et al., 2005).

As noted above, atopic dermatitis is often associated with significant morbidity. Pruritus (severe itching, often of undamaged skin) caused by atopic dermatitis can affect both sleep and mood, and affected individuals often must modify several aspects of their lives because of treatment regimens and associated lifestyle changes. Individuals with atopic dermatitis are also at risk for psychosocial difficulties that may have long-lasting consequences, potentially affecting career choices and personal relationships. Patients are thus affected both by the condition itself and by the stigma associated with its visibility. A number of studies have shown that people with atopic dermatitis tend to report lower health-related quality of life and greater psychological distress than the general population (Carroll et al., 2005). In addition, the effects of atopic dermatitis on the entire family can be extensive. Unfortunately, monetary assessments of these intangible costs in the U.S. are yet to come.

6. FUTURE RESEARCH

Further progress must be made in documenting and understanding aeroallergen response to climate, the role of aeroallergens in disease development, and the willingness to pay to avoid – the intangible costs of these allergic diseases.

A review of the literature indicates that there is limited data on aeroallergen trends in the United States. Integrated long-term data series on all aeroallergens is necessary to clearly document future changes in aeroallergen production and distribution, as well as allergen content. Additional research on the response of mold and indoor allergens to climate change would be of particular value. In addition, further experimental and field studies are needed to examine how allergen content and distribution of aeroallergens may be altered in response to climate change. Such studies could address a number of key issues, including: (1) the combined effects of CO_2 and temperature, as well as interactions between these and other important variables, such as water and nutrient availability, disturbance, and competition (Beggs, 2004); (2) within-species genetic variation in response to changing CO_2 concentration availability and temperature (Beggs, 2004); and (3) effects of urban warming or land use changes, which may alter observed impacts of climate change (Beggs, 2004).

There is a need for better understanding of the role of aeroallergens in disease development, especially asthma. Specifically, what is the relative contribution of different aeroallergens to the development of asthma (Selgrade et al., 2006). There is a need to know what levels of allergen exposure constitute a risk for development of asthma (Selgrade et al., 2006). There is also a need for standardized approaches for measuring exposures and outcomes in epidemiologic studies (Selgrade et al., 2006). Finally, the possible synergistic effects of aeroallergens and air pollutants on the development of allergenic illnesses could be an important area for future research. For example, changes in the timing of pollen seasons could result in some overlap between the peak pollen period and the ozone season.

Based on a review of the COI literature on allergic rhinitis, asthma, and atopic dermatitis, it is clear that an important research gap is the current lack of assessment of – and, in particular, estimation of willingness to pay to avoid – the intangible costs of these diseases. In addition, better methodologies are needed to address productivity losses, aeroallergen avoidance, and over-the-counter medication use. Finally, as noted in Section 5, a disease or condition may contribute to increased costs as a secondary diagnosis, or as a risk factor for other diseases and

conditions. These hidden costs of co-morbidity need to be properly estimated and, if possible, included in future COI studies.

7. SUMMARY AND CONCLUSIONS

This report reviewed the available literature on (1) aeroallergens and associated allergenic illnesses prevalent in the United States, (2) the potential effects of climate change on these aeroallergens and, by inference, on the allergenic illnesses associated with them, and (3) the economic and quality-of-life impacts of these illnesses. Although some of the relevant research cited was carried out in other countries, this report focuses on the United States.

Aeroallergens are distributed throughout the U.S., but some are concentrated in particular geographic regions. Three allergenic illnesses have been associated with aeroallergens in the U.S.: asthma, allergic rhinitis (hay fever), and atopic dermatitis (eczema). Although all aeroallergens have been linked to each of these three allergenic illnesses, the strongest associations appear to be between pollens (tree, grass, or weed) and allergic rhinitis (hay fever), and between house dust mite or mold and asthma.

Limited data suggest aeroallergen levels in the U.S. have remained relatively constant (though the period of record may be too short to assess trends). While significant increases in the prevalence of allergenic illnesses have been observed, the factors contributing to this increase remain unclear. At the same time, experts have hypothesized that an increase in the distribution and concentration of aeroallergens could further increase the economic and quality-of-life burdens imposed by these illnesses in the United States.

The literature does not provide definitive data or conclusions on how climate change might impact aeroallergens and subsequently the severity prevalence of allergenic illnesses in the U.S. There is also an inherent uncertainty as to how the climate will change, especially at a regional level. In addition, the etiology of allergic diseases, especially asthma, is complex and has a gene environment interaction that is poorly understood. Finally, there are numerous other factors that affect aeroallergen levels and the prevalence of associated allergenic illnesses, such as changes in land use, air pollution, adaptive responses, and modifying factors, many of which are difficult to assess.

Nevertheless, some tentative inferences can be drawn about the potential impact of climate change on aeroallergens and the associated allergenic illnesses by making reasonable inferences about the links between (1) climate change and the characteristics of aeroallergens and (2) those aeroallergen characteristics and the associated allergenic illnesses. Global climate change models developed for the National Assessment Synthesis Team predict that many areas of the United States will become warmer and wetter. In addition, research has shown that

preseason temperature and precipitation have been consistently important predictors of pollen and mold production. Overall, experimental and observational data as well as models indicate the following likely changes in aeroallergen production, distribution, dispersal, and allergen content as a result of climate change in the United States:

- Pollen production is likely to increase in many parts of the United States, with the possible exception of the Southeast;
- Phenologic advance is likely to occur for numerous species of plants, especially trees;
- There will likely be changes in the distribution of pollen producing species, including the possibility of extinction in some cases;
- Intercontinental dispersal (e.g., of pollen) is possible, facilitating the introduction of new aeroallergens into the United States; and
- Increases in allergen content of some aeroallergens are possible.

Aeroallergen (e.g., pollen) exposure in sensitized individuals is associated with allergic rhinitis and less clearly with asthma and atopic dermatitis. Furthermore, some studies have demonstrated links between weather, aeroallergen production, and subsequent increased illness. Therefore, we can infer that changes in the timing, severity, and possibly the prevalence of allergic rhinitis (hay-fever) are likely, given the clear association between allergen exposure and response in sensitized individuals. While recent research points to a link between aeroallergens and asthma, the complex etiology of this illness and the unclear link between indoor aeroallergens and climate change lead to greater uncertainty about how asthma severity or prevalence might change in response to climate change and corresponding impacts on aeroallergens.

Because the economic and quality-of-life impacts of these allergenic illnesses are substantial, the corresponding economic and quality-of-life impacts of increases in the prevalence of these illnesses could similarly be significant. It has been reported that 54.6 percent of people in the U.S. currently test positive to one or more allergens. Consequently, allergies are the sixth most costly chronic disease category in the United States, costing the health care system approximately $21 billion annually (in 2005 dollars). Although the allergenic illnesses discussed in this report – allergic rhinitis, asthma, and atopic dermatitis – are not the only allergenic

illnesses in the United States, they are among the most important ones, and the costs associated with them account for a substantial component of the total costs of allergies in the U.S.

Allergic rhinitis affects approximately 40 million people each year in the United States, 40 percent of whom are children. Estimated total direct costs of treatment are $6.2 billion per year (in 2005 dollars). Indirect costs include 3.8 million missed days of school and work per year.

Asthma is estimated to affect approximately 15 million Americans, and 30 percent of all patients are children. Asthma can be life-threatening – there were 1,669 deaths due to asthma in 2003. According to a 2000 study, direct costs totaled nearly $12.5 billion (in 2005 dollars) and indirect costs (lost earnings due to illness or death) totaled $9.1 billion (in 2005 dollars). For adults, asthma is the fourth leading cause of work losses, resulting in nearly 15 million missed or "reduced productivity" workdays each year. Among children, asthma is the leading cause of school absences from a chronic illness, resulting in an annual loss of more than 14 million school days per year.

Atopic dermatitis is one of the most common skin diseases, particularly in infants and children – 10 to 15 percent of the population is affected during childhood and there is considerable evidence that the prevalence is increasing. The direct medical costs associated with atopic dermatitis are estimated to be $1.2-$5.9 billion (in 2005 dollars) per annum.

The cost of illness studies for allergic rhinitis, asthma, and atopic dermatitis that contributed to this review were all based on U.S. data, but varied with respect to scope, perspective, reference year, cost components, and, in some cases, the definition of disease. None of the studies used the incidence approach or applied discount rates to the stream of lost earnings over future years.

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