DRAFT
APPENDIX

HEALTH EFFECTS

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HEALTH EFFECTS OF AIR POLLUTION

Ambient air pollution is a major public health concern. Excess deaths and increases in illnesses associated with high air pollution levels have been documented in several episodes as early as 1930 in Meuse Valley, Belgium; 1948 in Donora, Pennsylvania; and 1952 in London. Although levels of pollutants that occurred during these acute episodes are now unlikely in the United States, ambient air pollution continues to be linked to increases in respiratory illness (morbidity) and slight increase in death rates (mortality).

The adverse health effects associated with air pollution are diverse and include:

[[Do you want to mention premature death here?]]

- Increased health care utilization (hospitalization, physician and emergency room visits)
- Increased respiratory illness (symptoms, infections, and asthma exacerbation)
- Decreased lung function (breathing capacity)
- Lung inflammation
- Potential immunological changes
- Increased airway reactivity to a known chemical exposure - a method used in laboratories to evaluate the tendency of airways to have an increased possibility of developing an asthmatic response
- A decreased tolerance for exercise.

The evidence linking these effects to air pollutants is derived from population-based observational and field studies (epidemiological) as well as controlled laboratory studies involving human subjects and animals. There have been an increasing number of studies focusing on mechanisms (that is, on learning how specific organs, cell types, and biochemicals are involved in the human body's response to air pollution) and specific pollutants responsible for individual effects, yet the underlying biological pathways for these effects are not always clearly understood. Long-term effects of exposure, being more difficult to identify and measure, require further research and evaluation.

Although individuals inhale pollutants as a mixture under ambient conditions, ~~a focus on specific pollutants occurs because~~ the regulatory framework and the control measures developed are mostly pollutant-specific. This is appropriate in that different pollutants usually differ in their sources, their times and places of occurrence, the kinds of health effects they may cause, and their overall levels of health risk. Different pollutants, from the same or different sources, may sometimes act together to harm health more than they

would acting separately. Nevertheless, as a practical matter, health scientists as well as regulatory officials usually must deal with one pollutant at a time. A brief overview of the effects observed and attributed to various air pollutants is presented in this document.

This summary is drawn substantially from a review presented previously (SCAQMD, 1996), and from reviews on the effects of air pollution by the American Thoracic Society (ATS, 1996), the USEPA reviews for ozone (USEPA, 1996), and Particulate Matter (USEPA, 2001)[1].

OZONE

Ozone is a highly reactive compound, and is a strong oxidizing agent. When ozone comes into contact with the respiratory tract, it can react with tissues and cause damage in the airways. Since it is a gas, it can penetrate into the gas exchange region of the deep lung.

The EPA standards for ozone are 0.12 ppm averaged over 1 hour, and 0.08 ppm averaged over eight hours.

The major subgroups of the population considered to be at increased risk from ozone exposure are outdoor exercising individuals including children, and people with preexisting respiratory disease(s) such as asthma. The data base identifying the former group as being at increased risk to ozone exposure is much stronger and more quantitative than that for the latter group, probably because of a larger number of studies conducted with healthy individuals. The adverse effects reported with short-term ozone exposure are greater with increased activity because activity increases the breathing rate and the volume of air reaching the lungs, resulting in an increased amount of ozone reaching the lungs. Children may be a particularly vulnerable population to air pollution effects because they spend more time outdoors, are generally more active, and have a higher ventilation rate than adults.

A number of adverse health effects associated with ambient ozone levels have been identified from laboratory and epidemiological studies (EPA, 1996; ATS, 1996). These include increased respiratory symptoms, damage to cells of the respiratory tract, decreases in lung function, increased susceptibility to respiratory infection, and increased risk of hospitalization.

The Children's Health Study has been following a cohort of children that live in 12 communities in southern California with differing levels of air pollution for several years. A recent publication from this study has found that school absences in fourth graders for respiratory illnesses were associated with ambient ozone levels. An increase

[1] Most of the studies referred to in this appendix are cited in the above sources. Only recent, specific references will be cited in this summary.

of 20 ppb ozone was associated with an 83% increase in illness related absence rates (Gilliland, 2001).

The number of hospital admissions for all respiratory causes (infections, respiratory failure, chronic bronchitis, etc.) including asthma show a consistent increase as ambient ozone, sulfate or sulfur dioxide levels increase in a community. These excess hospital admissions and emergency room visits are observed when hourly ozone concentrations are as low as 0.08 to 0.10 ppm. However, limitations in the study designs preclude attributing the effects solely to ambient ozone concentrations.

Several population-based studies suggest that asthmatics are more adversely affected by ambient ozone levels, as evidenced by increased hospitalizations and emergency room visits. Laboratory studies have attempted to compare the degree of lung function change seen in age and gender matched healthy individuals versus asthmatics and those with chronic obstructive pulmonary disease. While the degree of change evidenced did not differ significantly, that finding may not accurately reflect the true impact of exposure on these respiration-compromised individuals. Since the respiration-compromised group may have lower lung function to begin with, the same degree of change may represent a substantially greater adverse effect overall.

In addition, human and animal studies involving both short-term (few hours) and long-term (months to years) exposures indicate a wide range of effects induced or associated with ambient ozone exposure. These are summarized in Table 1.

Some lung function responses (volume and airway resistance changes) observed after a single exposure to ozone exhibit attenuation or a reduction in magnitude with repeated exposures. Although it has been argued that the observed shift in response is evidence of a probable adaptation phenomenon, it appears that while functional changes may exhibit adaptation, biochemical and cellular changes which may be associated with episodic and chronic exposure effects may not exhibit similar adaptation. That is, internal damage to the respiratory system may continue with repeated ozone exposures, even if externally observable effects – chest symptoms and reduced lung function – disappear.

In a laboratory, exposure of human subjects to low levels of ozone causes reversible decrease in lung function as assessed by various measures such as respiratory volumes, airway resistance and reactivity, irritative cough and chest discomfort. Lung function changes have been observed with ozone exposure as low as 0.08 to 0.12 ppm for 6-8 hours under moderate exercising conditions. Similar lung volume changes have also been observed in adults and children under ambient exposure conditions (0.10 - 0.15 ppm). The responses reported are indicative of decreased breathing capacity and are reversible.

In laboratory studies, cellular and biochemical changes associated with respiratory tract inflammation have also been consistently reported in the airway lining after low level

exposure to ozone. These changes include an increase in specific cell types and in the concentration of biochemical mediators of inflammation and injury such as cytokines and fibronectin. These inflammatory changes can be observed in healthy adults exposed to ozone in the range of 0.08 to 0.10 ppm.

The susceptibility to ozone observed under ambient conditions could be due to the combination of pollutants that co-exist in the atmosphere, or ~~that~~ ozone may actually sensitize these subgroups to the effects of other pollutants.

Some animal studies show results that indicate possible chronic effects including functional and structural changes of the lung. These changes indicate that repeated inflammation associated with ozone exposure over a lifetime may result in sufficient damage to respiratory tissue such that individuals later in life may experience a reduced quality of life in terms of respiratory function and activity level achievable. An autopsy study involving Los Angeles County residents provided supportive evidence of lung tissue damage (structural changes) attributable to air pollution.

TABLE 1

Adverse Health Effects of Ozone (O_3)
(Summary of Key Studies)

0_3 Concentration and Exposure Hr, ppm	Health Effect
Ambient air containing 0.10 - 0.15 daily 1-h max over days to weeks	Decreased breathing capacity in children, adolescents, and adults exposed to 0_3 outdoors Exacerbation of respiratory symptoms (e.g., cough, chest pain) in individuals with preexisting disease (e.g., asthma) with low ambient exposure, decreased temperature, and other environmental factors resulting in increased summertime hospital admissions and emergency department visits for respiratory causes
≥0.12 (1-3h) ≥0.08 (6.6h) (chamber exposures)	Decrements in lung function (reduced ability to take a deep breath), increased respiratory symptoms (cough, shortness of breath, pain upon deep inspiration), increased airway responsiveness and increased airway inflammation in exercising adults
≥0.12 (1-3 h) ≥0.08 (6.6h) (chamber exposures)	Effects are similar in individuals with preexisting disease except for a greater increase in airway responsiveness for asthmatic and allergic subjects
≥0.12 (1-3h) ≥0.08 (6.6h) (chamber exposures)	Older subjects (>50 yr old) have smaller and less reproducible changes in lung function Attenuation of response with repeated exposure

≥0.12 with prolonged, repeated exposure (chamber exposures)	Changes in lung structure, function, elasticity, and biochemistry in laboratory animals that are indicative of airway irritation and inflammation with possible development of chronic lung disease Increased susceptibility to bacterial respiratory infections in laboratory animals

From: SCAQMD, 1996

A few studies have suggested that population exposure to community air pollution (ozone and particulate matter), ~~are~~ is related to genetic toxicity and increased incidence of cancer. In recent years, an increase in daily mortality has also been reported to be associated with ozone levels. Because of limitations in study design in a number of studies, as well as assumptions involved and coexisting pollutants, the severity of chronic effects associated with ozone exposure alone cannot be ascertained from these studies.

In summary, acute adverse effects associated with ozone exposures have been well documented, although the specific causal mechanism is still somewhat unclear. Additional research efforts are required to evaluate the long-term effects of air pollution and to determine the role of ozone in influencing chronic effects.

PARTICULATE MATTER

Airborne particulates are a complex group of pollutants that vary in size and composition, depending on location and time. The components include nitrates, sulfates, elemental carbon, organic carbon compounds, acid aerosols, trace metals, and material from the earth's crust. Substances of biological origin, such as pollen and spores, may also be present.

The health effects of particulates are focused on those sized 10 μm (micrometers) aerodynamic diameter and smaller. These can be inhaled through the upper airways and deposited in the lower airways and gas exchange tissues in the lung. These particles are referred to as PM_{10}. EPA promulgated ambient air quality standards for PM_{10} of 150 $\mu g/m^3$ averaged over a 24-hour period, and 50 $\mu g/m^3$ for an annual average.

In recent years additional focus has been placed on particles having an aerodynamic diameter of 2.5 μm or less ($PM_{2.5}$). A greater faction of particles in this size range can penetrate and deposit deep in the lungs. The EPA set air quality standards for $PM_{2.5}$ in 1997 at 65 $\mu g/m^3$ for a 24-hour average and 15 $\mu g/m^3$ for an annual average.

There are also differences in the composition and sources of particles in the different size ranges that may have implications for health effects. The particles larger than 2.5 μm (often referred to as the coarse fraction) are mostly produced by mechanical processes. These include automobile tire wear, industrial processes such as cutting and grinding,

and resuspension of particles from the ground or road surfaces by wind and human activities.

In contrast, particles smaller than 2.5 μm are mostly derived from combustion sources, such as automobiles, trucks, and other vehicle exhaust, as well as from stationary combustion sources. The particles are either directly emitted or are formed in the atmosphere from gases that are emitted. Components from material in the earth's crust, such as dust, are also present, with the amount varying in different locations.

The health effects of ambient particulate matter have been recently reviewed (ATS, 1996; EPA, 2001). The major types of effects associated with particulate matter include:

- Increased mortality
- Exacerbation of respiratory disease and of cardiovascular disease as evidenced by increases in:
  - -Respiratory symptoms
  - -Hospital admissions and emergency room visits
  - -Physician office visits
  - -School absences
  - -Work loss days
- Effects on lung function
- Changes in lung morphology

Short-Term Exposure Effects

Epidemiological studies have provided continued and consistent evidence for most of the effects listed above. An association between increased daily or several-day-average concentrations of PM_{10} and excess mortality and morbidity is consistently reported from studies involving communities across the U.S. as well as in Europe, Asia, and South America. A review and analysis of epidemiological literature for acute adverse effects was undertaken by Dockery and Pope to estimate these effects as percent increase in mortality associated with each incremental increase of PM_{10} by 10 $\mu g/m^3$. The estimates are presented in Table 2. It appears that individuals who are elderly or have preexistent lung or heart disease are more susceptible than others to the adverse effects of PM_{10}.

TABLE 2

Combined Effect Estimates of Daily Mean Particulate Pollution

	% Change in Health Indicator per each 10 $\mu g/m^3$ Increase in PM_{10}
Increase in daily mortality	
Total deaths	1.0
Respiratory deaths	3.4
Cardiovascular deaths	1.4
Increase in hospital usage (all respiratory diagnoses)	
Admissions	1.4
Emergency department visits	0.9
Exacerbation of asthma	
Asthmatic attacks	3.0
Bronchodilator use	12.2
Emergency department visits*	3.4
Hospital admissions	1.9
Increase in respiratory symptom reports	
Lower respiratory	3.0
Upper respiratory	0.7
Cough	2.5
Decrease in lung function	
Forced expiratory volume	0.15
Peak expiratory flow	0.08

* One study only

(Source: American Journal of Respiratory and Critical Care Medicine, Vol. 153, 113-50, 1996)

Many recent studies have confirmed that excess mortality and morbidity are associated with particulate matter levels. Estimates of mortality effects from these studies range from 0.3 to 1.7% increase for a 10 $\mu g/m^3$ increase in PM_{10} levels. The National Morbidity, Mortality, and Air Pollution Study (NMMAPS), a recent study of the 90 largest U.S. cities, determined a combined risk estimate of about a 0.5% increase in total mortality for a 10 $\mu g/m^3$ increase in PM_{10}. This study also analyzed the effects of gaseous co-pollutants. The results indicated that the association of PM_{10} and mortality were not confounded by the presence of the gaseous pollutants. When the gaseous

pollutants were included in the analyses, the significance of the PM_{10} estimates remained. The PM_{10} effects were reduced somewhat when O_3 was also considered and tended to be variably decreased when NO_2, CO, and SO_2 were added to the analysis. These results argue that the effects are likely due to the particulate exposures: they cannot readily be explained by coexisting weather stresses or other pollutants.

Studies of $PM_{2.5}$ also find associations with elevated mortality. The estimates for $PM_{2.5}$ generally are in the range of 2.0 to 8.5% increase in total deaths per 25 $\mu g/m^3$ increase in 24-hour $PM_{2.5}$ levels. The estimates for cardiovascular related mortality range from 3.0 to 7.0% per 25 $\mu g/m^3$ 24-hour $PM_{2.5}$, and for respiratory mortality estimates range from 2.0 to 7.0% per 25 $\mu g/m^3$ 24-hour $PM_{2.5}$.

Several studies have attempted to assess the relative importance of particles smaller than 2.5 μm and those between 2.5 μm and 10 μm ($PM_{10-2.5}$). While some studies report that $PM_{2.5}$ levels are better predictors of mortality effects, others suggest that $PM_{10-2.5}$ is also important. Most of the studies found higher mortality associated with $PM_{2.5}$ levels than with $PM_{10-2.5}$. For example, a study of six cities in the U.S. found that particulate matter less than 2.5 μm were associated with increased mortality, but that the larger particles were not. Other studies in Mexico City and Santiago, Chile reported that $PM_{10-2.5}$ was as important as $PM_{2.5}$. Overall effects estimates for $PM_{10-2.5}$ fall in the range of 0.5 to 6.0 % excess mortality per 25 $\mu g/m^3$ 24-hour average.

The relative importance of both $PM_{2.5}$ and $PM_{10-2.5}$ may vary in different regions depending on the relative concentrations and components, which can also vary by season. More research is needed to determine the relative effects of fine ($PM_{2.5}$) and course ($PM_{10-2.5}$) fractions of particulate matter on mortality.

A number of studies have evaluated the association between particulate matter exposure and indices of morbidity such as hospital admissions, emergency room visits or physician office visits for respiratory and cardiovascular diseases. The effects estimates are generally higher than the effects for mortality. The effects are associated with ~~both~~ measures of PM_{10} and ~~with~~ $PM_{2.5}$. Effects are also associated with $PM_{10-2.5}$. Thus, it appears that when a relatively small number of people experience severe effects, larger numbers experience milder effects, which may relate either to the coarse or to the fine fraction of airborne particulate matter.

In the recent NMMAPS study, hospital ~~emissions~~ admissions for those 65 years or older were assessed in 14 cities. Hospital admissions for these individuals showed an increase of 6% for cardiovascular diseases and a 10% increase for respiratory disease admissions, per 50 $\mu g/m^3$ increase in PM_{10}. The excess risk for cardiovascular disease ranges from 3-10% per 50 $\mu g/m^3$ PM_{10} and from 4-10% per 25 $\mu g/m^3$ $PM_{2.5}$ or $PM_{10-2.5}$.

Similarly, school absences, lost workdays and restricted activity days have also been used in some studies as indirect indicators of acute respiratory conditions. The results

are suggestive of both immediate and delayed impact on these parameters following elevated particulate matter exposures. These observations are consistent with the hypothesis that increased susceptibility to infection follows particulate matter exposures.

Some studies have reported that short-term particulate matter exposure is associated with changes in lung function (lung capacity and breathing volume); upper respiratory symptoms (hoarseness and sore throat); and lower respiratory symptoms (increased sputum, chest pain and wheeze). The severity of these effects is widely varied and is dependent on the population studied, such as adults or children with and without asthma. Sensitive individuals, such as those with asthma or pre-existing respiratory disease, may have increased or aggravated symptoms associated with short-term particulate matter exposures. Several studies have followed the number of medical visits associated with pollutant exposures. A range of increases from 3% to 42% for medical visits for respiratory illnesses was found corresponding to a 50 $\mu g/m^3$ change in PM_{10}. A limited number of studies also looked at levels of $PM_{2.5}$ or $PM_{10-2.5}$. The findings suggest that both the fine and course factions may have associations with some respiratory symptoms.

The biological mechanisms by which particulate matter can produce health effects are being investigated in laboratory studies. Inflammatory responses in the respiratory system in human and animals exposed to concentrated ambient particles have been measured. These include effects such as increases in neutrophils in the lungs. Other changes reported include increased release of cytokines and interleukins, chemicals released as part of the inflammatory process. The effects of particulate matter may be mediated in part through the production of reactive oxygen species during the inflammatory process.

Long-Term Exposure Effects

While most studies have evaluated the acute effects, some studies specifically focused on evaluating the effects of chronic exposure to PM_{10} and $PM_{2.5}$. Studies have analyzed the mortality of adults living in different U.S. cities. After adjusting for important risk factors, these studies found a consistent positive association of deaths and exposure to particulate matter. A similar association was observable in both total number of deaths and deaths due to cardiorespiratory causes. A shortening of lifespan was also reported in these studies.

Significant associations for $PM_{2.5}$ for both total mortality and cardiorespiratory mortality were reported in a study using data from the American Cancer Society. A recent re-analysis of the data from this study confirmed the finding. The Harvard Six Cities Study evaluated several size ranges of particulate matter and reported significant associations with PM_{15}, $PM_{2.5}$, sulfates, and non-sulfate particles, but not with course particles ($PM_{15} - PM_{2.5}$). These studies provide evidence that the fine particles, as measured by $PM_{2.5}$,

may be more strongly associated with mortality effects from long-term particulate matter exposures than are coarse compounds.

Recent studies report evidence indicating that particulate matter exposure early in pregnancy may be associated with lowered birth weights. Other studies from the U.S., the Czech Republic and Mexico City have reported that neonatal and early postnatal exposure to particulate matter may lead to increased infant mortality. These results suggest that infants may be a subgroup affected by particulate matter exposures.

In addition, long-term effect studies have reported an increased risk of mortality from lung cancer associated with particulate matter exposures. A study involving California Seventh Day Adventists, very few of whom smoke, has reported an association of cancer in females with increased particulate matter (total suspended particles) exposure. It is not clear from these studies whether the association relates to causation of disease, or whether individuals with cancer are more susceptible to other effects of particles leading to the observed mortality association. Other studies of larger populations in the U.S. have not found significant association of lung cancer with PM levels.

Evaluating mortality effects in a public health context is a complex task and requires information regarding the extent of life shortening or prematurity of death associated with Particulate matter exposures. The relative risk estimates vary considerably depending on the type of study (acute vs. chronic) and also among studies within each group. Some attempts have been made in a broad sense to calculate the number of deaths associated with PM_{10} exposure by applying different statistical methods using the relative risk estimates of specific studies. However, U.S. EPA has concluded that although a substantial portion of deaths associated with long-term PM_{10} exposure may be independent of the daily deaths associated with recent PM_{10}, quantification of the extent of life- shortening or the number of deaths directly associated with PM_{10} exposure from either type of studies is difficult.

Several studies have assessed the effects of long-term particulate matter exposure on respiratory symptoms and lung function changes. Associations have been found with symptoms of chronic bronchitis and decreased lung function. A study of school children in 12 communities in Southern California showed significant association of particulate matter with bronchitis or phlegm in children with asthma. These effects were also associated with NO_2 and acid vapor levels.

A cohort of 4^{th} graders from the Southern California communities were followed over a period of four years by the Children's Health Study. A lower rate of growth in lung function was found in children living in areas with higher levels of particulate pollution. Decreases in lung function growth were associated with PM_{10}, $PM_{2.5}$, $PM_{10\text{-}2.5}$, acid vapor, and NO_2. There was no association with ozone levels. The investigators were not able to identify independent effects of the pollutants, but noted that motor vehicle emissions are a major source of the pollutants.

Despite data gaps, the extensive body of epidemiological studies has both qualitative and quantitative consistency suggestive of causality. A considerable body of evidence from these studies suggests that ambient particulate matter, alone or in combination with other coexisting pollutants, is associated with significant increases in mortality and morbidity in a community.

In summary, the scientific literature indicates that an increased risk of mortality and morbidity is associated with particulate matter at ambient levels. The evidence for particulate matter effects is mostly derived from population studies with supportive evidence from clinical and animal studies. Although most of the effects are attributable to particulate matter, co-pollutant effects cannot be ruled out on the basis of existing studies. The difficulty of separating the effects may be due to the fact that particulate levels co-vary with other combustion source pollutants. ~~and may serve as an index of air pollution from these sources instead of a separate pollutant by itself.~~ That is, the particle measurements serve as an index of overall exposure to combustion-related pollution, and some component(s) of combustion pollution other than particles might be at least partly responsible for the observed health effects.

CARBON MONOXIDE

The high affinity of carbon monoxide (CO) to bond with oxygen-carrying proteins (hemoglobin and myoglobin) results in reduced oxygen supply in the bloodstream of exposed individuals. The reduced oxygen supply is responsible for the toxic effects of CO which are typically manifested in the oxygen-sensitive organ systems. The effects have been studied in controlled laboratory environments involving exposure of humans and animals to CO, as well as in population-based studies of ambient CO exposure effects. People with deficient blood supply to the heart (ischemic heart disease) are known to be susceptible to the effects of CO. Protection of this group is the basis of the existing National Ambient Air Quality Standards for CO at 35 ppm for one hour and 9 ppm averaged over eight hours. The health effects of ambient CO have been recently reviewed (USEPA, 2000).

Inhaled CO has no known direct toxic effect on lungs but rather exerts its effects by interfering with oxygen transport through the formation of carboxyhemoglobin (COHb, a chemical complex of CO and hemoglobin). Exposure to CO is often evaluated in terms of COHb levels in blood measured as percentage of total hemoglobin bound to CO. COHb levels in non-smokers range between 0.3 and 0.7% and 5 to 10% in smokers. COHb levels in excess of 1.5% in a significant proportion of urban nonsmoking populations can be considered as evidence of widespread exposure to environmental CO.

Under controlled laboratory conditions, healthy subjects exposed to CO sufficient to result in 5% COHb levels exhibited reduced duration of maximal exercise performance and consumption of oxygen. Studies involving subjects with coronary artery disease who engaged in exercise during CO exposures have shown that COHb levels as low as

2.4% can lead to earlier onset of electrocardiograph changes indicative of deficiency of oxygen supply to the heart. Other effects include an earlier onset of chest pain, an increase in the duration of chest pain, and a decrease in oxygen consumption.

Animal studies associated with long-term exposure to CO resulting in COHb levels that are equivalent to those observed in smokers have shown indication of reduction in birth weight and impaired neurobehavior in the offspring of exposed animals.

Recent epidemiological studies conducted in Southern California have indicated an association with CO exposure during pregnancy to increases in pre-term births. (Ritz, 2000). However, the results were not consistent in different areas studied. The increase in the pre-term births was also associated with PM_{10} levels.

NITROGEN DIOXIDE

Evidence for low-level nitrogen dioxide (NO_2) exposure effects is derived from laboratory studies of asthmatics and from epidemiological studies. Additional supportive evidence is derived from animal studies.

Epidemiological studies using the presence of an unvented gas stove as a surrogate for indoor NO_2 exposures suggest an increased incidence of respiratory infections or symptoms in children.

Recent studies related to outdoor exposure have found health effects associated with ambient NO_2 levels, including respiratory symptoms, respiratory illness, and decreased lung function. However, since NO_2 exposure generally occurs in the presence of other pollutants, such as particulate matter, these studies are often unable to determine the specific role of NO_2 in causing effects.

The Children's Health Study in Southern California found associations of air pollution, including NO_2, PM_{10}, and $PM_{2.5}$, with respiratory symptoms in asthmatics (McConnell, 1999). Particles and NO_2 were correlated, and effects of individual pollutants could not be discerned.

Ambient levels of NO_2 were also associated with a decrease in lung function growth in a group of children followed for four years. In addition to NO_2, the decreased growth was also associated with particulate matter and airborne acids.

Results from controlled exposure studies of asthmatics demonstrate an increase in the tendency of airways to contract in response to a chemical stimulus (bronchial reactivity). Effects were observed with an exposure to 0.3 ppm NO_2 for a period ranging from 30 minutes to 3 hours. A similar response is reported in some studies with healthy subjects at higher levels of exposure (1.5 - 2.0 ppm). Mixed results have been reported when people with chronic obstructive lung disease are exposed to low levels of NO_2.

Short-term controlled studies of animals exposed to NO_2 over a period of several hours indicate cellular changes associated with allergic and inflammatory response and interference with detoxification processes in the liver. In some animal studies the severity of the lung structural damage observed after relatively high levels of short-term ozone exposure is observed to increase when animals are exposed to a combination of ozone and NO_2.

In animals, longer-term (3-6 months) repeated exposures at 0.25 ppm appear to decrease one of the essential cell-types (T-cells) of the immune system. Non-specific changes in cells involved in maintaining immune functions (cytotoxic T cells and natural killer cells) have been observed in humans after repeated exposure (4-6 days) to >0.6 ppm of NO_2 (20 min. - 2 hours). All these changes collectively support the observation reported both in population and animal studies of increased susceptibility to infections, as a result of NO_2 exposure.

SULFUR DIOXIDE

Controlled laboratory studies involving human volunteers have clearly identified asthmatics as the most sensitive group to the effects of ambient sulfur dioxide (SO_2) exposures. Healthy subjects have failed to demonstrate any short-term respiratory functional changes at exposure levels up to 1.0 ppm over 1-3 hours.

In asthmatics, brief exposure (10 minutes) to SO_2 at levels as low as 0.25 ppm can result in significant alteration of lung function, such as increases in airway resistance and decreases in breathing capacity. In some, the exposure can result in severe symptoms necessitating the use of medication for relief. The response to SO_2 inhalation is observable within 2 minutes of exposure, increases further with continuing exposure up to 5 minutes then remains relatively steady as exposure continues. SO_2 exposure is generally not associated with any delayed reactions or repetitive asthmatic attacks.

No significant changes have been reported from studies, which have evaluated the effects of exposure to co-pollutants (ozone or nitrogen dioxide), prior to or in conjunction with SO_2 exposure.

Animal studies have shown that despite SO_2 being a respiratory irritant, it does not cause substantial acute or chronic toxicity in animals exposed at ambient concentrations. However, relatively high exposures (10 ppm of SO_2 for 72 hours) in mice can lead to tissue damage, fluid accumulation and sloughing of respiratory lining. Sensitization to allergies is observable in guinea pigs repeatedly exposed to high levels (72 ppm) of SO_2. This effect needs further evaluation in clinical and population studies to identify any chronic exposure impact on both asthmatic incidence and attacks in a population.

Some epidemiological studies indicate that the mortality and morbidity effects associated with the fine fraction of particles show a similar association with ambient SO_2 levels. In these studies, efforts to separate the effects of SO_2 from fine particles have not been

successful. Thus, it is not clear whether the two pollutants act synergistically, or whether being generated from similar combustion sources they represent the same pollution index for the observed effects.

SULFATES

Based on a level determined necessary to protect the most sensitive individuals, the California Air Resources Board in 1976 adopted a standard of 25 $\mu g/m^3$ (24-hour average) for sulfates.

In recent years, a vast majority of effects (mortality and morbidity) associated with fine particles ($PM_{2.5}$) and sulfur dioxide have shown a similar association with ambient sulfate levels in some population studies. The efforts to fully separate the effects of sulfates from other coexisting pollutants have not been successful. This may be due to the fact that these pollutants co-vary under ambient conditions having been emitted from common sources and the effects observed may be due to the combination of pollutants, rather than a single pollutant.

Clinical studies involving exposure of human subjects to sulfuric acid aerosol (<100 $\mu g/m^3$) have indicated that adolescent asthmatics may be a susceptible population subgroup. Lung function changes (volume and resistance to airflow) are observable in this subgroup as well as in people with chronic obstructive lung disease such as chronic bronchitis and emphysema.

Results from animal studies involving exposures to sulfuric acid aerosol, ammonium bisulfate and ammonium sulfate indicate that acidic particles (former two) are more toxic than non-acidic particles (latter). In addition, the severity or magnitude of both mortality and morbidity effects is relatively higher in population studies of the eastern United States and Canada where sulfate concentrations are higher than for those observed in the western United States. Mixed results have been reported from studies which attempted to ascertain the role of acidity in determining the observed toxicity.

CONCLUSION

The vast body of scientific evidence shows that the adverse impacts of air pollution in human and animal health are clear. A considerable number of population-based and laboratory studies have established a link between increased morbidity and in some instances, earlier mortality and air pollution.

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