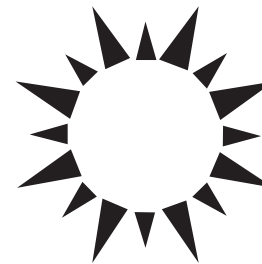


A0005 *Air Pollution, Health Effects of*

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- I. Historical Air Pollution Episodes
 - II. Types of Studies Used to Evaluate Health Impacts
 - III. Key Pollutants and Health Outcomes
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Glossary

- G0005 **cohort study** An epidemiological study in which a group of individuals is enrolled and tracked over time to evaluate whether more highly exposed individuals are more likely to develop disease or to die prematurely.
- G0010 **confounder** A variable independently associated with both the exposure and the health outcome in an epidemiological study, and could therefore be responsible for the observed relationship.
- G0015 **epidemiological study** An observational study of human populations (either occupational or general); designed to determine the association between exposure and disease.
- G0020 **inhalation unit risk** The excess lifetime cancer risk estimated to result from continuous lifetime exposure to a substance at a concentration of $1 \mu\text{g}/\text{m}^3$ in the air.
- G0025 **particulate matter (PM)** A solid or liquid suspended in the air; typically defined by the aerodynamic diameter of the particle and categorized as fine or respirable particles ($\text{PM}_{2.5}$, particles less than $2.5 \mu\text{m}$ in diameter), inhalable particles (PM_{10} , particles less than $10 \mu\text{m}$ in diameter), coarse particles ($\text{PM}_{2.5-10}$, particles between 2.5 and $10 \mu\text{m}$ in diameter), or total suspended particles (TSPs; suspended particles of all sizes).
- G0030 **reference dose** An estimate (with uncertainty spanning perhaps an order of magnitude) of the daily exposure to the human population (including sensitive subgroups) that is likely to be without an appreciable risk of adverse effects during a lifetime; used for the evaluation of noncancer risks of toxic chemicals.
- G0035 **time-series study** An epidemiological study in which changes in pollution levels over time are correlated with changes in health outcomes over time, capturing the short-term effects of pollution on health.

toxicological study A controlled laboratory experiment in which a small number of animals is given a gradient of doses of compounds with suspected health impacts, and the relationship between dose and disease rate is estimated. G0040

UNDERSTANDING THE HEALTH impacts of air pollution is a crucial step in the determination of appropriate energy policy. Although it has been well established that large increases in pollution exposures can lead to substantial increases in death and disease, it is somewhat more complex to quantify the precise impacts of an incremental change in exposures to a specific pollutant at the levels commonly faced by individuals. This is in part because there is an array of different air pollutants in outdoor and indoor air; pollutants can come from different sources and have different types of health effects, thus different forms of evidence are used to draw conclusions regarding pollutant health impacts. Broadly, air pollution causes health impacts through a pathway in which emissions lead to concentrations of key pollutants in the air, human activity patterns influence the exposures people face from these concentrations, and characteristics of the exposed populations help determine the types and magnitudes of health impacts. D0005

I. HISTORICAL AIR POLLUTION EPISODES

Although there have been a number of documented events whereby extreme levels of air pollution led to elevated death and disease rates, three episodes occurring near the middle of the 20th century are among the most well documented and were the first pollution events studied in great detail. In December 1930, an atmospheric inversion led to a thick pollution fog settling over the Meuse Valley in P0005

Belgium. During a 4-day period, 60 deaths were attributed to the pollution (10 times more than normal), and many individuals suffered from respiratory distress, with the elderly or those with respiratory or cardiovascular disease at greatest risk. Levels of a number of pollutants were increased during this episode, with extremely high concentrations of sulfur-based compounds. In the second event, in October 1948, a similar set of circumstances (temperature inversion in an area with substantial industrial activity) led to an air pollution episode in Donora, Pennsylvania. Nearly half of the residents of the town became ill, with 20 deaths attributed to the multiday episode. Finally, perhaps the most damaging and well-known pollution episode occurred in December 1952 in London, where a temperature inversion and associated elevated pollution levels led to 4000 deaths during the episode and to another 8000 deaths during the subsequent months (demonstrating a lagged or cumulative effect of exposure). As previously, elderly individuals and those with respiratory and cardiovascular disease were at greatest risk of health impacts.

P0010 These and other similar episodes provided clear evidence of the effects of extremely high levels of air pollution, which generally occurred when significant emissions from low stacks were trapped near the ground due to atmospheric conditions. Because of increased emission controls and taller stacks in many settings at the start of the 21st century, the pollution levels seen in the early studies are currently rarely seen in either developed or developing countries. Evidence from additional sources of information is therefore needed to understand health impacts of lower levels of air pollution, as well as to determine precisely which pollutants are responsible for mortality and morbidity impacts.

S0010 **II. TYPES OF STUDIES USED TO EVALUATE HEALTH IMPACTS**

P0015 The evidence used to determine the magnitude of mortality and morbidity effects of air pollution comes from two general types of studies. Toxicological studies are controlled laboratory experiments in which relatively high doses of compounds are administered to animals and rates of diseases (often cancer) are estimated. As controlled experiments, toxicological studies avoid some of the issues in observational studies, wherein a number of potential

causal factors can be changing at the same time. However, in order to determine health effects in humans, results from toxicological studies must be extrapolated in at least two important ways—results from animals must be applied to humans, and results from high doses necessary to see effects in a small number of animals must be used to draw conclusions about lower doses typically seen in humans. Because of these often substantial uncertainties, epidemiological studies, when they are available and interpretable, are generally preferred for quantifying the health impacts of air pollution, with toxicological studies providing supporting evidence for a causal effect.

Epidemiological studies are observational studies of human populations; they designed to show the relationship between exposure to an agent or set of agents and the development or exacerbation of disease. Although the focus on human populations and observed exposures removes some of the extrapolation issues associated with toxicological studies, epidemiological studies run a greater risk of yielding results that do not reflect a true causal relationship between exposure and disease (because correlation does not necessarily imply causation). This would occur if there were confounders, which are variables independently associated with both the exposure and the disease in question, that could actually be responsible for the observed relationship. For an epidemiological study to adequately determine the health effects of air pollution, it must use statistical techniques or a restrictive study design to remove the possibility of confounding by nonpollution variables. Also, unlike toxicological studies, which generally focus on a single pollutant or a defined list of pollutants, epidemiological studies measure health effects that could be associated with a number of pollutants that are often correlated with one another in time or space. Epidemiological studies must also be able to provide accurate exposure estimates, which can be more difficult than in toxicological studies, in which the doses can be measured in a controlled setting, particularly for large populations, for long-term exposures, or for pollutants that vary greatly in time or space.

There are three primary types of epidemiological studies used to understand the health effects of air pollution, each of which has different strengths and different issues related to potential confounders. The first is the cross-sectional study, in which disease rates in different locations are correlated with pollution levels in those settings, looking at a single point in time. Although these studies can generally be

conducted using only publicly available information, they can suffer both from confounding issues and from the ecological fallacy, which is the incorrect assumption that relationships evaluated from large groups are applicable to individuals. A classic example of the ecological fallacy involved a study that showed that whereas there was a correlation between race and illiteracy rates across states, this relationship was drastically reduced when considering individuals rather than states.

P0030 In terms of confounding issues, individual behaviors with important linkages to health (such as smoking status or occupation) cannot be incorporated into a cross-sectional study, making it difficult to interpret the causal association between air pollution and health. Therefore, although many of the original air pollution epidemiological studies were cross-sectional because of the availability of information, these studies are conducted less often at present.

P0035 Air pollution health effects are also determined through time-series studies, which are studies that compare changes in daily or multiday air pollution levels with changes in daily or multiday health outcomes (such as emergency room visits or deaths). These studies therefore yield information about the influence of air pollution on health over a relatively short number of days (known as acute health effects). Time-series studies have the strength of having a relatively limited set of potential confounding variables, because any confounder must be correlated with both air pollution levels and health impacts on a temporal basis. For example, cigarette smoking could only confound the relationship in a time-series study if more people smoked on high-pollution days than on low-pollution days, which is unlikely. However, cigarette smoking could act as an effect modifier, a variable that influences the relationship between exposure and disease but does not distort the true relationship between exposure and disease. Plausible confounders include weather variables such as temperature and relative humidity, which can affect both pollutant formation and population health, as well as air pollutants other than those studied or measured. Because time-series studies rely largely on publicly available information and are informative about the relationship between air pollution and health, the majority of air pollution epidemiological studies are time-series studies.

P0040 Despite the numerous advantages of time-series studies, they cannot provide information about the effects of longer term exposures to air pollution (known as chronic health effects). Time-series studies

can expand the time window under consideration beyond periods of days, but seasonal trends in health risks and statistical limitations of time-series studies make it impossible to evaluate the effects of daily exposure beyond about a couple of months. Information about long-term health risks is primarily taken from retrospective or prospective cohort studies, in which a group of individuals is tracked for a significant period of time (often decades) to evaluate whether their air pollution exposures are linked to higher risks of mortality or chronic disease. Because individual-level data about nonpollution risk factors can be collected, confounders can be dealt with in a more substantial way than in cross-sectional studies. However, there remain more plausible confounders for a cohort study than for a time-series study (including lifestyle factors such as smoking, diet, or occupation, which, similar to pollution levels, can theoretically vary spatially in patterns). Statistical methods are used to evaluate the independent effects of air pollution given the levels of other risk factors, which addresses this issue to an extent. The long time horizon to conduct a cohort study implies that fewer of these studies can be done, but the long-term exposure focus means that the health impacts estimated in cohort studies would be expected to be greater than the health impacts in time-series studies (which do not capture the effects of long-term exposures).

In addition, it should be noted that other types of studies provide evidence about the health effects of air pollution. Human chamber studies, in which people are exposed to a pollutant for a short period of time in a controlled laboratory setting, can help corroborate relationships observed in epidemiological studies (particularly for short-term and reversible health effects). Other epidemiological study designs can also be informative, such as case-crossover studies (in which individuals act as their own controls, comparing exposures when the health outcome of concern occurred with exposure levels during a comparable point in time) or panel studies (in which subjects are monitored intensively over a short period of time to evaluate the effects of exposure on outcomes such as daily symptoms or lung function).

Regardless of the type of toxicological or epidemiological information, a crucial final step in determining the health effects of an air pollutant is to evaluate whether the evidence is sufficient to infer a causal relationship rather than a simple association. Although proper statistical control of confounders is an important first step, inferences about

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causality require evidence that is outside of the domain of individual studies. To make this evaluation more systematic, Sir Austin Bradford Hill proposed nine “causal criteria” that could be applied. These include strength of the association, consistency across studies or techniques, specificity of the health effect, temporality (exposure preceding disease), biological gradient (higher exposures leading to greater health risks), biological plausibility, coherence with known facts about the disease, supporting experimental evidence, or analogy with other exposures. Although these provide a useful basis for analysis, Hill believed that these should not be interpreted as rules, all of which must be followed, but rather as a framework in which evidence about causality can be interpreted.

have largely been associated with cancer through a combination of toxicological and occupational epidemiology studies, along with miscellaneous neurological or reproductive end points. Another important difference between the two pollutant categories is that although it is assumed that cancer risks from air toxics have no threshold (meaning that any level of exposure would lead to some risk of cancer), criteria air pollutants or noncancer risks from air toxics are assumed to have thresholds (levels below which no population health impacts would occur) unless it can be demonstrated otherwise.

III.A. Particulate Matter

Of the criteria pollutants, particulate matter has received the greatest attention within the scientific community to date. PM can be simply defined as any solid or liquid substance suspended in the air. As such, PM can include many different substances, ranging from sea salt, to elemental carbon directly emitted by diesel vehicles, to sulfate particles secondarily formed from SO₂ emissions. Air quality regulations have focused historically on the size of particles rather than on the chemical composition, given the complexity of particulate matter, the difficulty of measuring numerous constituents, and the physiological importance of particle size.

Originally, regulations in the United States and elsewhere focused on total suspended particles (TSPs), which included airborne particles of all sizes. However, the largest particles seemed unlikely to cause significant health impacts, because they remain suspended in the air for brief periods of time and cannot travel into the lungs (see Fig. 1). In 1987, the U.S. EPA modified the particulate matter National Ambient Air Quality Standard (NAAQS) to focus on PM₁₀, defined as the fraction of particles less than 10 μm in aerodynamic diameter. PM₁₀ has also been referred to as inhalable particles, because these particles are sufficiently small to enter the respiratory system. The size fraction of interest was further constrained by the U.S. EPA in 1997, when they proposed to change the focus of the NAAQS to PM_{2.5}, the fraction of particles less than 2.5 μm in aerodynamic diameter. These smaller particles, known as fine particles or respirable particles, are most able to reach the lower portions of the lungs, where gas exchange occurs.

Historically, a large amount of the evidence of particulate matter health effects has come from epidemiological studies, in part because of the regulatory emphasis on total particulate matter

S0015 III. KEY POLLUTANTS AND HEALTH OUTCOMES

P0055 A number of air pollutants have been connected with human health impacts in epidemiological and/or toxicological studies. These pollutants are conventionally divided into two categories:

1. Criteria pollutants: particulate matter (PM), ozone (O₃), sulfur dioxide (SO₂), nitrogen dioxide (NO₂), carbon monoxide (CO), and lead (Pb), as defined by the United States Environmental Protection Agency (U.S. EPA) in the Clean Air Act. These pollutants are generally ubiquitous and have a range of health impacts at typical ambient levels.
2. Toxic air pollutants: also known as “hazardous air pollutants,” substances considered to cause cancer or to lead to other potential noncancer effects that might include reproductive, developmental, or neurological impacts. The U.S. EPA maintains a list of hundreds of toxic air pollutants that are anticipated to impact human health.

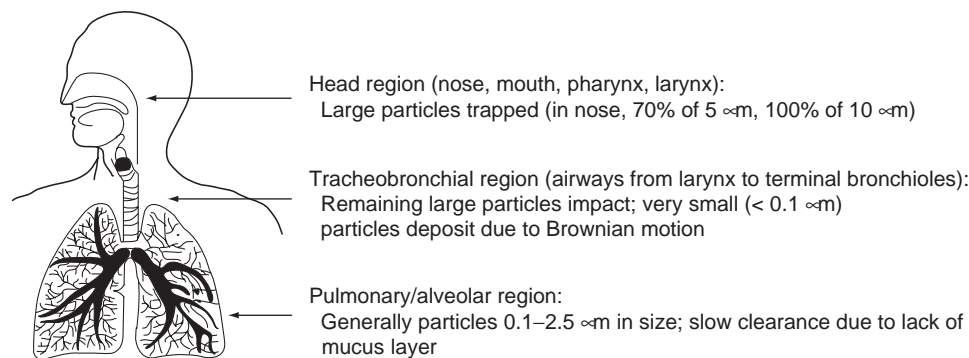
P0060 As might be expected, there is substantially more epidemiological evidence for criteria air pollutants than for toxic air pollutants, given the generally higher levels and shorter term effects (as well as the existence of monitoring networks necessary for most epidemiological investigations). In general, criteria air pollutants have been associated with respiratory or cardiovascular outcomes ranging from symptom exacerbation to premature death, with some limited evidence for lung cancer effects. Toxic air pollutants

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FIGURE 1 Relationship between particle size and site of particle deposition in the lung.

rather than chemical constituents. A number of time-series studies have evaluated the relationship between daily changes in particulate matter concentrations and daily changes in number of deaths, generally within a few days of the pollution increment. These studies have been conducted in both developed and developing country settings and in cities with a range of pollution types or levels, but they have largely demonstrated a consistent relationship between PM and mortality even when the effects of weather or other air pollutants are taken into account. Across the numerous studies that evaluated the relationship between PM₁₀ and daily mortality, estimates generally have been on the order of a 0.5–1% increase in deaths per 10 $\mu\text{g}/\text{m}^3$ increase in daily average PM₁₀ concentrations (although with selected studies yielding either nonsignificant or greater effects). These estimates have been similar in cities with different levels of other air pollutants, different sources of particulate matter, and different correlations between those pollutants and particulate matter, lending support to the hypothesis that particulate matter rather than other pollutants or confounders is responsible for this observed relationship. As anticipated, in most studies, the effects were greater for respiratory or cardiovascular causes of death than for other causes of death.

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A crucial issue for interpretation of time-series air pollution studies is whether they represent a significant loss of life expectancy or whether the deaths are simply a function of “harvesting,” whereby individuals who would have otherwise died the next day are dying one day earlier due to acute pollution exposure. If this were the case, then the death rate might increase above the expected level on one day but drop below the expected level the next day, with no net increase in deaths over the week following the pollution increase. Studies that have investigated the harvesting question have found that the relationship

between PM and mortality does not vanish as the time period after the exposure increases, indicating that harvesting is unlikely.

A final question from the time-series mortality literature is whether a threshold exists, and, if so, at what concentration. Studies have generally not found evidence of a population threshold within the range of ambient concentrations measured, although a threshold could exist at levels lower than those observed in the epidemiological studies. In contrast, there have been relatively fewer cohort mortality studies in the published literature, given the resource intensity of these investigations. Although multiple cohort mortality studies exist, two studies published in the mid-1990s were among the earliest completed and provided an important basis for subsequent regulatory decisions and assessments of the health effects of air pollution. The Six Cities Study tracked 8111 white adults who lived in six cities in the eastern half of the United States for 15–17 years. In each city, at the start of the study, the research team set up a centrally located monitoring station, where concentrations of both particulate matter of various sizes and gaseous pollutants were measured. As a cohort study, this study was able to collect detailed information about individual behaviors that could influence health, such as smoking, obesity, and occupational exposures.

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Controlling for these and other plausible confounders, the investigators found that mortality rates were significantly higher in the high-pollution cities compared with the low-pollution cities, with the strongest associations found for three different measures of particulate matter (PM₁₀, PM_{2.5}, and sulfate particles). The relationship for SO₂ was weaker than the PM relationships, and there was no association between mortality and ozone. Air pollution was significantly associated with death from cardiovascular and respiratory disease, was

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positively associated with lung cancer (although not statistically significantly so), and was not associated with other causes of death. The relative risk for mortality was reported to be 1.26 for an $18.6 \mu\text{g}/\text{m}^3$ increase in $\text{PM}_{2.5}$ concentrations (95% confidence interval: 1.08, 1.47), with no apparent threshold at the pollution levels documented in the study (between 11.0 and $29.6 \mu\text{g}/\text{m}^3$ of $\text{PM}_{2.5}$).

P0095 To determine if the conclusions from the Six Cities Study were robust, the American Cancer Society cohort study was conducted, in which individuals enrolled in the American Cancer Society Cancer Prevention Study II were matched with the nearest ambient air pollution monitoring data. This cohort contained over 500,000 United States subjects living in all 50 states, with detailed individual risk factor data collected. As in the Six Cities Study, the American Cancer Society study found a significant increase in mortality risks as levels of both $\text{PM}_{2.5}$ and sulfate particles increased across cities. Cardiopulmonary mortality was significantly elevated for both pollutants, whereas lung cancer mortality was significantly associated with sulfate particles but not $\text{PM}_{2.5}$. The relative risk for all-cause mortality was 1.17 for a $24.5 \mu\text{g}/\text{m}^3$ increase in median annual $\text{PM}_{2.5}$ concentrations (95% confidence interval: 1.09, 1.26), slightly lower than the relative risk from the Six Cities Study. No threshold for mortality risks was apparent across the range of fine particle concentrations in the study (between 9.0 and $33.5 \mu\text{g}/\text{m}^3$ of median annual $\text{PM}_{2.5}$ concentrations).

P0100 Additional analyses of these two cohorts emphasized the robustness of the findings across different statistical formulations and additional confounders. A detailed reanalysis of both studies by the Health Effects Institute concluded that the findings did not appear to be confounded by non-air-pollution variables and that there was an association between mortality and $\text{PM}_{2.5}$ and sulfate particles, as well as with gaseous SO_2 . A follow-up to the American Cancer Society study used more monitoring data and more years of population follow-up on the original cohort, along with a refined statistical approach and an increased number of behavioral confounders. The estimated effect of air pollution on mortality was similar to the earlier findings, but the follow-up study documented a statistically significant association between PM exposure and lung cancer (potentially due to the increased sample size given more years of follow-up).

P0105 Thus, these two seminal cohort mortality studies documented an effect of air pollution on mortality that is somewhat larger than the effect from the time-

series studies (even when both types of studies consider the same particle size) and was associated in large part with particulate matter. Furthermore, the cohort mortality studies likely represent both a greater loss of life expectancy potentially related to induction rather than exacerbation of disease (such as lung cancer, which cannot plausibly be related to air pollution in a time-series study). Although inherent limitations of epidemiology make it difficult to disentangle the effects of individual pollutants, and cohort studies have numerous behavioral confounders that must be addressed statistically, the cohort mortality studies supported the time-series mortality studies regarding the role of particulate matter and demonstrated a potentially greater effect for fine particles than for larger particles.

Along with the mortality effects, the epidemiological literature for PM has documented morbidity outcomes with a wide range of severity. Hospital admissions and emergency room visits for cardiovascular or respiratory causes have been studied extensively in time-series investigations, in part due to the publicly available information and the relative ease of defining the health end points. Other acute health end points that have been associated with particulate matter exposure include upper and lower respiratory symptoms, asthma attacks, and days with restricted activities. Long-term particulate matter exposure has also been associated with the development of chronic bronchitis, defined as inflammation of the lining of the bronchial tubes on a chronic basis, with the presence of mucus-producing cough most days of the month for at least 3 months of the year for multiple years, without other underlying disease. These morbidity end points are consistent with the types of premature deaths found in the mortality studies and are therefore supportive of the relationship between particulate matter exposure and respiratory and cardiovascular health.

III.B. Ozone

In contrast with the health evidence for PM, the primary studies documenting ozone health effects have been a combination of toxicological, human chamber, and epidemiological studies. This is in part because, unlike PM, ozone is a single substance with well-understood chemical properties. Ozone is an oxidant gas that is poorly water soluble. Ozone is therefore able to travel throughout the respiratory tract, reacting with molecules on the surface of the lung and leading to pulmonary edema, inflammation, and the destruction of epithelial cells that line the

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respiratory tract. These and other physical changes to the lung, many of which are transient but some of which may be permanent, could plausibly lead to a number of health outcomes documented in the epidemiological literature, given sufficient ozone exposure. As in any epidemiological analysis, the crucial question is what level of ozone exposure is sufficient to induce health effects (or whether population health effects are found for any level of ozone exposure) and what the magnitude of the relationship is between ozone exposure and various health outcomes.

P0120 As anticipated, epidemiological and human chamber studies have shown that ozone has an array of acute effects on the respiratory system. Short-term exposures to ozone have been associated with significant but reversible decreases in lung function as well as increases in pulmonary inflammation. As would be expected, these physiological changes have resulted in increases in both mild (respiratory symptoms and restrictions of activity) and severe (emergency room visits and hospitalizations) morbidity outcomes, depending on the health of the individual and the magnitude of the exposure.

P0125 Ozone has also been associated with premature death in some time-series studies; however, because high-ozone days tend to correspond with hot and humid days (which are associated with higher mortality rates), it can be difficult to determine the relative contributions of air pollution and weather. Ozone may also be correlated with particulate matter and other air pollutants in some settings, impairing the ability to determine the independent role of each pollutant. Finally, ozone does not penetrate indoors as readily as PM, making indoor exposures lower and outdoor monitor-based health evidence harder to interpret. Regardless, considering a subset of published studies that controlled both for other air pollutants (primarily PM) and for the nonlinear effects of weather on health, there appears to be an association between daily average ozone concentrations and premature death, with an approximate 1% increase in deaths per 10 parts per billion (ppb) increase in daily average ozone. Because fewer studies have focused on ozone mortality in detail than have focused on particulate matter mortality, both the existence and the magnitude of this effect are somewhat uncertain.

P0130 Ozone may also be associated with chronic, nonreversible health outcomes. Children who exercise outdoors in high-ozone areas have been shown to have increased risk of asthma development, demonstrating potential long-term effects of ozone

exposure as well as the importance of breathing rate and time spent outdoors (because ozone levels indoors are low, given the reactivity of ozone). Ozone exposure has also been linked with decreased lung function in young adults who lived for long periods of time in cities with high ozone levels. Although the Six Cities Study and the American Cancer Society study did not document an influence of long-term exposure to ozone on premature death, there is both epidemiological and physiological evidence supporting chronic pulmonary inflammation and other chronic health effects due to low-level ozone exposure.

III.C. Other Criteria Air Pollutants

Although PM and ozone are the two pollutants studied most extensively in many past epidemiological investigations (especially studies of mortality risk), there is also evidence of health effects of other criteria air pollutants. It has been well established that extremely high levels of carbon monoxide (CO) can lead to damage to the central nervous system, eventually leading to death at high enough concentrations. This is because hemoglobin preferentially reacts with CO over oxygen (forming carboxyhemoglobin), thereby reducing the oxygen-carrying capacity of the blood. Symptoms at lower levels of carboxyhemoglobin in the blood (below 30%) include headache, fatigue, and dizziness, with coma, respiratory failure, and subsequent death occurring at levels above 60%.

There has also been evidence that low levels of exposure to CO (corresponding to typical ambient levels in some settings) can lead to cardiovascular impairment. Time-series investigations have correlated cardiovascular hospital admissions with exposure to CO even when controlling for other pollutants, although the degree to which these effects are independent of the effects of other pollutants is difficult to determine. However, controlled human chamber studies have demonstrated that carboxyhemoglobin levels as low as 2% are associated with cardiovascular effects such as anginal pain or changes in electrocardiogram measures, providing support for the epidemiological findings.

Similarly, there is clear evidence that exposure to extremely high levels of nitrogen dioxide can lead to respiratory distress, with symptoms such as cough, shortness of breath, and chest tightness occurring given short-term exposures on the order of 1 part per million (ppm; a level rarely seen in outdoor air but occasionally found in poorly ventilated indoor settings containing combustion sources).

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These effects occur for reasons similar to those involved in ozone health impacts, with the insoluble nature of nitrogen oxides coupled with their oxidative properties leading to damage to epithelial cells and other forms of cytotoxicity.

P0150 At lower levels of air pollution, epidemiological studies have documented linkages between NO₂ exposures and outcomes such as decreased lung function or increased respiratory infections. A number of studies have investigated the relationship between NO₂ exposure and respiratory illness in children, often using the presence of gas stoves as a proxy for elevated exposures. These studies generally found that acute lower respiratory symptoms in children increased with incremental increases in NO₂ concentrations, down to fairly low levels. Children and individuals with preexisting respiratory disease have been most strongly linked with respiratory outcomes associated with NO₂ exposure.

P0155 As mentioned previously, there was an association between sulfur dioxide and premature mortality in the American Cancer Society cohort study. However, it was difficult to determine the relative importance of gaseous SO₂ versus PM_{2.5} or secondary sulfate particles, and this finding has generally not been interpreted as a definitive causal relationship, given the lack of supporting evidence for the lethality of low-level SO₂ exposure. Sulfur dioxide has been established as an irritant to the eyes and upper respiratory tract at high concentrations (multiple ppm). The site of the documented respiratory tract effect differs somewhat from the sites hypothesized for ozone or nitrogen oxides. This is because SO₂ is highly water soluble and can therefore react in the upper respiratory tract, making that the site of its irritant effects.

P0160 Considering acute SO₂ exposures at typical ambient concentrations, high-risk populations include children with mild to moderate asthma and others with preexisting respiratory disease. Short-term exposures to SO₂ concentrations on the order of 0.25–0.5 ppm have been associated with bronchoconstriction and subsequent decreases in lung function and increases in respiratory symptoms, for those with asthma or other respiratory diseases. In agreement with these findings, some epidemiological studies have associated respiratory hospital admissions or emergency room visits with SO₂, although the evidence supporting these more severe outcomes has not been substantial. However, it is clear that sulfur dioxide and its related secondary by-products have potential health impacts at higher pollution levels.

P0165 Finally, although the health effects of airborne lead have been drastically reduced in much of the

developed world due to the use of unleaded fuels, outdoor airborne lead can have significant health impacts near industrial sites (such as lead smelters) or in countries that still use a significant portion of leaded fuel. Although extremely high levels of blood lead have been associated with severe central nervous system problems, the more prevalent health impacts, which have been documented at blood lead levels as low as 10 µg/dl or lower, include incremental increases in blood pressure and incremental decreases in the IQ of children. Although both of these health end points are only incrementally affected by lead at generally seen blood lead levels, the population health implications of small shifts in blood pressure or IQ can be significant.

III.D. Toxic Air Pollutants

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Given the numerous toxic air pollutants (189 compounds are listed in Section 112 of the 1990 U.S. Clean Air Act Amendments) with both cancer and noncancer health effects, the anticipated health effects of each of these pollutants cannot be described in detail here. However, the severity of the carcinogenic effects of a toxic air pollutant can generally be described in one of three ways—its cancer classification, its inhalation unit risk, or its population cancer risk.

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Because evidence about carcinogenicity can arise from a number of sources, the U.S. EPA, the International Agency for Research on Cancer (IARC), and other similar organizations have developed methods to categorize the weight of evidence for carcinogenicity. As indicated in Table I, both the U.S. EPA and IARC evaluate evidence from animal and human studies, as well as available information about the mechanism of action of the compound, to draw conclusions about the likelihood that the substance is carcinogenic. In general, few substances have been categorized as known human carcinogens (EPA Category A, IARC Category 1), because this requires statistically significant epidemiological evidence, which is difficult to obtain, given the need for studies that follow exposed populations for decades, accurately characterize long-term exposures, and adequately control for potential confounders for cancer development (such as smoking). Similarly, few substances have been determined to be noncarcinogens, because most substances tested (which is only a subset of those substances to which humans are exposed) have some positive evidence of carcinogenicity in some test or species.

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Once the likelihood of carcinogenicity has been established, the inhalation unit risk is calculated,

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T0005 **TABLE I**

Cancer Classification Systems by the U.S. Environmental Protection Agency and International Agency for Research on Cancer

Category	Description	Animal evidence	Human evidence
U.S. EPA			
A	Known carcinogen	Any	Sufficient
B1	Probable carcinogen	Sufficient	Limited
B2	Probable carcinogen	Sufficient	Inadequate or none
C	Possible carcinogen	Limited	Inadequate or none
D	Not classifiable	Inadequate	Inadequate or none
E	Noncarcinogen	None	None
IARC			
1	Known carcinogen	Any Sufficient	Sufficient strong relevant mechanism
2A	Probable carcinogen	Sufficient	Limited, inadequate + strong relevant mechanism
2B	Possible carcinogen	<Sufficient	Limited
		Sufficient	Inadequate
3	Not classifiable	Inadequate or limited	Inadequate
4	Probable noncarcinogen	Negative	Negative, inadequate

given evidence from animal and human studies. The inhalation unit risk refers to the excess lifetime cancer risk estimated to result from continuous lifetime exposure to the given substance at a concentration of 1 µg/m³ in the air. For most compounds, the inhalation unit risk must be calculated from animal studies that use much higher doses than are commonly found for human populations. Statistical techniques based in part on hypothesized mechanisms of action for cancer development are used to determine appropriate inhalation unit risks at low doses, but this analytical process contains multiple steps that contribute uncertainty to the final quantitative estimate.

described focused on cancer risks; however, many air toxics also have noncancer risks that can be substantial. A prominent example is mercury, for which there is substantial evidence of neurological impairment (such as impaired motor skills or cognitive function) but limited evidence of carcinogenic effects. For these noncancer effects, the general analytical approach is to determine whether an adverse health effect is likely to occur, rather than quantifying a unit risk factor. This is done by determining a reference dose from animal or human studies, i.e., an estimate (with uncertainty spanning perhaps an order of magnitude) of the daily exposure to the human population (including sensitive subgroups) that is likely to be without an appreciable risk of adverse effects during a lifetime. As indicated by the careful language in the definition, this reference dose is not meant to be a definitive bright line, in part because of the number of uncertainties embedded in its calculation (i.e., extrapolation from short-term studies of genetically homogeneous rats to health effects from long-term exposures in heterogeneous human populations).

IV. HEALTH EFFECTS OF INDOOR AIR POLLUTION

The information discussed thus far was obtained from studies that largely focused on the effects of pollution generated outdoors (such as from power plants or motor vehicles) on population health, which includes exposure during time spent outdoors

P0185 As is clear from the definition of inhalation unit risk, the population cancer risk from an air toxic will be a function of both the inhalation unit risk and the level of population exposure to the substance. Investigations by the U.S. EPA provide some indication of the outdoor air toxics that contributed most substantially to cancer risk in the United States in 1990, based on estimated inhalation unit risks and modeled outdoor concentrations of the pollutants. In total, five substances contributed more than 75% of the total estimated cancer risk from outdoor air toxics—polycyclic organic matter, 1,3-butadiene, formaldehyde, benzene, and chromium. Along with their relatively high inhalation unit risks and ambient concentrations, these substances are all considered probable or known human carcinogens.

P0190 Although this captures some of the most substantial health effects from air toxics, there are a few important omissions. The analytical approach just

S0040

P0195

as well as exposure indoors from pollution penetrating from the outdoors. However, most of these studies did not consider indoor-generated pollution. Indoor-generated air pollution can be extremely important in both developing and developed country settings, both because of the amount of time people spend at home and because, in a confined space, pollution levels can quickly reach extremely high levels when a highly emitting fuel is burned indoors.

P0200 The uncontrolled combustion of biofuels, ranging from wood, to animal waste, to crop residues, to coal, is prevalent among poorer households in developing countries, with about 50% of the global population relying on these energy sources for heating and cooking. Numerous pollutants are emitted at high rates from biofuel combustion, including particulate matter, carbon monoxide, nitrogen oxides, and carcinogens such as formaldehyde or benzo[*a*]pyrene. The high emission rates into confined spaces result in extremely high indoor concentrations, with daily average levels as high as 50 ppm of CO and 3000 $\mu\text{g}/\text{m}^3$ of PM₁₀ (versus U.S. EPA primary health standards of 9 ppm of CO and 150 $\mu\text{g}/\text{m}^3$ of PM₁₀). As a result, rates of multiple diseases are elevated in homes burning biofuels, including acute respiratory infections, chronic obstructive pulmonary disease, cancer, and low birth weight. It has been estimated that indoor air pollution is responsible for nearly 3 million deaths per year globally, approximately two-thirds of which occur in rural areas of developing countries.

P0205 Although the health effects of indoor air quality and its linkage with energy are predominantly a developing country story, the developed world is not immune to these problems. Homes that have been tightened to improve energy efficiency can have reduced ventilation rates and subsequent increases in indoor pollution concentrations. As already mentioned, the use of gas stoves can increase indoor concentrations of nitrogen dioxide, which has been associated with increased respiratory disease in children. In addition, for many air toxics, exposure to indoor sources can exceed exposure to outdoor sources, due to the use of cleaning products, off-gassing from building materials, and other emission sources.

S0045 V. CONCLUSIONS

P0210 Although the evidence supporting the health impacts of air pollution is varied and evolving over time,

some general conclusions can be drawn based on existing information:

1. At current levels of air pollution in most developed and developing country settings, there is evidence of both mortality and morbidity effects. However, extreme episodes are rare and the relative risk of health effects of air pollution is low enough to necessitate incorporating evidence from a number of types of studies (including epidemiological and toxicological studies) to determine the magnitude of the effect and the likelihood of causality.

2. For criteria air pollutants, the most extensive evidence is related to particulate matter, which has been associated with premature death and cardio-pulmonary morbidity due to both short-term and long-term exposures. However, uncertainties exist regarding the components of particulate matter causally linked with health outcomes and the relative contributions of other criteria pollutants to the public health burden of air pollution. The fact that long-term cohort studies have been conducted only in developed countries also contributes uncertainty in extrapolating the findings to locations with much higher levels of pollution.

3. In most settings, a subset of toxic air pollutants contributes a substantial portion of the population cancer risk from outdoor air toxic emissions, with polycyclic organic matter, 1,3-butadiene, formaldehyde, benzene, and chromium among the most substantial contributors in the United States at present.

4. Indoor air pollution, compared to outdoor air pollution, could contribute more significantly to health impacts, given the amount of time spent indoors and the higher concentrations of combustion-related pollutants in indoor settings with limited ventilation. This problem is most severe in rural settings in developing countries, where the direct burning of biofuels has been associated with respiratory disease and other health end points.

SEE ALSO THE FOLLOWING ARTICLES

Acid Deposition and Energy Use (00389) • *Air Pollution from Energy Production and Use (00387)* • *Clean Air Markets (00492)* • *Climate Change and Public Health: Focus on Emerging Infectious Diseases (00432)* • *Gasoline Additives and Public Health (00541)* • *Indoor Air Quality in Industrial Nations (00391)* • *Radiation, Risks and Health Impacts of (00433)* • *Thermal Pollution (00416)*

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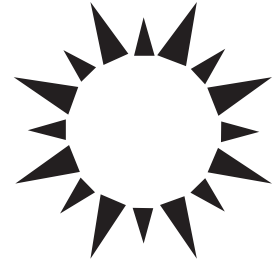
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