

Criteria Air Pollutants and Toxic Air Pollutants

Helen H. Suh,¹ Tina Bahadori,² Jose Vallarino,¹ and John D. Spengler¹

¹Harvard School of Public Health, Department of Environmental Health, Boston, Massachusetts, USA; ²Electric Power Research Institute, Palo Alto, California, USA

This review presents a brief overview of the health effects and exposures of two criteria pollutants—ozone and particulate matter—and two toxic air pollutants—benzene and formaldehyde. These pollutants were selected from the six criteria pollutants and from the 189 toxic air pollutants on the basis of their prevalence in the United States, their physicochemical behavior, and the magnitude of their potential health threat. The health effects data included in this review primarily include results from epidemiologic studies; however, some findings from animal studies are also discussed when no other information is available. Health effects findings for each pollutant are related in this review to corresponding information about outdoor, indoor, and personal exposures and pollutant sources. **Key words:** benzene, exposures, formaldehyde, health effects, ozone, particulate matter, VOCs. — *Environ Health Perspect* 108(suppl 4):625–633 (2000). <http://ehpnet1.niehs.nih.gov/docs/2000/suppl-4/625-633suh/abstract.html>

Criteria and toxic air pollutants represent two classes of air pollutants with diverse chemical and physical properties. Criteria pollutants, as designated under the Clean Air Act of 1971, include pollutants that are ubiquitous in the United States and are known or strongly suspected to be harmful to public health and the environment (1). Currently, six pollutants are designated as criteria pollutants: particles with aerodynamic diameters under 10 and 2.5 μm , ozone, sulfur dioxide, nitrogen dioxide, carbon monoxide, and lead. For each of these pollutants, a primary health-based National Ambient Air Quality Standard (NAAQS) under the Clean Air Act has been established, which sets the “safe” amount of the pollutant that can be present in the air (1).

One hundred eighty-nine other potentially harmful air pollutants are designated as toxic or hazardous air pollutants (HAPs) under the Clean Air Act (Table 1). HAPs include a diverse set of pollutants, including those that have multiple sources and that are prevalent in the environment, as well as other less prevalent pollutants that can be introduced by sudden accidental releases. HAPs include metals, other particles, gases adsorbed onto particles, and vapors from fuels and other sources. About 70% of the pollutants classified as hazardous air pollutants fall into the category of volatile organic compounds (VOCs). These compounds are the principal components in atmospheric reactions that form ozone and other secondary pollutants. Currently, industrial processes and fuel combustion sources account for 47% and less than 3% of the total VOC emissions, respectively (2). The diversity in chemical species and sources is reflected in the number of adverse health effects that may result from exposures to HAPs, including acute illnesses such as nausea, chronic diseases such as cancer, as well as a variety of immunologic,

neurologic, reproductive, developmental, and respiratory disorders.

This article is a brief overview of the health effects, properties, and exposures of a subset of criteria and toxic air pollutants, including ozone and particulate matter for the criteria pollutants and benzene and formaldehyde for the HAPs. This subset of pollutants was selected on the basis of their prevalence in the United States, their physicochemical behavior, and the magnitude of their potential health threat. Because of space limitations, discussions of their adverse health effects focus primarily on findings from epidemiologic studies.

Criteria Air Pollutants

Ozone

Ground-level ozone, the primary constituent of urban smog, is a secondary pollutant formed in the atmosphere through photochemical reactions involving nitrogen oxides and VOCs. It was first designated as a criteria pollutant under the Clean Air Act in 1971 (1). Its NAAQS was subsequently revised in 1979 and again most recently in 1997. In its current form, the primary NAAQS sets an 8-hr standard for ozone of 0.08 ppm (based on a 3-year average of the annual fourth highest daily maximum 8-hr ozone concentrations) to replace (in a phased-in manner) the previous standard based on a 1-hr averaging time. (Note that the NAAQS for ozone is currently undergoing judicial review. As a result, both the previous 1-hr ozone standard of 0.12 ppm and the new 8-hr standard are currently in effect.)

The NAAQS for ozone was established on the basis of its effects on the human respiratory system. Ozone is a known pulmonary irritant affecting the respiratory mucous membranes, other lung tissues, and

respiratory functions. It impairs the normal mechanical function of the human lung, the effects of which manifest themselves through symptoms such as chest tightness, cough, wheezing, and lung function decrements (3). Ozone-induced decrements in lung volume, specifically forced vital capacity (FVC) and forced expiratory volume in 1 sec (FEV₁) are primarily due to decreases in inspiratory capacity. With less severe exposures, lung volumes generally recover within 2–6 hr, with normal baseline function typically reestablished within 24 hr. Although small changes in lung function (when unaccompanied by discomfort symptoms or impairment of oxygen uptake) may not interfere with normal activity in healthy individuals, small changes in lung function for people with pre-existing disease could result in clinically significant adverse effects. The U.S. Environmental Protection Agency (U.S. EPA) has determined that these effects may arise in sensitive individuals, including children, the elderly, asthmatics and other individuals with preexisting respiratory conditions, and result in an approximately 10% decrease in pulmonary function, a level deemed by the U.S. EPA to be an adverse effect.

The adverse effects of ozone on the respiratory system may also manifest themselves as more serious clinical outcomes such as hospital admissions, emergency room visits, chronic illness, and possibly death. Numerous epidemiologic studies, for example, have shown ambient ozone concentrations to be associated with increased hospital admissions for pneumonia, chronic obstructive pulmonary disease (COPD), asthma, and other respiratory ailments. These associations have generally been shown for ozone, using multivariate models that included other pollutants, such as particulate matter, CO, and sulfur dioxide (SO₂). Burnett et al. (4), for example, compared air pollution data to hospital admissions for 16 cities across Canada for a 10-year period (1981–1991). During the months when ozone levels are high (April–December), the study found

This article is part of the monograph on Environmental and Occupational Lung Diseases.

Address correspondence to H.H. Suh, Harvard School of Public Health, 665 Huntington Ave., I-1309, Boston, MA 02115 USA. Telephone: (617) 432-0647. Fax: (617) 432-4122. E-mail: hsuh@hsph.harvard.edu

Received 8 March 2000; accepted 26 June 2000.

Table 1. List of Clean Air Act-designated hazardous air pollutants (1).

Chemical name			
Acetamide	DDE	Hexamethylphosphoramide	Propionaldehyde
Acetonitrile	Diazomethane	Hexane	Propoxur (Baygon)
Acetophenone	Dibenzofurans	Hydrazine	Propylene dichloride
2-Acetylaminofluorene	1,2-Dibromo-3-chloropropane	Hydrochloric acid	Propylene oxide
Acrolein	Dibutylphthalate	Hydrogen fluoride	1,2-Propylenimine
Acrylamide	1,4-Dichlorobenzene(p)	Hydrogen sulfide	Quinoline
Acrylic acid	3,3-Dichlorobenzidene	Hydroquinone	Quinone
Acrylonitrile	Dichloroethyl ether	Isophorone	Styrene
Allyl chloride	1,3-Dichloropropene	Lindane (all isomers)	Styrene oxide
4-Aminobiphenyl	Dichlorvos	Maleic anhydride	2,3,7,8-Tetrachlorodibenzo-
Aniline	Diethanolamine	Methanol	p-dioxin
<i>o</i> -Anisidine	<i>N,N</i> -Diethyl aniline	Methoxychlor	1,1,2,2-Tetrachloroethane
Asbestos	Diethyl sulfate	Methyl bromide	Tetrachloroethylene
Benzene	3,3-Dimethoxybenzidine	Methyl chloride	Titanium tetrachloride
Benzidine	Dimethyl aminoazobenzene	Methyl chloroform	Toluene
Benzotrithloride	3,3-Dimethyl benzidine	Methyl ethyl ketone	2,4-Toluene diamine
Benzyl chloride	Dimethyl carbamoyl chloride	Methyl hydrazine	2,4-Toluene diisocyanate
Biphenyl	Dimethyl formamide	Methyl iodide	<i>o</i> -Toluidine
Di(2-ethylhexyl)phthalate	1,1-Dimethyl hydrazine	Methyl isobutyl ketone	Toxaphene
Bis(chloromethyl)ether	Dimethyl phthalate	Methyl isocyanate	1,2,4-Trichlorobenzene
Bromoform	Dimethyl sulfate	Methyl methacrylate	1,1,2-Trichloroethane
1,3-Butadiene	4,6-Dinitro- <i>o</i> -cresol, and salts	Methyl tert butyl ether	Trichloroethylene
Calcium cyanamide	2,4-Dinitrophenol	4,4-Methylene bis(2-chloroaniline)	2,4,5-Trichlorophenol
Caprolactam	2,4-Dinitrotoluene	Methylene diphenyl diisocyanate	2,4,6-Trichlorophenol
Captan	1,4-Dioxane	4,4'-Methylenedianiline	Triethylamine
Carbaryl	1,2-Diphenylhydrazine	Naphthalene	Trifluralin
Carbon disulfide	Epichlorohydrin	Nitrobenzene	2,2,4-Trimethylpentane
Carbon tetrachloride	1,2-Epoxybutane	4-Nitrobiphenyl	Vinyl acetate
Carbonyl sulfide	Ethyl acrylate	4-Nitrophenol	Vinyl bromide
Catechol	Ethyl benzene	2-Nitropropane	Vinyl chloride
Chloramben	Ethyl carbamate	<i>N</i> -Nitroso- <i>N</i> -methylurea	Vinylidene chloride
Chlordane	Ethyl chloride	<i>N</i> -Nitrosodimethylamine	Xylenes (isomers, mixture)
Chlorine	Ethylene dibromide	<i>N</i> -Nitrosomorpholine	<i>o</i> -Xylenes, <i>m</i> -Xylenes
Chloroacetic acid	Ethylene dichloride	Parathion	<i>p</i> -Xylenes
2-Chloroacetophenone	Ethylene glycol	Pentachloronitrobenzene	Antimony compounds
Chlorobenzene	Ethylene imine	Pentachlorophenol	Arsenic compounds (inorganic)
Chlorobenzilate	Ethylene oxide	Phenol	Beryllium compounds
Chloroform	Ethylene thiourea	<i>p</i> -Phenylenediamine	Cadmium compounds
Chloromethyl methyl ether	Ethylidene dichloride	Phosgene	Chromium compounds
Chloroprene	Formaldehyde	Phosphine	Cobalt compounds
Cresols/Cresylic acid	Heptachlor	Phosphorus	Coke oven emissions
<i>o</i> -Cresol, <i>m</i> -Cresol	Hexachlorobenzene	Phthalic anhydride	Cyanide compounds ^a
<i>p</i> -Cresol	Hexachlorobutadiene	Polychlorinated biphenyls	Glycol ethers ^b
Cumene	Hexachlorocyclopentadiene	1,3-Propane sultone	Manganese compounds
2,4-Dichlorophenoxyacetic acid, salts and esters	Hexachloroethane	β -Propiolactone	Mercury compounds
Lead compounds	Hexamethylene-1,6-diisocyanate	Nickel compounds	Fine mineral fibers ^c
	Selenium compounds		Polycyclic organic matter ^d
			Radionuclides radon included ^e

NOTE: Listings containing the word "compounds" and for glycol ethers, unless otherwise specified, include any unique chemical substance that contains the named chemical as part of its infrastructure. *X'CN where X = H' or a group where a formal dissociation may occur. ^aIncludes mono- and di-ethers of ethylene, diethylene, and triethylene glycol R-(OCH₂CH₂)_n-OR' where n = 1, 2, or 3 R = alkyl or aryl groups R' = R, H, or groups which, when removed, yield glycol ethers: R-(OCH₂CH₂)_n-OH. Polymers are excluded from the glycol category. ^bIncludes mineral fiber emissions from facilities manufacturing or processing glass, rock, or slag fibers of average diameter 1 μ m or less. ^cIncludes organic compounds with more than one benzene ring, and which have a boiling point greater than or equal to 100°C. ^dA type of atom which spontaneously undergoes radioactive decay.

positive associations between the previous day's 1-hr maximum ozone concentration and respiratory admissions, after controlling for SO₂, NO₂, CO, soiling index, and dew point temperature. The authors found relative risk (RR) values ranging between 1.043 ($p < 0.0001$) and 1.024 ($p = 0.0258$) for a 30-ppb increase in ambient ozone, depending on the covariate selection and the cities examined. In addition to ozone, particulate matter and carbon monoxide were also positively associated with respiratory hospitalizations. Findings from this study were consistent with earlier studies of other U.S.

and Canadian cities (5–9). Together, they suggest that approximately 3–20% of respiratory admissions are associated with ambient ozone (10).

Ozone has also been linked to increased asthma-related emergency room visits for all age groups in studies by Cody et al. (9) and Weisel et al. (11) in New Jersey and by Stieb et al. (12) in New Brunswick, Canada. These associations were strongest when ambient ozone levels exceeded 75 ppb (12). Correspondingly, exposure to ozone has also been associated with acute respiratory problems in asthmatics, including increased

asthma symptoms (13), asthma rates (14), asthma attacks (15), wheeze (16), cough (17), reduced pulmonary function (16,17), and shortness of breath (18). These associations have been shown in both children (14,15,18) and adults and have been demonstrated for a number of U.S. cities.

Less consistent have been results from epidemiologic studies investigating associations between ozone and both chronic illness and premature mortality. Several recent studies have suggested that ambient ozone concentrations are associated with the development of chronic illnesses, such as adult onset of

asthma (19–21). These results are supported by data from animal studies in which exposure to ozone for months and years has been shown to cause structural changes in several regions of the respiratory tract, with the effects in the deep lung where most chronic airway diseases of the lung occur (3). These effects are not reversible, raising concerns that seasonal exposures to ozone may have a cumulative impact over many years (22–24). The sensitivity to chronic ozone exposures varies by species (25), with the rat having the lowest response (26,27) and the monkey the greatest (22,28). Together, these findings led the U.S. EPA (3) to conclude that prolonged ozone exposures cause structural changes in several regions of the respiratory tract, which in turn may lead to chronic adverse effects in humans. Evidence of these ozone-related chronic effects in humans, however, has not been conclusive in part because of the relatively small number of studies investigating this issue. A far greater number of epidemiologic studies have been performed to investigate associations between ozone and mortality, with most conducted over the past 5 years. While the growing body of epidemiologic studies suggests that there may be a positive association between ozone and premature mortality, possible confounding by other air pollutants such as particulate matter have made the interpretation of these results difficult.

Although many questions remain regarding ozone's health effects, it is clear that exposure to currently observed ambient ozone concentrations can result in adverse effects to the human respiratory system. As a result, substantial efforts have been made to reduce ozone concentrations in areas located throughout the United States, through reductions in anthropogenic emissions of VOCs and NO_x, which cause the bulk of ozone found in the troposphere.

Reductions in NO_x and VOC emissions can have long-reaching effects on ambient ozone concentrations. Like many secondary pollutants, ozone is regionally distributed and once formed tends to travel with the prevailing winds. Since ozone formation relies on sunlight, ambient ozone concentrations are highest during the summer months and during the early afternoon hours. In addition, ambient ozone varies spatially, as ambient concentrations tend to be higher in remote and suburban areas compared to urban areas (29,30), as the result of O₃ removal by NO emitted by motor vehicles. Ambient ozone concentrations also tend to increase with altitude, as ozone concentrations have been shown to be higher in mountain compared to valley communities (31).

In 1997, the revision to the O₃ NAAQS set forth that the 1-hr standard will no

longer apply to an area once the U.S. EPA determines that the area has air quality data meeting the 1-hr standards. In response to the revised ozone NAAQS, the U.S. EPA revoked the 1-hr O₃ NAAQS in most counties in the United States, leaving 226 counties (and 38 nonattainment areas) where the 1-hr standard still applies. Currently, 24 of the 38 one-hour ozone nonattainment areas are classified as either serious, severe, or extreme, with most of the 24 areas located in areas on the east or west coast of the United States (Table 2). Three areas, however, are located in Texas and two areas located near Chicago, Illinois. Together, the 24 one-hour nonattainment areas have a total population of about 84 million people.

Outdoor ozone concentrations, together with activity patterns and housing characteristics, are the primary determinants of exposures to ozone, since ozone has few indoor sources. Like outdoor concentrations, both indoor concentrations and personal exposures to ozone are highest in the summer months; however, both indoor and personal ozone levels tend to be substantially lower than those outdoors (29). Short-term (< 1 hr) personal ozone exposures, however, have been shown to be comparable to those outdoors, when monitored individuals spent their time in outdoor activities (32). Furthermore, both indoor concentrations and personal exposures to ozone tend to be highest for individuals living in non-air conditioned and other well-ventilated homes (29,33). Results from several exposure studies have shown that outdoor ozone concentrations are poor surrogates for personal exposures, as outdoor concentrations explain relatively little of the variability in personal exposures (29,31,33). Microenvironmental models developed to date have been able to explain little of the variability in personal ozone exposures; however, models do represent a slight improvement over outdoor concentrations alone (29). Poor model performance clearly demonstrates the need for additional research to improve our understanding of factors affecting personal ozone exposures and our ability to predict these exposures.

Particulate Matter

Epidemiologic studies have shown consistent and significant associations between ambient PM₁₀ (fine particulate matter with aerodynamic diameters less than or equal to 10 µm) concentrations and increased daily mortality and morbidity (34–38). The epidemiologic studies were conducted in communities across the United States using a variety of study designs, including short-term exposure, prospective cohort (time-series), cross-sectional, and meta-analyses studies. Despite their differences in design, methodology, and target population, findings from

Table 2. Serious, severe, or extreme ozone nonattainment areas in the United States in 1999.

Atlanta, GA	Serious
Baltimore, MD	Severe
Baton Rouge, LA	Serious
Boston-Lawrence-Worcester, MA-NH	Serious
Chicago, Gary-Lake County, IL-IN-WI	Severe
Dallas-Fort Worth, TX	Serious
El Paso, TX	Serious
Greater Connecticut, CT	Serious
Houston-Galveston, Brazoria, TX	Severe
Los Angeles-South Coast Air Basin, CA	Extreme
Milwaukee-Racine, WI	Severe
New York-New Jersey-Long Island, NY-NJ-CT	Severe
Phoenix, AZ	Serious
Philadelphia-Wilmington, Trenton, PA-NJ-DE-MD	Severe
Portsmouth-Dover-Rochester, NH-ME	Serious
Providence-Pawtucket-Fall River, RI-MA	Serious
Sacramento, CA	Severe
San Diego, CA	Serious
San Joaquin Valley, CA	Serious
Santa Barbara-Santa Maria-Lompac, CA	Serious
SE Desert Modified AQMA, CA	Severe
Springfield, MA	Serious
Ventura County, CA	Severe
Washington, DC-MD-VA	Serious

these studies were remarkably consistent, as the relative risk estimates for total mortality and morbidity were comparable across studies.

The time-series studies, in particular, provided evidence that ambient particulate pollution at currently observed levels is associated with increases in daily human mortality (39–42). Relative risk estimates from these mortality studies indicate that an increase in ambient particulate concentrations of 50 µg/m³ is associated with a relative risk of 1.015–1.085 in the general population. Even higher relative risks were observed for senior citizens and for those with preexisting respiratory conditions (39–42).

Despite the consistency of these findings, the interpretation of results from these studies remains controversial. Much of this controversy arises from the fact that the particulate component(s) responsible for the observed adverse health effects has not yet been identified nor has the biologic mechanism that results in the observed adverse effect been determined. These difficulties arise in large part from the fact that particulate matter is a mixture of pollutants. At its simplest, inhalable particulate matter is composed of two distinct size fractions, those with aerodynamic diameters (d_a) less than or equal to 2.5 µm (PM_{2.5}) or fine particles, and those with aerodynamic diameter between 2.5 and 10 µm or coarse particles (PM_{2.5–10}). The two size fractions have different origins and compositions. Fine particles originate primarily from combustion sources (such as automobiles, power plants, and wood stoves), either through the condensation of volatilized materials (primary particulate matter), or from precursor gases reacting

in the atmosphere to form secondary particles. The major components of fine particles often include sulfates, carbonaceous materials, nitrates, trace elements, and water (43). Coarse particles, in contrast, are formed by mechanical crushing, grinding, or abrasion of surfaces and are suspended and dispersed by wind and anthropogenic activity such as traffic and agricultural activities. Coarse particles are primarily composed of aluminosilicates and other oxides of crustal elements in soil and fugitive dust.

As a result of their physical and chemical differences, exposures to $PM_{2.5}$ and PM_{10} may have different adverse effects. Indirect evidence from studies using British Smoke, coefficient of haze (COH), or sulfates as indicators of fine particle concentrations suggest that $PM_{2.5}$ is most strongly associated with the observed increases in mortality and morbidity (44–46). Direct evidence was provided by the Six-Cities study, which found RR values ranging from 1.020 to 1.056 per $25 \mu g/m^3$ $PM_{2.5}$, whereas coarse particles generally showed small and nonsignificant RR values (except for Steubenville, Ohio, RR = 1.061 per $25 \mu g/m^3$) (47). On the basis of these results, the authors concluded that in most cases associations between excess mortality and PM_{10} were derived mainly from the $PM_{2.5}$ fraction. This conclusion is supported by results from a recent analysis of elemental data from the Six-Cities study (48). In a combined analysis of data from the six cities, a $10\text{-}\mu g/m^3$ increase in $PM_{2.5}$ from mobile sources accounted for a 3.4% increase in total mortality, whereas an equivalent increase in $PM_{2.5}$ from coal combustion sources accounted for a 1.1% increase. In contrast, $PM_{2.5}$ -associated crustal particle levels were not associated with daily mortality.

It is important to note that these results are not universal, as coarse—but not fine—particles have been implicated as the toxic agent in other epidemiologic studies. For example, in a study conducted in Mexico City, Mexico (49), ambient $PM_{2.5}$ was found to have no statistically significant impact on either total mortality or mortality by age or cause. A $10 \mu g/m^3$ increase in ambient coarse particle concentrations, however, was associated with a 4.5% [95% confidence interval (CI): 2.4–6.5%] increase in total mortality, a 9.8% increase in respiratory mortality (95% CI: 3.4–16.2%), a 3.9% increase in cardiovascular mortality (95% CI: 0.1–7.7%), and a 5.4% increase (95% CI: 2.6–8.1%) in mortality in individuals above 65 years of age. The apparent inconsistency in the study findings is not known but may be due to differences in particle composition or study population.

Recent findings from toxicologic studies and epidemiologic studies of cardiovascular effects have suggested a plausible biologic mechanism by which particles can cause

damage. In toxicologic studies, exposures to concentrated ambient air particles have been associated with significant alterations in breathing patterns and acute inflammatory responses, as demonstrated by neutrophil influx and increased vascular permeability in normal and chronic bronchitic rats (50,51). Concentrated ambient air particles (CAPs) have also been shown to result in hematologic changes in rats, including elevated polymorphonuclear leukocyte levels (52).

Consistent with these results, subtle alterations in pulmonary and systemic cell profiles were also found when normal canines were exposed to concentrated air particles (53). These changes were not associated with the total mass concentrations but were instead associated with specific particulate components (as identified using factor analysis techniques). Bronchoalveolar lavage (BAL), total peripheral white blood cell (WBC) counts, and circulating neutrophils and lymphocytes, for example, were correlated with an aluminum/silicon factor, which may result from an effect of crustal particles on pulmonary inflammation. The nickel/vanadium factor was associated with increased circulating neutrophils and BAL macrophages, suggesting a link between combustion-related metals and peripheral blood parameters. Significant red blood cell changes (e.g., decrements in red blood cell counts and hemoglobin levels), which were also observed in a study of elevated ambient particle levels (54), were associated with the sulfur factor. The authors suggested that these hematological alterations may potentially be linked to cardiac effects (54).

Support for this theory has been provided by recent epidemiologic studies of elderly individuals. In these studies, ambient $PM_{2.5}$ levels were associated with reduced cardiovascular function as assessed using heart rate variability (HRV) (55–57), defibrillator discharge measures (58), and increased plasma viscosity (59). Liao et al. (55) in Baltimore, Maryland, and Gold et al. (57) in Boston, for example, found elevated ambient $PM_{2.5}$ to be associated with reductions in time domain HRV measures—SDDN (standard deviation of normal RR intervals) and r-MSSD (square root of the mean of the squared differences between adjacent normal RR intervals). In the Boston study, a $14.3 \mu g/m^3$ increase in ambient $PM_{2.5}$ during the hour of and the three hours prior to cardiac monitoring resulted in a 6.1-ms reduction in r-MSSD during slow breathing. These findings differed from those reported by Pope et al. (56) in Utah, in which reduced SDNN but increased r-MSSD was associated with ambient $PM_{2.5}$ levels. Reasons for the inconsistency in the study findings are unclear, but may be due to differences in particle composition, sample size, or study population. Despite this inconsistency, findings

from these studies suggest that $PM_{2.5}$ exposures may disturb short-term autonomic function, which may partially account for observed associations between particulate pollution and cardiovascular mortality.

Considerable research has been conducted to assess the levels and nature of particulate exposures, particularly in the outdoor environment. These studies have demonstrated that ambient fine and coarse particle mass concentrations tend to be weakly correlated or uncorrelated, as would be expected due to their different sources (60). Ambient fine ($PM_{2.5}$) and inhalable (PM_{10}) particulate concentrations, however, tend to be strongly correlated with ozone in the “high-sulfur source” and downwind transport regions, and with sulfate, a fine particulate constituent, as well. These regions of the Eastern United States and Southern Canada experienced the greatest $PM_{2.5}$, PM_{10} , and SO_4^{2-} concentrations during the spring and summer months (May–September).

In the Eastern United States, ambient $PM_{2.5}$ and PM_{10} concentrations are relatively uniform across large metropolitan areas, especially in the summer months (61–63). This spatial uniformity suggests that concentrations measured at a single ambient monitoring site are able to reflect particulate concentrations across an urban area. For coarse particles, however, a single ambient monitoring site would not be sufficient, as coarse particles vary spatially with population density. In the Eastern United States, $PM_{2.5}$ comprises the majority of PM_{10} , accounting for approximately 75% of PM_{10} in Philadelphia, Pennsylvania (61).

Outdoor $PM_{2.5}$ concentrations may differ, at times substantially, from indoor concentrations. Indoors, cigarette smoke is the most significant particulate source, as mean indoor concentrations in homes with smoking have been shown to be approximately $20\text{--}30 \mu g/m^3$ higher than concentrations inside homes without smokers (64–66). Although less significant, kerosene heaters, cooking, and cleaning have also been identified as important indoor particulate sources (67–69). The influence of these indoor particulate sources is strongest in indoor environments with low air exchange rates, as these low air exchange rates provide sufficient time for the particles emitted from indoor sources to accumulate (68,69).

Similarly, personal $PM_{2.5}$ exposures have been shown to differ from corresponding outdoor concentrations, as personal $PM_{2.5}$ exposures have been shown to be both higher (70,71) and lower (72–74) than corresponding outdoor levels. These personal-outdoor differences have been attributed to the varying activity level of the study cohorts, in which individuals who were relatively sedentary,

such as those with COPD, measured in the Bahadori et al. (73) study had lower indoor, and thus lower personal, exposures to particulate matter.

Despite these observed differences, longitudinal associations between personal $PM_{2.5}$ and PM_{10} exposures and outdoor concentrations are relatively strong (71,73–75). For example, cross-sectional analysis of data from Phillipsburg, New Jersey, where personal PM_{10} exposures of 14 individuals were measured for 14 days, resulted in an R^2 of only 0.037 ($p = 0.008$). When analyzed by individual across time, however, a median R^2 value of 0.46 was found (75). Similar results were found in studies conducted in a variety of other cities and for diverse study populations.

The strength of the personal-ambient associations has also been shown to be strongly influenced by the indoor ventilation conditions (33,76). Associations between personal $PM_{2.5}$ exposures and ambient concentrations were strongest when individuals spent most of their time in well-ventilated environments ($R^2 = 0.80$) and lowest when individuals spend most of their time in poorly ventilated environments ($R^2 = 0.25$) (Figure 1) (33). Similar analyses for SO_4^{2-} , a fine particulate constituent with no major indoor sources, showed that the strength of the personal-ambient association varied little with the indoor ventilation conditions (Figure 2). The weaker personal-ambient associations for individuals spending time in poorly ventilated indoor environments for $PM_{2.5}$ compared to SO_4^{2-} were attributed to the greater influence of indoor particulate sources in these environments (33).

Upon review of the available scientific evidence linking exposures to ambient particulate matter to adverse health and welfare effects, the U.S. EPA revised the NAAQS for particulate matter (77). These new rules include a new $PM_{2.5}$ annual standard set at $15 \mu\text{g}/\text{m}^3$ and a new 24-hr standard of $65 \mu\text{g}/\text{m}^3$.

Although now in effect, the new standard is currently undergoing judicial review and is clearly the subject of considerable controversy, with much of this scientific controversy focusing on the ability of outdoor concentrations to estimate exposures. The studies conducted to date have provided important information about the relationship between personal particulate exposures and corresponding outdoor concentrations. However, they have also raised significant questions about the nature of personal exposures, the relative contributions of both outdoor and indoor concentrations to overall exposure levels, and the factors that may influence these relationships. In this context, the link between ambient air pollution and adverse health effects remains ambiguous, thus making it difficult to identify the toxic agent

responsible for the observed adverse effects. Addressing these issues will be critical to our ability to protect the public from particulate air pollution.

Hazardous Air Pollutants

In contrast to the criteria pollutants, relatively little has been done to characterize the concentrations, exposures, and health risks for most of the HAPs. Still less is known about the human health effects of HAP exposures at concentrations found in the ambient environment, as most of what is known has been obtained from occupational and animal studies. These studies, along with efforts to characterize the potential public health impacts of HAPs using monitoring data, dispersion models, and emission estimates, have implicated 189 air pollutants as chemicals whose presence in the air may be associated with adverse human health effects.

Sources of HAPs are numerous and include outdoor (i.e., industrial processes, motor vehicles), indoor (i.e., building materials) and activity-based sources (i.e., smoking, dry cleaning). Studies characterizing concentrations and exposures to numerous HAPs suggest that concentrations for most HAPs are higher indoors as compared to levels found outdoors (78,79). Similarly, these studies have found that personal exposures typically exceed both outdoor and indoor sources. These results can be explained by a number of factors including the accumulation of HAP concentrations within enclosed indoor environments as well as the importance of indoor and activity-specific or occupational sources of HAP exposure. In a review of VOC levels, Wallace (78) found that indoor VOC concentrations were twice that of concentrations found outdoors. Similarly, personal exposures were found to be 3 times that of corresponding outdoor concentrations. Higher personal VOC exposures were attributed to the fact that individuals spend a majority (~90%) of their time indoors (80), where numerous

indoor sources exist. These indoor sources include dry-cleaned clothing (tetrachloroethylene), mothballs and restroom deodorizers (*para*-dichlorobenzene), building materials (formaldehyde, styrene) and office products such as glues and correction fluid (1,1,1-trichloroethane). Identification of these sources and reducing or eliminating the use of products containing these HAPs can help in reducing or minimizing exposures to various VOCs.

Despite the findings that show higher indoor concentrations than outdoor concentrations, a number of recent studies suggest that outdoor HAPs concentrations in several U.S. cities may also constitute a health concern. In the U.S. EPA's Assessment System for Population Exposure Nationwide (ASPEN) study (81), emissions data for various HAPs were inputted into an atmospheric dispersion model to estimate outdoor concentrations in each of the 60,803 census tracts of the contiguous United States for 1990. Model results showed outdoor concentration estimates for benzene and formaldehyde, for example, were greater than the cancer benchmark concentrations in over 90% of the census tracts. Approximately 200 census tracts had modeled air pollution levels over 100 times the benchmark for at least one of the HAPs (82). These estimates of high outdoor HAP concentrations strongly support the need for further characterization of HAPs concentrations and exposures.

Estimates of high cancer risks from HAP exposures are supported by a report presented before Congress on March 1, 1999, in which outdoor Los Angeles, California, basin levels were characterized for 10 HAPs (83). Results from this report indicated that 9 of the 10 HAPs were present outdoors at levels that exceeded additional lifetime cancer risks of one in a million—the health-based goal for HAPs outlined in the Clean Air Act. Outdoor concentrations of benzene and formaldehyde in particular were exceptionally high and were

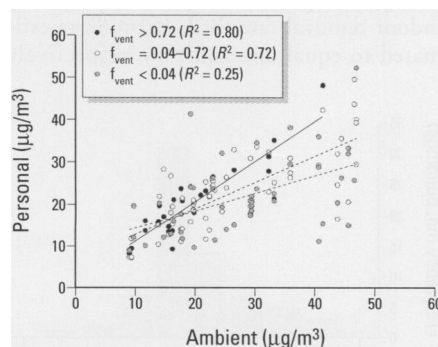


Figure 1. Personal vs ambient $PM_{2.5}$ by ventilation status: results from Baltimore, Maryland, older adult study. f_{vent} represents the fraction of time the monitored individual spent in indoor environments with open windows. Adapted from Samat et al. (33).

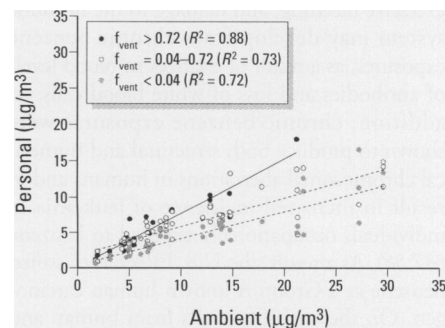


Figure 2. Personal vs ambient SO_4^{2-} by ventilation status: results from Baltimore, Maryland older adult study. f_{vent} represents the fraction of time the monitored individual spent in outdoor environments with open windows. Adapted from Samat et al. (33).

49 and 72 times greater than their respective benchmark doses for cancer risk. The health effects and exposures for benzene and formaldehyde are discussed briefly below.

Benzene

Of the HAPs, benzene is perhaps the most widely studied. Benzene is a gaseous pollutant that is ubiquitous in the environment. It is used as a constituent in motor fuels; as a solvent for fats, waxes, resins, oils, inks, paints, plastics, and rubber; in the extraction of oils from seeds and nuts; and in photogravure printing. It is also used in the manufacture of detergents, explosives, pharmaceuticals, and dyestuffs (84,85). In addition, the public is exposed to benzene as a result of direct and indirect cigarette smoke, home use of solvents and gasoline, and leaking underground storage tanks.

Benzene is absorbed into the human body via various pathways, including inhalation, dermal contact, and ingestion. Exposures to benzene, even at low doses, have been linked to a variety of acute and chronic adverse health effects. Inhalation exposures to benzene, for example, may result in a variety of neurologic symptoms, including drowsiness, dizziness, headaches, unconsciousness, and even death after exposures to very high levels. Similarly, ingestion exposures to large amounts of benzene may result in vomiting, dizziness, convulsions, and may be fatal (84).

In animal studies, neurologic, immunologic, and hematologic effects from inhalation and oral exposures to benzene have been observed. Laboratory tests in rats, mice, rabbits, and guinea pigs have shown benzene to have low acute toxicity through inhalation, moderate acute toxicity through ingestion, and low or moderate acute toxicity through dermal exposure. Benzene toxicity can be enhanced with co-exposure to ethanol (86). Hematologic effects have also been observed after chronic or long-term inhalation of benzene, which has been shown to cause blood disorders through damage to the bone marrow. Aplastic anemia, excessive bleeding, and damage to the immune system may develop from chronic benzene exposures, as a result of changes in blood levels of antibodies and loss of white blood cells. In addition, chronic benzene exposures were shown to produce both structural and numerical chromosomal aberrations in humans and to result in increased incidence of leukemia in individuals occupationally exposed to benzene (87,88). As a result, the U.S. EPA has classified benzene as a Group A known human carcinogen. On the basis of results from human and animal studies, benzene has been estimated to have an inhalation unit risk for cancer of $8.3 \times 10^{-6} (\mu\text{g}/\text{m}^3)^{-1}$ (86).

Several studies have been performed to characterize benzene exposures. In an

Environment Canada-sponsored outdoor monitoring study, 5,000 twenty-four-hour benzene samples were collected at 40 urban and rural monitoring stations (89). Median benzene concentrations were highest at urban street sites and at sites influenced by point sources, whereas median benzene concentrations were lowest at rural and suburban sites. Significantly higher 95th percentile benzene concentrations were reported at sites influenced by point sources (89).

Twelve-hour outdoor benzene concentrations—along with 12-hr personal exposures and exhaled breath values—were also measured in a variety of communities across the United States in the U.S. EPA Total Exposure Assessment Methodology (TEAM) study, which was conducted in the early 1980s (78). Results from this study showed that as was the case in the Canadian study, outdoor concentrations were also higher in urban compared to suburban cities. In addition, benzene was found at all of the TEAM sites. Major sources of benzene exposures were identified and included active (39%) and passive (5%) cigarette smoking, automobiles (18%), and industrial (3%), home (16%), and personal (18%) sources (78).

Because many of these sources are located indoors, benzene concentrations inside homes are generally higher than those outdoors (78). In Elizabeth–Bayonne, New Jersey, one of the TEAM studies, for example, the geometric mean indoor benzene concentration was substantially higher than that outdoors, with indoor concentrations highest inside homes with smokers (78). Median and 95th percentile indoor concentrations in Elizabeth–Bayonne were 15 and 78 $\mu\text{g}/\text{m}^3$. These high concentrations may specifically be attributed to the presence of indoor benzene sources. In areas with high outdoor concentrations, the ability of benzene to penetrate indoors may be an important exposure factor. In a study of 10 Boise, Idaho, homes with no major indoor VOC sources, the penetration efficiency and the indoor removal rate for benzene were estimated to equal one and zero, respectively

(90). Indoor benzene concentrations have been found to be substantially lower in large, nonresidential buildings, as mean, median, and 95th percentile indoor concentrations in the U.S. EPA Building Assessment Survey and Evaluation (BASE) study of 69 buildings were only 1.3, 1.2, and 2.8 $\mu\text{g}/\text{m}^3$, respectively (Figure 3). Lower concentrations observed in the BASE study may be attributed to the fact that measurements were made in large office buildings compared to homes, where large HVAC systems are more prevalent and the penetration efficiency of benzene from outdoor to indoor environments may be lower.

Personal benzene exposures also tend to be higher than those outdoors. As was the case outdoors, personal levels were highest in urban than in suburban locations. Median daytime and nighttime outdoor, personal, and breath concentrations, for example, ranged between 10 and 20 $\mu\text{g}/\text{m}^3$ in the industrialized Elizabeth–Bayonne (Figure 4) and urban Los Angeles communities (Figure 5), whereas median concentrations in suburban Antioch–Pittsburg, California, were lower, ranging between 1 and 10 $\mu\text{g}/\text{m}^3$ (Figure 6). As shown in Figure 7, concentration distributions observed in Antioch and Pittsburg were comparable to those reported for most of California in the 1990–1996 California Air Resources Board-sponsored statewide benzene summary (mean and median outdoor concentrations ranged

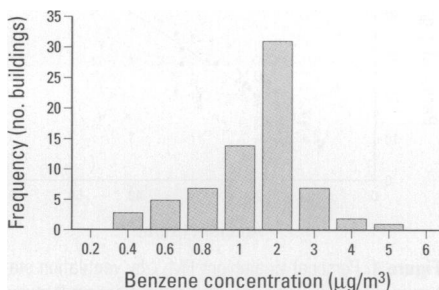


Figure 3. The distribution of indoor benzene concentration measurements, from the U.S. EPA BASE study of 69 buildings from 1996 through 1998 (103).

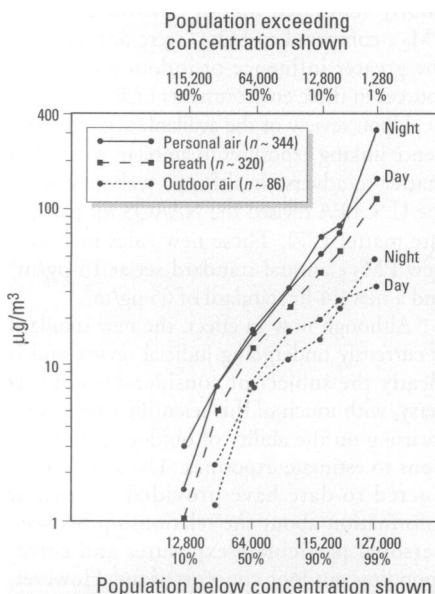


Figure 4. The estimated frequency distributions of benzene personal air exposures, outdoor air concentrations, and exhaled breath values for the combined Elizabeth–Bayonne, New Jersey, target population ($n = 128,000$). All air values are for 12-hr integrated samples. The breath value was taken following the daytime air sample (6:00 AM–6:00 PM). All outdoor samples were in the vicinity of the participants' homes (78).

between 0.82 and 7.38 $\mu\text{g}/\text{m}^3$). It should also be noted that the exposure assessment in the Antioch and Pittsburg areas was conducted in well-ventilated indoor environments, another factor leading to lower personal benzene exposures.

Benzene concentrations have been shown to be highest in motor vehicles, with concentrations inside motor vehicles up to 8 times that of corresponding ambient concentrations (78). Correspondingly, short-term (1-hr) personal benzene exposures have also been shown to be highest during motor vehicle-related activities, such as commuting by car or bus and during activities at gasoline stations (32,78,90–94).

Formaldehyde

Formaldehyde is a gaseous pollutant with many outdoor and indoor sources. Outdoors, major formaldehyde sources include power plants, manufacturing facilities, incinerators, and automobile exhaust emissions (95). In addition, forest fires and other natural combustion sources also introduce formaldehyde into the ambient air. The highest levels of airborne formaldehyde have been detected in indoor air, where it is released from various building materials, such as processed particleboard and plywood, and consumer products and are emitted from tobacco smoke. Formaldehyde may also be present in food, either naturally or as a result of contamination.

Formaldehyde is used predominantly as a chemical intermediate. As a chemical building block, its use can be traced to consumer goods through a wide spectrum of manufacturing processes. Formaldehyde, for example, is used in the manufacture of urea, phenol, and melamine resins and for a variety of special industrial chemicals. In addition, formaldehyde is used as a preservative in medical laboratories and as an embalming agent in mortuaries. It also has minor uses in agriculture, as an analytical reagent, in concrete and plaster additives, cosmetics, disinfectants, fumigants, photography, and wood preservation (96). Formaldehyde (as urea formaldehyde foam) was extensively used as an insulating material until 1982, when it was banned by the U.S. Consumer Product Safety Commission. Formaldehyde can be emitted from the coating that provides permanent press quality to fabrics and draperies.

Exposures to formaldehyde have been shown to result in a variety of acute adverse effects. Airborne concentrations of formaldehyde above 100 ppb, for example, can cause irritation of the eye, nose, and throat irritation and effects on the nasal cavity. The severity of irritation increases as concentrations increase; at 100 ppm, formaldehyde is immediately dangerous to life and health. Dermal contact causes various skin reactions including sensitization, which might force persons thus, sensitized to

find other work. Coughing, wheezing, chest pains, and bronchitis are also symptoms of formaldehyde exposure. Formaldehyde is ranked as a non-threshold contaminant by the U.S. EPA Office of Planning and Standards. The RfD (reference dose) for formaldehyde is 0.2 mg/kg/day based on a decrease in body weight gain and effects on the stomach in rats (97).

As with acute effects, chronic inhalation exposures to formaldehyde have been associated with respiratory symptoms and eye, nose, and throat irritation (98). Results from animal studies suggest that the adverse health mechanism may occur through damage to the nasal respiratory epithelium and lesions in the respiratory system (99). In addition, chronic formaldehyde exposures were linked, in one study to an increased incidence of menstrual disorders and pregnancy problems in women workers using urea-formaldehyde resins; however, potential confounding factors were not examined in this study, making results from this study difficult to interpret. In another study, an association between formaldehyde exposure and increased spontaneous abortions was not found for hospital equipment-sterilizing workers.

Chronic formaldehyde exposures have also been associated in occupational studies with increased incidence of lung and nasopharyngeal cancer (100). This association is considered to be "limited," rather than "sufficient," due to possible exposure to other agents that may have contributed to the excess cancers. An increased incidence of nasal squamous-cell carcinomas due to inhalation exposures to formaldehyde has been observed in animal studies (101). Formaldehyde is classified as a probable human carcinogen (cancer-causing agent) by the U.S. EPA, with an estimated inhalation unit risk of $1.3 \times 10^{-5} (\mu\text{g}/\text{m}^3)^{-1}$. Average lifetime inhalation exposures to formaldehyde concentrations of 8 $\mu\text{g}/\text{m}^3$, for example, would result in an approximate one-in-a-ten thousand increased chance of developing cancer over the span of a lifetime.

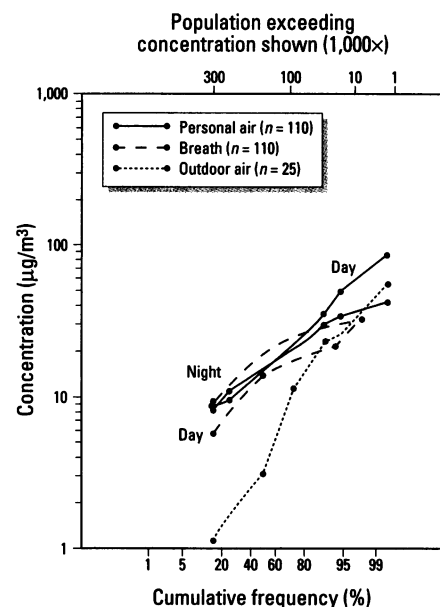


Figure 5. The estimated frequency distributions of benzene personal air exposures, outdoor air concentrations, and exhaled breath values for the South Bay section of Los Angeles, California. California target population ($n = 360,000$). All air values are for 10- to 14-hr integrated samples. The breath value was taken following the daytime air sample (6:00 AM–6:00 PM). All outdoor samples were in the vicinity of the participants homes (February 1984) (78).

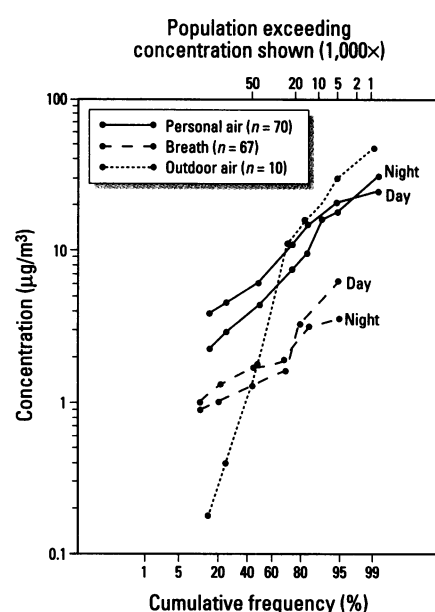


Figure 6. The estimated frequency distributions of benzene personal air exposures, outdoor air concentrations, and exhaled breath values for the residents of Antioch and Pittsburg, California (population = 360,000). All air values are for 10- to 14-hr integrated samples. The breath value was taken following the daytime air sample (6:00 AM–6:00 PM). All outdoor samples were in the vicinity of the participants homes (June 1984) (78).

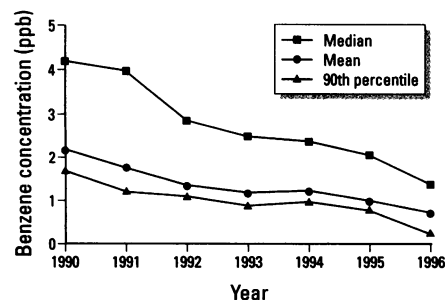


Figure 7. The 1990–1996 statewide benzene summary for California, measured by the California Environmental Protection Agency, Air Resources Board (104).

Ambient formaldehyde concentrations of this magnitude are common in the United States, where the average ambient formaldehyde concentrations reported in U.S. urban areas ranges between 11 and 20 ppb (13.5–24.6 $\mu\text{g}/\text{m}^3$). Figure 8 shows the distribution of 24- and 3-hr time integrated measurements collected in New York City and Los Angeles in 1997. Environment Canada has reported maximum ambient formaldehyde of 31.15 $\mu\text{g}/\text{m}^3$, with means ranging from 1.8 to 8.8 $\mu\text{g}/\text{m}^3$ in urban areas. Formaldehyde levels in homes have been reported ranging between 100 and 3,680 ppb in homes (123–4,526 $\mu\text{g}/\text{m}^3$) (78). As was the case with benzene, indoor formaldehyde concentrations inside large, nonresidential

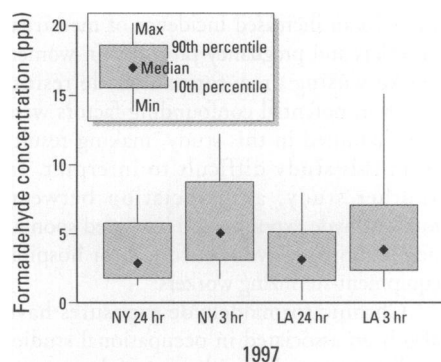


Figure 8. The distribution of 24- and 3-hr time integrated measurements collected in New York City and Los Angeles, California, 1997 (105).

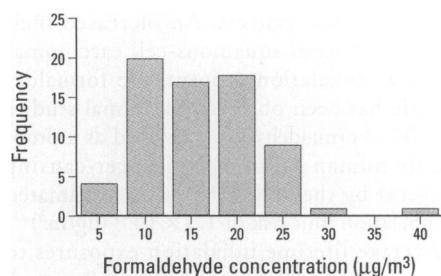


Figure 9. The distribution of indoor formaldehyde concentration measurements, from the U.S. EPA BASE study of 69 buildings from 1996 through 1998 (103).

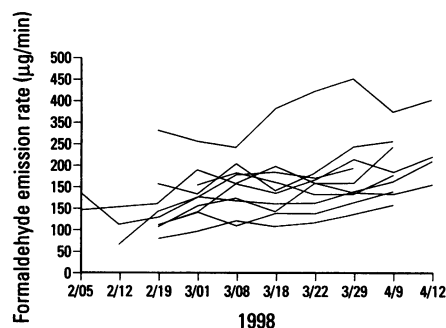


Figure 10. The measured formaldehyde emission rates of 10 homes measured over 10 consecutive weeks in northern Japan from February 5 through April 14 (106).

buildings are much lower, with mean, median, and 95th percentile formaldehyde levels in the U.S. EPA BASE study of 13.6, 13.1, and 22.8 $\mu\text{g}/\text{m}^3$, respectively (Figure 9).

There are several factors that influence the emission of formaldehyde from materials. Two of the best understood are temperature and relative humidity. As the temperature and humidity increase, the emission rate of formaldehyde also increases. The measured formaldehyde emission rates of 10 homes measured over 10 consecutive weeks in Northern Japan, from February 5 through April 14 are shown in Figure 10. The formaldehyde emission rate in all homes increased on average with the increasing air temperature and humidity as winter transitioned into spring. A third important factor is the age of the home. As the home ages, the building materials emit less formaldehyde. Since the early 1980, as a result of the rash of formaldehyde poisonings attributable to urea-formaldehyde foam insulation, low-level exposure to formaldehyde has been suspected of initiating chemical hypersensitivity (102).

REFERENCES AND NOTES

- Clean Air Act, 33 United States Code Sec. 1241 Et Seq., 1971.
- U.S. EPA. National Air Quality and Emissions Trend Report. Washington, DC:U.S. Environmental Protection Agency, 1998.
- U.S. EPA. Air Quality Criteria for Ozone and Related Photochemical Oxidants. Research Triangle Park, NC:U.S. Environmental Protection Agency, National Center for Environmental Assessment, Office of Research and Development, 1996.
- Burnett RT, Brook JR, Yung WT, Dales RE, Krewski D. Association between ozone and hospitalization for respiratory diseases in 16 Canadian cities. *Environ Res* 72:24–31 (1997).
- Özkaynak H, Xue J, Severance P, Burnett RT, Raizenne ME. Associations between daily mortality, ozone, and particulate air pollution in Toronto, Canada. Paper presented at the Colloquium on Particulate Air Pollution and Human Mortality and Morbidity, Irvine, California, 1994.
- Thurston GD, Ito K, Kinney PL, Lippmann M. A multi-year study of air pollution and respiratory hospital admissions in three New York State metropolitan areas: results for 1988 and 1989 summers. *J Expos Anal Environ Epidemiol* 2:429–450 (1992).
- Thurston GD, Ito K, Hayes CG, Bates DV, Lippmann M. Respiratory hospital admissions and summertime haze air pollution in Toronto, Ontario: consideration of the role of acid aerosols. *Environ Res* 65:271–290 (1994).
- Schwartz J. Air pollution and hospital admissions for the elderly in Birmingham, Alabama (1994). *Am J Epidemiol* 139:589–598 (1994).
- Cody RP, Weisel CP, Birnbaum G, Lioy PJ. The effect of ozone associated with summertime photochemical smog on the frequency of asthma visits to the hospital emergency departments. *Environ Res* 58:184–194 (1992).
- American Lung Association. Breathless: air pollution and hospital admissions/emergency room visits in 13 cities. New York:American Lung Association, 1998.
- Weisel CP, Cody RP, Lioy PJ. Relationship between summertime ambient ozone levels and emergency department visits for asthma in central New Jersey. *Environ Health Perspect* 103(suppl 2):97–102 (1995).
- Stieb DM, Burnett RT, Beveridge RC, Brook JR. The association between ozone and asthma emergency department visits in Saint John, New Brunswick, Canada. *Environ Health Perspect* 104:1354–1360 (1996).
- Holguin AH, Buffler PA, Contant CF, Stock TH, Kothmar D, His BP, Jenkins DE, Gehan BM, Noel LM, Mei M. The effects of ozone on asthmatics in the Houston area. In: *Evaluation of the Scientific Basis for Ozone/Oxidants Standards: Proceedings of the APCA International Specialty Conference*, November 1984.
- Bates DV, Baker-Anderson M, Sizto R. Asthma attack periodicity: a study of hospital emergency visits in Vancouver. *Environ Res* 51:51–70 (1990).
- Whitemore AS, Korn EL. Asthma and air pollution in the Los Angeles area. *Am J Public Health* 70:687–696 (1980).
- Lebowitz MD, Collins L, Holberg CJ. Time series analyses of respiratory responses to indoor and outdoor phenomena. *Environ Res* 43:332–341 (1987).
- Krzyzanowski M, Quackenboss JJ, Lebowitz MD. Relation of peak expiratory flow rates and symptoms to ambient ozone. *Arch Environ Health* 47:107–115 (1992).
- Ostro BD, Lipsett MJ, Mann JK, Krupnick A, Harrington W. Air pollution and respiratory morbidity among adults in Southern California. *Am J Epidemiol* 137:691–700 (1993).
- Abbey DE, Moore J, Petersen F, Beeson L. Long-term ambient concentrations of total suspended particulates and oxidants as related to incidence of chronic disease in California Seventh-Day Adventists. *Environ Health Perspect* 94:43–50 (1991).
- Abbey DE, Petersen F, Mills, PK, Beeson WL. Long-term ambient concentrations of total suspended particulates, ozone, and sulfur dioxide and respiratory symptoms in a nonsmoking population. *Arch Environ Health* 48:33–46 (1993).
- McDonnell WF, Abbey DE, Nishino N, Lebowitz MD. Long-term ambient ozone concentrations and the incidence of asthma in nonsmoking adults: the AHSMOG study. *Environ Res* 80:110–121 (1999).
- Tyler WS, Tyler NK, Last JA, Gillespie MJ, Barstow TJ. Comparison of daily and seasonal exposures of young monkeys to ozone. *Toxicology* 50:131–144 (1988).
- Tepper JS, Costa DL, Lehmann JR, Weber MF, Hatch GE. Unattenuated structural and biochemical alterations in the rat lung during functional adaptation to ozone. *Am Rev Respir Dis* 140:493–501 (1989).
- Tepper JS, Wiester MJ, Weber MF, Fitzgerald S, Costa DL. Chronic exposure to a simulated urban profile of ozone alters ventilatory responses to carbon dioxide challenge in rats. *Fundam Appl Toxicol* 17:52–60 (1991).
- Travis CC, White RK, Ward RC. Interspecies extrapolation of pharmacokinetics. *J Theor Biol* 142:285–304 (1990).
- Chang LY, Huang Y, Stockstill BL, Graham JA, Grose EC, Menache MG, Miller FJ, Costa DL, Crapo JD. Epithelial injury and interstitial fibrosis in the proximal alveolar regions of rats chronically exposed to a simulated pattern of urban ambient ozone. *Toxicol Appl Pharmacol* 115:241–252 (1992).
- Chang LY, Stockstill BL, Menache MG, Mercer RR, Crapo JD. Consequences of prolonged inhalation of ozone on F344/N rats: collaborative studies. VIII: Morphometric analysis of structural alterations in alveolar regions. 3–39 Research Rep no. 65. Cambridge, MA:Health Effects Institute, 1995.
- Harkema JR, Plopper CG, Hyde DM, St. George JA, Wilson DW, Dungworth DL. Response of macaque bronchiolar epithelium to ambient concentrations of ozone. *Am J Pathol* 143:857–866 (1993).
- Liu L-JS, Koutrakis P, Suh HH, Mulik JD, Burton RM. Use of personal measurements for ozone exposure assessment: a pilot study. *Environ Health Perspect* 101:318–324 (1993).
- Waldman JM, Lioy PJ, Thurston GD, Lippmann M. Spatial and temporal patterns in summertime sulfate aerosol acidity and neutralization within a metropolitan area. *Atmos Environ (B)* 24:115–126 (1990).
- Geyh AS, Xue J, Özkaynak H, Spengler JD. The Harvard Southern California Chronic Ozone Exposure Study: assessing ozone exposures of grade-school-age children in two southern California communities. *Environ Health Perspect* 108(3):1–6 (2000).
- Chang LT, Koutrakis P, Catalano P, Suh HH. Hourly personal exposures to fine particles and gaseous pollutants: results from Baltimore, MD. *J Air Waste Manag* (in press).
- Sarnat J, Koutrakis P, Suh HH. Assessing the relationship between personal particulate and gaseous exposures of senior citizens living in Baltimore, MD. *J Air Waste Manag* (in press).
- Dockery DW, Pope CA III, Xu X, Spengler JD, Ware JH, Fay ME, Ferris BGJ, Speizer FE. An association between air pollution and mortality in six U.S. cities. *N Engl J Med* 329(24):1753–1759 (1993).
- Dockery DW, Schwartz J, Spengler JD. Air pollution and daily mortality: associations with particulates and acid aerosols. *Environ Res* 59:362–373 (1992).
- Özkaynak H, Thurston GD. Associations between 1980 U.S. mortality rates and alternative measures of airborne particle concentration. *Risk Anal* 7(4):449–461 (1987).
- Pope CA III, Dockery DW, Spengler JD, Raizenne ME. Respiratory health and PM_{10} pollution: a daily time series

- analysis. *Am Rev Respir Dis* 144:668–674 (1991).
38. Schwartz J, Dockery DW. Increased mortality in Philadelphia associated with daily air pollution concentrations. *Am Rev Respir Dis* 145:600–604 (1992).
 39. Ito K, Thurston GD. Daily PM₁₀ mortality associations: an investigation of at-risk subpopulations. *J Expos Anal Environ Epidemiol* 6(1):79–95 (1996).
 40. Kinney PL, Ito K, Thurston GD. A sensitivity analysis of mortality/PM-10 associations in Los Angeles. *Inhalat Toxicol* 7:59–69 (1995).
 41. Schwartz J. Air pollution and hospital admissions for respiratory disease. *Epidemiology* 7(1):20–28 (1996).
 42. Styer P, McMillan N, Gao F, Davis J, Sacks J. Effect of outdoor airborne particulate matter on daily death counts. *Environ Health Perspect* 103(5):490–497 (1995).
 43. Wilson WE, Suh HH. Fine particles and coarse particles: concentration relationships relevant to epidemiologic studies. *J Air Waste Manag* 47(12):1238–1249 (1997).
 44. Katsouyanni K, Karakatsani A, Messari I, Touloumi G, Hatzakis A, Kalandari A, Trichopoulos D. Air pollution and cause specific mortality in Athens. *J Epidemiol Commun Health* 44:321–324 (1990).
 45. Thurston GD, Ito K, Lippman M, Hayes C. Reexamination of London, England, mortality in relation to exposure to acid aerosols during 1963–1972 winters. *Environ Health Perspect* 79:73–82 (1989).
 46. Touloumi G, Pocock SJ, Katsouyanni K, Trichopoulos D. Short-term effects of air pollution on daily mortality in Athens: a time-series analysis. *Int J Epidemiol* 23:957–967 (1994).
 47. Schwartz J, Dockery DW, Neas LM. Is daily mortality associated specifically with fine particles? *J Air Waste Manag* 46:2–12 (1996).
 48. Laden F, Neas LM, Dockery DW, Schwartz J. Association of fine particulate matter from different sources with daily mortality in six U.S. cities. *Environ Health Perspect* (in press).
 49. Castillejos M, Borja-Aburto VH, Dockery DW, Loomis D. Coarse particles and mortality in Mexico City. *Inhalat Toxicol* 12(suppl 1):61–72 (2000).
 50. Clarke RW, Catalano P, Murthy GG, Koutrakis P, Wolfson JM, Sioutas C, Godleski JJ. Pulmonary function and inflammatory response alterations following inhalation of concentrated urban air. *Inhalat Toxicol* 11:101–120 (1999).
 51. Clarke RW, Catalano P, Coull B, Koutrakis P, Murthy GG, Rice T, Godleski JJ. Age-related responses in rats to concentration urban air particles (CAPs). *Inhalat Toxicol* (in press).
 52. Gordon T, Nadziejko C, Schlesinger R, Chen LC. Pulmonary and cardiovascular effects of acute exposure to concentrated ambient particulate matter in rats. *Toxicol Lett* 96–97:285–288 (1998).
 53. Clarke RW, Coull B, Reinisch U, Catalano P, Killingsworth CR, Koutrakis P, Kavouas I, Murthy GG, Lawrence J, Lovett E, et al. Inhaled concentrated air particles induce pulmonary inflammation and hematological changes in canines. *Environ Health Perspect* (in press).
 54. Godden DJ, Seaton A, Soutar A, Crawford V, Elton R, McNerlan S, Cherrie J, Watt M, Agius J, Stout R. Hematological changes associated with exposure to particulate air pollution: results of a panel study. In: *Proceedings Third Colloquium Particulate Air Pollution and Human Health*, 6–8 June 1999, Durham, North Carolina.
 55. Liao D, Creason J, Shy C, Williams R, Watts R, Zweidinger R. Daily variation of particulate air pollution and poor cardiac autonomic control in the elderly. *Environ Health Perspect* 107:521–525 (1999).
 56. Pope CA III, Verrier RL, Lovett EG, Larson AC, Raizenne ME, Kanner RE, Schwartz J, Willegas GM, Gold DR, Dockery DW. Heart rate variability associated with particulate air pollution. *Am Heart J* 138:890–899 (2000).
 57. Gold DR, Litonjua A, Schwartz J, Lovett E, Larson A, Nearing B, Allen GA, Verrier M, Cherry R, Verrier R. Ambient pollution and heart rate variability. *Circulation* 126:1273–1277 (2000).
 58. Peters A, Liu E, Verrier RL, Schwartz J, Gold DR, Mittleman M, Baliff J, Oh JA, Allen GA, Monahan K, et al. Air pollution and incidence of cardiac arrhythmia. *Epidemiology* 11:11–17 (2000).
 59. Peters A, Doring A, Wichmann HE, Koenig W. Increased plasma viscosity during the 1985 air pollution episode: a link to mortality? *Lancet* 349:1582–1587 (1997).
 60. Spengler JD, Thurston GD. Mass and elemental composition of fine and coarse particles in six U.S. cities. *J Air Pollut Contr Assoc* 33(12):1162–1171 (1983).
 61. Burton RM, Suh HH, Koutrakis P. Spatial variation in particulate concentrations within metropolitan Philadelphia. *Environ Sci Technol* 30:400–407 (1996).
 62. Suh HH, Allen GA, Koutrakis P. Spatial variation in acidic sulfate and ammonia concentrations within metropolitan Philadelphia. *J Air Waste Manag* 45:442–452 (1995).
 63. Suh HH, Nishioka Y, Allen GA, Koutrakis P, Burton RM. The Metropolitan Acid Aerosol Characterization study: results from the summer 1994 Washington, DC field study. *Environ Health Perspect* 105(7):826–834 (1997).
 64. Spengler JD. Harvard's indoor air quality respiratory health study. Paper presented at the Indoor Air '87: The 4th International Conference on Indoor Air Quality and Climate, Berlin, Federal Republic of Germany, 1987.
 65. Özkaynak H, Xue J, Weker RA, Butler DA, Koutrakis P, Spengler JD. The Particle TEAM (PTEAM) Study: Analysis of the Data; Volume III: Final Report (EPA/600/R-95/098). Washington, DC:U.S. Environmental Protection Agency, 1996.
 66. Özkaynak H, Xue J, Weker RA, Butler DA, Koutrakis P, Spengler JD. Project Summary, The Particle TEAM Study (PTEAM): Analysis of the Data (EPA/600/SR-95/098). Research Triangle Park, NC:U.S. Environmental Protection Agency, 1997.
 67. Koutrakis P, Briggs SLK, Leaderer BP. Source apportionment of indoor aerosols in Suffolk and Onondaga counties, New York. *Environ Sci Technol* 26(3):521–527 (1992).
 68. Abt E, Suh HH, Allen GA, Koutrakis P. Characterization of indoor particle sources: a study conducted in the metropolitan Boston area. *Environ Health Perspect* 108:35–44 (1999).
 69. Long CM, Suh HH, Koutrakis P. Characterization of indoor particle sources using continuous mass and size monitors. *J Air Waste Manag* (in press).
 70. Spengler JD, Treitman RD, Tosteson TD, Mage DT, Soczek ML. Personal exposures to respirable particulates and implications for air pollution epidemiology. *Environ Sci Technol* 19:700–707 (1985).
 71. Rojas L, Suh H, Koutrakis P. Relationships among personal, indoor, and outdoor fine and coarse particulate concentrations for individuals with COPD. *J Expos Assess Environ Epidemiol* 10:294–306 (2000).
 72. Tamura K, Ando M, Sagai M, Matsumoto Y. Estimation of levels of personal exposure to suspended particulate matter and nitrogen dioxide in Tokyo. *Environ Sciences (Tokyo)* 4:37–51 (1996).
 73. Bahadori T, Suh HH, Rojas L, Koutrakis P. Characterization of personal PM₁₀ and PM_{2.5} exposures for individuals with COPD: results from a pilot study in Nashville, TN. *J Environ Epidemiol Expos Assess* (in press).
 74. Janssen NAH, Hoek G, Harssema H, Brunekreef B. A relationship between personal and ambient PM₁₀. *Epidemiology* (suppl) 6(4):S45 (1995).
 75. Lioy PJ, Waldman JM. The personal, indoor, outdoor concentrations of PM-10 measured in an industrial community during the winter. *Atmos Environ* 24B:57–66 (1990).
 76. Suh HH, Koutrakis P, Spengler JD. Validation of personal exposure models for sulfate and aerosol strong acidity. *J Air Waste Manag* 43:845–850 (1993).
 77. U.S. Environmental Protection Agency. 40 CFR, Part 50: National Ambient Air Quality Standards for Particulate Matter, Final Rule (Regulation). *Fed Reg* 62:38651–38701 (1997).
 78. Wallace LA. The TEAM Study: Summary and Analysis. Vol I. U.S. EPA, EPA 600/6-87/002a, NTIS PB 88-100060. U.S. Washington, DC:Environmental Protection Agency, 1987.
 79. Tucker WG. Characterizing emissions and health effects of sources of indoor air contaminants-Introduction. *Ann NY Acad Sci* 641:1–6 (1992).
 80. Robinson J, Thomas J. Time Spent in Activities, Locations, and Microenvironments: A California-National Comparison. EPA/600/4-91/006. Washington, DC:U.S. Environmental Protection Agency, 1991.
 81. Rosenbaum AS, Axelrad DA, Woodruff TJ, Wei YH, Ligocki MP, Cohen JP. National estimates of outdoor air toxics concentrations. *J Air Waste Manag* 49(10):1138–1152 (1999).
 82. Woodruff TJ, Axelrad, Caldwell J, Morello-French R, Rosenbaum A. Public health implications of 1990 air toxics concentrations across the United States. *Environ Health Perspect* 106(5):245–251 (1998).
 83. Exposure To Hazardous Air Pollutants in Los Angeles. Prepared for Rep. Henry A. Waxman, Minority Staff Report, Committee on Government Reform, U.S. House of Representatives, March 1, 1999.
 84. Sittig M. Handbook of Toxic and Hazardous Chemicals and Carcinogens. 2nd ed., Noyes Publications, Park Ridge, NJ, 1985.
 85. The Merck Index: An Encyclopedia of Chemicals, Drugs, and Biological (Annual) (Budavari S, O'Neil MJ, ed). Rahway, NJ:Merck & Co 1996.
 86. ATSDR. Toxicological Profile for Benzene (Draft). Atlanta, GA:Agency for Toxic Substances and Disease Registry, 1991.
 87. Rinsky RA, Young RJ, Smith AB. Leukemia in benzene workers. *Am J Ind Med* 2:217–245 (1981).
 88. Rinsky RA, Smith AB, Hornung R, Filloon TG, Young RJ, Okun AH, Landrigan PJ. Benzene and leukemia: an epidemiologic risk assessment. *N Engl J Med* 316(17):1044–1050 (1987).
 89. Dann T. Ambient air measurements of benzene at Canadian monitoring sites, 1987–1993. Ottawa, Ontario:Canada Environment, Canada Environmental Technology Centre, 1994.
 90. Lewis CW. Sources of air pollutants indoors: VOC and fine particulate sources. *J Expos Anal Environ Epidemiol* 1(1):31–44 (1991).
 91. Chan CC, Özkaynak H, Spengler JD, Sheldon L. Driver exposure to volatile organic compounds, CO, ozone, and NO₂ under different driving conditions. *Environ Sci Technol* 25:964–972 (1991).
 92. Jo WK, Park KH. Concentration of volatile organic compounds in the passenger side and the back seat of automobiles. *J Expos Anal Environ Epidemiol* 9:217–227 (1999).
 93. Lawryk NJ, Weisel CP. Concentrations of volatile organic compounds in the passenger compartments of automobiles. *Environ Sci Technol* 30:810–816 (1996).
 94. Weisel CP, Nicholas NJ, Lioy PJ. Exposure to emissions from gasoline within automobile cabins. *J Expos Anal Environ Epidemiol* 2:79–96 (1992).
 95. U.S. EPA. Technical Background Document to Support Rulemaking Pursuant to the Clean Air Act – Section 112 (g). Ranking of Pollutants with Respect to Hazard to Human Health. EPA-450/3-92-010. Research Triangle Park, NC:U.S. Environmental Protection Agency, 1994.
 96. WHO. Environmental Health Criteria for Formaldehyde. Vol 89. Geneva:World Health Organization, 1989.
 97. U.S. EPA. Integrated Risk Information System (IRIS) on Formaldehyde. Cincinnati, OH:U.S. Environmental Protection Agency, 1993.
 98. Calabrese EJ, Kenyon EM. Air Toxics and Risk Assessment. Chelsea, MI:Lewis Publishers, 1991.
 99. National Library of Medicine. Hazardous Substances Databank (HSDB, online database). Bethesda, MD:National Institutes of Health, 1993.
 100. Blair A, Stewart PA, Hoover RN, et al. Mortality among industrial workers exposed to formaldehyde. *J Natl Cancer Inst* 76(6):1071–1084 (1986).
 101. Kerns WD, Pavkov KL, Donofrio DJ, Gralla EJ, Swenberg JA. Carcinogenicity of formaldehyde in rats and mice after long-term inhalation exposure. *Cancer Res* 43:4382–4392 (1983).
 102. Levine SA, Reinhardt MS. Biochemical-pathology initiated by free radicals, oxidant chemicals, and, therapeutic drugs in the etiology of chemical hypersensitivity disease. *J Orthomol Psych* 12(3):166–183 (1983).
 103. Spengler JD. Personal communication.
 104. California Air Resources Board. Air Quality Database. Air Quality Branch. PT SD-99-011-CD, 1999.
 105. U.S. Environmental Protection Agency. AIRS: Aerometric Information Retrieval System. [Available: <http://www.epa.gov/airs/>].
 106. Vallarino J, Spengler J, Nishioka Y, Kawai S, Yanagisawa Y. Evaluation of material selection as a strategy for improving indoor air quality in new residential construction. Presented at Indoor Air 99, 8–13 August 1999, Edinburgh, Scotland.