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Office of
HealthHazard
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STAFF REPORT

Adequacy of California Ambient Air Quality Standards: Children's Environmental Health Protection Act



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GLOSSARY OF TERMS

AAQS	Ambient Air Quality Standards
AQAC	Air Quality Advisory Committee
ARB	California Air Resources Board
CAD	Coronary Artery Disease
Cal/EPA	California Environmental Protection Agency
CO	Carbon Monoxide
COHb	Carboxyhemoglobin
H_2S	Hydrogen Sulfide
H_2SO_4	Sulfuric Acid
mg/m^3	milligrams per cubic meter of air
NO_2	Nitrogen Dioxide
NO_x	Oxides of Nitrogen
OCHP	Office of Children's Health Protection (U.S. EPA)
OEHHA	Office of Environmental Health Hazard Assessment
Pb	Lead
PM	Particulate Matter
PM2.5	Particulate matter equal to or less than 2.5 microns aerodynamic diameter
PM10	Particulate matter equal to or less than 10 microns aerodynamic diameter
ppb	parts per billion
ppm	parts per million
ROG	Reactive Organic Gases
SO_2	Sulfur Dioxide
SO_4	Sulfate
SO_x	Oxides of Sulfur
TAC	Toxic Air Contaminants
TOG	Total Organic Gases
TSP	Total Suspended Particles
U.S. EPA	United States Environmental Protection Agency
$\mu g/m^3$	Micrograms per cubic meter of air

1. Executive Summary

Under the Children's Environmental Health Protection Act (SB 25, authored by Senator Martha Escutia), the California Air Resources Board (ARB), in consultation with the Office of Environmental Health Hazard Assessment (OEHHA), is required, no later than December 31, 2000, to "review all existing health-based ambient air quality standards to determine whether, based on public health, scientific literature, and exposure pattern data, the standards adequately protect the health of the public, including infants and children, with an adequate margin of safety" (California Health & Safety Code section 39606(d)(1); see Appendix A) . This initial review is intended to: (1) examine the health protectiveness of each of the standards and (2) set priorities for more extensive review and possible revision of those standards not considered sufficiently protective of public health, especially with respect to infants and children.

The initial Children's Environmental Health Protection Act assessments were accomplished through critical reviews of recent health effects literature on each pollutant. The critical reviews were performed by well-recognized experts on each of the specific pollutants, including consultants from academia as well as from the staff of OEHHA. The pollutants reviewed are particulate matter with an aerometric diameter 10 microns or less in diameter, sulfates, ozone, nitrogen dioxide, carbon monoxide, hydrogen sulfide, sulfur dioxide, and lead. The standards for these pollutants are set forth in the Table of Standards in section 70200 of the California Code of Regulations, and are presented in Table 2.2.4-1 of this report, on page 14.

Five factors were considered in assessing the standards' health protectiveness and the need for further review:

(1) The extent of the evidence of effects reported to occur at or near the existing ambient air quality standard.
(2) The nature and severity of those effects.
(3) The magnitude of risk of effects anticipated to occur when ambient (outdoor) levels are at or near the level of the existing standard.
(4) Any evidence indicating that children may be more susceptible to effects than adults.
(5) The degree of outdoor exposure in California relative to the level of the standard.

The critical reviews indicate that health effects may occur in infants, children, and other potentially susceptible subgroups exposed to pollutants at or near levels corresponding to several existing California ambient air quality standards. Based on these factors, the pollutants fell into two tiers, the first representing greater potential risks to public health at the concentrations of the current air quality standards. The first tier includes particulate matter less than 10 microns in aerodynamic diameter (PM10), ozone, and nitrogen dioxide, with the recommended review priority in that order. Although California also has a separate standard for sulfates, this class of pollutants represents a subset of particulate matter, and should therefore be considered in conjunction with PM10. Recent scientific publications suggest that health effects may occur when ambient levels of these pollutants are at or near the current State ambient air quality standards. Key evidence for ranking these pollutants into the first tier is discussed below.

Recent epidemiological literature on PM10 suggests the potential for health effects in infants and children, including mortality, reduced birth weight, premature birth,

asthma exacerbation, and acute respiratory infections. Epidemiological studies suggest that increased mortality and hospital admissions among the elderly and those with chronic heart and lung diseases may also be associated with exposure to PM10. Almost everyone in California is exposed to levels at or above the current State PM10 standard during parts of the year. The review of PM10 should include an assessment of the sulfate standard as well, since sulfates are a component of particulate matter.
Epidemiological studies suggest effects of ozone exposure on lung function, asthma exacerbation, and other indices of acute respiratory morbidity in children and adults at ozone levels lower than the current State standard. A large segment of California's population is exposed to levels at or above the current State standard, primarily during daylight hours in the summer.

Several recent controlled exposure studies suggest indirect effects of nitrogen dioxide on allergic asthmatics (i.e., it may enhance the response to airborne allergens) when exposure levels are quite close to the existing standard. Allergy is a prominent feature of most childhood asthma and it is possible that there could be an impact on children. California has been in attainment of the ambient air quality standard for nitrogen dioxide since 1995; however, levels close to the standard are occasionally recorded at some sites.

The second tier includes lead, carbon monoxide, hydrogen sulfide, and sulfur dioxide. Exposure to lead has significant effects on the development of children's nervous systems, including impacts on intelligence and behavior. The scientific literature indicates that exposure to an airborne lead level at the current State standard would not be protective of the health of infants and children, and lead is currently listed pursuant to Health and Safety Code section 39657 as a Toxic Air Contaminant (TAC) with no safe threshold. However, exposures to levels of concern occur in a relatively small segment of the population since the statewide average lead level is well below the ambient air quality standard. Since there are few areas of the State where ambient lead is a concern, and since it will be regulated through the TAC control program, the review of the ambient air quality standard for lead is a low priority and it was not placed into the first tier.

Evidence from controlled exposure studies suggests that the existing State ambient air quality standards for carbon monoxide, hydrogen sulfide, and sulfur dioxide are reasonably health protective. However, some evidence from observational epidemiological studies suggests the potential for adverse health effects related to carbon monoxide and sulfur dioxide, including increased risks of hospitalization and premature mortality in the general population at relatively low ambient levels. In contrast, there is little evidence for effects in infants and children. Epidemiological studies suggesting effects attributable to these pollutants are complicated by their correlation with other traffic-related pollutants. Epidemiological studies of health effects associated with exposure to carbon monoxide are likely to be based on ambient measurements that bear little relationship to individual exposures. Moreover, for hydrogen sulfide and sulfur dioxide, ambient levels are very low relative to the standard throughout most of the State. In addition, the hydrogen sulfide standard received a lower priority for review since it is intended primarily to prevent odor annoyance and associated symptoms, outcomes that are clearly not as serious as those associated with pollutants ranked in the first tier. The prioritization of the criteria air pollutants in the second tier is subject to change, based on scientific evidence available at the time.

Our recommendations were presented for review and comment at public workshops on September 19, 2000, in Sacramento and on September 26, 2000, in Los Angeles. A public meeting of the Air Quality Advisory Committee (AQAC), OEHHA's external scientific peer review group for health-based ambient air quality standards, was held on October 12 and 13, 2000 in Oakland. (Further details are available at the ARB website (http://www.arb.ca.gov/ch/ceh/workshops.htm or by calling Joann Myhre at 916-327-2997). Transcripts of the AQAC meeting are available on the OEHHA website (http://oehha.org/air/toxic_contaminants/AQAC1.html) The AQAC has generally endorsed the recommendations provided in this report. The provisions of the Children's Environmental Health Protection Act require that review of the highest priority pollutant be completed by December 31, 2002. Review of other pollutants found to be insufficiently protective of public health with an adequate margin of safety will take place at the rate of one per year thereafter. Written comments on the recommended order for review of the ambient air quality standards may be addressed to Dr. Bart Ostro, Ph.D., Chief, Air Pollution Epidemiology Unit, Office of Environmental Health Hazard Assessment, 1515 Clay St., 16th Floor, Oakland, CA 94612 (bostro@oehha.ca.gov, 510-622-3150), or to Bart Croes, P.E., Chief, Research Division, Air Resources Board, PO Box 2815, Sacramento, CA 95612-2815 (bcroes@arb.ca.gov, 916-323-4519) prior to, or at the Air Resources Board public hearing, scheduled for December 7 and 8, 2000.

2. Environmental Protection of Children

2.1 Summary and Requirements of Children's Environmental Health Protection Act

The Children's Environmental Health Protection Act, (SB 25,authored by Senator Martha Escutia, Stats. 1999, Ch. 731, set forth in Appendix A) was approved by the Governor on October 7, 1999. The bill requires the California Air Resources Board (ARB), in consultation with the Office of Environmental Health Hazard Assessment (OEHHA), to review all existing health-based State Ambient Air Quality Standards (AAQS) by December 31, 2000, to determine whether the standards protect the health of the public, including infants and children, with an adequate margin of safety. This report provides the ARB with information and recommendations to make this determination. If there is uncertainty about the health-protectiveness provided by a standard or standards, the highest priority air quality standard must be revised no later than December 31, 2002. Following the revision of the highest priority standard, the ARB is directed to review, and if necessary, revise any additional standards where health protection, particularly for infants and children, may not be sufficient. Such reviews shall be completed at the rate of one standard per year. Any revision to a health-based standard will be based on the recommendation of OEHHA. Further, OEHHA is to take into account exposure patterns, special susceptibilities, and interaction of multiple pollutants on infants and children, including the interaction of criteria pollutants with toxic air contaminants, in making its recommendations.

To assist in reviewing the adequacy of the State's health-based ambient air quality standards, OEHHA entered into an interagency agreement with the University of California, Irvine, which developed agreements with recognized experts on particulate matter (PM), sulfate (SO_4), ozone (O_3), nitrogen oxides (NO_x), carbon monoxide (CO), and sulfur dioxide (SO_2). Each prepared a literature review assessing whether their assigned California ambient air quality standard provided an adequate margin of safety with respect to infants and children.

The pollutant reviews were conducted by the following researchers:

- Carbon monoxide - Michael Kleinman, Ph.D., University of California at Irvine
- Nitrogen dioxide - Mark Frampton, M.D., University of Rochester Medical Center
- Ozone clinical studies - John Balmes, M.D., University of California, San Francisco
- Ozone epidemiology studies - Ira Tager, M.D., University of California, Berkeley
- Particulate matter and sulfates - George Thurston, Sc.D., New York University
- Sulfur dioxide - Jane Koenig, Ph.D., University of Washington

OEHHA reviewed hydrogen sulfide (H_2S) and lead. OEHHA and ARB used these reviews and other scientific information in the assessment of the health-protectiveness of the standards and the setting of priorities for possible revision. This report was available for review and comment at two public workshops (September 19, 2000 in Sacramento and September 26, 2000 in Los Angeles) and at a meeting of the

Air Quality Advisory Committee, OEHHA's external peer review group for health-based ambient air quality standards (October 12 and 13, 2000, in Berkeley).

The Children's Environmental Health Protection Act further requires OEHHA, in consultation with the ARB, to establish by July 1, 2001, a list of five toxic air contaminants (TACs) that may cause illness especially to infants and children. The bill requires the ARB to review and, if appropriate, revise any control measures for TACs to reduce exposure to those toxic compounds (Health and Safety Code section 39669.5). The Children's Environmental Health Protection Act also creates the Children's Environmental Health Center within the California Environmental Protection Agency to advise the Secretary for Environmental Protection and the Governor on matters within the jurisdiction of the agency relating to environmental health and environmental protection as it relates to children (Health and Safety Code section 900).

The Children's Environmental Health Protection Act requires the ARB to expand its existing monitoring program in six communities around the State which are in non-attainment areas, and to conduct special monitoring to better assess children's exposure to air pollutants (Health and Safety Code section 39617.5). The ARB is to use this information to evaluate the adequacy of the current monitoring network for assessing children's exposure to air pollutants.

The initial tasks of the Children's Environmental Health Protection Act are to review the health-protectiveness of the standards and to set priorities for more extensive review and revision of those standards considered insufficiently protective of public health. This report addresses these initial tasks. The background information, the legal authority for setting ambient air quality standards, information on exposure to air pollutants, review of health-based information, and the basis for recommendations for priority standards to review is presented herein.

2.2 Ambient Air Quality Standards

2.2.1 Definition of Ambient Air Quality Standard

An "Ambient Air Quality Standard" (AAQS) represents the legal definition of clean air by specifying concentrations and durations of exposure to air pollutants that reflect the relationship between the intensity and composition of air pollutantion and undesirable effects (see Health and Safety Code section 39014). The AAQS's establish the maximum allowable levels of air pollutants.

2.2.2 National Ambient Air Quality Standards

Two provisions (sections 108 and 109 of the Federal Clean Air Act (42 USC section 7401 *et seq*.) govern the establishment, review, and revision of National Ambient Air Quality Standards (NAAQS). Section 108 directs the U.S. Environmental Protection Agency (U.S. EPA) to list pollutants that may reasonably be anticipated to endanger public health or welfare and to issue air quality criteria for them, hence the name "criteria air pollutants" to characterize those air pollutants for which there are ambient air quality standards. The air quality criteria ("Criteria Documents") are to reflect the latest scientific information useful in indicating the kind and extent of all exposure related effects on public health and welfare that may be expected from the presence of the pollutant in ambient air. Section 109 directs U.S. EPA to establish "primary" (health-based) and "secondary" (welfare-based) NAAQS for pollutants listed under section 108 and based

upon the information contained in the "Criteria Documents". More information on the NAAQS can be obtained at the U.S. EPA website at: http:/www.epa.gov.oar/oaqps/.

The Federal Clean Air Act also permits the states to adopt additional or more stringent air quality standards when they are needed to address local problems (see Clean Air Act section 116). California has vigorously exercised this option. California Ambient Air Quality Standards were established by the ARB in 1969, prior to the establishment of NAAQS. California's ability to set its own ambient air quality standards allows the State to respond more rapidly to new information regarding the effects of air pollutants on public health and welfare. It also allows the State to address situations and pollutants important or unique to California, but not as important or relevant to the national perspective.

An example which illustrates California's timely response to new scientific evidence is the State ozone standard of 0.09 ppm, averaged over one hour, which was set in 1987. The ARB acted to protect public health from injury to the respiratory system. The NAAQS of 0.12 ppm averaged over one hour was established in 1971 and not revised until 1997. The revised standard of 0.08 ppm for eight hours is pending review by the U.S. Supreme Court. Moreover, for some California standards, either the pollutant or the circumstances of exposure are not a nationwide problem. For example, the Lake Tahoe Air Basin carbon monoxide standard of 6 ppm for 8-hours is more protective than the general standard of 9 ppm for 8-hours because the high altitude of the area worsens the effect of carbon monoxide on the many visitors to this region.

2.2.3 State Ambient Air Quality Standards

California Health and Safety Code section 39606(b) authorizes the ARB to adopt standards for ambient air quality "in consideration of public health, safety, and welfare, including but not limited to health, illness, irritation to the senses, aesthetic value, interference with visibility, and the effects of air pollution on the economy". The objective of ambient air quality standards is to provide a basis for preventing or abating adverse health or welfare effects of air pollution (title 17, California Code of Regulations (Cal Code Regs.) section 70101).

Ambient air quality standards establish the maximum allowable levels of air pollutants deemed to be healthy. However, standards should not be interpreted as permitting, encouraging, or condoning the degradation of present air quality that is superior to that stipulated in the standards. The ambient air quality standards adopted by the Air Resources Board are to be achieved and maintained by rules and regulations – primarily emission limitations- established by the regional and local air pollution control and air quality management districts for stationary sources such as industrial smoke stacks, and by the State Board for vehicular (mobile) sources (ie., generally Health and Safety Code sections 39002, 40000, and 40001). OEHHA provides detailed analyses of the available health information for each criteria pollutant, and in conjunction with the Air Quality Advisory Committee (AQAC), OEHHA's peer review body, provides health recommendations for the standards (Health and Safety Code sections 39606 (a) and (b)). The current California Ambient Air Quality Standards and their health bases are set forth in 17 Cal. Code Regs. section 70200, and are summarized in Table 2.2.4-1.

During the adoption of a State AAQS, a number of factors are evaluated and reviewed by the ARB, OEHHA, AQAC, and the public. An important underlying premise of the AAQS evaluation process is to assure that sensitive sub-populations are protected

from exposures to levels of pollutants that may cause adverse health effects. For example, the one-hour standard for SO_2 of 0.25 ppm was adopted to protect exercising individuals with asthma. The standards for carbon monoxide (CO) in California were adopted to protect sensitive individuals with cardiovascular disease. Although many of the studies that were instrumental in supporting ambient air quality standards have incorporated sensitive sub-populations in their analyses, most have not specifically included infants or children. California has been in the forefront of studies involving the health effects on children exposed to air pollutants. Examples of these studies conducted in California are summarized in Appendix B.

Table 2.2.4-1. California Ambient Air Quality Standards and the primary health basis of the standard.

Pollutant [1]	Averaging Time	Concentration [2]	Health Effects Basis of Standard
Ozone (O_3)	1 Hour	0.09 ppm (180 $\mu g/m^3$)	Short-term exposures: Human clinical studies - decreases in lung function, and lung inflammation that are indicative of lung injury. Altered lung structure and changes in immune defense systems in animals. Long-term exposures: Community health (epidemiological) studies – Decrease in lung function in chronically exposed people. Animal studies - Altered lung connective tissue metabolism and altered pulmonary morphology.
Respirable Particulate Matter (PM10)	Annual Geometric Mean	30 $\mu g/m^3$	Epidemiological studies – Seasonal declines in lung function, especially in children.
	24 Hour	50 $\mu g/m^3$	Epidemiological studies – Excess deaths from short-term exposures and exacerbation of symptoms in sensitive patients with respiratory disease.
Carbon Monoxide (CO)	8 Hour	9.0 ppm (10 mg/m^3)	Human clinical studies – Chest pain (angina) in heart patients (decreased time before onset of angina in exercising heart patients). Decreased tolerance to exercise in persons with circulatory and lung disease. Impairment of central nervous system functions. Possible increased risk to fetuses.
	1 Hour	20 ppm (23 mg/m^3	
	8 Hour (Lake Tahoe)	6 ppm (7 mg/m^3)	Human clinical studies – Combined effects of altitude and CO resulting in increased angina in exercising heart patients.
Nitrogen Dioxide (NO_2)	1-Hour	0.25 ppm (470 $\mu g/m^3$)	Human clinical studies – Potential to aggravate chronic respiratory disease and respiratory symptoms in sensitive groups. Animal studies – Lung irritation and damage. Changes in lung cells (including cells associated with allergic and inflammatory responses) and biochemistry. Reacts in the atmosphere to form ozone and acid rain.
Lead (Pb)	30 days Average	1.5 $\mu g/m^3$	Epidemiological studies – Increased accumulation of lead in the body. Impairment of blood formation and nerve conduction.

Pollutant [1]	Averaging Time	Concentration [2]	Health Effects Basis of Standard
Sulfur Dioxide (SO_2)	**24 Hour**	**0.04 ppm (105 µg/m^3)**	**Epidemiological studies – Increased incidence of lung disease and symptoms, decreased lung function, and increased risk of death**
	1 Hour	**0.25 ppm (655 µg/m^3)**	**Human clinical studies – Bronchoconstriction (the narrowing of airways) in asthmatics accompanied by symptoms including wheezing, shortness of breath, and chest tightness during exercise or physical activity.**
Sulfates (SO_4)	**24 Hour**	**25 µg/m^3**	**Epidemiological studies – Decrease in lung function, aggravation of asthmatic symptoms, aggravation of heart and lung diseases.**
Hydrogen Sulfide (H_2S)	**1 Hour**	**0.03 ppm (42 µg/m^3)**	**Human clinical study - Odor nuisance (rotten egg smell). Limits, but does not prevent, odor nuisance.**

1. California standards for O_3, CO (except Lake Tahoe), SO_2 (1 and 24 hour), NO_2, and PM10 are values that are not to be exceeded. California ambient air quality standards are listed in the Table of Standards in section 70200 of the California Code of Regulations.

2. Concentration expressed first in units in which it was promulgated. Equivalent units given in parentheses are based upon a reference temperature of 25 degrees C and a reference pressure of 760 mm of mercury. Most measurements established at 1,013.2 millibar; ppm in this table refers to ppm by volume, or micromoles of pollutant per mole of gas.

3. Exposure to Air Pollutants

3.1 Introduction

Exposure to air pollutants occurs when we breath the air around us. Important factors that determine the degree of exposure are “when”, “where”, and “how long” air pollutants are inhaled. Individual behavior of where we are during the day can influence our exposure and can be different for children and adults. For example, during the summer and midday when certain air pollutant concentrations are at their seasonal and daily high, children may spend a longer time outdoors than adults. During the school year, the majority of school age children spend most of their time in the classroom, childcare facility, and on the playground. Children also participate in sports activities after school. Susceptible sub-population groups such as the elderly with medical conditions often stay inside their homes. Since exposure to air pollutants can take place throughout the day in any environment and can cause adverse health effects at certain levels, the airborne concentrations of these pollutants are routinely measured throughout the State.

To provide an introduction to air quality issues and an overview of air pollutant concentrations in California, we discuss in the following sections information on ambient air quality, pollutant sources in California, monitoring, and indoor and personal exposure.

3.2 Ambient Air Quality

Outdoor (ambient) air pollutant concentrations are measured in the State over time intervals that are pertinent to protect the public from potential adverse health effects. For example, a one-hour average concentration for SO_2 was adopted to protect sensitive individuals with asthma.

This monitoring, or regular measurement of pollutants in community air, allows determination of the quality of the air we breathe, and further allows determination of which geographic areas within California are meeting (in compliance with) the standards. If an area is not in compliance, the monitoring information will show by how much and how frequently the standards have been exceeded. Each year, more than ten million air quality measurements are collected from over 200 monitoring sites located throughout California and are stored in a comprehensive database maintained by the ARB called ADAM (Aerometric Data Analysis and Management). ADAM is capable of processing interactive data queries of the entire California database in several formats, including the four highest values and number of days above the standards for O_3, PM10, fine particles, CO, SO_2 and NO_2. ADAM can be accessed at: www.arb.ca.gov./adam. A summary of air pollutant concentrations and days exceeding the State standard are described in the next section.

3.3 Ambient Air Quality Summaries

Summaries of selected California ambient air quality data for major populated air districts are presented for 1999 in Table 3.3-1. The maximum concentrations of air pollutants, and the number days exceeding the standards, are provided for each district. PM10 has the greatest number of days exceeding the 24-hour standard of 50 $\mu g/m^3$. For example, the South Coast district exceeded the standard for 258 days during 1999, and the San Joaquin Valley district exceeded the standard for 174 days. The maximum 24-

hour average PM10 concentration recorded for each of these districts was 183 $\mu g/m^{3.}$ The South Coast, San Joaquin Valley, and San Diego districts had maximum PM10 annual geometric mean concentrations of approximately 65, 50, and 48 $\mu g/m^3$, respectively, all of which exceeded the annual standard of 30 $\mu g/m^3$. The Bay Area Air Quality Management District and Lake County (not shown in Table 3.3-1) did not exceed the annual PM10 standard for 1999.

Statewide, there are a number of days each year during which the ozone concentration exceeds the standard (0.09 ppm for 1 hour). For example, the South Coast district exceeded the standard for 111 days, and the San Joaquin district exceeded the standard for 122 days. The maximum 1 hour concentration for ozone recorded in the South Coast district was 0.174 ppm.

Nitrogen dioxide, sulfate, and sulfur dioxide, generally do not exceed the standard, and were not exceeded in 1999. Los Angeles County and Calexico each had several exceedances of the CO standard. Information on air quality including statewide trends, emissions, and sources for each pollutant spanning the period from 1980 through 1999 are summarized in Appendix B of this report. Additional information regarding air quality data can be reviewed at the ARB worldwide website at: http://www.arb.ca.gov/aqd/aqd.htm

3.4 Pollutant Sources in California

Air pollutants can be classified as being directly emitted from sources (referred to as "primary air pollutants"), or formed in the atmosphere by chemical reactions between sunlight and the compounds directly emitted from sources (referred to as "secondary air pollutants"). Examples of air pollutants that are directly emitted include CO, NO_x, SO_x, and PM. An example of an air pollutant that is formed in the atmosphere is ozone, the formation of which involves a complex set of chemical reactions between hydrocarbons, oxides of nitrogen, and sunlight. The peak level of ozone is detected near midday, for example, and reflects the timing of these concentration-dependent photochemical reactions. There are also chemical reactions that take place during the night in the absence of sunlight-dependent chemistry. The typical smog in Los Angeles and other metropolitan areas is a complex mixture of primary and secondary air pollutants.

Primary pollutant sources in California can be classified into four major categories:

- Stationary - fixed-site establishments such as those having emission stacks.
- Area – widespread sources such as road dust, consumer products, and landfills.
- Mobile – cars, trucks, trains, boats, etc.
- Natural – windblown dust, wildfires and other non-anthropogenic sources.
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To estimate the sources and quantities of air pollutants, the ARB, in cooperation with local air pollution control districts and industry, maintains an emission inventory of California emission sources. Total amounts of air pollutants that are emitted (usually reported as tons per day) from specific source types are calculated. Emission values for individual air pollutants and their sources are presented in Appendix C.

Emissions data are important in an air pollution control program. Developing statewide, regional, and neighborhood emissions inventories identifies the sources contributing to air pollution, quantifies the mass emissions for each source type, and provides information concerning the public's exposure to air pollution.

Additional information regarding air pollutant sources and emissions in California can be reviewed at the ARB worldwide website at: http://www.arb.ca.gov/emisinv/eib.htm.

3.5 Monitoring

Monitoring for ambient air quality includes measurement of airborne pollutant concentrations that results in development of a long-term database. The instrumentation used for monitoring is generally placed near locations where people live and work, but also can be placed near emission sources. Some of the important factors to consider when monitoring include: 1) the population exposed to the specific air pollutant, 2) the frequency of monitoring in relation to the averaging time of the standard, and 3) the placement of the monitoring instrumentation consistent with the monitoring objective. The latter is especially important with respect to measuring exposure to infants, children and other susceptible populations.

Additional information of the ARB monitoring program or monitoring information as it specifically relates to the Children's Environmental Health Protection Act can be accessed on the worldwide web at: www.arb.ca.gov/ch/ceh.htm.

3.6 Indoor and Personal Exposure

Indoor exposures to air pollutants are important in assessing health risks because we spend considerable amounts of time indoors and the concentration of pollutants indoors can be higher or lower than ambient levels. The results of studies of adults and children in California and the percent time spent in various locations are summarized in Table 3.6.1. Children (0-11 years old) spend approximately 86% of their time in indoor environments (including activities of sleeping, eating, classroom learning, and playing, for example), and spend a greater time outdoors than adults. About 70% of the total time that these children spend outdoors occurs between noon and 8 p.m. The home environment is especially important for sensitive groups of the population, such as infants, toddlers, and the elderly because they spend a substantial portion of their time indoors at home.

For many pollutants, indoor levels are elevated due to sources located indoors, the trapping effect of buildings, and re-emission, re-suspension, or reactivity of pollutants previously emitted into the indoor environment. Important indoor sources for air pollutants include combustion appliances such as gas stoves and space heaters that emit CO, NO_2, and PM10.

Personal exposure to air pollutants is the measurement of concentrations near a person's breathing zone over a certain period of time, and is an indicator of individual exposure to pollutants. Individual activities and behavior may elevate exposure relative to levels typically measured at established monitoring sites. This is a consideration when evaluating exposures to air pollutants for susceptible populations including infants and children, and is further addressed in the Children's Environmental Health Protection Act.

Table 3.6-1. Percent time spent in different environments [1]

(Californians, population averages)

	Infants 0-2 years	Children 3-5 years	Children 6-11 years	Adolescents and Adults (12 and older)
Indoors at Home	**85%**	**76%**	**71%**	**62%**
Other Indoor	**4%**	**9%**	**12%**	**25%**
Inside Vehicles	**4%**	**5%**	**4%**	**7%**
Outdoors	**6%**	**10%**	**13%**	**6%**

[1] From: Wiley et al., 1991; Jenkins et al., 1992.

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4. OEHHA Summary of Air Pollutant Assessments

4.1 Summary and Guidelines for Evaluation

4.1.1 Summary

Under The Children's Environmental Health Protection Act, the California Air Resources Board (ARB), in consultation with the Office of Environmental Health Hazard Assessment (OEHHA), is required by December 31, 2000, to "review all existing health-based ambient air quality standards to determine whether, based on public health, scientific literature, and exposure pattern data, the standards adequately protect the health of the public, including infants and children, with an adequate margin of safety" (Health & Safety Code section 39606(d)(1)). To assist the ARB in fulfilling this legislative mandate, OEHHA has undertaken a critical literature review for the pollutants governed by health-based ambient air quality standards: carbon monoxide, hydrogen sulfide, lead, nitrogen dioxide, ozone, sulfur dioxide, particulate matter (measured as PM10, or particulate matter with mean aerodynamic diameter less than 10 microns), and sulfates. This initial review was intended to: (1) examine the health-protectiveness of each of the standards, and (2) prioritize for more extensive review and revision those standards considered insufficiently protective of public health, including infants and children.

Our review indicates that health effects may occur in infants, children, and other potentially susceptible subgroups exposed to several pollutants at or near levels corresponding to existing California ambient air quality standards. We categorized the pollutants into two tiers, based on our assessment of potential risks to public health. The first tier includes PM10, ozone, and nitrogen dioxide. Although California also has a separate standard for sulfates, this class of pollutants represents a subset of particulate matter, and should therefore be considered in conjunction with PM10. The second tier is comprised of pollutants for which there is weaker and more uncertain evidence that exposures at or near the levels of the current California ambient standards may cause adverse effects in the most susceptible populations, or which are adequately controlled under other regulatory programs. This pollutant group includes lead, carbon monoxide, sulfur dioxide, and hydrogen sulfide. Based on the evidence for effects that may occur with exposures at or near the levels of the current standards, the severity of the effects, the degree of current exposure, and the possible effects on children, OEHHA staff believe that PM10 should be prioritized as the first pollutant to be reviewed for possible revision.

4.1.2 Guidelines for Assessing Health Protectiveness of Ambient Air Quality Standards and for Prioritization of Review

Bearing in mind that the overarching goal of this review has been to protect public health, particularly for infants and children, this section provides a description of the criteria used by OEHHA staff in making these assessments, as well as judgments for prioritization. The specific information utilized during this process included the following: (1) the extent of the evidence of effects reported to occur at or near the existing ambient air quality standard; (2) the nature and severity of those effects; (3) the level of risk of effects anticipated at or near the level of the existing standard; (4) whether there is evidence indicating that infants and/or children may be more susceptible than adults; and (5) the degree of exposure in California relative to the level of the standard. These are described in greater detail below. With respect to the initial assessment of the standards' health-protectiveness, the principal focus was on guidelines (1), (2) and (4), while all five factors entered into decisions regarding priority for

further review and revision. During this initial SB25 review, OEHHA staff found that several ambient pollutant standards were candidates for more extensive evaluation. In each instance, research findings suggested the potential for the occurrence of adverse health effects among sensitive populations, including infants and children, in relation to exposures that might occur at or near the level(s) of the existing standard(s).

4.1.2.1 Evidence of effects reported at or near the existing standard

The primary consideration in this review by OEHHA staff has been whether there is evidence of effects reported in either animal or human studies when exposures to the pollutant of concern have been at or near the existing California ambient air quality standard for that pollutant. In general, we accorded greater weight to studies involving humans (controlled exposures and epidemiological investigations) than to toxicological studies of experimental animals. Pollutants governed by ambient air quality standards typically have been extensively studied for their effects in humans, unlike the pollutants designated as toxic air contaminants. We also examined the quality and quantity of data indicating that there might be an inadequate margin of safety to protect against the occurrence of adverse effects. As a starting point for this review, OEHHA obtained assessments of the scientific literature from several experts (see Appendix D). All other things being equal, the more extensive the database suggesting the potential for adverse health effects from exposure to a given pollutant at the level of the current standard, the higher the priority that pollutant received.

4.1.2.2 Nature and severity of effects

This aspect of the process involved consideration of the severity of the adverse effects associated with various pollutant exposures. All of the pollutants subject to ambient standards in California are capable of causing severe injury and death from high-level exposures. However, our review focused on adverse effects likely to occur upon exposure to concentrations at or near existing standards or current ambient concentrations. Such exposures have been linked with a spectrum of effects ranging from premature mortality (PM10) to odor annoyance and discomfort (H_2S). Decisions about the severity of effects are clear-cut at the extremes, but are less so for intermediate outcomes, such as increased daily reporting of asthma symptoms versus, for example, small decrements in lung growth in nonasthmatic children. Reversibility of effect also entered into these deliberations. In assessing the severity of effects, we were guided in part by the recent revision of the American Thoracic Society's position paper on "What Constitutes an Adverse Health Effect from Air Pollution?" (Samet et al., 2000). Ultimately, however, decisions regarding the relative weighting of the severity of "intermediate" health impacts was a matter of informed, professional judgement. Clearly, those exposures considered to contribute to premature mortality would be given higher priority than those thought to increase the risk of rhinitis.

4.1.2.3 Magnitude of risk anticipated at the level of the current standard

Another criterion relied upon by OEHHA staff was the magnitude of risk expected if people were exposed to a given pollutant at the level of the existing standard. This represents two factors -- the anticipated increment in the level of risk and the background risk faced by the general population or an identifiable susceptible subpopulation. The greater the magnitude of risk (represented in epidemiological studies, for example, by the relative risk), the higher the ranking that pollutant would theoretically receive. However, if the background or baseline level of occurrence of that outcome were extremely uncommon, this would tend to decrease the priority assigned to that pollutant. In general, this criterion played less of a role than the others, because the levels of risk for the relevant effects of most of the pollutants examined were generally of similar magnitude.

4.1.2.4 Evidence indicating that children may be more susceptible than adults

Evidence of susceptibility in children was also an important factor considered in this review, consistent with one of the principal objectives of The Children's Environmental Health Protection Act, that is, the protection of the health of children and infants. Therefore, our review focused particularly on both the exposure patterns and potential susceptibility of children to the pollutants under study. In evaluating the toxicological and epidemiological evidence, the existence of studies suggesting potential effects among infants and children resulted in a higher priority consideration for a given pollutant.

In this regard, Appendix F summarizes some of the important exposure and physiological differences between adults and children that may affect susceptibility to the toxicity of ambient pollutants. Developmental differences, in particular, increase the difficulty in examining potential risks to children in toxicological studies. For instance, there may be a critical window of time during which a given exposure may result in no obvious immediate toxicity, but may produce significant chronic effects, which are not manifested for many years. During the interim, other risk factors may be present, thereby making it difficult to isolate the influence of any single exposure. Moreover, there may be no appropriate animal models for the effects in question, or inter-species differences in the stages of development may render examination of relative age-dependent toxicities uncertain, at best.

In epidemiological studies of the relationships between ambient air pollution and children's health, short-term effects of acute exposure (e.g., school absenteeism, the occurrence of respiratory symptoms) are less problematic. However, in epidemiological studies of chronic exposure, the identification of developmentally significant exposures represents a significant challenge. Despite these obstacles in examining children's susceptibility, however, the reviewers' critical examination of the most relevant published literature revealed important research findings bearing on these issues. Such findings have been taken into account in the priority weightings for the various pollutants.

4.1.2.5 Degree of exposure relative to the level of the standard

Recent air quality monitoring data also played an important role in this review. Widespread exposures occurring at or near the current standard for any candidate pollutant were given greater priority weighting than ambient concentrations well below the standard. To the extent that current State ambient concentrations already provide a *de facto* margin of safety for any pollutant, even if the corresponding standard itself does not, that pollutant was given a lower priority ranking. Lead provides an illustrative example. Though we considered the neurodevelopmental effects of lead in young children to be serious adverse outcomes at the level of the existing standard, current exposures in most of California are nearly an order of magnitude lower than the standard, largely because of highly successful control measures implemented years ago, including the elimination of leaded gasoline as a conventional motor vehicle fuel. Information on current and historical ambient concentrations can be obtained at the ARB website (http://www.arb.ca.gov/aqd/aqd.htm).

The above factors were applied as guidelines, not rigid criteria, in arriving at the assessments of health-protectiveness and the priorities for more extensive review. Given the time constraints on this process, OEHHA staff believed that a formal, decision-analytical framework was neither feasible nor likely to have produced markedly different results. As is true of all aspects of this report, OEHHA's recommendations regarding priorities for more extensive review have been subject to peer review of outside experts.

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4.2 Summaries of Air Pollutant Assessments

4.2.1 PM10

4.2.1.1 Summary

The review of the scientific literature on PM10 (particulate matter less than 10 microns in diameter) indicates that adverse health effects resulting from exposure to ambient PM10 could occur when ambient concentrations are near or below the current State standards of 30 $\mu g/m^3$ (annual average) and 50 $\mu g/m^3$ (24-hour average). PM10 is a heterogeneous mix consisting of both fine particles (PM2.5 or particles less than 2.5 microns in diameter) and coarse particles (2.5 to 10 microns in diameter). Fine particles result from fuel combustion (from motor vehicles, power generation, and industrial facilities), residential fireplaces and wood stoves, and agricultural burning. They can also be formed in the atmosphere from gases such as sulfur dioxide, nitrogen dioxide and volatile organic compounds. Coarse particles are generally emitted from sources such as windblown dust, unpaved roads, materials handling, and crushing and grinding operations. The PM10 standard is often exceeded throughout the State.

The review suggests several factors that may render children and infants more susceptible to PM10, including a greater amount of time spent outdoors, greater activity levels and breathing rates, higher doses per body weight and lung surface area, and potential irreversible effects on children's developing lungs. A large body of epidemiological studies indicates an association between current ambient concentrations of PM10 and a suite of adverse outcomes including changes in lung function, respiratory symptoms, asthma exacerbation, doctor visits, emergency room visits, hospital admissions, and premature mortality. The more severe outcomes are experienced primarily by the elderly and by people with pre-existing chronic heart or lung disease. However, several epidemiological studies suggest that children under age 5, and possibly under age 1, may also experience adverse responses from exposure to PM10. Studies have found association between PM10 and changes in lung function, asthma, respiratory symptoms, doctor visits, and premature mortality in this subgroup. A threshold concentration, below which no effects are observed, has not been demonstrated for these outcomes. The precise particle size(s) and biologically active constituents within PM10 are uncertain. Therefore, the review of the PM10 standard, which is assigned a high priority, should also examine the effects of subspecies such as fine and coarse particles.

4.2.1.2 Review of the health assessment

Beginning with the London smog episodes in the 1950s, the quantification of adverse health effects of particulate matter (PM) have been well documented, with evidence provided primarily from the epidemiological literature, as summarized by the U.S. Environmental Protection Agency (U.S. EPA, 1995, 1998). Over the last decade, over 100 studies have been published suggesting associations between various measures of PM and a large suite of adverse outcomes. Many of these studies indicate that the elderly and those with chronic heart and lung conditions are particularly susceptible to PM10. However, there is evidence to suggest that children may constitute another group that is particularly vulnerable to exposure to ambient PM10. Specifically, children spend more time outdoors and are more active than adults. When indoors, children's personal exposures to PM10 appears to be more than twice as high as that of adults, possibly due to the "personal cloud" effect (Janssen et al., 1998). Lung deposition of PM10 (in μg/day) may be slightly lower for children under age 14 relative to older adolescents and adults, but is higher when adjusted for body weight and lung surface

area. Finally, there is limited experimental and epidemiological information suggesting that the early post-neonatal period of lung development is a time of high susceptibility for irreversible effects on lung growth associated with injury from exposure to environmental toxicants. This may be because this period is a time of rapid development of the respiratory system.
There is a large body of literature on the effects of particle exposure in animal models. This work has aided our understanding of the size distribution, composition, and deposition patterns that contribute to the injury observed with particle exposure.

Epidemiological studies have reported associations of PM10 or other measures of PM with premature mortality, hospital admissions for cardiovascular and respiratory conditions, emergency room and unscheduled physician visits, asthma exacerbation, respiratory symptoms and reductions in lung function. The long-term mean concentrations in a number of these studies have been below the current State annual average standard of 30 $\mu g/m^3$ PM10. For example, in its last review of the Federal PM standard, the U.S. EPA (1996) used three different approaches to help determine possible cutpoints, or levels of concern in PM concentrations: the lower limit of detection, the minimum mean concentration, and the visual interpretation. Though they indicate there is little evidence of a threshold from a population exposure point of view, these approaches point to a range of 20 to 40 $\mu g/m^3$ PM10 based on short-term exposure studies, and 24 to 32 $\mu g/m^3$ based on long-term exposure studies. For example, recently Schwartz (2000) reported an association between PM10 and mortality among persons 65 years of age and older in 10 U.S. cities collecting daily PM10 concentrations. Mean PM10 over an eight-year period ranged from 27 to 41 $\mu g/m^3$.

Among the many epidemiological studies published on PM10 health effects, several demonstrate effects at lower levels. For example, associations between PM10 and hospital admissions for respiratory disease have been reported at ambient concentrations near the current California annual average standard including Schwartz (1995) in Tacoma (mean 24-hr average PM10 concentration = 36 $\mu g/m^3$), Schwartz (1994) in Minneapolis (mean 24-hr average PM10 concentration = 36 $\mu g/m^3$) and Bremner et al. (1999) in London (mean 24-hr average PM10 concentration = 29 $\mu g/m^3$). Associations between cardiovascular hospital admissions and relatively low concentrations of PM10 were reported by Schwartz (1999) for eight U.S. counties. Sheppard et al. (1999) reported an association between asthma hospital admissions and PM10 in Seattle (mean 24-hr average PM10 concentration = 27 $\mu g/m^3$). Associations between PM10 and adult asthma symptoms at relatively low ambient concentrations have been reported by Ostro et al. (1991) in Denver (mean 24-hr average PM10 concentration = 22 $\mu g/m^3$). Finally, associations between low concentrations of PM10 and decrements in lung function have been reported by Timonen and Pekkanen (1997) and Vedal et al. (1998) in Finland (mean 24-hr average PM10 concentration = 18 $\mu g/m^3$), and British Columbia (median 24-hr average PM10 concentration = 22 $\mu g/m^3$), respectively. The studies cited above relating PM10 to increased mortality and hospital admissions primarily reflect effects on the elderly or people with chronic heart or lung conditions. However, they may also include, to a lesser extent, impacts on children and infants, as well.

Studies specifically involving children below age 14 suggest small reductions in lung function, exacerbation of asthma, and increased medical or hospital visits associated with PM10 or PM in general (U.S. EPA, 1998). For example, among studies conducted using U.S. data, short-term exposure to PM10 has been associated with asthma exacerbation in Los Angeles (Ostro et al., 1995), cough among non-asthmatic children (Schwartz et al., 1994), and lung function (Hoek et al., 1998). In addition, several studies have reported effects on children resulting from chronic exposure to PM. For example, in a study conducted in southern

California, associations have been reported between PM10 and both measures of lung function and exacerbation of asthma in children (Peters et al, 1999; McConnell et al., 1999). Long-term exposure to PM10 has also been associated with both decrements in lung function and increased bronchitis in children (Raizenne et al., 1996; Dockery et al., 1989).

In a large, longitudinal study in Southern California funded by the Air Resources Board (the Children's Health Study, a copy of which is attached in Appendix B), several measures of particulate matter have been recently reported to be associated with diminished lung function growth (Gauderman et al. 2000). During a four-year period, significant deficits in several measures of lung function were found to be associated with PM10, PM2.5, and PM10-PM2.5 (the coarse fraction), as well as with nitrogen dioxide and acid vapors. These associations were statistically significant for children who were in the fourth grade at the outset of the study, but not for older children and adolescents who entered the study in seventh or tenth grade. The effects appeared to be generally larger for those who spent more time outdoors, enhancing the likelihood of a causal association. Because the gaseous and particulate pollutants were so highly correlated over the study period, however, it was not possible to identify which pollutants were responsible for the observed deficits in lung function growth.

In addition, both time-series using short-term exposure and cross-sectional studies incorporating longer-term exposure demonstrate associations between PM and adverse outcomes in young children and infants. Most of these time-series studies, indicating a mortality effect, have been conducted outside of the United States in cities such as Mexico City and Bangkok, Thailand, which have mean and peak concentrations of PM much higher than those observed in the U.S. Cross-sectional studies of the impact of PM on infant health have also been conducted primarily on data from outside the U.S. and include effects such as infant mortality, low birth weight and gestational age, and sudden infant death syndrome. As for the other outcomes listed above, no study has provided evidence of a threshold concentration below which these outcomes would not occur.

Taken together, the available evidence suggests that significant adverse health effects may occur among both children and adults when ambient PM10 concentrations are at or near the current State standards. This conclusion is based primarily on the results of numerous epidemiological studies conducted throughout the world, which (despite local differences in pollutant sources and co-pollutants) produce a picture of remarkable consistency. However, the role of particle size and the identification of the biologically active constituents of PM10 are unknown, as are the biological mechanisms of action. In addition, the chemical and size distributions in California are quite different from those found in other parts of the U.S. During a formal review of the standard, these issues will be examined.

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4.2.2 Sulfates

4.2.2.1 Summary

The review of the scientific literature on sulfates indicates that clinically significant effects may occur when ambient sulfate concentrations are below the current State standard of 25 $\mu g/m^3$ (24-hour average). The review suggests several factors that may render children more susceptible to sulfates, including greater amounts of time spent outdoors and greater activity levels. Many epidemiological studies suggest that children may experience adverse responses from exposure to current ambient concentrations of sulfates, including changes in lung function, respiratory symptoms, asthma exacerbation, hospital admissions, and premature mortality. In addition, since sulfates are constituents of PM10 and the fine particulate mode (i.e., particulate matter < 2.5 microns in diameter), the health effects attributed to exposure to these measures of particulate matter may also be applicable to sulfates (See section 4.2.1). A threshold for these effects has not been demonstrated for sulfates. Since sulfates are a subspecies of PM10, the sulfate standard should be reviewed along with the PM10 standard and afforded a high priority.

4.2.2.2 Review of the health assessment

Sulfates are generally defined as the atmospherically transformed products of sulfur dioxide, including strong acids and sulfate salts. Although both clinical and epidemiological studies have been conducted on sulfates, the strongest evidence of an effect is provided by several dozen epidemiological studies suggesting an association between sulfates, broadly defined, and several adverse health outcomes. However, the sulfate ion itself may not be a causal factor in these associations since ambient sulfate concentrations are a measure of several compounds, including strong acids such as sulfuric acid and, more commonly, ammonium bisulfate. These acidic aerosols are often represented in epidemiological studies by strong acid hydrogen ion (H+).

Generally, controlled clinical studies of various sulfates have not detected significant respiratory effects at concentrations near the current ambient standard. However, there is evidence from these studies to indicate that, at high concentrations, strong acids produce functional and structural changes in the human respiratory system, including decrements in lung function, slowing of mucociliary clearance, increased airway responsiveness and respiratory symptoms (Lippmann and Thurston, 1996). These studies indicate that healthy subjects experience only modest changes in respiratory mechanics following single exposures to sulfuric acid at levels orders of magnitude (500 – 1,000 $\mu g/m^3$) above the current standard. Asthmatics appear to be more sensitive than healthy subjects to the effects of acid aerosols, but the effective dose (concentration x duration x ventilation rate) differs widely among available studies. Generally, asthmatic subjects experience modest bronchoconstriction after exposure to 400 – 1000 $\mu g/m^3$ of sulfuric acid. In addition, there is some evidence that adolescent asthmatics may be more sensitive than adults. For example, mild bronchoconstriction was reported after short exposures to as low as 68 $\mu g/m^3$ sulfuric acid in exercising adolescent asthmatics and 90 $\mu g/m^3$ in exercising adult asthmatics, although other researchers have not found effects at such low levels of exposure. Several studies have failed to find effects in asthmatics (U.S. EPA, 1996).

Available epidemiological evidence for sulfates suggests associations with premature mortality, primarily among the elderly and those with chronic heart or lung disease, from both daily (Schwartz et al., 1996; Gwynn et al, 2000) and long-term (over several years) exposure (Dockery et al., 1993; Pope et al., 1995). The mean ambient sulfate concentrations in the two

short-term exposures were both around 6 $\mu g/m^3$, while the mean concentrations in the two multi-city long-term studies ranged from 5 to 13 $\mu g/m^3$ and 4 to 24 $\mu g/m^3$, respectively. Associations have been reported between sulfates and hospital admissions for respiratory disease (Gwynn et al, 2000; Thurston et al., 1994; Burnett et al. 1994), asthma exacerbation in children and nonasthmatic respiratory symptoms (Ostro 1990; Ostro et al., 1991), and bronchitis in children (Dockery et al., 1996). In all of these cases, the mean 24-hr sulfate concentration was well below 25 $\mu g/m^3$.

Since sulfate is included within the fine particulate mode (i.e., < 2.5 microns in diameter or PM2.5), the health effects attributed to exposure to PM2.5 mass may be extended to sulfates, unless only the nonsulfate portion of PM2.5 is biologically active. In many parts of the country, sulfates appear to constitute 50% of the PM2.5 mass. PM2.5 has only recently been monitored on a regular basis, but typically is highly correlated with PM10. This relationship and the fact that more of the smaller particles will penetrate into the deep lung, have led many to speculate that the health effects associated with PM10 in epidemiological studies may be driven by PM2.5 (U.S. EPA, 1996b). Thus, potential effects of sulfates may be inferred not only from those studies in which these substances have been directly measured, but also from studies using PM2.5 (and indirectly, from those studies using PM10) as the particulate exposure metric.

There is also a wide array of adverse health outcomes attributed to PM2.5, which may have implications for exposure to sulfates. Among the more severe outcomes is premature mortality from both short-term (Schwartz et al., 1996) and long-term exposure (Pope et al., 1995; Dockery et al., 1993). For cities included in these studies, the annual average of PM2.5 ranged from 9 to 34 $\mu g/m^3$. Again, these findings apply primarily, although not exclusively, to the elderly and those with chronic heart or lung conditions. PM2.5 has also been directly associated with increased respiratory symptoms and decreased lung function (U.S. EPA, 1996b). The mean PM2.5 concentration for these studies ranged from 11 to 30 $\mu g/m^3$. In a study conducted in Santa Clara County, California, Fairley (1999) found associations between PM2.5 and mortality at a mean concentration of 13 $\mu g/m^3$. Among the morbidity effects, an association between PM2.5 and emergency room visits for children was reported for Seattle, with a mean PM2.5 concentration of 12 $\mu g/m^3$ (Norris et al, 1999).

It is unclear why epidemiological studies appear to find several different adverse effects associated with exposure to current ambient concentrations of sulfates, while human clinical studies fail to find such effects. This may be a result of self-selection in the clinical studies as well as deliberate exclusion of potentially susceptible subjects, such as poorly controlled asthmatics, young children, and individuals with severe heart or lung disease. In addition, the effective doses used in the clinical studies may be insufficient to trigger a response in the (basically healthy) or the studies may be underpowered. It may also be the case that in epidemiologic studies sulfates are only a surrogate for some other, correlated component of PM10.

There is also evidence for an interactive effect of sulfates and other pollutants. For example, in a toxicological study of rats exposed to a concentration mixture of ozone and sulfuric acid-coated carbon particles (0.2 ppm, and 50 $\mu g/m^3$, respectively), Kleinman et al. (1999) found that exposure to ozone and sulfuric acid-coated particles generated an inflammatory response that was greater than the response to either pollutant alone. In addition, in a human chamber experiment with asthmatic subjects, Frampton et al. (1995) found that prior exposure to 100 $\mu g/m^3$ sulfuric acid aerosol may enhance the subsequent

response to ozone (at 0.08 ppm) in adult asthmatics. Though the relevance of these studies to effects that might occur at current ambient conditions is uncertain, they suggest that exposure to sulfuric acid (and possibly other sulfates) may heighten the impact of subsequent exposure to other pollutants.

Taken together, the available evidence from sulfate studies, as well as those using PM2.5 mass as the measure of exposure to PM, suggests the possibility of significant health effects below the current State standard for sulfates. However, since sulfates are a component of both PM2.5 and PM10, the necessity for an independent sulfate standard in California should be examined within the context of the review of the PM10 standard, which may have implications for establishing a standard for smaller sized particles such as PM2.5. An appropriately designed PM standard should provide protection from exposure to sulfates, as well.

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4.2.3 Ozone

4.2.3.1 Summary

The review of the scientific literature on ozone indicates the potential for biologically significant effects when exposure concentrations are at or below 0.09 ppm (the current State standard (1-hr average)). The review suggests several factors that may render children and young adolescents more susceptible to ozone exposure, including activity and exposure patterns, higher doses per unit of body weight and lung surface area, and the potential for effects on lung growth and development. Controlled exposure studies, which have mainly been conducted with adult subjects, indicate that multi-hour ozone exposures at concentrations as low as 0.08 ppm have resulted in significant transient decreases in lung function, increases in respiratory symptoms and airway responsiveness, as well as cellular and biochemical evidence of airway injury and inflammation. Epidemiological studies suggest effects on lung function, asthma exacerbations, increased use of hospital emergency departments, and other indicators of acute respiratory morbidity in adults and children at ozone concentrations lower than 0.09 ppm. Several recent studies also suggest potential long-term effects on lung function related to cumulative lifetime exposure to ozone, though how these findings may relate to daily average exposures is unknown. A large fraction of California's population resides in areas in which ozone concentrations occur at or above the current State standard, primarily during daylight hours in the summer. Based on a considered assessment of these factors, the ozone ambient air quality standard was prioritized to the first tier of review.

4.2.3.2 Review of the health assessment

The California ozone standard is based primarily on controlled human exposure studies and epidemiological investigations, with some supportive evidence from animal toxicology experiments. Therefore, for the purposes of the SB25 review, OEHHA has focused on research involving human subjects exposed to ozone in controlled settings, in field studies, and in epidemiological investigations.

Since 1987, several controlled exposure studies in adults published by U.S. EPA investigators document effects of multi-hour (6.6 hr) exposures on lung function, respiratory symptoms, airway responsiveness, and inflammation at ozone concentrations as low as 0.08 ppm (Folinsbee et al. 1988, 1994; Horstman et al. 1990; McDonnell et al 1991). At each concentration, there was a progressive decrease in lung function during the exposure, measured as FEV_1 (forced expiratory volume in one second), with statistically significant mean decrements at the end of the exposures of 7 - 8%, 5 - 11%, and 13% for 0.08, 0.10 and 0.12 ppm, respectively (there were 2 experiments using 0.08 and 0.10 ppm ozone). Some individuals showed declines as great as 50%. There is no specific FEV_1 cut-point demarcating what constitutes a physiologically significant decrement in lung function; however, historically FEV_1 decrements greater than 10% have been considered adverse, particularly when coupled with respiratory symptoms (U.S. EPA, 1996). The proportions of subjects with decreases in $FEV_1 > 10\%$ in all the U.S. EPA multi-hour exposure experiments were 26%, 31%, and 46% after exposures to 0.08, 0.10 and 0.12 ppm, respectively (Folinsbee et al. 1994). Moreover, there were significant increases in respiratory symptoms (cough, chest tightness) and in airway responsiveness (a measure of the lung's reactivity to a variety of irritants) after exposure to each concentration as well. In an experiment involving young adult males (aged 18-35), significant increases in the quantities of a variety of cellular and biochemical markers of airway injury and inflammation were identified in bronchoalveolar lavage fluid collected 18 hours after a 6.6-hr exposure to either 0.08 or 0.10 ppm ozone (Devlin et al. 1991).

These U.S. EPA studies were intended to mimic exposures likely to be experienced by outdoor workers and convincingly demonstrated the importance of exposure duration in the elicitation of ozone-related effects. The acute toxicity of ozone appears to be due to the short-term cumulative dose (or "effective dose") inhaled, which is roughly proportionate to the product of the ozone concentration, the exposure duration and the subjects' ventilation or breathing rate. Earlier studies had involved exposure durations of one or two hours and, even though subjects in several experiments sustained high ventilation rates, no compelling evidence of lung function changes or symptoms had been demonstrated below 0.12 ppm ozone, which was somewhat at variance with the epidemiological results.

There is considerable inter-individual variability in responsiveness (lung function and symptoms) to ozone, with up to 25-30% of study populations experiencing markedly greater effects than other subjects. For a given dose of ozone, inter-subject differences in FEV_1 decrements may be 10-fold or greater. These results are highly reproducible over periods from 3 weeks to 14 months, which suggests the existence of an intrinsic responsiveness to ozone (McDonnell 1985; Gliner 1983). The degree of ozone responsiveness, as measured by lung function changes, does not correspond to the extent of ozone-related inflammation (Aris 1993; Balmes 1996). Although the determinants of individual ozone susceptibility are not well understood, increasing age and current cigarette smoking seem to blunt ozone's acute effects (McDonnell 1993; Drechsler 1989; Frampton 1997). Ozone's effects on asthma are addressed below.

There are several lines of evidence suggesting that children may constitute a potentially vulnerable subpopulation with respect to ozone toxicity, most of which relate to their spending more time outdoors engaged in vigorous activities than older adolescents and adults (Wiley et al. 1991; see also section 3.6, above). Moreover, for any given level of activity, children (more so than infants) will have a greater breathing rate, and therefore a greater dose of ozone delivered to the lung on a weight basis than will adults (See Figure 1 of Tager and Balmes 2000, Appendix C to this review). Thus, because of both exposure patterns and respiratory physiology, children are more likely to receive proportionately greater exposure to ozone than adults.

Although almost all of the controlled exposure studies of ozone toxicity conducted since 1987 have involved adults, there is no reason to think that the results of these studies should not be extended to children as well. Therefore, to the extent that children may be subject to prolonged exposures to ozone concentrations comparable to those used in the above controlled exposure investigations, they may well be at risk for decrements in lung function, respiratory symptoms, increased airway responsiveness, and respiratory tract inflammation. Two field studies conducted in Germany found evidence of inflammation of the upper respiratory tract in approximately 200 children, with statistically significant increases in markers of inflammation when the daily half-hour maximum was $\geq$ 0.09 ppm ozone compared with days when the daily half-hour maximum was $\leq$ 0.07 ppm (Frischer et al. 1993; Kopp et al. 1999). Several investigations have also reported that, for a given ozone concentration, children appear to be less likely to report symptoms than adults, suggesting that they may be less aware or able to recognize somatic warnings to curtail exposure. In addition, there is reason to believe, based on animal experiments, that repeated episodes of injury and inflammation may lead to long-term damage to the developing respiratory tract, there is as yet no compelling evidence of this in humans, two recent studies provide some support for this proposition (Kunzli 1998; Galizia 1999; see below).

Since 1987, the results of two controlled exposure studies have been published involving adolescents (including some subjects with mild asthma) (Koenig 1987, 1988). The lowest exposure concentration used was 0.12 ppm for either 30 minutes or one hour. In one study there was no effect on lung function in either the asthmatics or the nonasthmatics, while in the other there was a statistically significant decrease in one measure of lung function related to the caliber of the small airways. In neither case was there evidence that the adolescents were differentially susceptible to the bronchoconstrictive effects of ozone than adults, which was consistent with earlier work addressed in the 1987 review of the California ambient ozone standard.

In 1996, the U.S. EPA undertook an exhaustive review of the epidemiological literature on ozone, and based on its evaluation of all the evidence, articulated the following:

> "Children who are active outdoors... appear to be the at-risk population group examined with the highest percentage and number of individuals exposed to O_3 concentrations at and above which there is evidence of health effects, particularly for 8-hour average exposures at moderate O_3 concentrations $\geq$ 0.08 ppm." (US EPA 1996).

More recent studies indicate potential effects may also occur at concentrations lower than 0.08 ppm.

Recent field studies suggest potential thresholds of between 0.04 and 0.08 ppm (1-hr average) for effects on lung function in children exercising for 1 hour on a treadmill in Mexico City (Castillejos et al. 1995 - see figure 4 in Tager and Balmes 2000, Appendix D to this review). Similarly, in an epidemiological study of lung function of children in Taiwan, ozone had a significant effect on lung function, but only when one-hour peaks exceeded 0.06 ppm (Chen et al. 1999). In a study of adult hikers in New Hampshire, where the 1-hour ozone maximum concentration did not exceed 0.074 ppm, Korrick et al (1998) reported similar relationships between ozone levels and lung function, with an apparent threshold at an ozone concentration between 0.04 and 0.055 ppm, (see figure 5 in Tager and Balmes 2000, in Appendix C to this review). Other studies of lung function in women in Virginia and in berry-pickers in British Columbia, as well as emergency room visits for asthma in New Brunswick, Canada, also suggest population-level effects of ozone when 1-hour ambient concentrations are lower than 0.09 ppm (Stieb et al. 1996, Naeher et al. 1999, Brauer et al. 1996).

Cross-sectional epidemiological data from the Children's Health Study in 12 southern California communities suggest no effect of average 1-hr peak ozone on a variety of chronic respiratory symptoms or on most measures of lung function, except for peak expiratory flow (PEFR) and maximum mid-expiratory flow (FEF_{25-75}). However, two recent studies of college freshmen at U.C. Berkeley and at Yale both suggest that increasing lifetime exposure to ozone may permanently affect lung function, particularly in measurements of flows governed by the dimensions of the small airways (Kunzli et al. 1998; Galizia et al. 1999). While these latter two studies provide evidence consistent with ozone dosimetry studies and the sites of ozone-related lung injury in experimental animals, they need to be confirmed with larger studies before drawing any causal inferences. Moreover, assuming the existence of a causal relationship, it is not clear whether the observed decrements in lung function may have been due to peak concentrations higher than the reported mean ozone levels, to the cumulative lifetime ozone dose regardless of peak exposures, or to some other measure of exposure. Autopsies of young adults in Los Angeles who died from violent injuries suggest the presence of chronic lung (centriacinar) inflammation, even in nonsmokers, providing circumstantial

histological evidence supporting the findings of lung function decrements in college students (Sherwin et al. 1998, 2000).

Asthma is a disease characterized by chronic inflammation of the airways, with episodic exacerbation of symptoms and decreased lung function. In controlled exposure studies, adult asthmatics appear to be more susceptible to the inflammatory effects of low-level ozone than nonasthmatics (Basha et al 1994; Scannell et al. 1996). Several studies suggest that short (1-hour) ozone exposure at concentrations of 0.12 ppm or higher can render allergic adult asthmatics more susceptible to allergen exposure, though these results are not entirely consistent (Molfino et al. 1991; Ball et al. 1996).

Some controlled exposure studies, as well as several field studies, suggest that there may be some interaction between ozone and other pollutants at low ambient concentrations; however, in general, most studies do not show effects greater than those attributable to ozone alone (Koenig et al. 1990, 1994; Linn et al 1995, 1997).

There appears to be evidence for a variety of health effects of exposure to ambient ozone at concentrations lower than the current State standard of 0.09 ppm, although these appear to be related to exposures lasting longer than one hour, the averaging time of the standard. On the other hand, exposure durations greater than one hour are routine in urban and suburban areas. Multi-hour controlled exposure studies using ozone concentrations as low as 0.08 ppm indicate progressive adverse effects on the lung (respiratory symptoms, decreased lung function, increased airway responsiveness, and evidence of intra-pulmonary inflammation) with increasing duration of exposure. In these multi-hour investigations, the effects observed at 0.08 ppm were of lesser magnitude than those seen at 0.12 ppm; nevertheless, similar effects may be expected to occur at lower exposure concentrations of similar or greater durations. Moreover, in the controlled exposure studies the subjects are self-selected and generally do not include substantial numbers of “susceptible” individuals whose experience might be captured in epidemiological investigations (e.g., asthmatics who are experiencing a flare-up of their condition).

While clinical studies have been inconclusive, epidemiological studies suggest that effects may occur at ambient ozone concentrations below 0.09 ppm. Nevertheless, even though in these studies the results have typically been presented in terms of peak one-hour averages, the exposures experienced by the study subjects are likely to have exceeded one hour. Most of the acute effects observed are thought to be related to the cumulative short-term dose of ozone inhaled over the course of the day, with some carry-over from prior days’ exposures. The effects most consistently reported at low ambient concentrations in the epidemiological studies include decrements in several measures of lung function. In the absence of symptoms, the biological significance of such effects on lung function is uncertain. Chronic effects on lung function, such as those suggested in the reports by Kunzli et al. (1998) and Galizia et al. (1999), would clearly be important from a public health standpoint; however, the relationships between short-term responses and chronic changes require further study.

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4.2.4 Nitrogen Dioxide

4.2.4.1 Summary

Controlled exposure studies of human volunteers generally fail to show effects of exposure to NO_2 at or below the current California standard of 0.25 ppm. However, recent studies suggest that exposure to NO_2 at concentrations only slightly above 0.25 ppm enhances bronchial or airway responses to challenge with common aeroallergens in subjects with allergic asthma. NO_2 exposure could therefore render asthmatics more susceptible to effects from other environmental exposures. Epidemiological studies have reported relationships between both outdoor and indoor NO_2 concentrations and a variety of adverse health outcomes, including decrements in lung function, increased risks of respiratory symptoms and illness, exacerbation of asthma, especially in children, and increased risks of daily mortality. However, in many of the epidemiological studies an independent role of NO_2 cannot be determined, because of high covariation between NO_2 and other pollutants, or because the investigators did not adjust for the effects of important confounders (especially different measures of particulate matter), or both. NO_2 may represent a marker for exposure to traffic emissions generally or to combustion-related pollution, or may play an etiologic role in the observed health effects. Though recent trends suggest nearly complete statewide compliance with the current California NO_2 ambient air quality standard, the results of some of the recent clinical and epidemiological studies suggest that examination of the basis for the standard is warranted. Based on our consideration of the relevant evidence, notably the potential impacts on asthmatic childhood, the NO_2 standard was allocated to the first tier of review.

4.2.4.2 Review of Health Assessment

NO_2 is produced by high-temperature combustion, particularly of fossil fuels. The primary sources for NO_2 include diesel and gasoline-powered engines, as well as industrial point sources, especially power plants. Local urban concentrations of NO_2 are related to traffic density; therefore, people working or residing near busy streets, as well as individuals driving in heavy traffic, may be exposed to higher concentrations of NO_2 than those indicated by regional air quality monitors. It is important to recognize that outdoor NO_2 levels can contribute a substantial fraction of indoor concentrations, up to 50% according to one estimate (Marbury et al., 1988).

There is little convincing evidence that exposure of healthy volunteers to NO_2 at levels as high as 4.0 ppm is associated with effects on lung function alterations or respiratory symptoms. (See Frampton 2000, Appendix D to this review). NO_2 exposures in the range of 1.5-2.0 ppm cause small but significant increases in airway responsiveness in healthy individuals; this effect can be observed in asthmatics at lower exposure concentrations (Mohsenin 1988). Other studies indicate that exposure to NO_2 at concentrations well above the ambient standard (2.0 ppm and above) may cause a modest inflammatory response and alterations of lymphocyte subsets in peripheral blood as well as in the airways (Azadniv 1998; Blomberg 1997, 1999; Sandström 1991, 1992). Repeated exposures using 2.0 ppm NO_2 appear to result in persistent mild airway inflammation (Blomberg 1999). In contrast, exposure using 0.30 ppm NO_2 produced no detectable inflammation in healthy subjects, or in subjects with asthma or chronic obstructive pulmonary disease (COPD) (Vagaggini 1996).

Some animal studies seem to show effects on immune function at exposure concentrations near the standard (Richters 1988, 1989). However, overall the clinical studies provide little evidence for effects on lung function, airway inflammation, or host defense

impairment in healthy subjects at outdoor ambient exposure concentrations (See Frampton 2000, Appendix D to this review).

Among asthmatic study subjects, exposure to as little as 0.10 to 0.60 ppm NO_2 has been reported to enhance airway responsiveness but has not typically resulted in increased symptoms or decrements in lung function. However, the numerous studies examining changes in airway responsiveness have been somewhat inconsistent (See Frampton, 2000, Appendix D to this review, and California Air Resources Board 1995). The results of one early study that reported an effect at 0.10 ppm could not be replicated in subsequent investigations (Orehek 1976). The inter-study discrepancies are likely to be related to differences in baseline disease severity of the subjects and differences in study protocols (exposure durations and concentrations, intensity of exercise, methods of assessing airway responsiveness). Although few of these studies have found any immediate symptoms or changes in lung function after low-level NO_2 exposures, one implication of increased airway responsiveness is that asthmatics may be rendered more susceptible to the effects of exposure to aeroallergens or to other respiratory irritants. Overall, based on the data from controlled exposure studies, short-term exposures to NO_2 at outdoor ambient concentrations are unlikely to significantly alter lung function or non-specific airway responsiveness in most people with mild asthma. However, outdoor NO_2 augments indoor NO_2 concentrations, which may reach peak levels that are clinically important for some adults and children with asthma.

In addition, several recent investigations indicate that controlled exposures to NO_2 at concentrations as low as 0.26 ppm for 30 minutes can enhance the response of allergic asthmatics to subsequent challenge with common inhaled allergens (Tunnicliff 1994; Strand 1997; See Table 3 of Frampton (2000) in Appendix C). These studies are reasonably consistent with each other and with the studies noted above, as well as with animal studies conducted at higher concentrations, and suggest that low-level NO_2 may be important in augmenting the expression of allergic asthma.

Epidemiological studies have also examined the potential health impacts of both acute and chronic exposures to NO_2. There have been numerous investigations examining the relationship of indoor NO_2 concentrations or gas stove use to respiratory illness and lung function in adults and children. While these are useful in assessing the potential impacts of NO_2 exposure, they are not informative in evaluating the health-protectiveness of the ambient standard. Many studies examining the impact of ambient pollutants have not identified effects of NO_2 independent of those of other pollutants. In particular, NO_2 often tends to be so highly correlated with one or more measures of particulate matter, carbon monoxide, or both, that the multicollinearity precludes analytical isolation of the effects of NO_2. Measurement error of NO_2 or other pollutants compounds this problem, as inaccurate measurements will affect inter-pollutant correlations and make it difficult to control for confounding in the analysis. Some have hypothesized that NO_2 may serve as an indicator for a complex mixture of traffic-related pollutants, notably fine particles. However, several studies have noted effects of NO_2 independent of other pollutants, as listed below.

Ambient NO_2 levels have been linked with daily mortality, though many studies show no association (e.g., Zmirou 1996, Ostro 1996). In a cohort of patients with chronic obstructive pulmonary disease in Barcelona, significant associations were reported for daily mortality and 1-hour maximum NO_2 as well as 24 hour average NO_2 (Garcia-Aymerich et al. 2000). In a Brazilian study of air pollution and mortality among children < age 5, Saldiva et al. (1994) reported that NO_2, but not PM10, ozone, SO_2, or CO, was associated with an increased risk of mortality. In this study, the mean NO_2 (NOx) level was 0.127 ppm. In a more recent study in

Sao Paulo, Pereira et al. (1998) found that the strongest single-pollutant predictor of intrauterine mortality was NO_2 (see Figure 2 in Frampton (2000) in Appendix D).
Peters and colleagues (Peters et al. 2000) reported that ambient NO_2 levels in Boston were better predictors of cardiac arrhythmias in subjects with heart disease than were two measures of particles (PM2.5 or black carbon). As in many other epidemiological studies, NO_2 may represent a general indicator for local traffic-related pollution. However, the data are also consistent with toxicity related to NO_2 as a component of the ambient pollutant mixture.

Time-series studies have identified other linkages with ambient NO_2 and adverse health events. Associations have been observed in several studies between ambient NO_2 levels and emergency visits for asthma in Spain (Tenias et al. 1998), Israel (Garty et al. 1998), and Santa Clara County, California (Lipsett et al. 1997). At least one study suggests the existence of stronger associations between daily air pollution levels (including NO_2) and the occurrence of physician visits for asthma and other lower respiratory conditions in children compared with those in adults (Hajat 1999). In a Swiss time-series study of daily respiratory symptoms in children, NO_2 exposures were estimated using passive samplers placed outside the residence location and inside in the room where the child spent the most time (Braun-Fahrlander et al., 1992). Neither indoor nor outdoor NO_2 concentration was associated with symptom incidence; however, symptom duration was associated with outdoor NO_2 concentrations, supporting the idea that NO_2 serves as an indicator for other correlated ambient pollutants.

Several studies of the chronic effects of air pollution suggest a potential role for NO_2 in relation to children's lung growth as well as to respiratory symptoms in adults and children; however, the strong correlations of NO_2 concentrations with ambient particulate matter make causal inference problematic. For instance, McConnell et al (McConnell et al. 1999), reporting data from the Southern California Children's Health Study, found positive associations between several indices of air pollution, including NO_2, and respiratory symptoms in children with asthma. The strongest association was with NO_2 (See Figure 1 in Frampton (2000), in Appendix D to this review). No association was seen for children without asthma. However, particles, NO_2, and acids were too highly correlated to allow estimation of individual pollutant effects. Likewise, NO_2, acid vapors and several measures of particulate matter were associated with decrements in lung function growth, but the pollutant co-variation made it impossible to attribute such decrements specifically to any single pollutant (Gauderman et al. 2000). Outdoor NO_2 (one-week average), but not NO_2 measured with personal monitors, was significantly associated with the prevalence of atopy and rhinitis in 9-year-old children in Düsseldorf (Krämer et al. 2000). These results also suggest that a NO_2 may be serving as a surrogate for the ambient pollutant mix.

The Swiss Study on Air Pollution and Lung Disease in Adults examined the long-term effects of air pollution exposure in a cross-sectional and longitudinal study of 8 areas in Switzerland. Significant associations were observed between symptoms (chronic phlegm, chronic cough, breathlessness at rest, dyspnea on exertion) and both NO_2 and particles, while NO_2 was also associated with lower lung function indices (FVC and FEV_1) (Zemp et al., 1999). However, as NO_2 concentrations were strongly correlated with PM10 levels ($r = 0.91$), the roles of specific pollutants in the observed associations could not be ascertained.

In summary, though the clinical studies are somewhat inconsistent in their results, several key recent investigations suggest that at near-ambient levels, NO_2 may potentiate the response to aeroallergens in allergic asthmatics. The epidemiological evidence suggests that exposure to traffic or combustion-related pollutants is associated with a variety of adverse

health outcomes in adults and children, and that measurements of ambient NO_2 may be a good atmospheric marker of exposure. As part of the mixture of outdoor pollutants, NO_2 may play a role in causing the observed health effects. In view of the results of recent research, more extensive review and analysis of the literature on NO_2 in relation to the current California ambient standard should be considered.

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4.2.5 Lead

4.2.5.1 Summary

The review and analysis of the scientific literature indicates that exposure to an airborne lead concentrations at the current State standard of 1.5 $\mu g/m^3$ (30-day average) would not be protective of the health of children and infants. Specifically, an increase in ambient lead from current concentrations to the level of the standard could be expected to drive blood lead levels of an additional 40% of 1- and 2-year old children to exceed 10 $\mu g/dL$, the level of concern specified by the U.S. Centers for Disease Control and Prevention (CDC). At this blood lead level, there is consistent evidence from several well-conducted prospective cohort studies that demonstrate an association between blood lead and several adverse neurological outcomes in children, including decreases in IQ. Even an increase in airborne lead to an ambient concentration of 0.50 $\mu g/m^3$ would theoretically result in an additional 10% of children having blood lead concentrations above the CDC level of concern. However, lead is currently listed as a Toxic Air Contaminant (TAC) and statewide average ambient air exposures to lead are about an order of magnitude lower than the standard. Therefore, review of the lead standard for possible revision was given a lower level of priority.

4.2.5.2 Review of the health assessment

The adverse health effects of lead are well documented, with evidence provided from the toxicological, clinical and epidemiological literature, as summarized by the U.S. Environmental Protection Agency (U.S. EPA, 1986, 1990), the Agency for Toxic Substances and Disease Registry (ATSDR, 1990) the National Research Council (NRC, 1993), and the California Office of Environmental Health Hazard Assessment (OEHHA, 1997). Children are more vulnerable than adults when exposed to lead partly because they: (1) have hand-to-mouth behaviors that result in more ingestion of lead in soil and dust (This is relevant since lead emitted into the air will increase lead concentrations in soil.); (2) absorb substantially more lead from the gut than adults, especially children below 2 years of age; (3) have a faster metabolic rate, resulting in a proportionately greater daily intake of lead through food; (4) have a less developed blood-brain barrier and therefore greater neurological sensitivity; (5) have a faster resting inhalation rate; and (6) have a rapidly developing nervous system. Furthermore, children from economically disadvantaged backgrounds are especially vulnerable because they are more likely to have diets deficient in elements that suppress lead absorption, such as iron and calcium (OEHHA, 1997). At current ambient concentrations, air lead contributes to about 5 to 18% of total blood lead. Increases in air lead from current statewide average ambient concentrations of around 0.06 $\mu g/m^3$ to a concentration of 0.50 $\mu g/m^3$ would increase the contribution of air lead to blood lead to about 50% (OEHHA, 1997).

Unlike many other pollutants, the health effects associated with exposure to lead have been quantitatively tied to measures of the pollutant found in the blood. Therefore, to assess the impact of any given airborne lead concentration, one must first determine the relation between air lead and blood lead, and then blood lead with the adverse health effect. There is substantial evidence linking air lead and blood lead concentrations from both clinical and epidemiological studies. Population-based studies include the effect of changes in ambient air on the deposition, accumulation and exposure from other environmental pathways (e.g., soil and dust) as well, so the total impact of lead can be estimated. Quantitative assessment of the association between air lead and blood lead have been conducted by both U.S. EPA (1989) and OEHHA (1997) using three different models: (1) disaggregate (pathway specific); (2) aggregate (all pathways combined); and (3) integrated biokinetic. The results are consistent and provide a reasonable range for estimating the effects of air lead on blood lead.

The scientific evidence suggests that lead exposure is associated with neurological effects in children and infants, resulting in diminished measures of intelligence such as IQ, short-term memory loss, reading and spelling underachievement, impairment of visual motor functioning, disruptive classroom behavior, and impaired reaction time (NRC, 1993). These findings are based on both cross-sectional and prospective studies of human populations. In these studies, effects have been noted at blood lead levels of 10 to 20 μg/dL and lower. Reviewing this body of evidence, the CDC identified 10 μg/dL as a "level of concern." and recommended the initiation of community-wide childhood lead poisoning prevention activities when children in a community have blood lead levels between 10 and 14 μg/dL. Thus, it is reasonable to estimate, as an indicator of the protectiveness of the standard, the increase in the proportion of children that will move above 10 μg/dL as ambient lead increases above current concentrations.

While there have been substantial decreases in average blood lead levels over the last 15 years, mostly associated with the reduction of lead in gasoline (Pirkle et al., 1994), there are still many children in California with blood lead levels above 10 μg/dL (OEHHA, 1997). Since there are no population-based blood lead data that are both specific to and representative of California, it is reasonable to assume that the results of a national probability sample – the National Health and Nutrition Examination Survey (NHANES III) - are representative of children in California. These results were used as a starting point to estimate the impact of changes in air lead on the percent of 1- and 2-year olds that will move above a blood lead level of 10 μg/dL. Sensitivity analyses conducted with alternative geometric means and geometric standard deviations (which describe the spread of a log normally-distributed exposure like blood lead), demonstrated that the results were robust.

At the baseline average ambient air lead level existing when the NHANES III was undertaken of 0.055 $\mu g/m^3$, about 5.9% of young children had blood lead levels above 10 μg/dL. This baseline includes lead exposure from all media including air, dust, soil, paint, water and diet. At an air lead concentration equivalent to the current ambient standard of 1.5 $\mu g/m^3$, more than 45% of children aged 1 and 2 would be expected to have blood lead levels above the CDC guideline of 10 μg/dL. For African-American children, who have much higher baseline blood lead levels, the percent moving above 10 μg/dL in any of these scenarios would be much greater.

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4.2.6 Hydrogen Sulfide

4.2.6.1 Summary

There is little recent published literature relevant to the ambient air quality standard for hydrogen sulfide (H_2S) of 30 ppb (1-hr average). Although at high concentrations, H_2S is an asphyxiant and has been associated with industrial fatalities, its principal effects at ambient levels are odor annoyance, sometimes accompanied by symptoms of headache and nausea. The ambient standard was originally set in 1969 to protect against odor annoyance, based on a small study of adults' H_2S odor perception thresholds. A report prepared for the Air Resources Board in 1985 indicated that, at the level of the current ambient standard, approximately 40% of adults would be likely to be annoyed by the odor of H_2S. Young adults and children are likely to be more sensitive with suspect to the odor perception and annoyance than older adults. In light of recent guidance from the American Thoracic Society (Samet et al. 2000), such annoyance should be considered an adverse effect from exposure to air pollution. The H_2S standard was allocated to the second tier because there is little exposure in California and because the health impacts related to low-level exposures to H_2S are not as serious as those identified for the other criteria pollutants. Nevertheless, consideration should be given to revising the ambient standard at some future date.

4.2.6.2 Review of H_2S Health Effects Assessment

The principal sources of H_2S in California are geothermal power plants, petroleum and natural gas production and refining, and sewage. Schools located near industrial sources of H_2S have been subject to accidental releases of this compound, resulting in the implementation of emergency protection measures, including "shelter-in-place."
Most of what is known about the toxicity of H_2S has come from industrial accidents or studies involving exposure concentrations orders of magnitude above the current ambient standard. The biochemical mechanism of action of H_2S is similar to that of cyanide. Interestingly, however, small quantities of H_2S are also produced endogenously, and may be important in modulating neurotransmission.

Effects associated with exposure to 50 ppm and above include conjunctivitis and eye pain, respiratory tract irritation, pulmonary edema and sudden death (Spiers and Finnegan, 1986; ACGIH 1992; NIOSH 1977). Several controlled experiments of healthy adult volunteers (total n = 86) at concentrations of 2.5 to 10 ppm are somewhat inconsistent. Bhambhani and Singh (1985, 1991) showed that at exposure concentrations of 2.5 and 5 ppm H_2S, study subjects experienced coughing and throat irritation, as well as impaired lactate metabolism and oxygen uptake in the blood. In two subsequent reports, Bhambhani et al. (1994, 1996) reported no significant increase in symptoms or changes in a variety of respiratory and cardiovascular parameters in subjects exposed to either 5 or 10 ppm H_2S. One other controlled exposure study of 10 mild asthmatics to 2 ppm for 30 minutes showed no significant changes in several measures of lung function, though 2 subjects experienced increases in specific airway resistance (Sraw) in excess of 30%. All subjects reported detecting a "very unpleasant" odor, to which they "rapidly" adapted (Jappinen et al. 1990). These small controlled studies were all conducted using exposure concentrations at or near the occupational exposure limit (20 ppm ceiling), which is over two orders of magnitude higher than the 1-hour ambient standard for H_2S. It should be noted that olfactory fatigue is common with relatively high levels of exposure and can prevent workers from recognizing continuing exposure to H_2S.

The H_2S ambient standard was originally established in 1969 by the former State Department of Public Health to protect against odor annoyance, and was based on rounding of the geometric mean odor threshold of 29 ppb (range = 12 – 69 ppb; geometric SD = 5 ppb) measured in adults (California State Department of Public Health 1969). In a report prepared for the Air Resources Board, Amoore (1985) reviewed 26 published studies (not including the California Department of Public Health study), which reported average odor detection thresholds for H_2S ranging from 0.07 to 1400 ppb H_2S. In this review, the geometric mean was 8 ppb, approximately ¼ the level of the standard.

Earlier work indicated that olfactory sensitivity declines with age (Venstrom et al 1968). In his 1985 report to the ARB, Amoore indicated that an average 18-year old would be predicted to have an odor perception threshold of 4 ppb, while a 62-year-old would have a threshold of 16 ppb. Recent work suggests that nine-year-olds may not be as sensitive as 15-year-olds in odor identification (Koelega 1994); however, this may be partly explained by the results of another study in which children aged 8 – 14 had an odor sensitivity similar to that of young adults, but appeared not have the knowledge to identify odors by name (Cain et al. 1995).

Exposure to high concentrations of unpleasant odorants can cause annoyance as well as symptoms of headache and nausea (Amoore 1985; Reynolds and Kauper 1984). Several studies have examined the ratio of annoyance threshold to odor detection threshold for a variety of odorants (Winneke 1975; Winneke and Kastka 1977; Hellman and Small 1974; Adams *et al.* 1968; and NCASI 1971); the geometric mean of these ratios is five. If the mean detection concentration for H_2S is 8 ppb, the mean theoretical odor annoyance threshold would therefore be 40 ppb. At the level of the current ambient standard, approximately 40% of adults would likely be annoyed by the odor of H_2S (Amoore 1985). In a semi-quantitative "reality test" of this theoretical construct, Reynolds and Kauper (1984) reported that ambient concentrations of 30 ppb H_2S from geyser emissions have resulted in odor complaints and reports of nausea and headache in the general population. In an epidemiological study of a Finnish community exposed to pulp mill emissions (H_2S and methyl mercaptan), odds ratios for several symptoms among children were elevated (cough, nasal symptoms, eye symptoms, and headache), though none was statistically significant (Jaakkola 1990, Marttila 1994). To prevent odor nuisance from H_2S, the World Health Organization recommends a more stringent ceiling of 5 ppb, 30-minute average (WHO 1981).

Several studies have examined the reproductive and developmental toxicity of H_2S in experimental animals using exposure concentrations up to 3 orders of magnitude higher than the current ambient standard. All but one of these studies showed no biologically significant effects, suggesting that toxicological investigations of similar outcomes in experimental animals using lower concentrations more relevant to the ambient standard are unlikely to be informative. The sole exception might be the study by Hannah and Roth (1990), which examined the impacts of H_2S exposure on developing neurons in rat brains. The authors reported that maternal exposure to 20 and 50 ppm resulted in severe alterations in neuron growth and development.

The American Thoracic Society has recently indicated that symptom-related impairment of quality of life resulting from exposure to air pollution should be deemed an adverse health effect (Samet et al. 2000). In view of this, the distinction that is sometimes made between odor annoyance and an adverse health effect should no longer be drawn, at least from a standard-setting perspective. In view of the observation that exposure to H_2S at the level of the current standard is likely to elicit odor annoyance and accompanying

symptoms in a large percentage of people so exposed, consideration should be given to revision of the ambient standard. However, symptoms related to H_2S exposure are generally not as serious as those linked with the Tier 1 pollutants. In addition, H_2S exposures near the level of the ambient standard are relatively uncommon compared with the Tier 1 pollutants. There fore, H_2S was relegated to Tier 2.

As the primary symptoms associated with environmental exposures to this pollutant are nausea and headache, consideration should be given to its potential to aggravate similar symptoms occurring in, for instance, pregnant women or patients undergoing cancer chemotherapy. In any future revision of the standard, however, the principal difficulty that will be faced by OEHHA and ARB is the dearth of research on the impacts of this toxicant at exposure concentrations near the level of the ambient standard.

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4.2.7 Carbon Monoxide

4.2.7.1 Summary

There are several State standards for CO, including 20 ppm for one hour, 9 ppm for eight hours, and 6 ppm for eight hours in the Lake Tahoe basin. The standards for CO are based on the critical endpoint of exacerbation of pre-existing coronary artery disease (CAD) among susceptible individuals. Justification of this standard rests upon a substantial body of peer-reviewed literature, and in particular on several controlled human exposure studies. Review and analysis of the current scientific literature on CO indicates that a reasonable margin of safety for the current ambient air quality standard continues to exist in terms of protection against exacerbation of CAD among susceptible adults. Other health endpoints, including fetotoxic effects as well as adult mortality and hospitalization for cardiovascular disease, have been associated with ambient CO in epidemiological analyses. However, considerable uncertainties exist in these studies due to potential confounders and the large exposure measurement error related to use of fixed site monitors for CO. Based on the above findings, there is only weak evidence that the current California ambient CO standards may not be protective against adverse effects of infants, children or other potentially susceptible populations. Therefore, review of the carbon monoxide standard for possible revision was given a lower level of priority.

4.2.7.2 Review of the health assessment

CO is a colorless, odorless gas with no substantial warning properties. It is produced by various combustion processes, including motor vehicles, fireplaces, home furnaces and heaters, numerous industries, and burning cigarettes. Individuals in motor vehicles are at the greatest risk from ambient CO exposure, followed by pedestrians, bicyclists and joggers in the proximity of roadways, and roadworkers (U.S. EPA, 2000). CO acts in the body as a “chemical asphyxiant” by interfering with the transportation of oxygen by hemoglobin molecules found in red blood cells. Critical targets of CO are those organs with a high metabolic oxygen demand and limited metabolic reserve. These include the nervous system, heart, and the developing fetus.

Characterizing exposure to and assessing the risk of CO is helped by the availability of an excellent biomarker of exposure: carboxyhemoglobin (or COHb). Experimental studies looking at biological effects in both animals and humans can tailor exposures to achieve target COHb levels, which in turn provide a common denominator for describing “internal exposure.” Toxicokinetic modeling is utilized with a variety of assumptions in order to predict the relationship between ambient exposure and COHb levels.

The current California ambient air quality standard for CO is based on the critical endpoint of exacerbation of pre-existing CAD among susceptible individuals. Justification of this standard rests upon a substantial body of peer-reviewed literature, and in particular on several controlled human exposure studies. Most important of these are two showing a decrease in exercise tolerance among CAD patients exposed to CO experimentally. One study showed a decreased exercise time to both angina (chest pain caused by insufficient oxygen delivery to the heart muscle) and electrocardiographic abnormalities among CAD patients exposed to CO (Allred, 1989). Another study showed a similar decrease for the endpoint of single and multiple premature ventricular contractions (PVCs), a potentially dangerous cardiac rhythm abnormality (Sheps, 1990). Together these two studies – and several that preceded them – suggest that relatively low COHb levels (e.g., 2.0 to 2.5% for exercise-induced angina, and 6% for PVCs) may impair oxygen delivery to the heart of CAD

patients in clinically important ways. Using these studies, together with toxicokinetic calculations presented at the time of the last CO Criteria Air Pollutant Review (1991), OEHHA scientists concluded that the current ambient air quality standards adequately protect the most vulnerable segment of the public – CAD patients. Specifically, the current ambient air quality standards for CO are intended to keep COHb levels well below 2.1% to protect these individuals.

Other health endpoints considered at the time of the last review, but not designated as critical for standard-setting purposes, were: 1) neurobehavioral impairment, and 2) prenatal effects (in particular, intrauterine growth retardation or IUGR). At the time of that review, no convincing evidence could be found for neurobehavioral impairment with COHb levels below approximately 10-20% in human volunteers (Benignus et al., 1990), nor for perinatal effects with maternal COHb levels below approximately 16% in experimental animals (Singh and Scott, 1984). IUGR / low birthweight has been observed among the offspring of human mothers with lower COHb levels, but these are smokers who were also exposed to a variety of other toxic agents in cigarette smoke (Mactutus, 1989).

Since the above review, several new research findings – including publications pertaining to children and/or fetuses – have appeared in the scientific literature. In addition, a major review was recently published by the US Environmental Protection Agency (U. S. EPA, 2000) looking at the adequacy of the current national ambient air quality standards for CO (25 ppm for one hour and 9 ppm for eight hours). US EPA concluded that their standards – likewise based upon the protection of individuals with CAD – continue to be adequately protective, and that the intervening literature on the subject did not support a change in the standards.

Most of the newer literature pertaining to CO exposure in humans has been epidemiological in nature, and has several methodological shortcomings. Two recent studies cited in the accompanying literature review (Kleinman, 2000) examined neonatal birth weight as a function of ambient CO levels recorded at the air monitoring station located closest to the mother's residence (Alderman et al., 1987; Ritz and Yu, 1999). In the first study, conducted in Denver, the authors found no association between imputed CO exposure and birth weight. In the second study (conducted in Los Angeles), the authors concluded that the likelihood of a full-term neonate having low birth weight was significantly elevated if the 3-month average of nearest CO measurements exceeded 5.5 ppm. These latter results were reportedly unaffected by adjustment for a number of potential confounders, including commuting habits of the mother, sex of the child, level of prenatal care, and age, ethnicity, and education of the mother.

However, because of issues related to potential confounders and measurement error, the study can only be viewed as suggestive. Specifically, the authors were unable to control for a number of potential confounders, including maternal nutrition, prior adverse pregnancy outcomes, occupational exposures, and personal (or passive) smoking. Perhaps more importantly, classification of CO exposure by sampling results at the nearest air pollution monitoring station is problematic, since CO – perhaps more than any other criteria air pollutant – tends to show sharp concentration gradients over relatively short distances, with proximity to major roadways being an important variable. As indicated by the U.S. EPA (U.S. EPA, 2000), there is poor correlation between personal exposure and ambient CO as measured at fixed-site monitors due to personal mobility, and the spatial and temporal variability of CO measurements. Thus, there may also be significant misclassification, possibly non-random, of exposure in these studies.

This same problem of measurement error exists for a series of epidemiological studies of adults showing associations between CO and both daily mortality and cardiovascular-related hospital admissions. Among the mortality studies in the U.S. finding an association with daily mortality are Kinney and Ozkaynak (1991) in Los Angeles County. However, in that study and in many other similar studies, the traffic-related pollutants – CO, NO_2, and particulate matter – were highly correlated ($r \sim 0.8$), so a separate effect of CO is impossible to discern. Among other U.S. studies examining CO, Ito et al. (1996) in Chicago, Kelsall et al. (1997) in Philadelphia and Fairley (1999) in Santa Clara County, failed to find any association between CO and mortality. In studies using data from outside the U.S., the results for CO are mixed (U.S. EPA, 2000).

Associations between CO and hospitalization for cardiovascular disease have been reported by Morris et al. (1995) and Schwartz (1999). However, the Morris et al. study did not include measures of particulate matter, despite the large body of evidence associating exposure to this pollutant with hospitalization. In discussing the positive findings for CO at levels much lower than that observed in toxicological investigations, Schwartz (1999) suggests two possible explanations. First, he suggests that the CO effects may be occurring among a part of the population with concurrent respiratory and cardiovascular illness; individuals who are not typically studied in controlled exposure settings. Second, CO may be serving as a marker for traffic-related pollutants, including volatile and semivolatile organic aerosols. The U.S. EPA did not find compelling toxicological evidence of biological plausibility for the associations reported in epidemiological studies, specifically between current low-level ambient CO and mortality and hospitalization (U.S. EPA, 2000). In fact, the EPA indicates that a CO concentration of 100 ppm or higher would be needed to obtain a 5% COHb level. The low levels of ambient CO found in urban area (typically < 5.0 ppm average daily 1-hour maximum) would be projected to increase COHb levels by barely detectable amounts (U.S. EPA, 2000). Therefore, it is challenging to reconcile these findings resulting from such small changes in CO on pathophysiological grounds.

Another study suggesting CO-induced decrements in video game performance with COHb levels in the 2-4% range also has potential methodological limitations. Specifically, the study employed a small number of subjects (n= 9), and was single (rather than double) blinded (Insogna and Warren, 1994). Thus, these discrepant results cannot, by themselves, challenge the larger body of literature that suggests that neurobehavioral effects occur at much higher COHb levels.

In summary, there is no evidence in the peer-reviewed scientific literature to challenge the place of CAD in susceptible individuals as the critical health endpoint for CO standard-setting. Notwithstanding this observation, significant uncertainties exist regarding the epidemiological studies that report associations between ambient CO measurements and various adverse outcomes, such as birthweight, mortality and hospitalization. These epidemiological studies may not only be subject to differential measurement error, but also generally cannot control for potential impacts of highly correlated traffic-related pollutants, especially PM10 and PM2.5. Based on these findings, there is only weak evidence that the current California ambient CO standards may not be protective against adverse effects in the most susceptible populations. In this instance, older adults with serious chronic disease represent a more susceptible population than infants and children, so that a standard protective of individuals with heart disease will also be protective of infants and children.

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4.2.8 Sulfur Dioxide

4.2.8.1 Summary

California has two Ambient Air Quality Standards for SO_2, which are intended to protect different sets of potentially susceptible subpopulations. The short-term standard (0.25 ppm, 1-hr average) is based on the results of controlled exposure studies, and is intended to protect exercising asthmatics against effects of acute exposure. The longer-term standard (0.04 ppm, 24-hr average) is based on the results of epidemiological studies, and is intended to protect not only asthmatics, but also individuals at risk for exacerbation of other chronic lung or heart diseases, as well as children and the elderly.

Many asthmatic subjects exposed briefly in controlled settings to low levels of SO_2 have demonstrated increased respiratory symptoms such as shortness of breath, coughing and wheezing, and decrements in lung function. By virtue of their activity patterns and generally greater ventilation rates, children may receive greater exposures to SO_2 than adults (Wiley et al. 1991; see also section 3.6, above); therefore active asthmatic children may represent a particularly susceptible subgroup. There is evidence that some nonasthmatic individuals with allergies and airway hyperresponsiveness may also be susceptible to bronchoconstriction induced by short-term exposure to SO_2.

Controlled exposure studies suggest consistent effects (changes in lung function and increased lower respiratory symptoms) in vigorously exercising asthmatics at exposure concentrations of 0.40 ppm and above. Changes in airway caliber unaccompanied by any symptoms have been observed at concentrations of 0.10 to 0.25 ppm in studies using mouthpiece exposures, a method of SO_2 administration that bypasses normal anatomic defenses.

Epidemiological studies have examined a variety of outcomes in relation to ambient SO_2 concentrations, specifically daily mortality, increases in hospital admissions for cardiac and respiratory causes, asthma exacerbations, decrements in children's lung function, and increased risks for other respiratory symptoms and illness. In many epidemiological studies that purport to show an SO_2 effect, there is substantial covariation of SO_2 with ambient particles or other pollutants, so that an independent effect of SO_2 cannot be identified. However, several studies appear to demonstrate associations of adverse health outcomes with ambient SO_2 levels, when measured ambient concentrations were near the current 24-hour California standard.

Based on these findings, there is some evidence that the current California ambient SO_2 standards may not be protective against adverse effects in the most susceptible populations. Coupled with the evidence that SO_2 levels in California are generally very low, these standards were assigned to the second tier for review.

4.2.8.2. Review of the health assessment

Sulfur dioxide is a highly irritating, colorless, soluble gas with a pungent odor and taste. In contact with water it forms sulfurous acid, which accounts for its significant respiratory tract irritancy. Principal sources of SO_2 include paper and pulp mills, coal-fired power plants, refineries, smelters, and food processing facilities. In ambient air, sulfur dioxide is slowly oxidized to sulfur trioxide, which, because of its strong affinity for water, is rapidly hydrated to form sulfuric acid (H_2SO_4) (World Health Organization 1987). The indirect health impacts of

SO_2 mediated through exposure to H_2SO_4 and other acid aerosol derivatives are reviewed in the assessment of sulfates, not in this section.

The prevalence of enhanced susceptibility to the bronchoconstrictive effects of SO_2 has been estimated to be about 5.4% among adults aged 20-44 years in Europe (Nowak et al, 1997). The population subgroups with the greatest response to SO_2 at low levels include primarily asthmatics and some individuals with allergies and airway hyperresponsiveness (Linn 1987, Sheppard 1980, 1981, Koenig 1981, 1998; Horstman 1986). Even among asthmatics there is wide variability in SO_2 susceptibility: one investigation of adult asthmatics suggests a seven-fold range of lung function responses to fixed levels of SO_2 exposures (Horstman 1986). Low humidity and exercise (or voluntary hyperventilation) augment the responses observed in asthmatics (Sheppard 1981, 1984, Bethel 1984, Linn 1983, 1985).

Pre-exposure to a low concentration of ozone (0.12 ppm) for 45 minutes potentiates the bronchoconstrictive effect of an otherwise subthreshold dose of SO_2 (0.10 ppm) in adolescent asthmatics, suggesting the possibility of interactions with other pollutants in urban environments (Koenig 1990). With moderate exercise or voluntary rapid breathing, lower respiratory symptoms and/or effects on lung function have been consistently observed in asthmatics after short (several minutes) exposures to SO_2 concentrations of 0.4 - 0.5 ppm and above, and in some cases in the range of 0.2-0.3 ppm (California Air Resources Board 1994). Though many asthmatics experience exercise-induced bronchospasm, controlled exposure studies adjust for this phenomenon by comparing the effects observed in asthmatics exercising in clean air with effects seen when they are exercising during an SO_2 exposure. In experimental settings, SO_2-induced bronchospasm in asthmatics often appears to be reversible within a half-hour even without treatment; however, a number of study subjects have required rescue bronchodilator administration. Pre-treatment with a variety of asthma medications can blunt the effects of SO_2 exposure (Koenig 1987; Gong 1996).

Two controlled studies have reported SO_2-related effects on lung function using an exposure concentration of 0.10 ppm (Koenig 1990, Trenga 2000). In both of these studies, SO_2 was administered via a mouthpiece, which completely bypasses the nose. At rest most (80-85%) people breathe through the nose, which filters out most inhaled SO_2, preventing its passage to sensitive irritant receptors at and below the larynx (Speizer et al, 1966, Frank et al. 1969). With exercise, people begin oronasal breathing, at which point about 60% of inhaled air passes through the nose, declining to 40% at very high ventilation rates (Ninimaa 1981). The mouth and throat cannot scrub SO_2 as efficiently as the nose; therefore, breathing through the mouth alone, as was done in these and several other controlled exposure studies, increases the penetration of SO_2 into the lungs substantially beyond that which would happen in real life in most individuals. Mouthpiece exposure was also used in one of the two studies that reported an SO_2-related effect on specific airway resistance (SRaw – a measure of the caliber of the airways and possibly the larynx) at 0.25 ppm (Sheppard 1981). The only other controlled study that reported an effect at 0.25 ppm was unable to replicate this result using a higher workload and ventilation rate (Bethel et al. 1985).

While mouthpiece administration of SO_2 represents and unnatural mode of exposure, many asthmatics also have allergies that can contribute to nasal congestion and increased mouth-breathing. Thus, SO_2 penetration to the lungs during mouthpiece exposures may be representative of what some, but not most, individuals would experience with unencumbered ambient exposures to this pollutant. One expert has opined that lower airway exposure to SO_2 administered by mouthpiece at rest may be equivalent to that experienced by exercising

children exposed to similar ambient concentrations (M.T. Kleinman, personal communication, October 12, 2000).

There has been little research into the determinants of SO_2 susceptibility: one pilot study found that there were no differences in results of lung function testing or nasal lavage in black versus white adult asthmatics exposed to SO_2 in a controlled setting (Heath 1994). In another study of mild and moderate/severe asthmatics, the latter group manifested somewhat greater SO_2-induced bronchoconstriction; however, because the more severe asthmatics started with less functional reserve, such exposures in real life could produce effects that are more severe clinically (Linn 1987; California Air Resources Board 1994). Nonasthmatic adolescents (and possibly individuals in other age groups) with allergy and airway hyperresponsiveness (as manifested by exercise-induced bronchospasm) may also constitute an SO_2-susceptible subgroup (Koenig 1998). However, there have been no direct comparisons of the relative age-related susceptibility to SO_2 (Koenig 1998).

Increased ambient SO_2 concentrations have been linked epidemiologically with acute morbidity and mortality as well. In the London smog episode of 1952 and several other major events, excess morbidity and mortality were clearly associated with the air pollution mixture, though the relative etiologic roles of particulate matter, SO_2, aerosol acidity, or other unmeasured pollutant(s) cannot be delineated. Numerous other time-series analyses conducted since the mid-1980s suggest associations of several adverse outcomes with SO_2, as well as with airborne particles, aerosol acidity, and other pollutants, though the associations with SO_2 are often inconsistent or not statistically significant. Outcomes linked with SO_2 include modest decrements in children's lung function, increased risks of respiratory symptoms, hospital admissions for cardiac and respiratory illness, and increased daily mortality. (California Air Resources Board 1991; Dockery 1982; Charpin 1988; Derrienic 1989; Hatzakis 1986; Spix 1993; Dab 1996; Peters 1996; Touloumi 1996; Schwartz 1995; Burnett 1999; Ballester 1996; Wong 1999). Some of these associations between ambient SO_2 and adverse health outcomes have been reported when 24-hour SO_2 averages were near the range of the current California ambient standard (0.04 ppm, 24-hr average).

In many analyses that included particles or ozone as well as SO_2 in the regression models, the SO_2 effect diminishes substantially or is no longer associated with the health outcome (Spix; 1993 Schwartz 1995; Burnett 1999, Schwartz and Dockery 1992). This would suggest that the apparent SO_2 effect may in some cases be due to covariation with particles or other pollutants. In other analyses, however, there appear to be effects related to SO_2 but not particles, indicating that the explanation is not so simple (Charpin 1988; Hatzakis 1986). The series of recent articles from the APHEA study (Air Pollution and Health: a European Approach) suggest small, but significant SO_2-related effects on mortality and hospital admissions (Sunyer 1996; Katsouyanni 1997; Vigotti 1996). Interestingly, however, SO_2-related effects appear weaker in Central Europe, where SO_2 levels are generally higher than in the Western European cities studied (Zmirou 1998). In addition, many of the European studies did not utilize some of the more sophisticated statistical techniques that are considered state-of-the-art to control for both long- and short-term trends in the data. Some studies suggest greater magnitudes of association between SO_2 and adverse outcomes in children than adults (Hajat 1999). Several recent time-series studies also suggest an effect of ambient SO_2 on exacerbations of asthmatic symptoms or changes in lung function in children (Segala 1999; Chew 1999; Timonen and Pekkanen 1997). Other recent publications also suggest potential linkages between ambient SO_2 levels and adverse pregnancy outcomes (Rogers 2000, Wang 1999).

These epidemiological studies suggest that children and those with pre-existing respiratory and cardiac conditions (including asthma) may be particularly susceptible to the effects of exposure to ambient air pollution mixtures that include SO_2. However, there are no animal toxicology studies at such low concentrations that can provide a framework for understanding how SO_2, per se, could cause the effects observed in the epidemiological studies. Controlled human exposure studies using higher-than-ambient SO_2 concentrations suggest a linkage with a modest degree of inflammation of the lower and upper respiratory tract (Sandström 1989; Bechtold 1993). In any case, there is insufficient information to provide a mechanistic explanation for direct SO_2-related associations observed at low ambient concentrations. In addition to any possible direct toxic effects of SO_2, it is possible that this substance is an indicator for a complex mixture of pollutants, including acid sulfates, other particles, or unmeasured pollutants.

In summary, recent reports suggest that the current ambient standards of SO_2 may not provide an adequate margin of safety for potentially susceptible subpopulations, which include exercising asthmatics (1-hr standard), as well as children and those with pre-existing respiratory and cardiac conditions (24-hr standard). However, because of long-standing pollution control measures, concentrations of SO_2 monitored throughout California are generally well below the levels of the ambient air quality standards. Therefore, this pollutant was assigned to the second tier for review.

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5. OEHHA Recommendations on the Prioritization of Review and Revision

Recent evidence summarized in the preceding sections indicates that health effects may occur in infants, children, and other potentially susceptible subgroups exposed to pollutants at or near levels corresponding to several existing California ambient air quality standards. The quality and quantity of the evidence varied by pollutant. As indicated in section 4.1.2, five factors were involved in prioritizing the ambient standards for more extensive review:

(1) The extent of evidence of effects reported to occur at or near the existing ambient air quality standard.

(2) The nature and severity of those effects.

(3) The level of risk of effects anticipated to occur when ambient concentrations are at or near the level of the existing standard.

(4) Any evidence indicating that children may be more susceptible to effects than adults.

(6) The degree of outdoor exposure in California relative to the level of the standard.

Based on OEHHA staff's application of these factors, the criteria air pollutant standards were categorized into two tiers, with the first tier representing greater potential risks to public health. The first tier includes PM10, ozone, and nitrogen dioxide with the recommended review priority in that order. Although California has a separate standard for sulfates, this class of pollutants represents a subset of PM, and should therefore be considered in conjunction with PM10. Key evidence for ranking these pollutants into the first tier is discussed below.

There is substantial evidence of health effects associated with ambient PM10 levels at and possibly below the current State 24-hour and annual standards. These effects range from transient decrements in lung function to severe outcomes, including premature mortality and hospitalization for cardiovascular or pulmonary disease. In addition, the literature suggests the potential for significant health effects occurring in infants and children, including mortality, reduced birth weight, premature birth, asthma exacerbation, and acute respiratory infections. While the levels of risks when ambient concentrations of PM are at or near the standard are of similar magnitude to those of other pollutants, almost everyone in California is exposed at times to levels at or above the current State standard during parts of the year.

Epidemiological studies suggest effects of ozone exposure on lung function, asthma exacerbation, and other indices of acute respiratory morbidity in adults and children at ozone levels lower than the current State standard. Controlled studies involving multi-hour exposures also suggest the potential for respiratory symptoms, lung function decrements, airway inflammation and hyper-responsiveness when ambient concentrations are at or near the level of the current ozone standard. A large fraction of California's population resides in areas in which ozone concentrations occur at or above the current State standard, primarily during daylight hours in the summer.

Several recent controlled exposure studies suggest that nitrogen dioxide exposures quite close to the existing ambient standard may enhance the response of allergic asthmatics to airborne allergens. Most childhood asthma has an allergic component, which suggests that ambient NO_2 may exert an indirect effect on children. Although California has met the ambient

air quality standard for nitrogen dioxide since 1996, levels close to the standard are occasionally recorded at some sites.

The second tier includes lead, carbon monoxide, hydrogen sulfide, and sulfur dioxide. Exposure to lead can affect the development of children's nervous systems, including impacts on intelligence and behavior. Exposure to airborne lead at a level corresponding to the current State standard would not be protective of the health of infants and children, and lead is currently listed as a Toxic Air Contaminant (TAC) with no safe threshold. However, throughout most of California, ambient air exposures to lead are about an order of magnitude lower than the standard. Since there are few areas of the State where ambient lead represents an ongoing public health concern, the review of the ambient air quality standard for lead was placed in the second tier.

Evidence from controlled exposure studies suggests that the existing State ambient air quality standards for carbon monoxide and sulfur dioxide are reasonably health protective. However, some evidence from observational epidemiological studies suggests the potential for adverse health effects related to carbon monoxide and sulfur dioxide, including increased risks of hospitalization and premature mortality in the general population at relatively low ambient levels. In contrast, there is little evidence for effects in infants and children. Epidemiological studies suggesting adverse effects attributable to these pollutants are complicated by their correlation with other traffic-related pollutants. Environmental epidemiological studies of health effects associated with exposure to carbon monoxide are likely to be based on ambient measurements that bear little resemblance to individual exposures. Moreover, for hydrogen sulfide and sulfur dioxide, ambient levels are very low relative to the standard throughout most of the State. In addition, the hydrogen sulfide standard received a lower priority for review since it is intended primarily to prevent odor annoyance and associated symptoms, outcomes that are clearly not as serious as those associated with pollutants ranked in the first tier.

The prioritization of the ambient standards into first and second tiers may be revised in light of comments from the public and new scientific evidence. Nevertheless, at this juncture, OEHHA staff members believe that the weight of the evidence currently favors the designation of particulate matter as the highest priority pollutant class for review.

Appendices

STAFF REPORT

Adequacy of California Ambient Air Quality Standards: Children's Environmental Health Protection

Appendix A. **Text of Bill**

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December 22, 2000

Appendix A

Adequacy of California Ambient Air Quality Standards: Children's Environmental Health Protection

Text of Bill

December 22, 2000

BILL NUMBER: SB 25 CHAPTERED
BILL TEXT

CHAPTER 731
FILED WITH SECRETARY OF STATE OCTOBER 10, 1999
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AMENDED IN SENATE JUNE 1, 1999
AMENDED IN SENATE APRIL 28, 1999
AMENDED IN SENATE MARCH 22, 1999

INTRODUCED BY Senator Escutia
(Principal coauthors: Assembly Members Kuehl and Villaraigosa)
(Coauthors: Senators Alarcon, Figueroa, Ortiz, Perata, Polanco, Sher, Solis, and Speier)
(Coauthors: Assembly Members Alquist, Aroner, Firebaugh, Honda, Jackson, Knox, Lempert, Mazzoni, Romero, Shelley, Steinberg, Thomson, Vincent, Washington, and Wildman)

DECEMBER 7, 1998

An act to amend Sections 39606, 39660, and 40451 of, to add Section 39617.5 to, to add Part 3 (commencing with Section 900) to Division 1 of, and to add Article 4.5 (commencing with Section 39669.5) to Chapter 3.5 of Part 2 of Division 26 of, the Health and Safety Code, relating to environmental health protection.

LEGISLATIVE COUNSEL'S DIGEST

SB 25, Escutia. Environmental health protection: children.
(1) Existing law requires the State Air Resources Board to adopt ambient air quality standards in consideration of specified factors, including public health effects, as provided, and to specify threshold levels for health effects in listing substances determined to be toxic air contaminants. Existing law requires the Office of Environmental Health Hazard Assessment, upon request of the state board, to evaluate the health effects of and prepare recommendations regarding specified substances which may be or are emitted into the

ambient air and that may be determined to be toxic air contaminants. Under existing law, the state board's request is required to be in accordance with an agreement that ensures that the office's workload in implementing these provisions will not be increased over that budgeted for the 1991-92 fiscal year, as provided.

This bill would eliminate the requirement for that agreement, and would impose specified requirements on the state board and the office generally relating to the protection of infants and children from environmental health hazards. The bill would require the state board, not later than December 31, 2000, to review all existing health-based ambient air quality standards to determine whether the standards adequately protect the health of the public, including infants and children, and to revise the highest priority air quality standard determined to be inadequate, not later than December 31, 2002. The bill would require the office, by July 1, 2001, to establish a list of up to 5 specified toxic air contaminants that may cause infants and children to be especially susceptible to illness. The bill would require the state board to review and, as appropriate, revise any control measures adopted for those toxic air contaminants, to reduce exposure to those toxic air contaminants, as provided.

(2) Existing law requires the South Coast Air Quality Management District to notify all schools in the South Coast Air Basin whenever any federal primary ambient air quality standard is predicted to be exceeded.

This bill would also require the south coast district to notify day care centers in that basin, to the extent feasible and upon request. The bill would create a state-mandated local program by imposing new duties on the south coast district.

(3) The bill would create the Children's Environmental Health Center within the Environmental Protection Agency to, among other things, serve as chief advisor to the Secretary for Environmental Protection and to the Governor on matters within the jurisdiction of the agency relating to environmental health and environmental protection as it relates to children.

(4) This bill would incorporate additional changes to Section 40451 of the Health and Safety Code, proposed by SB 1195, to be operative only if SB 1195 and this bill are both chaptered on or before January 1, 2000, and this bill is chaptered last.

(5) The California Constitution requires the state to reimburse local agencies and school districts for certain costs mandated by the state. Statutory provisions establish procedures for making that reimbursement, including the creation of a State Mandates Claims Fund to pay the costs of mandates that do not exceed $1,000,000 statewide and other procedures for claims whose statewide costs exceed $1,000,000.

This bill would provide that, if the Commission on State Mandates determines that the bill contains costs mandated by the state, reimbursement for those costs shall be made pursuant to these statutory provisions.

THE PEOPLE OF THE STATE OF CALIFORNIA DO ENACT AS FOLLOWS:

SECTION 1. The Legislature finds and declares all of the following:
(a) Infants and children have a higher ventilation rate than adults relative to their body weight and lung surface area, resulting in a greater dose of pollution delivered to their lungs.
(b) Children have narrower airways than adults. Thus, irritation or inflammation caused by air pollution that would produce only a slight response in an adult can result in a potentially significant obstruction of the airway in a young child.
(c) Children spend significantly more time outdoors, especially in the summer, when ozone air pollution levels are typically highest. National statistics show that children spend an average of 50 percent more time outdoors than adults.
(d) Air pollution is known to exacerbate asthma and be a trigger for asthma attacks in infants and children, 500,000 of whom are afflicted with this chronic lung disease in California.
(e) Infant's and children's developing organs and tissues are more susceptible to damage from some environmental contaminants than are adult organs and tissues.
(f) It is the intent of the Legislature in enacting this act, to require that the state's air quality standards and airborne toxic control measures be reviewed to determine if they adequately protect the health of infants and children, and that these standards and measures be revised if they are determined to be inadequate.
(g) It is also the intent of the Legislature in enacting this act to require the State Air Resources Board and the Office of Environmental Health Hazard Assessment to consider the health impacts to all populations of children, including special subpopulations of infants and children that comprise a meaningful portion of the general population, such as children with asthma, cystic fibrosis, or other respiratory conditions or diseases, in setting or revising standards pursuant to this act.
SEC. 2. Part 3 (commencing with Section 900) is added to Division 1 of the Health and Safety Code, to read:
PART 3. CHILDREN'S ENVIRONMENTAL HEALTH CENTER

900. There is hereby created the Children's Environmental Health

Center within the Environmental Protection Agency. The primary purposes of the center shall include all of the following:
(a) To serve as the chief advisor to the Secretary for Environmental Protection and to the Governor on matters within the jurisdiction of the Environmental Protection Agency relating to environmental health and environmental protection as each of those matters relates to children.
(b) To assist the boards, departments, and offices within the Environmental Protection Agency to assess the effectiveness of statutes, regulations, and programs designed to protect children from environmental hazards.
(c) To coordinate within the Environmental Protection Agency and with other state agencies, regulatory efforts, research and data collection, and other programs and services that impact the environmental health of children, and coordinate with appropriate federal agencies conducting related regulatory efforts and research and data collection.
(d) In consultation with the State Air Resources Board and the Office of Environmental Health Hazard Assessment, and notwithstanding Section 7550.5 of the Government Code, to report to the Legislature and the Governor no later than December 31, 2001, on the progress of the state board and the office toward implementing the act that added this part during the 1999-2000 Regular Session and to make recommendations for any statutory or regulatory changes that may be necessary to carry out the intent of that act to protect the public health, including infants and children, from air pollutants and toxic air contaminants.
SEC. 3. Section 39606 of the Health and Safety Code is amended to read:
39606. (a) The state board shall do both of the following:
(1) Based upon similar meteorological and geographic conditions and consideration for political boundary lines whenever practicable, divide the state into air basins to fulfill the purposes of this division.
(2) Adopt standards of ambient air quality for each air basin in consideration of the public health, safety, and welfare, including, but not limited to, health, illness, irritation to the senses, aesthetic value, interference with visibility, and effects on the economy. These standards may vary from one air basin to another. Standards relating to health effects shall be based upon the recommendations of the Office of Environmental Health Hazard Assessment.
(b) In its recommendations for submission to the state board pursuant to paragraph (2) of subdivision (a), the Office of Environmental Health Hazard Assessment, to the extent that information is available, shall assess the following:

(1) Exposure patterns, including, but not limited to, patterns determined by relevant data supplied by the state board, among infants and children that are likely to result in disproportionately high exposure to ambient air pollutants in comparison to the general population.
(2) Special susceptibility of infants and children to ambient air pollutants in comparison to the general population.
(3) The effects on infants and children of exposure to ambient air pollutants and other substances that have a common mechanism of toxicity.
(4) The interaction of multiple air pollutants on infants and children, including the interaction between criteria air pollutants and toxic air contaminants.
(c) In assessing the factors specified in subdivision (b), the office shall use current principles, practices, and methods used by public health professionals who are experienced practitioners in the field of human health effects assessment. The scientific basis or scientific portion of the method used by the office to assess the factors set forth in subdivision (b) shall be subject to peer review as described in Section 57004 or in a manner consistent with the peer review requirements of Section 57004. Any person may submit any information for consideration by the entity conducting the peer review, which may receive oral testimony.
(d) (1) No later than December 31, 2000, the state board in consultation with the office, shall review all existing health-based ambient air quality standards to determine whether, based on public health, scientific literature, and exposure pattern data, the standards adequately protect the health of the public, including infants and children, with an adequate margin of safety. The state board shall publish a report summarizing these findings.
(2) The state board shall revise the highest priority ambient air quality standard determined to be inadequate to protect infants and children with an adequate margin of safety, based on its report, no later than December 31, 2002. Following the revision of the highest priority standard, the state board shall revise any additional standards determined to be inadequate to protect infants and children with an adequate margin of safety, at the rate of at least one per year. The standards shall be established at levels that adequately protect the health of the public, including infants and children, with an adequate margin of safety.
(e) Nothing in this section shall restrict the authority of the state board to consider additional information in establishing ambient air quality standards or to adopt an ambient air quality standard designed to protect vulnerable populations other than infants and children.
SEC. 4. Section 39617.5 is added to the Health and Safety Code, to

read:
39617.5. (a) Not later than January 1, 2003, the state board shall do all of the following:
(1) Evaluate the adequacy of the current monitoring network for its ability to gather the data necessary to determine the exposure of infants and children to air pollutants including criteria air pollutants and toxic air contaminants.
(2) Identify areas where the exposure of infants and children to air pollutants is not adequately measured by the current monitoring network.
(3) Recommend changes to improve air pollution monitoring networks and data collection to more accurately reflect the exposure of infants and children to air pollutants.
(b) In carrying out this section, the state board, in cooperation with the districts, shall expand its existing monitoring program in six communities around the state in nonattainment areas, as selected by the state board, to include special monitoring of children's exposure to air pollutants and toxic contaminants. The expanded program shall include placing air pollution monitors near schools, day care centers, and outdoor recreational facilities that are in close proximity to, or downwind from, major industrial sources of air pollutants and toxic air contaminants, including, freeways and major traffic areas. The purpose of the air pollution monitors shall be to conduct sampling of air pollution levels affecting children. Monitoring may include the use of fixed, mobile, and other monitoring devices, as appropriate.
(c) The expanded monitoring program shall include the following:
(1) Monitoring during multiple seasons and at multiple locations within each community at schools, day care centers, recreational facilities, and other locations where children spend most of their time.
(2) A combination of upgrading existing fixed monitoring sites, establishing new fixed monitoring sites, and conducting indoor and outdoor sampling and personal exposure measurements in each community to provide the most comprehensive data possible on the levels of children's exposure to air pollutants and toxic air contaminants.
(d) Data collected from expanded air quality monitoring activities conducted pursuant to this section may be used for any purpose authorized by law, including, but not limited to, determinations as to whether an area has attained or has not attained the state and national ambient air quality standards, if the monitoring devices from which the data was collected meet the monitoring requirements specified in Section 58.14 of Title 40 of the Code of Federal Regulations for special purpose monitors, all other monitoring requirements of Part 58 of Title 40 of the Code of Federal Regulations, and all applicable requirements specified in regulations

adopted by the state board.
SEC. 5. Section 39660 of the Health and Safety Code is amended to read:
39660. (a) Upon the request of the state board, the office, in consultation with and with the participation of the state board, shall evaluate the health effects of and prepare recommendations regarding substances, other than pesticides in their pesticidal use, which may be or are emitted into the ambient air of California and that may be determined to be toxic air contaminants.
(b) In conducting this evaluation, the office shall consider all available scientific data, including, but not limited to, relevant data provided by the state board, the State Department of Health Services, the Occupational Safety and Health Division of the Department of Industrial Relations, the Department of Pesticide Regulation, international and federal health agencies, private industry, academic researchers, and public health and environmental organizations. The evaluation shall be performed using current principles, practices, and methods used by public health professionals who are experienced practitioners in the fields of epidemiology, human health effects assessment, risk assessment, and toxicity.
(c) (1) The evaluation shall assess the availability and quality of data on health effects, including potency, mode of action, and other relevant biological factors, of the substance, and shall, to the extent that information is available, assess all of the following:
(A) Exposure patterns among infants and children that are likely to result in disproportionately high exposure to ambient air pollutants in comparison to the general population.
(B) Special susceptibility of infants and children to ambient air pollutants in comparison to the general population.
(C) The effects on infants and children of exposure to toxic air contaminants and other substances that have a common mechanism of toxicity.
(D) The interaction of multiple air pollutants on infants and children, including the interaction between criteria air pollutants and toxic air contaminants.
(2) The evaluation shall also contain an estimate of the levels of exposure that may cause or contribute to adverse health effects. If it can be established that a threshold of adverse health effects exists, the estimate shall include both of the following factors:
(A) The exposure level below which no adverse health effects are anticipated.
(B) An ample margin of safety that accounts for the variable effects that heterogeneous human populations exposed to the substance under evaluation may experience, the uncertainties associated with

the applicability of the data to human beings, and the completeness and quality of the information available on potential human exposure to the substance. In cases in which there is no threshold of significant adverse health effects, the office shall determine the range of risk to humans resulting from current or anticipated exposure to the substance.

(3) The scientific basis or scientific portion of the method used by the office to assess the factors set forth in this subdivision shall be reviewed in a manner consistent with this chapter by the Scientific Review Panel on Toxic Air Contaminants established pursuant to Article 5 (commencing with Section 39670). Any person may submit any information for consideration by the panel, which may receive oral testimony.

(d) The office shall submit its written evaluation and recommendations to the state board within 90 days after receiving the request of the state board pursuant to subdivision (a). The office may, however, petition the state board for an extension of the deadline, not to exceed 30 days, setting forth its statement of the reasons that prevent the office from completing its evaluation and recommendations within 90 days. Upon receipt of a request for extension of, or noncompliance with, the deadline contained in this section, the state board shall immediately transmit to the Assembly Committee on Rules and the Senate Committee on Rules, for transmittal to the appropriate standing, select, or joint committee of the Legislature, a statement of reasons for extension of the deadline, along with copies of the office's statement of reasons that prevent it from completing its evaluation and recommendations in a timely manner.

(e) (1) The state board or a district may request, and any person shall provide, information on any substance that is or may be under evaluation and that is manufactured, distributed, emitted, or used by the person of whom the request is made, in order to carry out its responsibilities pursuant to this chapter. To the extent practical, the state board or a district may collect the information in aggregate form or in any other manner designed to protect trade secrets.

(2) Any person providing information pursuant to this subdivision may, at the time of submission, identify a portion of the information submitted to the state board or a district as a trade secret and shall support the claim of a trade secret, upon the written request of the state board or district board. Subject to Section 1060 of the Evidence Code, information supplied that is a trade secret, as specified in Section 6254.7 of the Government Code, and that is so marked at the time of submission, shall not be released to any member of the public. This section does not prohibit the exchange of properly designated trade secrets between public agencies when those

trade secrets are relevant and necessary to the exercise of their jurisdiction if the public agencies exchanging those trade secrets preserve the protections afforded that information by this paragraph.

(3) Any information not identified as a trade secret shall be available to the public unless exempted from disclosure by other provisions of law. The fact that information is claimed to be a trade secret is public information. Upon receipt of a request for the release of information that has been claimed to be a trade secret, the state board or district shall immediately notify the person who submitted the information, and shall determine whether or not the information claimed to be a trade secret is to be released to the public. The state board or district board, as the case may be, shall make its determination within 60 days after receiving the request for disclosure, but not before 30 days following the notification of the person who submitted the information. If the state board or district decides to make the information public, it shall provide the person who submitted the information 10 days' notice prior to public disclosure of the information.

(f) The office and the state board shall give priority to the evaluation and regulation of substances based on factors related to the risk of harm to public health, amount or potential amount of emissions, manner of, and exposure to, usage of the substance in California, persistence in the atmosphere, and ambient concentrations in the community. In determining the importance of these factors, the office and the state board shall consider all of the following information, to the extent that it is available:

(1) Research and monitoring data collected by the state board and the districts pursuant to Sections 39607, 39617.5, 39701, and 40715, and by the United States Environmental Protection Agency pursuant to paragraph (2) of subsection (k) of Section 112 of the federal act (42 U.S.C. Sec. 7412(k)(2)).

(2) Emissions inventory data reported for substances subject to Part 6 (commencing with Section 44300) and the risk assessments prepared for those substances.

(3) Toxic chemical release data reported to the state emergency response commission pursuant to Section 313 of the Emergency Planning and Community Right-To-Know Act of 1986 (42 U.S.C. Sec. 11023) and Section 6607 of the Pollution Prevention Act of 1990 (42 U.S.C. Sec. 13106).

(4) Information on estimated actual exposures to substances based on geographic and demographic data and on data derived from analytical methods that measure the dispersion and concentrations of substances in ambient air.

SEC. 6. Article 4.5 (commencing with Section 39669.5) is added to Chapter 3.5 of Part 2 of Division 26 of the Health and Safety Code,

to read:

Article 4.5. Special Provisions For Infants And Children

39669.5. The Legislature finds and declares that certain toxic air contaminants may pose risks that cause infants and children to be especially susceptible to illness and that certain actions are necessary to ensure their safety from toxic air contaminants.
(a) By July 1, 2001, the following shall occur:
(1) The office, in consultation with the state board, shall establish a list of up to five toxic air contaminants identified or designated by the state board pursuant to Section 39657 that may cause infants and children to be especially susceptible to illness. In developing the list, the office shall take into account public exposures to toxic air contaminants, whether by themselves or interacting with other toxic air contaminants or criteria pollutants, and the factors listed in subdivision (c) of Section 39660. The office shall submit a report containing the list and its reasons for including the toxic air contaminants on the list to the Scientific Review Panel on Toxic Air Contaminants established pursuant to Article 5 (commencing with Section 39670).
(2) The scientific review panel, in a manner consistent with this chapter, shall review the list of toxic air contaminants submitted by the office pursuant to paragraph (1). As part of the review, any person may submit any information for consideration by the panel, which may receive oral testimony.
(b) (1) Within two years of the establishment of the list required pursuant to subdivision (a), the state board shall review and, as appropriate, revise any control measures adopted for the toxic air contaminants identified on the list, to reduce exposure to those toxic air contaminants pursuant to Article 4 (commencing with Section 39665), to protect public health, and particularly infants and children.
(2) Within three years of the establishment of the list required pursuant to subdivision (a), for up to five of those toxic air contaminants for which no control measures have been previously adopted, the state board shall prepare a report on the need for regulations, following the procedure specified in Section 39665. The state board shall adopt within that same three-year timeframe, as appropriate, any new control measures to reduce exposure to those toxic air contaminants pursuant to Article 4 (commencing with Section 39665), to protect public health, particularly infants and children.

(c) Beginning July 1, 2004, the office shall annually evaluate at least 15 toxic air contaminants identified or designated by the state board pursuant to Section 39657, and provide threshold exposure

levels and nonthreshold health values, as appropriate, for those toxic air contaminants. The activities required pursuant to this subdivision shall continue until all toxic air contaminants are evaluated. The levels shall be established pursuant to the procedures adopted for health and risk assessments pursuant to paragraph (2) of subdivision (b) of Section 44360, and taking into account the factors listed in subdivision (c) of Section 39660. Based on this evaluation, and after review by the scientific review panel as prescribed in paragraph (2) of subdivision (a), the office shall update the list established pursuant to subdivision (a), by July 1, 2005, and each year thereafter. Within three years of the initial or subsequent listing update, for up to five of the toxic air contaminants contained on that list for which no control measures have been previously adopted, or for at least five of the toxic air contaminants if more than five toxic air contaminants have been identified, the state board shall prepare a report on the need for regulation, following the procedure specified in Section 39665. The state board shall adopt within that three-year timeframe, as appropriate, new control measures, pursuant to Article 4 (commencing with Section 39665), to reduce exposure to those toxic air contaminants, to protect public health, and particularly infants and children.

(d) Toxic air contaminants evaluated and listed pursuant to this section shall not include substances in those uses that are not subject to regulation by the state board pursuant to this chapter.

SEC. 7. Section 40451 of the Health and Safety Code is amended to read:

40451. (a) The south coast district shall use the Pollutant Standards Index developed by the Environmental Protection Agency and shall report and forecast pollutant levels daily for dissemination in the print and electronic media.

(b) Using existing communication facilities available to it, the south coast district shall notify all schools and, to the extent feasible and upon request, daycare centers in the South Coast Air Basin whenever any federal primary ambient air quality standard is predicted to be exceeded.

(c) Whenever it becomes available, the south coast district shall disseminate to schools, amateur adult and youth athletic organizations, and all public agencies operating parks and recreational facilities in the south coast district the latest scientific information and evidence regarding the need to restrict exercise and other outdoor activities during periods when federal primary air quality standards are exceeded.

(d) Once every two months and annually, the south coast district shall report on the number of days and locations that federal and state ambient air quality standards were exceeded and the number of

days and locations of these occurrences.
SEC. 7.5. Section 40451 of the Health and Safety Code is amended to read:
40451. (a) The south coast district shall use the Pollutant Standards Index developed by the United States Environmental Protection Agency and shall report and forecast pollutant levels daily for dissemination in the print and electronic media. Commencing July 1, 2001, the south coast district shall also include in its report and forecast levels of PM2.5 in excess of the 24-hour federal ambient air standard, as adopted in July 1997, or any standard adopted by the United States Environmental Protection Agency that succeeds that standard.
(b) Using existing communication facilities available to it, the south coast district shall notify all schools and, to the extent feasible and upon request, daycare centers in the South Coast Air Basin whenever any federal primary ambient air quality standard is predicted to be exceeded. Commencing July 1, 2001, using communication facilities available to it, the south coast district shall also notify all schools in the South Coast Air Basin when the ambient level of PM2.5 is predicted to exceed the 24-hour federal ambient air standard, as adopted in July 1997, or any standard adopted by the United States Environmental Protection Agency that succeeds that standard.
(c) Whenever it becomes available, the south coast district shall disseminate to schools, amateur adult and youth athletic organizations, and all public agencies operating parks and recreational facilities in the south coast district the latest scientific information and evidence regarding the need to restrict exercise and other outdoor activities during periods when federal primary air quality standards and the 24-hour federal ambient air standard for PM2.5, as adopted in July 1997, or any standards adopted by the United States Environmental Protection Agency that succeed those standards, are exceeded.
(d) Once every two months and annually, the south coast district shall report on the number of days and locations that federal and state ambient air quality standards were exceeded. Commencing July 1, 2001, the south coast district shall also include in that report the number of days and locations on and at which the 24-hour federal ambient air standard for PM2.5, as adopted in July 1997, or any standard adopted by the United States Environmental Protection Agency that succeeds that standard, is exceeded.
SEC. 8. Section 7.5 of this bill incorporates amendments to Section 40451 of the Health and Safety Code proposed by both this bill and SB 1195. It shall only become operative if (1) both bills are enacted and become effective on or before January 1, 2000, (2) each bill amends Section

40451 of the Health and Safety Code, and (3) this bill is enacted after SB 1195, in which case Section 7 of this bill shall not become operative.

SEC. 9. Notwithstanding Section 17610 of the Government Code, if the Commission on State Mandates determines that this act contains costs mandated by the state, reimbursement to local agencies and school districts for those costs shall be made pursuant to Part 7 (commencing with Section 17500) of Division 4 of Title 2 of the Government Code. If the statewide cost of the claim for reimbursement does not exceed one million dollars ($1,000,000), reimbursement shall be made from the State Mandates Claims Fund.

Appendix B

Children's Health Studies in California

December 22, 2000

B.1 Children's Health Study – Southern California

The ARB Children's Health Study is designed to assess the health effects on children of long-term exposures to southern California's mix of air pollutants (Peters et al., 1999). For up to eight years, the respiratory health of 5,000 children from 12 southern California communities, is being assessed annually. Initial findings indicate an association between poor air quality and lower lung function. Slower lung growth appears to be associated with exposure to particulate matter, nitrogen dioxide, and acid vapor. In communities with high ozone levels, lower lung capacity was seen in boys spending extensive amounts of time outdoors and in girls with asthma. The study will continue through 2003.

B.2 Fresno Asthmatic Children's Environment Study (FACES)

This ARB-sponsored study, about to begin in Fresno, will focus on childhood asthma and how air pollution exposures impact the progression and severity of the disease and overall respiratory health of 450 asthmatic children. The children will be followed for up to four years. The overall goal is to determine the effects of exposure to particulate matter air pollution in combination with other pollutants, on asthmatic children. The study addresses the concern that repeated short-term responses to air pollution may translate into long-term health effects, that include the worsening of asthma over time.

B.3 L.A. Children's Asthma Studies

OEHHA has completed two studies, sponsored by the Centers for Disease Control and Prevention (CDC) with supplemental funding from ARB, examining the effects of air pollution on asthma among African-American children living in Los Angeles. The sutdy focused on African-American children since this subgroup appears to be driving the significant increase in asthma morbidity and mortality observed throughout the United States over the last two decades. In a pilot study, 83 children aged 7 to 12 years, were recruited from allergy and pediatric clinics in central Los Angeles. Daily data on asthma symptoms were obtained over a three-month period, along with daily pollution and meteorological data. This study demonstrated an association between PM10 and several different asthma symptoms, including shortness of breath (Ostro et al., 1995).

In the full epidemiological study, 138 children in central Los Angeles and Pasadena were recruited. Daily data on respiratory symptoms and medication use were recorded for 13 weeks and examined in conjunction with data on ozone, nitrogen dioxide, particulate matter (PM10 and PM2.5), meteorological variables, pollens, and molds. Using generalized estimating equations, an association was found between daily PM10 and several different asthma symptoms including shortness of breath, cough and wheeze (Ostro et al., 2000). In addition, nitrogen dioxide and outdoor molds were associated with asthma exacerbation. The impact of air pollution on this population of African-American children in Los Angeles with asthma was clinically meaningful. For example, for an interquartile change in PM10 of 17 $\mu g/m^3$, there were 14% increase in daily shortness of breath and 10% increase in daily cough.

B.4 Pediatric Asthma in Sacramento

OEHHA has completed a study to determine whether indigent populations might be at increased risk of asthmatic exacerbation from exposure to ambient air pollution relative to the general population (Lipsett et al., 1999). To begin to address this issue, the potential associations between ambient air pollution and asthma exacerbation among young Medi-Cal beneficiaries in the Sacramento metropolitan area was examined. Hospital admission and emergency room visit claims were aggregated to create daily counts of asthma-related Medi-Cal events for beneficiaries under age 20 for the period January 1992 to April 1994. Daily population exposures to ambient levels of nitrogen dioxide, carbon monoxide, ozone, and coefficient of haze (a measure particulate matter) were measured. Significant associations were found between claims and daily concentrations of ozone, nitrogen dioxide, and coeffficient of haze. This study suggests significantly increased risks of clinically meaningful, air pollution-related asthma exacerbations in an indigent population.

B.5 Children's Activity Pattern Study and Breathing Study

ARB sponsored a study, completed in 1991, that examined the activity patterns of 2000 children ages 0-11, especially those aspects most relevant to air pollutant exposures (Wiley et al., 1991a). Diary information was obtained on the time spent in different locations and activities throughout the day, and on the children's proximity to, and use of, specific sources of pollutants throughout the day. A prior, similar study of adult Californians obtained similar data on teenagers (Wiley et al., 1991b). ARB also sponsored a study of Californians' pulmonary ventilation (breathing) rates and volumes during normal activities, such as walking and playing, on the largest group of children to date (Adams, 1993). These studies together have been used extensively to improve estimates of children's exposures to air pollutants.

B.7 References

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Lipsett M, Campleman S, Ostro B (1999) Air Pollution and Pediatric Asthma Exacerbation in Sacramento, California. Presented at the Annual Meetings of the American Thoracic Society, San Diego.

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Wiley, JA, Robinson, JP, Piazza, T, Garrett, K, Cirksena, K, Cheng, YT, Martin, G, (1991a), *Activity Patterns of California Residents*, Final Report to the California Air Resources Board, contract no.A6-177-33.

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Appendix C

ARB Air Pollutant Summaries

December 22, 2000

C.1 Introduction

Appendix C contains brief summaries of air quality, trends, emissions and sources for each criteria pollutant. There are several ways in which air quality information is commonly presented. Concentrations measured over 1-hour, 8-hours or 24-hours, annual averages, and the number of days above the State and national standards are actual measured values. These data for 1999 are presented in Table 3.3-1 on page 10.

Air quality trends are frequently reported as "Expected Peak Daily Concentrations" (EPDCs), or "peak indicators". A peak indicator is a calculated value based on measured data that represents the maximum concentration of a pollutant that is expected to occur once per year. It is based on a robust statistical calculation that provides a trend indicator that is less influenced by year-to-year changes in meteorology than actual measured data often is.

Except for sulfates, for which there are insufficient data available to calculate peak indicators, the air quality trends data presented below represent peak indicator values. All values on the x-axis are years. Further information on air quality, trends, and emissions for specific locations throughout the State, including information on site openings, site closures, and data completeness is available from the ARB's websites www.arb.ca.gov/aqd/almanac/almanac99.htm and www.arb.ca.gov, or from the ARB's Planning and Technical Support Division.

Indoor and outdoor air pollutant exposures in California are also summarized in this Appendix for the studies that provided parallel monitoring. However, note that the averaging times for the pollutants in many cases were not the averaging times for the ambient air quality standards. The information provides some relative comparisons for indoor and outdoor concentrations for the pollutants measured.

C.2 Background Pollutant Concentrations

There is a background concentration of many air pollutants. Background concentration is defined as the concentration that would be observed in the absence of anthropogenic emissions, ie., those resulting from human activities, such as from industrial facilities, and motor vehicles. Emissions of VOC, NO_x, and SO_x from natural processes are the precursors of background O_3. The background concentration of ozone is currently about 1/2 of the state standard, or about 0.04 PPM. Sources of background PM include particles of soil and crustal material, organic particles resulting from natural combustion processes such as wildfires, and organic aerosols formed from VOC emissions from vegetation. The background concentration of PM10 is approximately 1/3 of the state standard, or about 10 $\mu g/m^3$ annual geometric mean (Stefan and Husar, 1997). In addition, natural emissions of gaseous sulfur compounds contribute to the background sulfate concentration.

The Intergovernmental Panel on Climate Change (IPCC) Special Report on Emission Scenarios (http://www.unep.ch/ipcc/pub/sres-e.pdf) has presented several scenarios on growth in NO_x, VOC, CO, and methane (CH_4) emissions that suggest a significant increase in background levels of near- surface ozone throughout much of the northern mid-latitudes. As background pollution levels increase, they make up a larger

fraction of the total pollution allowed before the ambient air quality standards are exceeded. Increases in background concentrations result in the need to gain greater reductions from controllable sources. For example, if an area's background ozone concentration increased from 0.04 to 0.05 PPM, the emission reductions needed to attain the state standard could easily increase by 10 percent or more.

C.3 Airborne Particulate Matter (PM10)

C.3.1 Introduction

Airborne particulate matter with an aerodynamic diameter of 10 microns or less (PM10) is composed of a mixture of substances that includes elements (such as carbon, lead, nickel and iron), compounds (such as nitrates, sulfates, and polycyclic aromatic hydrocarbons), and complex mixtures (such as diesel exhaust and soil). Also present on particles are allergens and compounds derived from bacteria called endotoxins. Particles can be emitted directly into the atmosphere, such as from diesel vehicles, or can be formed gases that are transformed into particles through physical and chemical processes in the atmosphere (for example, nitrates from gaseous nitric acid).

C.3.2 Air Quality, Sources, and Emissions

Currently, over 99 percent of Californians breathe air that violates the State PM10 standards during at least part of the year. Consequently, particulate matter is receiving greater attention.

Maximum peak indicator concentrations of PM10 are illustrated in Figures C.3-1, C.3-2, and C.3-3. Maximum peak indicator information illustrated in Figure C.3-1 incorporates all sites in California, and shows large peaks in 1990, 1994, and 1998. The influence of specific monitoring sites on these peaks and trends can be evaluated by re-analyzing data with and without specific sites. This analysis is illustrated in Figures C.3-2 and C.3-3. When the data from the Great Basin Valley sites are excluded from the analysis (Figure C.3-2), increases are observed in 1990, and an increasing trend is observed through 1999. The increase in 1994 therefore appears to have been influenced by the Great Basin Valley sites. When in addition to the Great Basin Valley sites, the Mojave Desert and Salton Sea sites are excluded from the analyses (Figure C.3-3), there are few increases observed, indicating that these sites also were responsible for the peak occurrences for certain years. The PM sources for the Great Basin, Mojave Desert, and Salton Sea sites are thought to be wind-blown dust.

An analysis of the maximum annual geometric mean PM10 concentrations without the Great Basin Valley sites is presented in Figure C.3-4. There is a peak observed in 1996. The maximum annual geometric mean PM10 analysis without the Great Basin Valley, Mojave Desert, and Salton Sea sites is illustrated in Figure C.3-5. The maximum PM concentrations decreased throughout the years and there are no peak years observed. The Mojave Desert and Salton Sea sites therefore contribute to the highest annual geometric mean PM10 concentrations observed in the State.

The emissions and sources of PM10 statewide are illustrated in Figure C.3-6. The most prominent source is “area-wide” that includes wind-blown dust, and dust from roadways. Activities that contribute to high PM10 can include wood burning, agricultural activities, and driving on unpaved roads. The PM10 concentrations do not relate well to

population growth or vehicle usage, and high PM10 concentrations do not always occur in high population areas.

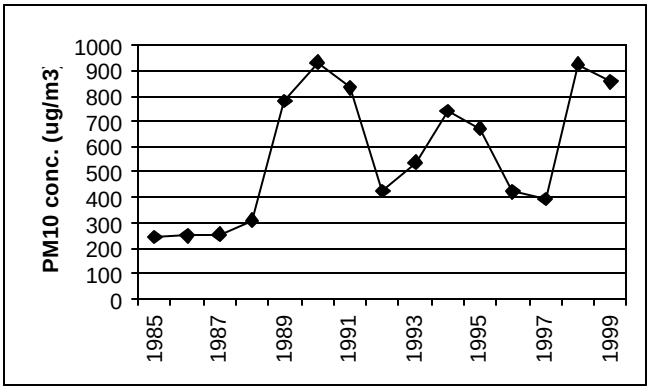


Figure C.3-1. Maximum 24-hour peak indicator for Statewide PM10 (μg/m^3).

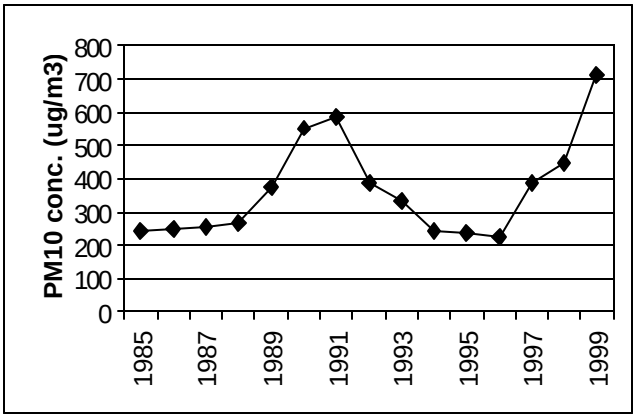


Figure C.3-2. Maximum 24-hour peak indicator for Statewide PM10 (μg/m^3), not including Great Valley Basin sites

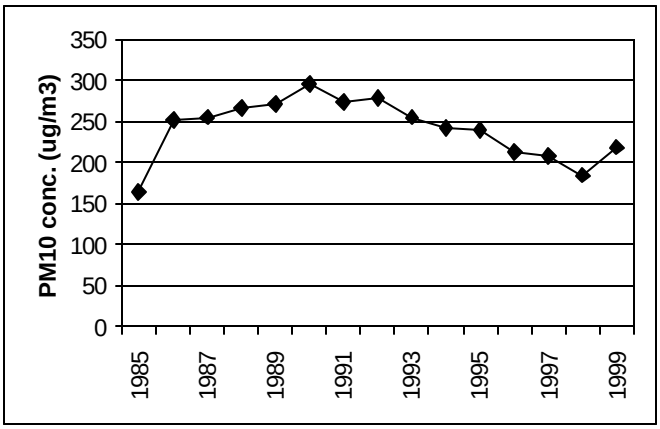


Figure C.3-3. Maximum 24-hour peak indicator for Statewide PM10 (µg/m^3), not including Great Basin Valley, Mojave Desert, and Salton Sea sites.

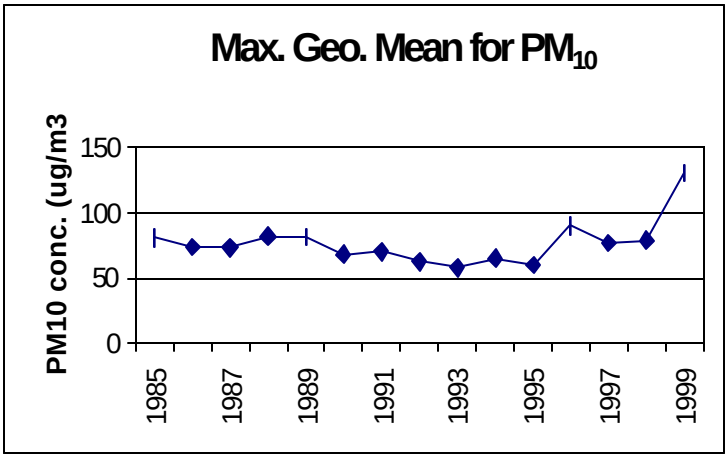


Figure C.3-4. Maximum annual geometric mean concentrations of PM10, not including the Great Basin Valley sites (µg/m^3).

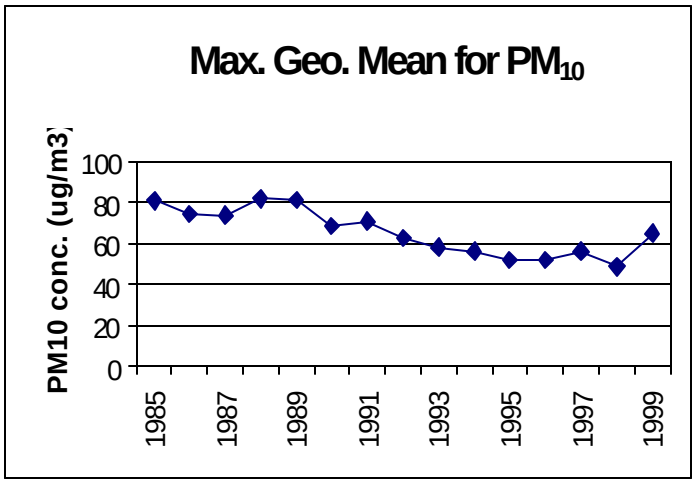


Figure C.3-5. Maximum annual geometric mean concentrations of PM10, not including the Great Basin Valley, Mojave Desert, and Salton Sea sites ($\mu g/m^3$).

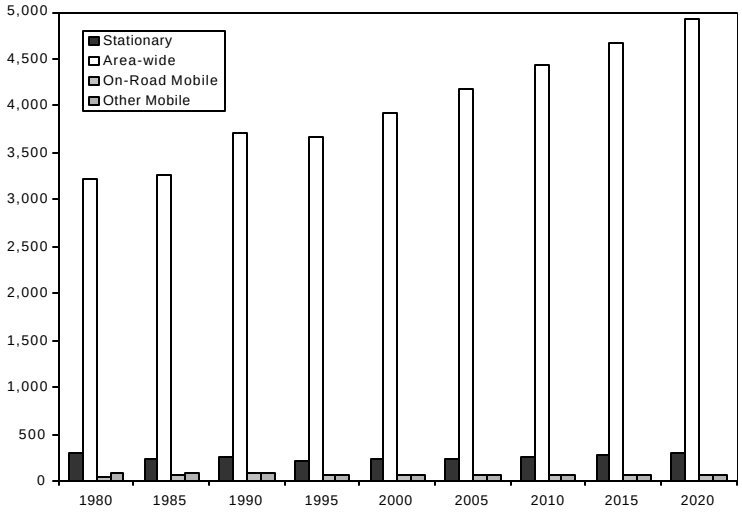


Figure C.3-6. Emissions (tons/day) and sources of PM10, projected through 2020.

C.4 Sulfates

C.4.1 Introduction

Sulfates are present in the atmosphere typically in combination with other substances to form compounds such as ammonium sulfate and sulfuric acid. Sulfates are typically present on particulate matter that can be directly emitted (primary particles) or formed in the atmosphere (secondary particles). Examples of sources for primary sulfate particles include dry lakebeds, desert soils, and emissions from combustion of fossil fuels from stationary and mobile sources. Secondary sulfate particles are produced in the atmosphere from directly emitted oxides of sulfur (SO_x). These SO_X emissions are generally from fossil fuel combustion. Secondary sulfate particles are transported over long distances.

C.4.2 Air Quality

Sulfate concentrations have steadily decreased in California, with some notable exceptions. The maximum concentration of sulfates for the years 1980 through 1999 is illustrated in Figure C.8-1 (Note: 1999 data is only for the South Coast Air Quality Management District). There is an observed an increase in maximum concentration during 1985 and 1986. Following this increase, the maximum concentration is observed to be approximately 20-30 µg/m^3 except for 1994. To evaluate the influence of a single site for the 1985-1986 increase, the highest maximum site (China Lake) was not included in the analysis. The results are presented in Figure C.4-2. When the China Lake site is not included in the analysis, a decreasing trend is observed.

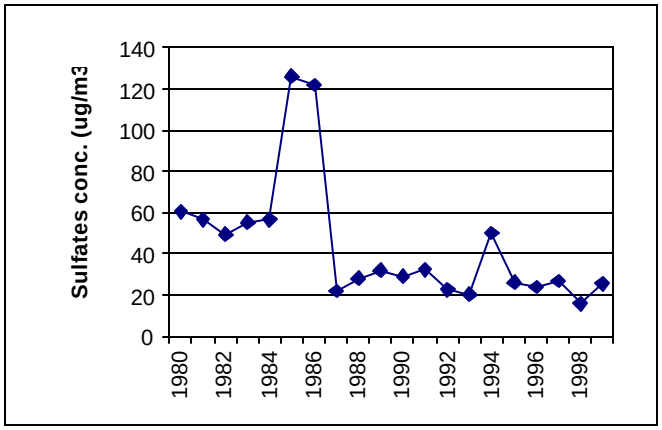


Figure C.4-1. Maximum concentration for sulfates (µg/m^3). All statewide sites.

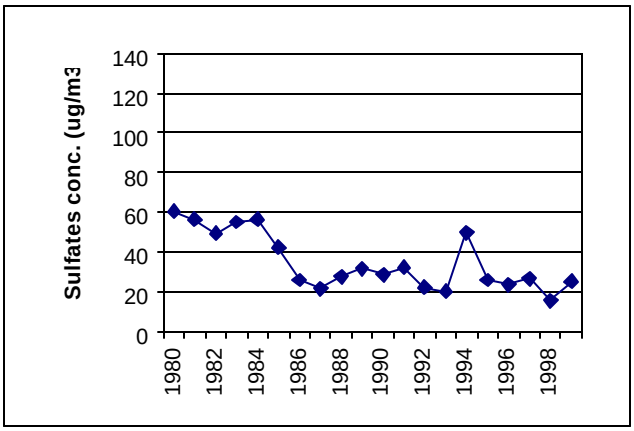


Figure C.4-2. Maximum concentration for sulfates not including the China Lake site ($\mu g/m^3$).

C.5 Ozone (O_3)

C.5.1 Introduction

Ozone is a colorless gas with a pungent odor. It is the chief component of urban smog. Ozone is not directly emitted as a pollutant, but is formed in the atmosphere when hydrocarbon and NO_x precursor emissions react in the presence of sunlight. Meteorology and terrain play major roles in ozone formation. Generally, low wind speeds or stagnant air coupled with warm temperatures and cloudless skies provide for the optimum ozone conditions. As a result, summer is generally the peak ozone season. Because of the reaction time involved, peak ozone concentrations often occur far downwind of the precursor emissions. Therefore, ozone is a regional pollutant that often impacts a widespread area.

C.5.2 Air Quality, Emissions, and Sources

Air quality with respect to ozone has improved greatly in all areas of California over the last 19 years, despite significant population growth. The statewide trend is illustrated in Figure C.5-1, and principally reflects values for the Southern California area. The maximum peak 1-hour indicator declined 53 percent from 1980 to 1999. During this same time period, however, the State's population has grown by 43 percent and the number of vehicle miles traveled each day has increased by more than 75 percent. Motor vehicles are the largest source of hydrocarbon precursor emissions as illustrated in Figure C.5-2, followed by stationary source emissions. Motor vehicles are also the largest source of NOx precursor emissions as illustrated in Figure C.5-2. Reducing vehicular emissions with ARB's low emission vehicle standards will help to reduce ROGs considerably. However, increases in population and driving will partially offset the benefits of cleaner vehicles. In addition to motor vehicle controls, the ARB is establishing controls for other sources of ozone precursor emissions, such as consumer

products. The ARB and other agencies are also investigating new approaches such as implementing market incentives to improve air quality.

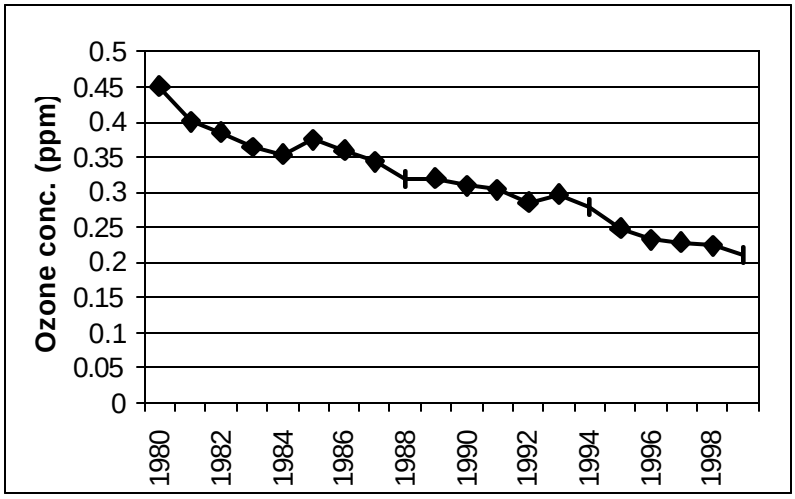


Figure C.5-1. Maximum 1-hour peak indicator for statewide ozone concentrations from 1980 through 1999 (ppm).

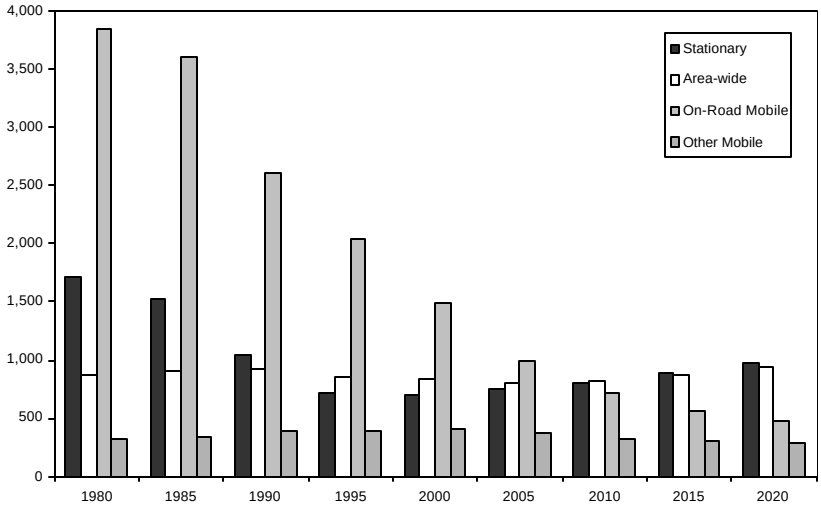


Figure C.5-2. Emissions (tons/day) and sources of reactive organic gases (ROG) that form ozone, projected through 2020.

C.6 Nitrogen Dioxide (NO_2)

C.6.1 Introduction

Nitrogen dioxide (NO_2) is a red-brown gas that is derived from both direct emissions (generally from the combustion of fossil fuels) and from the conversion of nitric oxide (NO) to nitrogen dioxide (NO_2). During combustion, nitrogen, present as a major component of air, combines with oxygen to produce oxides of nitrogen. Both NO and NO_2 are important compounds in a series of chemical reactions in the ambient air to produce secondary compounds including ozone, nitrate aerosols, nitric acid, and other nitrogen-containing compounds that are toxic.

C.6.2 Air Quality, Sources, and Emissions

The concentrations of nitrogen dioxide have decreased by 57% since 1980, as illustrated by the maximum 1-hour peak indicator concentrations in Figure C.6-1. The decrease is directly attributed to more stringent controls on both mobile and stationary sources.

The emissions of nitrogen dioxide are projected to decrease through 2020 with the emissions principally from mobile sources as illustrated in Figure C.6-2.

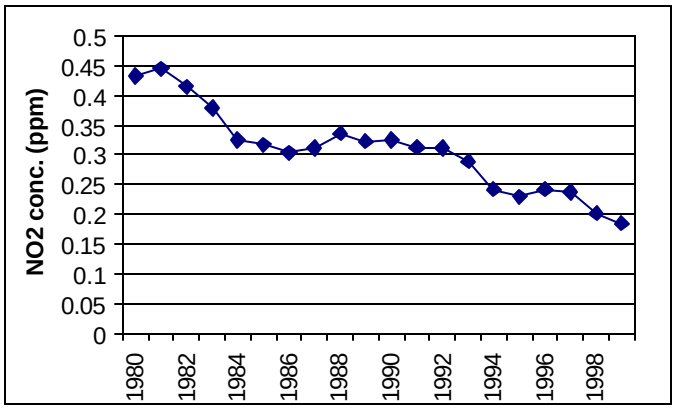


Figure C.6-1. Maximum 1-hour peak indicator concentrations for nitrogen dioxide (ppm).

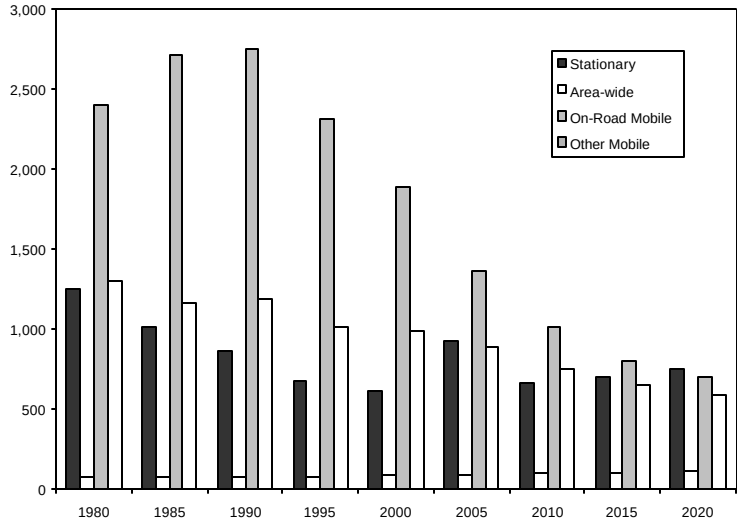


Figure C.6-2. Emissions (tons/day) and sources of nitrogen dioxide, projected through 2020..

C.7 Carbon Monoxide (CO)

C.7.1 Introduction

Carbon monoxide is a colorless and odorless gas that is directly emitted as a product of incomplete combustion. The highest concentrations are generally associated with cold stagnant weather conditions that occur during winter. In contrast to ozone, which tends to be a regional pollutant, CO problems tend to be localized.

C.7.2 Air Quality, Sources, and Emissions

The maximum 1-hour peak indicator for carbon monoxide concentrations statewide is illustrated in Figure C.7-1. As with ozone, carbon monoxide concentrations in all areas of California have decreased substantially over the last 19 years. Statewide, the maximum peak 8-hour indicator declined 35 percent from 1980 to 1999. Currently, the State carbon monoxide standard is violated in two areas: the South Coast Air Basin portion of Los Angeles County and the city of Calexico, in Imperial County.

The emissions for carbon monoxide are predominantly from mobile sources, followed by area-wide and other mobile sources as illustrated in Figure C7-2. By year 2015, these sources are projected to have similar emissions.

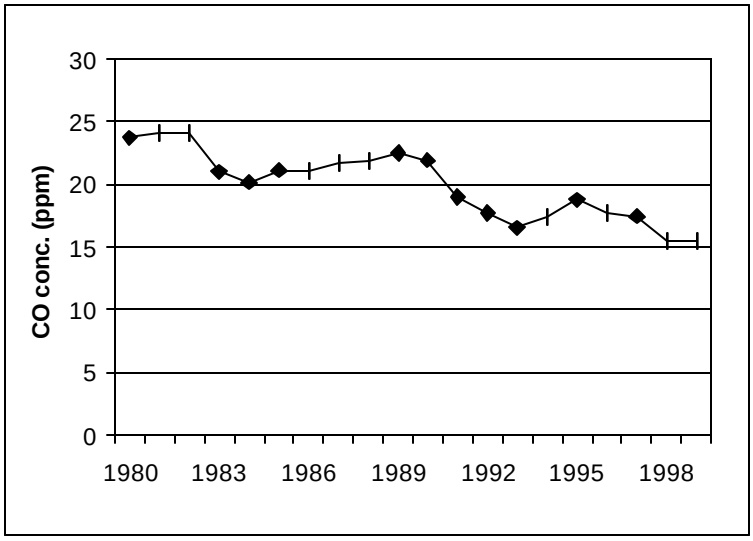


Figure C.7-1. Maximum 8-hour peak indicator carbon monoxide (ppm).

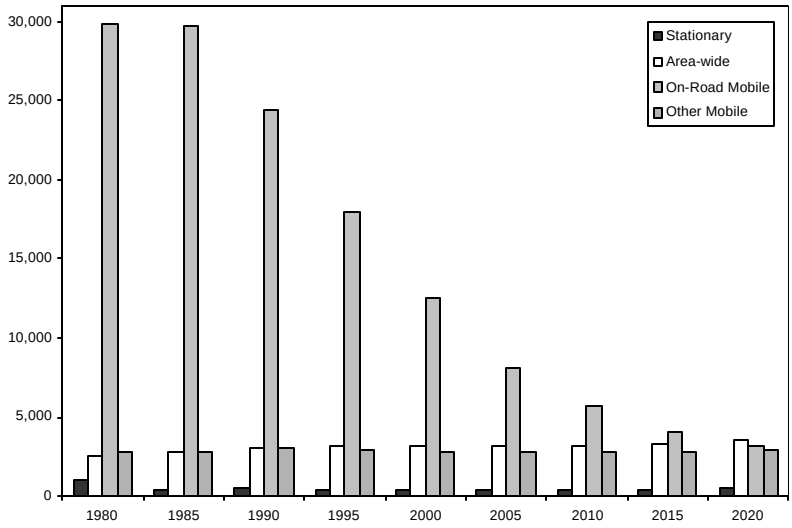


Figure C.7-2. Emissions (tons/day) and sources for carbon monoxide, projected through 2020..

C.8 Hydrogen Sulfide (H_2S)

C.8.1 Introduction

Hydrogen sulfide (H_2S) is a colorless, acidic gas with a strong unpleasant (rotten egg) odor. At the highest concentrations measured in California, hydrogen sulfide is considered a nuisance.

Statewide 1-hour peak indicator concentrations are illustrated in Figure C.8-1 from 1980 to 1999. There are increases observed in peak concentrations in 1982 (approximately 0.2 ppm), 1996 (approximately 0.35 ppm), and for 1991 through 1995 (approximately 0.3 ppm). Again, an analysis of the dependence of peak occurrence on certain sites was conducted. The city of Trona had the highest maximum concentrations. When the Trona site was not included in the analyses, the only increase remaining was for 1981-1982 (Figure C.8-2). The rest of the years from approximately 1985 through 1999 had concentrations of approximately 0.03 ppm.

Trona is the site of an industrial plant that uses salts from the Searles dry lake. The hydrogen sulfide may be attributable to the mining of the salts.

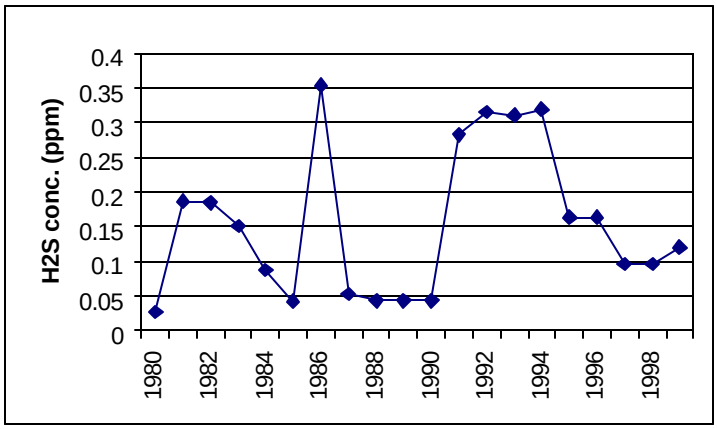


Figure C.8-1. Maximum 1-hour peak indicator for hydrogen sulfide (ppm), including Trona.

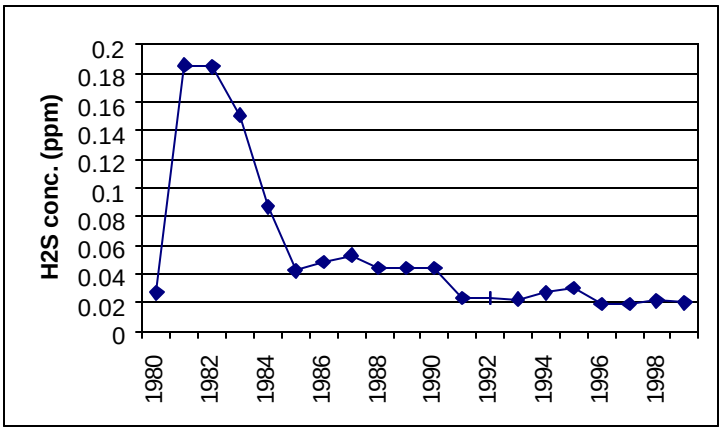


Figure C.8-2. Maximum 1-hour peak indicator for hydrogen sulfide (ppm), not including the Trona site.

C.9 Lead (Pb)

C.9.1 Introduction

Lead (Pb) is a bluish-gray metal that occurs naturally in the earth's crust. Lead typically is present in the environment in combination with organic or inorganic compounds. Organic lead consists of compounds containing carbon, while inorganic lead consists of compounds containing lead but no carbon. Airborne lead in California is generally inorganic lead.

C.9.2 Air Quality

The maximum 30-day average concentrations of airborne lead are presented in Figure C.9-1. There has been a rapid decrease in airborne lead concentrations due to removal of lead from gasoline. This phase-out began during the 1970s, and subsequent ARB regulations have virtually eliminated all lead from the gasoline now sold in California. All areas of the State are currently designated as attainment for the State lead standard. Although the ambient lead standards are no longer violated, lead emissions from stationary sources still pose "hot spot" emissions in some areas. Because of this, the ARB identified lead as a toxic air contaminant (TAC) in 1997.

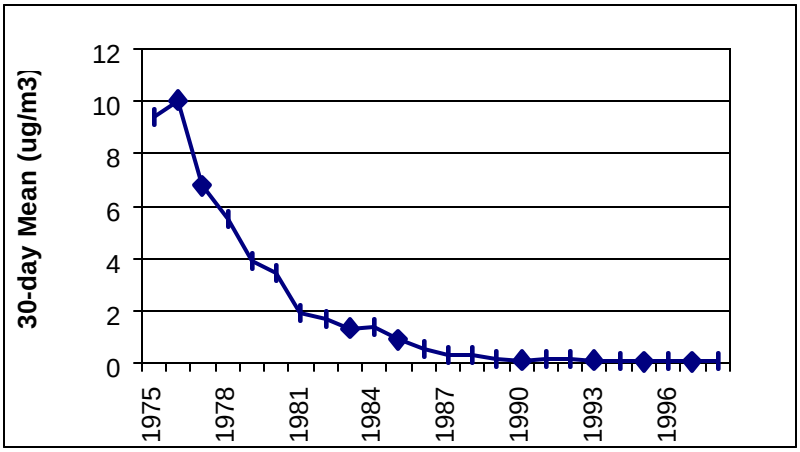


Figure C.9-1. Maximum 30-day average statewide lead concentrations ($\mu g/m^3$).

C.10 Sulfur Dioxide (SO_2)

C.10.1. Introduction

Sulfur dioxide (SO_2) is a colorless, non-flammable gas with a sulfurous odor. Sulfur dioxide is primarily produced from the combustion of sulfur-containing fuels and can be chemically transformed in the atmosphere into sulfuric acid and sulfates.

C.10.2. Air Quality, Sources, and Emissions

Sulfur dioxide emissions are from both mobile and stationary sources. While SO_2 poses significant problems in other parts of the nation such as the East Coast, emissions in California have been reduced sufficiently over the last 20 years so that all areas of California now attain both of the State standards for sulfur dioxide. The ambient concentrations of SO_2 have decreased over the last 20 years as illustrated in Figure C.10-1 for the 1- hour peak indicator for SO_2 concentrations and illustrated in Figure C.10-2 for the 24-hour peak indicator for SO_2. The decrease is attributed to a number of control measures implemented during this time period including: 1) the use of alternative fuels such as natural gas; 2) the use of lower sulfur-containing fuels; and 3) emission controls on sources. The emissions and sources of SO_2 are illustrated in Figure C-10-3. The two source categories that have the highest, yet similar emissions starting from 1985 through 2020, are stationary and other mobile sources.

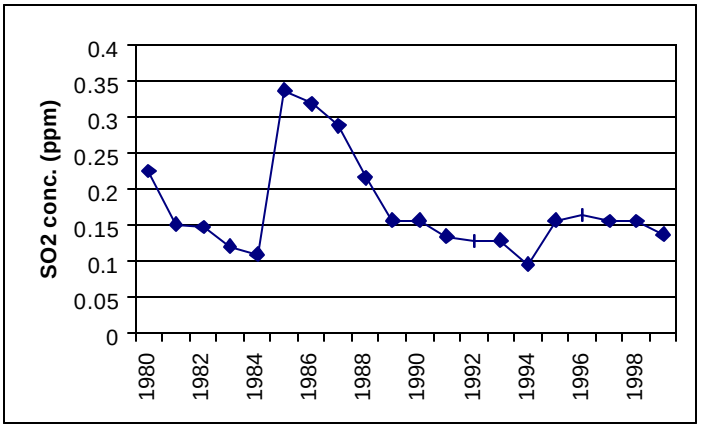


Figure C.10-1. Maximum 1-hour peak indicator for sulfur dioxide (ppm). Note that in 1985 a new site opened in Nipomo (San Luis Obispo County), near a petroleum reprocessing plant.

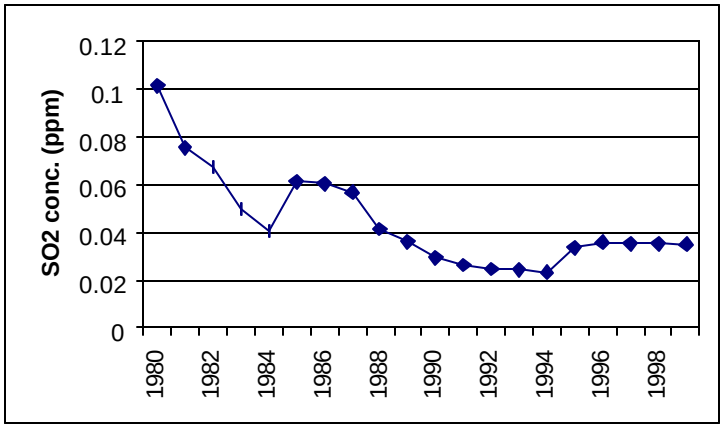


Figure C.10-2. Maximum 24-hour peak indicator for sulfur dioxide (ppm).

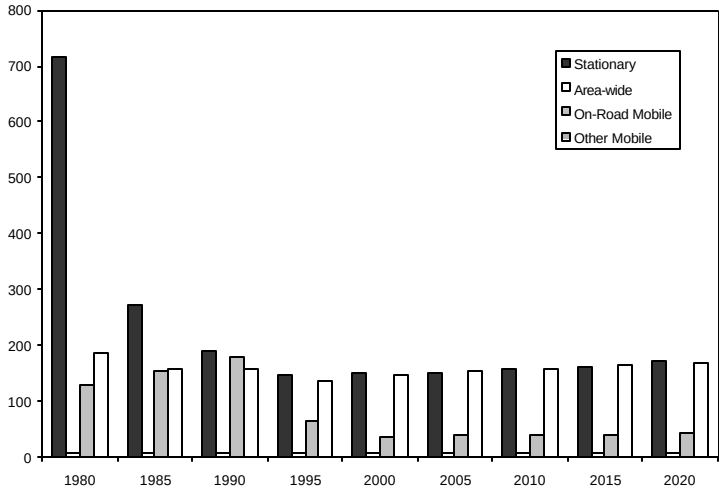


Figure C.10-3. Emissions (tons/day) and sources of sulfur dioxide (SO_2), projected through 2020.

C.11 Indoor and Outdoor Measurements of Criteria Pollutants

Indoor and outdoor concentrations of criteria pollutants are summarized in Table C.11-1. Parallel indoor and outdoor samples were obtained during each of the reported studies. However, the sampling times are generally longer than the averaging times of the ambient air standards. The one exception was for PM10, which was studied for a 24-hour sampling time. The indoor and outdoor PM10 was investigated in 90 homes in Southern California and there were slightly higher indoor concentrations (median concentrations: indoor = 33 $\mu g/m^3$; outdoor = 29 $\mu g/m^3$).

Table C11-1. Residential Concentrations of Criteria Pollutants Recent California Studies*

Pollutant	Concentrations			Comments	Reference
	Indoor	Outdoor	Averaging Time		
Ozone	6 ppb (median) 2-16 ppb (25-75 percentile) 50 ppb (99 percentile)	34 ppb (median) 23-51 ppb (25-75 percentile) 89 ppb (99 percentile)	24 hour	Southern California 241 homes	Avol et al., 1996
Particulate Matter (PM10)	98 μ/m^3 (daytime mean) 65 μ/m^3 (nighttime mean)	97 μ/m^3 (daytime mean) 87 μ/m^3 (nighttime mean)	12 hour	Riverside, CA 165 homes, Fall, 1990 PTEAM Study	Clayton et al., 1993 Ozkaynak et al., 1996
	33 μ/m^3 (median) 24-47 μ/m^3 (25-75 percentile) 295 μ/m^3 (99 percentile)	29 μ/m^3 (median) 18-44 μ/m^3 (25-75 percentile) 141 μ/m^3 (99 percentile)	24 hour	Southern California 90 homes	Avol et al., 1996
Fine Particulate Matter (PM2.5)	49 μ/m^3 (daytime mean) 37 μ/m^3 (nighttime mean)	48 μ/m^3 (daytime mean) 52 μ/m^3 (nighttime mean)	12 hour	Riverside, CA, 167 homes, Fall, 1990 PTEAM Study	Clayton et al., 1993 Ozkaynak et al., 1996
	13.7 μ/m^3 (median) 10-23 μ/m^3 (25-75 percentile) 107 μ/m^3 (99 percentile)	10.7 μ/m^3 (median) 7-20 μ/m^3 (25-75 percentile) 77 μ/m^3 (99 percentile)	24 hour	Southern California 67 homes	Avol et al., 1996
Carbon Monoxide	2.93 ppm (arithmetic mean) 0.26-7.45 ppm (range)	5.10 ppm (arithmetic mean) 0.21-16.74 ppm (range)	48 hour	passive samplers statewide monitoring 102 homes	Wilson et al., 1993
Nitrogen Dioxide	25 ppb (arithmetic mean) 0-177 ppb (range)	23 ppb (arithmetic mean) 0-80 ppb (range)	48 hour	passive samplers statewide monitoring 214 homes	Wilson et al., 1993

*Note—Direct comparison with ambient air quality standards can not be made because averaging times are not comparable. Residential indoor data for criteria pollutants are very limited.

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PARTICULATE MATTER AND SULFATE: EVALUATION OF CURRENT CALIFORNIA AIR QUALITY STANDARDS WITH RESPECT TO PROTECTION OF CHILDREN

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A. Abstract

Epidemiological evidence indicates that present-day ambient particulate matter (PM) and/or sulfate air pollution exposures are associated with adverse health effects in children, including that:

Short-term PM and/or sulfate exposures to children are associated with:

- reduced pulmonary function;
- increased respiratory symptoms in asthmatics (e.g., asthma attacks) and non-asthmatics;
- increased incidence of respiratory doctor's visits;
- increased incidence of emergency department (ED) visits and hospital admissions (HA's);
- increased mortality, and;
- especially increased infant morbidity and mortality;

Long-term chronic PM and/or sulfate exposures to children are associated with:

- reduced lung function;
- increased respiratory symptoms; and,
- increased infant mortality, intrauterine growth reduction, or pre-term delivery.

Especially apparent in the many studies examined, and of notable concern, are results indicating much higher risks for children in the neonatal (< 1 month) and post-neonatal (1-12 months) age groups. Furthermore, an examination of key medical visits and hospital admissions studies indicates that the existing Federal and California PM_{10} and $PM_{2.5}$ mass and sulfate ambient air quality standards are not presently sufficiently protective of public health, as significant adverse health impacts have been documented in published studies at mean ambient levels below these standards.

Both biological and physical exposure-related factors enhance the risk to children from PM and sulfate exposures. These risk-enhancing factors include:

- higher PM concentration exposures resulting from children's greater activity levels;
- larger PM doses in children from increased ventilation rates;
- greater doses of ultrafines among children 14-18 years of age;
- enhanced PM doses in children, especially infants, per body weight and lung surface area;
- diminished and developing defense systems in infants;
- higher prevalence of children with asthma than in other age groups;
- larger percentage of children made susceptible by poverty than other age groups; and,
- gas-particle interactions and particle-allergen interactions, potentially making the individual pollutant standards not fully protective to susceptible populations, such as children.

Based on the above insights, it is recommended that future PM research should focus on:

- improved identification of the specific characteristics of PM (e.g., ultrafines, acidity, elemental composition, etc.) that are contributing most to noted PM effects, and quantification of their relative roles in PM toxicity;
- further investigation as to whether acute exposures less than one day in length (e.g., 1-hr. daily maximum), or longer multi-day exposures (e.g., 2 or more day average PM), also have health importance, over and above that captured by the 24-hr. PM peak PM concentration measurement;
- further investigations into particle-gas and particle-allergen interactions;
- using both experimental and epidemiological methods, conduct further investigations of apparently larger acute and long-term effects of PM on children, and especially infants.

B. Background

This section briefly summarizes the existing California state and federal ambient standards for particulate matter (PM) and sulfate ($SO_4^=$), and the rationale for these standards.

According to California State Code of Regulations Section 39606 (b), the state board shall adopt standards of ambient air quality for each air basin in consideration of the public health, safety, and welfare, including, but not limited to, health, illness, irritation to the senses, aesthetic value, interference with visibility, and effects on the economy. These standards may vary from one air basin to another. Standards relating to health effects are to be based upon the recommendations of the State Department of Health Services. The term "Ambient air quality standards" means specified concentrations and exposure durations of air pollutants that reflect the relationship between the intensity and composition of air pollution to undesirable effects established by the state board or, where applicable, by the federal government. "Air contaminant" or "air pollutant" means any discharge, release, or other propagation into the atmosphere and includes, but is not limited to, smoke, charred paper, dust, soot, grime, carbon, fumes, gases, odors, particulate matter, acids, or any combination thereof.

The present particulate matter (PM) mass-based ambient air quality standard in California is indexed to PM_{10}, which refers to atmospheric particles, solid and liquid, except uncombined water, as measured by a PM_{10} sampler that collects 50 percent of all particles of 10 micrometers (um) aerodynamic diameter, and that collects a declining fraction of particles as their diameter increases and an increasing fraction of particles as their diameter decreases, reflecting the characteristic of lung deposition. Suspended particulate matter (PM_{10}) is to be measured by the size selective inlet high volume (SSI) PM_{10} sampler method in accordance with ARB Method P, as adopted on August 22, 1985, or by an equivalent PM_{10} sampler method, for purposes of monitoring for compliance with the PM_{10} standards.

As noted in Table 1, the State of California, unlike the Federal government, also has an air quality standard that was promulgated in the 1970s for the sulfate portion of PM_{10}. Sulfates are the water soluble fraction of suspended particulate matter containing the sulfate radical

($SO_4^=$) including, but not limited to, strong acids and sulfate salts, as measured by AIHL Method No. 61 (Turbidimetric Barium Sulfate) (December 1974, as revised April 1975 and February 1976) or equivalent method. The present sulfate standard is a 24-hour average concentration not to be exceeded more than once per year. In recognition of an inability to discern a threshold at and below which no effects can occur from exposure to this pollutant, this standard is set at a "Critical Harm" level.

Currently, most of the state is in non-attainment with the PM10 standard. The PM_{10} air quality levels dropped from a statewide average of approximately 80 ug/m^3 in 1988 to about 50 ug/m^3 in 1995 and 1996, but rose again to almost 60 ug/m^3 in 1997 (CARB, 1999). State average annual maximum sulfate concentrations dropped by about half between 1980 and 1990 (from about 60 ug/m^3 to about 30 ug/m^3), and have remained fairly stable since that time. Peak summer sulfate in the LA Basin in 1996 was about 17 ug/m^3, and for the last 10 years the mean summer 24-hour concentrations were less than 8 ug/m^3. Thus, typical concentrations are now below the existing sulfate standard, but this is not the case for PM_{10}.

The United States Environmental Protection Agency ("EPA") also recognized the adverse health effects of small particulate pollution as early as 1987 when, pursuant to its authority under the Clean Air Act, it promulgated a National Ambient Air Quality Standard ("NAAQS") for particulate matter that is 10 micrometers in diameter or smaller (PM_{10}). The NAAQS promulgated by EPA are required for certain air pollutants "that may reasonably be anticipated to endanger public health and welfare." The NAAQS' air criteria must be "requisite to protect the public health" with an "adequate margin of safety." Under the particulate matter NAAQS, states must reduce PM_{10} concentrations in their ambient atmosphere to no more than 50 micrograms per cubic meter on an annual average basis, and to no more than 150 micrograms per cubic meter on an average 24-hour period. Prior to 1987, EPA's particulate NAAQS had only regulated total suspended particulate matter. Its focus in 1987 on smaller particles -- that is, 10 micrometers or less -- resulted from increasing scientific evidence that human inhalation of smaller particles had more serious respiratory effects than larger particles.

Table 1. Present California Ambient Air Quality Standards for Particulate Matter and Sulfates
(Source: California State Code of Regulations)

Substance	Concentration and Methods	Duration of Averaging Periods	Most Relevant Effects	Comments
Suspended Particulate Matter (PM_{10})	50 ug/m^3 PM_{10} 30 ug/m^3 PM_{10}	24 hour sample Annual Geometric Mean of 24 hr. Samples	Prevention of excess deaths from short-term exposures and of exacerbation of symptoms in sensitive patients with respiratory disease. Prevention of excess seasonal declines in pulmonary function, especially in children	The standard applies to suspended particulate matter as collected by a PM_{10} sampler, which collects 50% of all particles of 10 um aerodynamic diameter and collects a decreasing fraction of particles as diameter increases, and an increasing fraction as their diameter decreases, reflecting the characteristics of lung deposition.
Sulfates	25 ug/m^3 Total Sulfates AIHL #61 (Turbidimetric Barium Sulfates)	24 hour sample	a. Decreases in ventilatory function b. aggravation of asthmatic symptoms c. Aggravation of cardio-pulmonary diseases d. Vegetative Damage e. Degradation of visibility f. Property damage.	This standard is based as a Critical Harm Level, not a threshold value.

In 1994, the EPA began the process of re-reviewing its particulate matter standards. In 1996, the EPA proposed a new NAAQS for even smaller particles -- those that are 2.5 micrometers in diameter or smaller ($PM_{2.5}$). This new proposed standard was based on an increasing scientific consensus that the current NAAQS for PM_{10} was not sufficiently protective of human health. EPA's scientific review concluded that fine particles, in the 2.5 micrometer and smaller range, penetrate more deeply into the lungs, and may be more likely than coarse particles to contribute to the health effects (e.g., premature mortality and hospital admissions) found in a number of recently published community epidemiological studies at concentrations that extend well below those allowed by the current U.S. PM_{10} standards. As EPA stated in its proposed regulation, a greatly expanded body of community epidemiological studies provide "evidence that serious health effects (mortality, exacerbation of chronic disease, increased hospital admissions, etc.) are associated with exposures to ambient levels of PM, even in concentrations below current U.S. PM standard" (*Federal Register*, July 18, 1997, Vol. 62, No. 138, pg. 38655).

The recently promulgated NAAQS for $PM_{2.5}$ is 15 micrograms per meter cubed (ug/m^3) based upon the 3-year average of annual arithmetic mean $PM_{2.5}$ concentrations at multiple

sites, and 65 ug/m^3 based upon the 3-year average of the 98^{th} percentile of the 24-hour PM_{10} concentration at individual sites. These standards are presently being contested in Federal courts (See: American Trucking Associations, Inc. v. USEPA, 175 F.3d 1027 (D.C. Cir. 1999), modified, 190 F.3d 4 (D.C. Cir. 1999), cert. granted in Browner v. American Trucking Associations, 120 S. Ct. 2003 (2000) (No. 99-1257), and in American Trucking Associations v. Browner, 120 S. Ct. 2193 (2000) (No. 99-1426)).

C. Factors in Particulate Matter (PM) and Sulfate Exposure and Dose Assessment

This section includes, to the extent that information is available, a description of exposure patterns among infants and children that are likely to result in disproportionately high exposures to ambient air pollutants in comparison to the general population.

C.1. PM Concentration Exposures from Children's Activities

Personal activities, such as exercise, cigarette smoking, hobbies, and occupational tasks generate a plume of particles that surround the person generating the particles. Such personal activity sources can exist either indoors or outdoors. These are microscale PM generating activities that primarily influence the exposure of the person performing the activity. Thus, personal activity PM exposure is only measured by a personal monitor carried by the subject, because a stationary monitor located nearby will not measure the high PM concentration generated by that activity. The difference between a personal monitor measurement and an area-representative measurement several meters away is sometimes called a "personal cloud" (Wallace, 1999).

However, personal PM exposure monitoring studies have indicated that personal activities, along with PM generated by personal and indoor sources (e.g., cigarette smoking), can lead to PM indoors and personal exposures to total PM that exceed the concentration of the PM found in the immediate outdoor air or in the local ambient air (Binder et al., 1976; Repace and Lowrey, 1980; Spengler et al., 1980). Fine particles have been found to readily penetrate buildings, but indoor activity adds incrementally to outdoor levels and, frequently, somewhat

higher levels of fine particles are observed indoors. Indeed, human activity, such as smoking and cooking, does generate fine particles (<2.5 um); cooking, dusting, vacuuming and general activity can generate coarser particles (>2.5 um), or can resuspend coarse particles that previously had settled out (Litzistorf et al., 1985; Thatcher and Layton, 1995; Abt et al., 1999, 2000).

Children are well documented to have greater activity levels than adults, and therefore are likely to have increased personal exposures, relative to adults, because of an enhanced personal cloud of particles. In recent surveys of the activity patterns of California children and adults (Wiley et al, 1991a,b), it was found that children 11 years of age and under spend an average of 124 minutes/day doing active sports, walking/hiking, or outdoor recreation, vs. only 21 minutes for adults. In personal exposure studies in the Netherlands, it has been found that, given roughly the same outdoor concentrations, children have a much higher personal PM_{10} exposure than adults (Janssen, et al. 1997, 1998). While children's homes in these studies had a mean outdoor concentration similar to that of adults (41.5 ug/m^3 vs. 38.5 ug/m^3 for adults), children's personal exposures averaged 66.8 ug/m^3 above ambient vs. 26.9 ug/m^3 above ambient for adults. This indicates a much higher "personal cloud" for children than adults. In regressions, personal activity was one of the more important contributors to the children's extra personal exposure concentration, contributing approximately 12 ug/m^3. The children's personal exposure was also some 43 ug/m^3 higher than their time-weighted average of indoor and outdoor concentrations, indicating most of the personal vs. outdoor PM_{10} difference to be due to their personal cloud, rather than generally higher PM_{10} concentrations indoors. Most of these particles are likely to be of indoor origins, however. Thus, PM exposure of a child can be substantially higher than that for adults because of the extra PM that is generated by their own increased activity levels, but the importance of this effect to outdoor air pollution standard setting is limited by the fact that most of these activity generated particles are of indoor origins.

For sulfates, the "personal cloud" phenomenon apparently does not apply as it does for PM mass in general, as sulfate is derived almost exclusively from the outdoors. Indeed, in the

PTEAM study (Ozkaynak et al, 1996) conducted in Riverside, CA in 1990, it was found that sulfate concentrations indoors and outdoors were the same, and the researchers concluded that there appeared to be no indoor or personal sources of exposure to sulfate particles. As shown in Figure 1, $SO_4^=$ measured at central monitoring stations in the PTEAM study is closely correlated with $SO_4^=$ as measured by personal exposure monitors. In that figure, the deviations from the line of identity can be largely accounted for by a model that incorporates other known influences. Such close correspondence between personal and outdoor concentrations was not seen for PM_{10} or $PM_{2.5}$ mass concentrations, or for other measured constituents. The close correspondence for $SO_4^=$ can be attributed to it being: a) chemically and physically stable in the air and on sampling filters; b) present primarily as submicrometer-sized particles which penetrate into indoor spaces efficiently with infiltrating air; c) a secondary aerosol that is distributed quite uniformly across large geographic areas; and d) without common indoor sources.

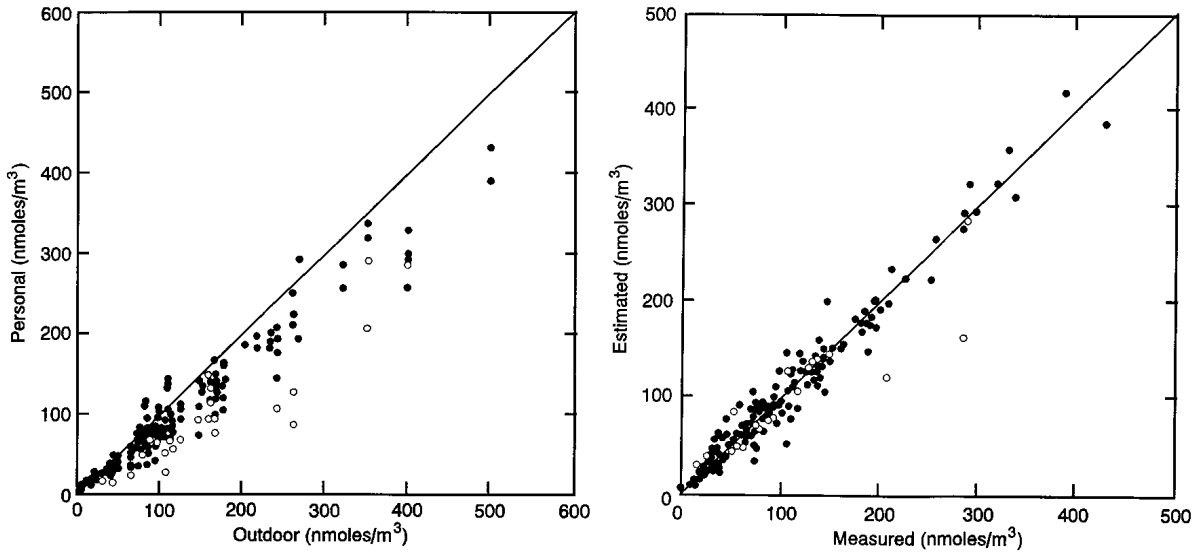


Figure 1. Left Panel: Comparison of personal monitoring data on $SO_4^=$ concentration with temporally coincident central monitoring station $SO_4^=$ in California. (Open circles are air-conditioned residences.)
Right panel: Comparison of measured ambient $SO_4^=$ concentrations with estimated personal $SO_4^=$ exposures based on PTEAM model incorporating known influences on personal exposures.
From: U.S. EPA (1995).

Thus, unlike for PM_{10}, children's personal concentration exposures to sulfates are similar to those of adults, and are well represented by a central site monitors. However, the acidity of

sulfates has been found to differ indoors and outdoors, with diminished acidity indoors due to ammonia sources indoors that can convert the acidic sulfates to ammonium sulfate (e.g., see Suh et al, 1994). Thus, while total sulfate exposures are similar for adults and children, the sulfates that children are exposed to are likely more acidic as a result of their greater time spent outdoors, as sulfates are more likely to be in an acidic form outdoors (i.e., as sulfuric acid and/or ammonium bisulfate). Therefore, the greater outdoor time and activity of children outdoors places them at greater risk than adults of exposure to acidic sulfates and acidic gases (e.g., nitric acid).

C.2. Variations in Lung Deposition Fraction in Children vs. Adults

Lung and airway characteristics vary with age, and these variations can change the deposition pattern of inhaled particles. The limited experimental studies available indicate results ranging from no clear dependence of total deposition on age to slightly higher deposition in children than in adults. Potential deposition differences between children and adults have been assessed to a greater extent using mathematical models, as shown in Figure 2, as derived from the ICRP model (U.S. EPA, 1995). These results indicate that extra-thoracic (ET) deposition (i.e., to the nose, naso-oropharyngeal passages, and larynx) in children is generally higher than in adults, but that tracheo-bronchiolar (TB) and alveolar (A) regional deposition in children may be either higher or lower than the adult, depending upon particle size and age of the child. Overall, available studies do not provide clear evidence for significant differences in deposition fraction between adults and children.

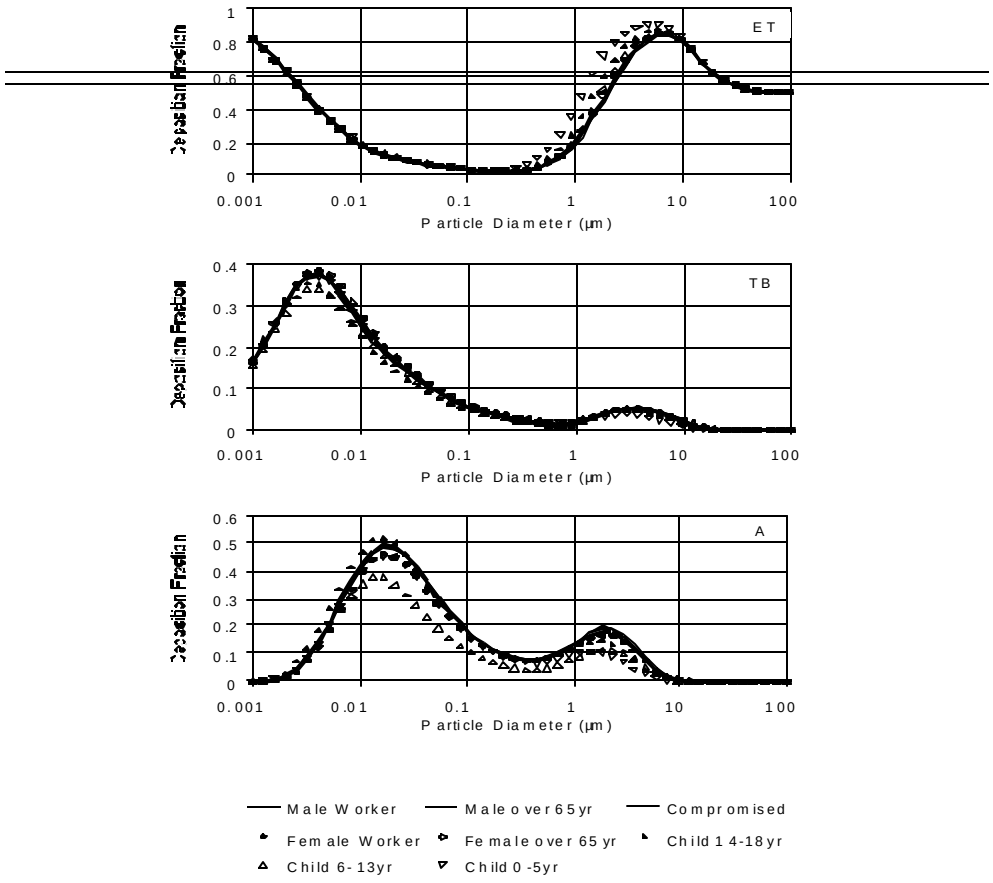


Figure 2. Daily mass particle deposition fraction in each respiratory tract region as predicted by the International Commission on Radiological Protection (ICRP66) (Source: U.S. EPA, 1995).

C.3. PM Doses in Children from Increased Ventilation Rates

While the fraction deposited on a mass basis is not generally very different between adults and children, differences in levels of activity between adults and children play a large role in age-related differences in their respective doses of ambient particles. Children generally have higher activity levels during the day (as noted above), yielding higher daily minute ventilation, especially when viewed on a per body weight basis. The typical total volume (m^3) breathed in 24 hours for children (0-5 years) is 11.6; children (6-13 years) is 18.2; and for children (14-18 years) is 25.5. The above childhood ventilation rates compare with an average 19.4 m^3 breathed in 24 hours for male worker (18-44 years of age). Thus, even without adjusting for body weight or lung surface area, teenagers breathe a greater volume of air than adults, due to their more active lifestyles, which increases the PM pollution dose they receive. Combining the deposition information in Figure 2 with these ventilation rates, it is seen in Figure

3 that children generally receive a greater inhaled dose of particle mass per given ambient PM mass concentration, especially in children aged 14-18.

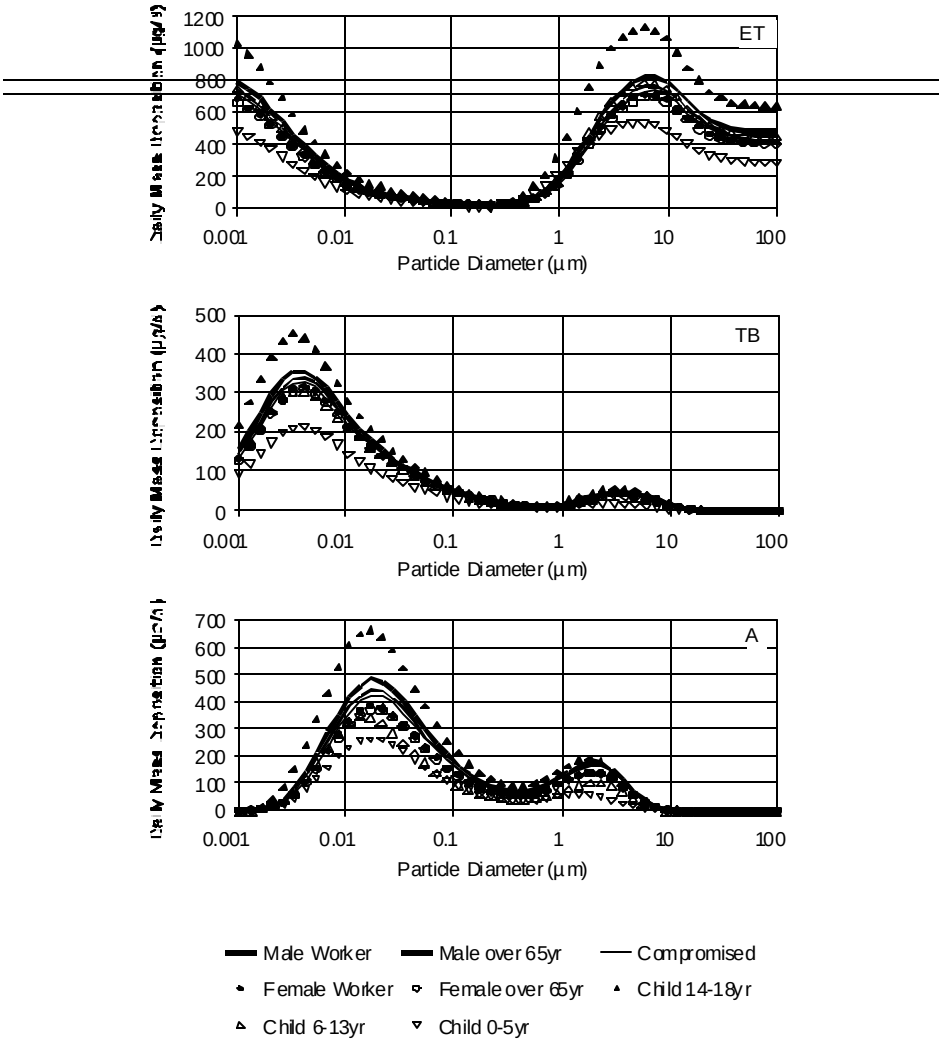


Figure 3. Daily PM deposition rates (ug/day) for 24 hour exposure at 50 ug/m^3 in each respiratory tract region as predicted by the International Commission on Radiological Protection (ICRP66).(U.S. EPA, 1996).

C.4. Doses of Ultrafines among Children 14-18 Years of Age

It is important to note, when evaluating the enhanced mass deposition in the ultrafine fraction for children 14-18 years of age, that the number of particle "hits" may be of paramount importance to health, rather than the PM_{10} mass. Thus, the enhanced alveolar deposition mass shown in Figure 3 in the ultrafine range represents a significant increase in the total number concentration dose experienced by children. The enormous numbers and huge surface area of the ultrafine particles demonstrate the importance of considering the size of the particle in assessing response. Ultrafine particles with a diameter of 20 nm when inhaled at the same mass concentration have a number concentration that is approximately 6 orders of magnitude higher

than for a 2.5 um diameter particle, and particle surface area is also greatly increased, as shown in Table 2.

Table 2. Numbers and Surface Areas of Monodisperse Particles of Unit Density of Different Sizes at a Mass Concentration of 10 mg/m^3

Particle Diameter (mm)	Particle Number (per cm^3 Air)	Particle Surface Area (mm^2 per cm^3 Air)
0.02	2,400,000	3,016
0.1	19,100	600
0.5	153	120
1.0	19	60
2.5	1.2	24
Source: Oberdorster et al. (1995).		

If the number concentration exposure in the alveolar part of the lung is of great health significance, as has been hypothesized by Seaton et al. (1995), then the greater ultrafine exposure in children 14-18 could take on greater importance than the disparities indicated by adult versus childhood mass concentration exposures and doses. Indeed, many studies summarized in the U.S. Environmental Protection Agency's PM Criteria Document (1995) suggest that the surface of particles, or substances that are on or are released from the surface (e.g., acids and/or transition metals), interact with the biological system and that surface-associated free radicals or free radical-generating systems may be responsible for toxicity. Thus, if ultrafine particles were to cause toxicity by a transition metal-mediated mechanism, for example, then the relatively large surface area for a given mass of ultrafine particles would mean higher concentrations of transition metals being available to cause oxidative stress to cells in the lungs of children vs. adults who breathe these aerosols.

C.5. Biological Factors that Increase PM Susceptibility in Children

In addition to differences in the ambient concentrations that children are exposed to relative to adults, the implications of those exposures are different due to biological differences between adults and children. In this section, these differences and their implications are discussed.

C.5.1. Enhanced PM Doses in Children per Body Weight and Lung Surface Area:

In addition to the fact that children can get higher absolute PM doses due to their greater activities and higher PM personal clouds, children also have smaller lungs and much lower body weights, both of which increase the toxicity of a given PM dose. For example, a newborn typically weighs 3 kg, a young child 10 kg, an older child 33 kg, and an adult 70 kg (Snodgrass, 1992). Thus, PM doses, when viewed on a per kg body weight basis, are much higher for children than adults. This is graphically displayed in Figure 4, which indicates that the amount of air inhaled per kg body weight increases dramatically as age decreases below adult levels, with the inhalation rate (in m^3/kg/day) of a 10-year old being roughly twice that of a 30-year old person, and this estimate does not even consider the higher personal exposure concentrations that a child is usually exposed to as a result of his or her high activity levels. Thus, for a given exposure concentration, young children get roughly 3 times higher air pollution doses than do adults, when viewed on a per unit body weight basis.

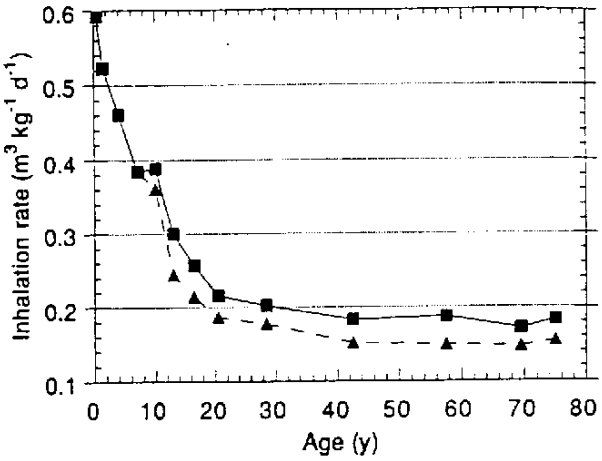


FIGURE 4. Age specific inhalation rates on a per body-weight basis for males (■) and females (▲). (Adapted from Layton, 1993).

Child-adult dosage disparities are even greater when viewed on a per lung area basis, which may be more important than body weight if the number of particle "hits" per unit lung surface is the important health impact metric, which may well be the case for ultrafine particles. A newborn infant has approximately 10 million alveoli vs. some 300 million as an adult. The alveolar surface area increases from approximately 3 m^2 at birth to about 75 m^2 in adulthood,

causing infants' and children's doses per lung surface area to be much higher than in adults, even given the same personal exposures (which is not the case, as they generally have greater PM_{10} personal exposures than adults, as noted above). Thus, PM air pollution doses are significantly higher in children than adults when one considers their higher personal exposures, their greater activity rates, and their smaller body weights and lung surface areas.

C.5.2. Diminished and Developing Defense Systems in Infants: As discussed by Plopper and Fanucchi (2000), the limited experimental and epidemiologic studies currently available identify the early post neonatal period of lung development as a time of high susceptibility for lung damage created by exposure to environmental toxicants. For example, due to the relatively diminished defenses of their developing immune systems, infants are disproportionately susceptible to infections and other diseases. Indeed, in 1998 in the U.S., the rate (per 1000) of Meningococcal disease by age group was 11.47 for <1 year versus: 2.75 for 1-4 years; 0.90 for 5-14 years; 1.27 for 15-24 years, 0.41 for 25-39 years; 0.49 for 40-64 years; and, 1.13 for >=65 years (CDC, 1999). Recent research indicates that there is a relationship between respiratory infections and air pollution effects in children (Sarafino et al., 1998). Thus, the higher rate of infectious diseases among infants is an indicator of diminished defenses against health insults, and is likely to cause them to have diminished reserves, and therefore to be more greatly affected by exposures to air pollution.

In addition to their insufficiently developed immune systems, infants are growing rapidly, and limited recent evidence supports the hypothesis that environmental pollution can significantly alter development of the respiratory system at that period of life. In experimental animals, for example, elevated neonatal susceptibility to lung-targeted toxicants has been reported at doses "well below the no-effects level for adults" (Plopper and Fanucchi, 2000; Fanucchi and Plopper, 1997). In addition, acute injury to the lung during early postnatal development causes a failure of normal repair processes, including down-regulation of cellular proliferation at sites of injury in animals. (Smiley-Jewel, et al., 2000, Fanucchi et al., 2000). Thus, it may be that both infants' diminished defenses and pollution-induced impairment of

repair mechanisms can therefore coincide during infancy, making the neonatal and post-neonatal period one of especially elevated susceptibility to damage by environmental toxicants like PM.

D. Key Studies of PM and Sulfate Health Effects

As discussed by Bates (1995), air pollution has been documented for many decades to be associated with a wide variety of health impacts in humans, and especially among the elderly and children. Indeed, as shown in the table below, infants less than one year of age (0-1 months Neonatal, 1-12 months Post-neonatal) experienced larger increases in mortality than older children or young adults during the notorious London Fog air pollution episode of 1952, and infants are indicated to be an especially susceptible subgroup of children. Among adults, recent research indicates that those with prior or coincident respiratory infections are among those especially affected by air pollution (Zanobetti et al, 2000), which may also be a factor placing infants at higher risk of being affected by air pollution, given their high rates of infectious diseases.

Table 3. Deaths Registered in London by Age Group (Adapted from Bates, 1995)

	< 1 Month of Age	1-12 Mo. Old	1-14 Years of Age	15-44 Years of Age	45-64 Years of Age	65-74 Years of Age	75+ Years of Age
Week Before the Episode	16	12	10	61	237	254	335
Week After the Episode	28	26	13	99	652	717	949
Before/After Episode Ratio	1.75	2.17	1.3	1.62	2.75	2.82	2.83

More recent epidemiological evidence indicates that lower present-day ambient PM air pollution exposure is also associated with adverse health effects in children in general, and, as will be discussed in detail below, these effects can include:

From short-term PM exposures to children:

- reduced pulmonary function;
- increased respiratory symptoms in asthmatics (e.g., asthma attacks) and non-asthmatics;
- increased incidence of respiratory doctor's visits;
- increased incidence of emergency department (ED) visits and hospital admissions (HA's);

- increased mortality, and;
- especially increased infant morbidity and mortality;

From long-term chronic PM exposures to children:

- Reduced lung function;
- increased respiratory symptoms; and,
- Increased infant mortality, intrauterine growth reduction, or pre-term delivery.

The PM indices most commonly evaluated in epidemiological and toxicological studies are those that have been most routinely measured: PM_{10}, total suspended particulate matter (TSP), and Black Smoke (BS, an index of primary carbonaceous particle mass collected primarily in Britain and Europe). However, significant effects are also reported for less often measured $PM_{2.5}$, sulfates ($SO_4^{=}$), and acidic aerosols (H^+).

This section seeks to summarize the most pertinent available evidence for acute and chronic health impacts of particulate matter and sulfates (including relevant toxicology, controlled exposures, and epidemiological studies, as available). These discussions emphasize studies involving children and adolescents, but rely on studies among adults when children's studies are not available. This section will also include, to the extent that information is available, a discussion of any special biological reasons for, or scientific evidence of, elevated susceptibility of infants and children to particulate matter and sulfates, in comparison to the general population.

D.1. Lung Function and/or Respiratory Symptom Effects from Acute PM Exposures

While not as adverse as more severe outcomes, such as medical visits or hospital admissions, symptom and lung function impacts do provide supportive evidence of consistent effects across outcomes, and can become medically important in health impaired individuals (e.g., children with asthma). A variety of PM and or sulfate symptom effects have been found in children, particularly in U.S. studies conducted in California. Cough, phlegm, and lower respiratory infections (LRI) are sometimes found to be associated with air pollution in these

studies. Delfino and colleagues' (1998) California study reported stronger symptom effects for 1-h and 8-h PM_{10} exposures, rather than 24-hr average PM_{10}, is noteworthy. This may indicate the need for a PM standard applicable to more acute exposure peaks of only a few hours.

Many asthmatics self-medicate with bronchodilators, which may also be a useful indicator of respiratory distress in these subjects. In the case of the Thurston et al. (1997) study of children with asthma at a summer camp, the medications were prescribed in cases where an asthma exacerbation was verified by a resident physician, indicating this to be a metric of severe air pollution effects associated with acidic sulfates (and ozone) in this case. A number of investigators have found statistically significant peak expiratory flow reduction (PEFR) associated with PM_{10} and other PM indices, and some have reported significant reduction in FEV_1 and FVC. For example, Figure 5 shows the relationship found between sulfates and PEFR, lower respiratory chest symptoms, and medication use in children with asthma in the Thurston et al summer camp study.

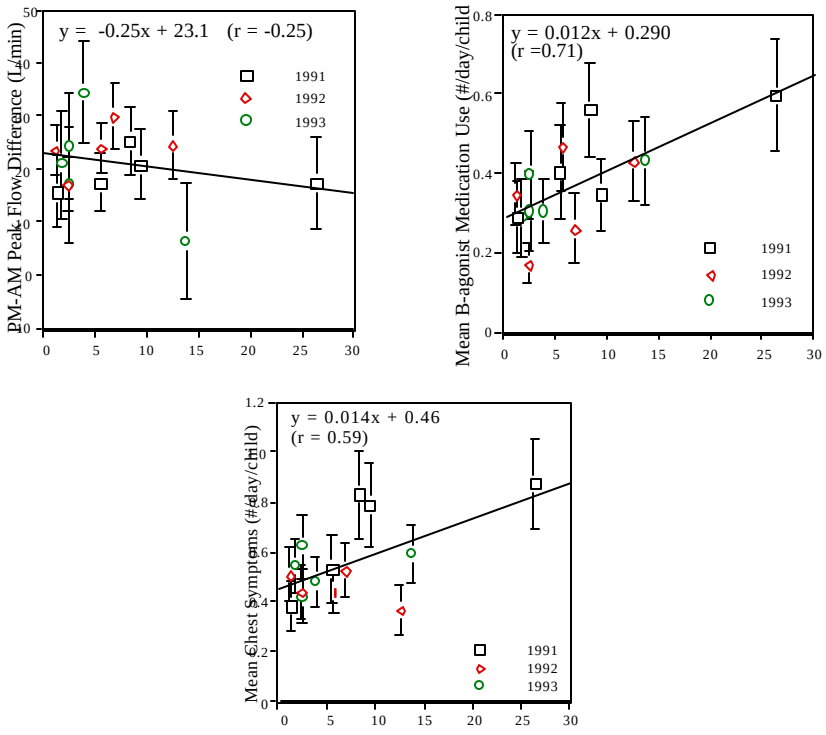


Figure 5. Lung Function, Symptom, and Inhaler Medication Use Association with Sulfate Concentration in Asthmatic Children (ages 8-12). (Adapted from Thurston et al., 1997).

Thus, as indicated by the studies summarized in Table 4, there is an overall indication that respiratory symptoms in children are exacerbated by exposure to airborne particles and sulfates. These effects have greater health implications in children with asthma, and can and do lead to an increased incidence of asthma attacks. Since the prevalence of asthma is much higher among children than among adults (CDC, 1996a,b), these enhanced acute effects of air pollution on those with asthma put more children at higher risk of PM health effects than adults.

D.2. Lung Function and/or Respiratory Symptoms from Long-Term PM Exposures

For decades, there has been accumulating evidence suggesting that higher long-term ambient particulate matter exposures are associated with higher rates of chronic respiratory disease. Much of this evidence has been based on cross-sectional analyses, comparing disease or symptom prevalence rates in different communities with different average pollution levels (e.g., Ferris et al., 1973; 1976; Hodgkin et al., 1984; Mullahy and Portney, 1990). This type of study is able to indicate associations, but they are often criticized because these analyses cannot be controlled for confounding factors on an individual level, and are more likely to be subject to ecological confounding than prospective cohort studies. Also, chronic symptoms presumably occur as a result of long-term exposures, but cross-sectional analyses are not very informative as to whether, for example, it is the five-year average, the twenty-year average, or the number of times a given level is exceeded that is the relevant health effects exposure measure.

TABLE 4. Recent U.S. Panel Studies Of Pulmonary Function Tests or Acute Respiratory Symptoms Associated with PM Exposure in North American Children

Study	Health Endpoints	Ages (yrs.)	PM Effects	Pollutants Considered	Remarks (N)
Ostro et al. (1995) Los Angeles, CA	Asthma symptoms for at least six weeks	7-12	Shortness of breath risk, 9% per 10 ug/m^3 PM_{10}	PM_{10}, TSP, SO_4, NO_3, O_3, SO_2, NO_2	African-American (N = 83)
Delfino et al. (1998) Alpine, CA	Bothersome asthma symptoms	9-17	Symptoms signif. 1-h, 8-h PM_{10}, 24-h less signif.	PM_{10}, O_3 (others low)	Panel of asthmatics (N = 25)
Delfino et al. (1997) Alpine CA	Symptom score, bronchodilator use		PM_{10} signif. dilator use	PM_{10}, O_3	Asthmatics (N = 13)
Delfino et al. (1996), San Diego, CA	Symptom scores, bronchodilator use		Signif. O_3 personal monitor, N.S. SAM O_3, $PM_{2.5}$	$PM_{2.5}$, O_3	Asthmatics (N = 12)
Hoek et al. (1998) re-analyses of 4 other studies in the U.S. and the Netherlands	PEF, large changes related to symptoms		Signif. PEFR, Cough PEFR N.S. PEFR N.S. PEFR N.S.	PM_{10}	Utah Valley Bennekom Uniontown St. College
Linn et al. (1996) southern CA	Pulmonary function		Morning FVC signif. PM5?, NO_2	PM5?, NO_2	School children (N = 269)
Thurston et al. (1997) Connecticut summer camp	lung function, symptoms, dilator use	8-12	SO_4, O_3 assoc. with symptoms, PEFR, dilator use	PM_{10}, SO_4, H+, O_3,	Asthmatic children (n=55)

Key: PEF = peak expiratory flow; PEFR = reduction in PEF; N.S.= not statistically significant (two-tailed, P > 0.05).

Source: Adapted from US EPA (1998)

More recently published articles have followed cohorts, answering the major criticisms of past studies by allowing confounder controls at the individual level. Abbey and colleagues (1991; 1993; 1995a,b) have reported results of a 10-year cohort study conducted at Loma Linda University in California with a large sample of nonsmoking adults. This follow-up allowed for measures of exposure over the 10-year period and for obtaining information on changes in chronic respiratory disease incidence over time. Abbey et al. (1995a) extends those earlier studies by analyzing associations between these chronic respiratory disease outcomes and both fine particles and sulfates. Logistic models were fitted using the mean concentration of these two pollutants, along with PM_{10}, ozone, and other pollutants. Fine particles were estimated from empirical estimates related to airport visibility. Regarding sulfates, a statistically significant association was observed with airway obstructive disease (AOD). Abbey and colleagues found no association with either SO_2 or NO_x, but sulfate exposure was associated with changes in the severity of AOD and chronic bronchitis over the ten-year study period.

Thus, new cases of disease were able to be analyzed in relation to pollution exposure for a matching time period in these studies, providing a more definitive concentration-response function for chronic respiratory disease, while confirming past "ecological" study results.

Children are likely to be at greater risk from long-term exposures because their bodies are growing, and their developmental processes, especially in the lung, may well be interfered with by air pollution exposures. Table 5 shows a number of recent studies involving school-age children indicating adverse respiratory effects from longer-term PM exposures. PM_{10} is not always significantly associated with adverse health effects in these studies, although other PM indicators sometimes are (e.g., $SO_4^=$, H^+). The mechanisms by which elevated PM exposure over long periods of time may be associated with increased risk of respiratory symptoms or decreased pulmonary function in children are not now understood, but may be analogous to the cumulative effects of smoking or environmental tobacco smoke (ETS) on the human respiratory system.

TABLE 5. Recent PM Studies Of Pulmonary Function Tests Or Respiratory Symptoms Associated With Long-Term PM Exposure In North American School-Age Children

Study	Endpoint	Ages (years)	Significant PM Associations	Pollutants Considered	Remarks (N)
Dockery et al. (1996) 24 U.S. & Can.. Communities	Various	8-12	SO_4 signif. bronchitis; PM_{10} N.S. any endpoint	PM_{10}, PM2.1, SO_4, H+, SO_2, O_3	
Raizenne et al. (1996) 24 U.S., Canadian Communities	Pulmonary function	8-12	Strong signif. H+, Signif. PM_{10}	PM_{10}, PM2.1, SO_4, H+, SO_2, O_3	
Peters et al. (1999a,b) 12 So. CA communities	Asthma, bronchitis, cough, wheeze, lung function	9-12	PM_{10} signif. FVC, FEF25-75% N.S. FEV_1, symptoms, PEFR,		(N =150 each, in grades 4, 7)

Source: Adapted from US EPA (1998)

D.3. Incidence of Medical Visits and Hospital Admissions from Acute PM Exposures

Numerous studies have related acute PM exposure with an increased incidence of hospital admissions (e.g., see Figure 6), but only a limited number have specifically studied the subgroup that are children. Burnett et al (1994) examined the differences in air pollution-hospital admissions associations as a function of age in the province of Ontario. As shown in

Table 6, this analysis indicated that the largest percentage increase in admissions was found among infants (neonatal and post-neonatal, one year or less in age), just as was the case for the mortality effects during the London fog of 1952 (see Table 3).

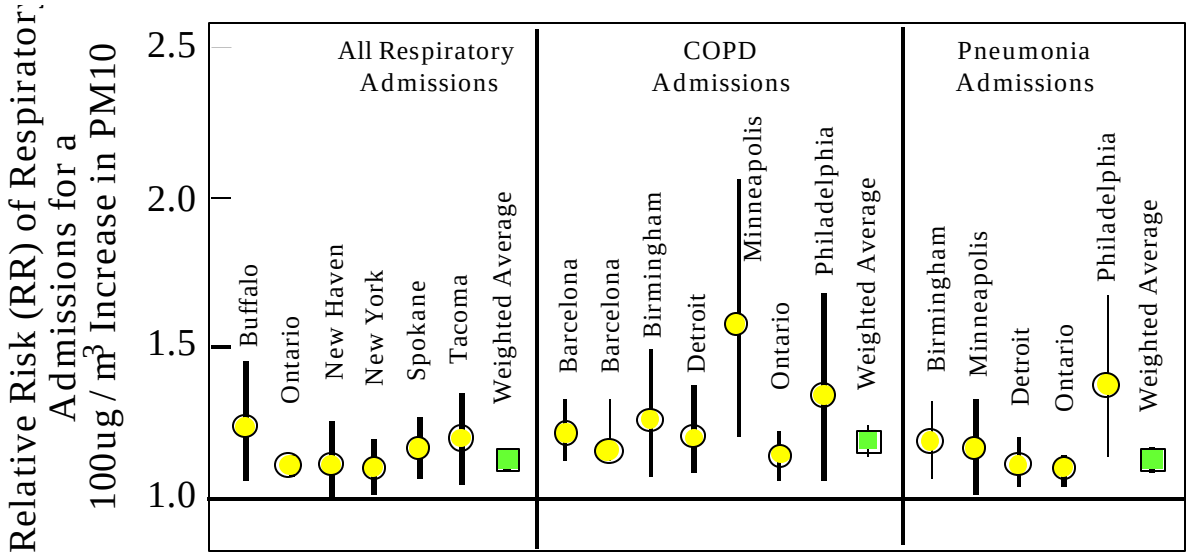


Figure 6. Relative Risk Estimates for Respiratory Hospital Admissions versus PM_{10}. (Adapted from Schwartz, 1997)

Table 6. Age-Specific Percent Increase in Respiratory Hospital Admissions Associated with Sulfate (5.3 ug/m^3) and Ozone (50 ppb) in Ontario, Canada. (Adapted from Burnett et al, 1994)

	< 1 Year of Age	2-34 Years of Age	35-64 Years of Age	75+ Years of Age
Asthma Admissions	13.0	5.5	9.8	7.0
Total Respiratory Admissions	14.8	5.5	7.2	4.3

More recent hospital admissions studies listed in Table 7 also indicate positive and often statistically significant associations between PM exposures and medical visits or hospital admissions by children. However, some of these PM-health effect associations listed in Table 7 became statistically non-significant when gaseous co-pollutants were included in the model, including O_3, SO_2, NO_2, CO. This may be due to a statistical artifact of pollutant inter-correlations over time causing enlarged coefficient standard errors, or may suggest that the co-pollutant mixture can collectively play a role in the effects of PM on children (e.g., through gas-particle interactions).

Looking in more detail at the results from each study in Table 7, as provided in Appendix A, reveals that the PM RR's for all children (e.g., 0-14 yrs.) are not usually noticeably larger than those for adults, but such comparisons of RR's must adjust for differences in the baseline risks for each group. For example, if hospital admissions per 100,000 per day for young children are double the rate for adults, then they will have a pollution relative risk (RR) per ug/m^3 that is half that of the adults given the exact same impact in admissions/100,000/ug/m^3/day. Thus, it is important to adjust RR's or Excess Risks (ER's) for each different age groups' baseline, but this information is usually not available (especially the population catchment for each age group in each study). One of the only signals that comes out clearly when comparing children with adults in Appendix A is for the group <1 yr. of age, which (despite higher baseline rates) usually has RR's larger than for other children or adults, as previously found in the Burnett (1994) study.

TABLE 7. Recent Key PM Studies Of Associations Between Medical Visits Or Hospital Admissions and Short-Term PM Exposure In Children

Study	Endpoint	Ages (yrs.)	PM Effects	Pollutants	Remarks (N)
Delfino et al. (1997) Montreal PQ	Emergency Dept. Visits (EDV), 1992-1993	0-1	H+ signif. only 1993	PM_{10}, $PM_{2.5}$, SO_4, H+, O_3	
Medina et al. (1997) Paris, France	Doctor's house calls	0-14	Asthma signif. BS.	PM_{13}, BS, SO_2, NO_2, O_3	Similar RR for PM13, SO_2, NO_2
Sunyer et al. (1997) Barcelona Helsinki London, Paris	emergency hospital admissions (HA's) for asthma	0-14	BS positive, N.S. NO_2 and SO_2 signif.	BS, NO_2, SO_2	
Anderson, et al. (1998) London, UK	HA's for asthma	0-14	BS positive, Signif.	BS, O_3, SO_2, NO_2	O_3, SO_2, NO_2, BS all pos. assoc.
Garty et al. (1998) Israel	EDV for asthma	1-18	PM_{10} N.S.	PM_{10}, O_3, SO_2, NO_2	N = 1076
Morgan et al, 1998 Sydney, AU	Asthma, COPD, and Cardiac HA's	0-14	PM (nephelometry) NS, NO_2 signif.	PM (nephelometry), O_3, and NO_2	
Rosas et al. (1998) Mexico City	emergency HA's for asthma	0-15	PM_{10} N.S.	PM_{10}, TSP, O_3, SO_2, NO_2	grass, fungal spores signif.
Atkinson et al. (1999) London UK	EDV for respiratory complaints	0-14	PM_{10} signif. total resp., asthma	PM_{10}, BS, O_3, SO_2, NO_2, CO	N.S. in 2-poll. models w. SO_2, NO_2
Atkinson et al. (1999) London UK	Hospital admissions for respiratory complaints	0-14	PM_{10} signif. total resp., asthma	PM_{10}, BS, O_3, SO_2, NO_2, CO	N.S. in 2-poll. models w. SO_2, NO_2
Norris et al. (1999) Seattle WA	EDV for asthma	0-17	PM_{10} signif. all hosp., lt.-scatter each	PM_{10}, light scatter, CO, SO_2, NO_2	PM_1 index from light scattering
Lin et al. (1999) Sao Paulo, Brazil	Respiratory emergency visits	0-12	PM_{10} signif. w. and w/o co-pollutants	PM_{10}, O_3, SO_2, NO_2, CO	LRI, URI, wheezing w. co-pollutants
Braga et al. (1999) Säo Paulo, Brazil	Hospital admissions	0-12	PM_{10} signif., not w. O_3, CO	PM_{10}, SO_2, NO_2, CO	
Ostro et al. (1999) Santiago, Chile	Medical visit for LRI, URI	<2 2-15	LRI 4-12% LRI 3-9%	PM_{10}, O_3	
Hajat et al. (1999) London U.K.	GP visits for asthma, LRI	0-14	PM_{10} N.S., BS signif. LRI	PM_{10}, BS, O_3, SO_2, NO_2, CO	
Wong, et al (1999) Hong Kong, CH	Respiratory HA's	0-4	PM_{10} NO_2, and O_3 signif., SO_2 not signif.	PM_{10}, NO_2, SO_2, O_3	
Gouveia et al (2000) Sao Paulo, BR	Respiratory, Pneumonia, and asthma HA's	<1 <5	Only PM signif., with larger RR than for <5 (pneumonia) All poll RR's>1, but NS. for asthma. Only SO_2 signif for Pneum., and only O_3 signif. for all resp.	PM_{10}, NO_2, SO_2, O_3	

Source: Adapted from US EPA (1998)

Two recent studies have found that air pollution-admissions associations are also stronger for the poor, which has special implications for children. Nauenberg et al. (1999) analyzed the effect of insurance status on the association between asthma-related hospital admissions and exposure to atmospheric particulate matter (PM_{10}) and ozone (O_3) using hospital discharge and air quality data for 1991-1994 for central Los Angeles. They used regression techniques with weighted moving averages (simulating distributed lag structures) to

measure the effects of exposure on overall hospital admissions, admissions of uninsured patients, admissions for which MediCal (California Medicaid) was the primary payer, and admissions for which the primary payer was another government or private health insurance program. No associations were found between asthma admissions and O_3 exposure in LA. An estimated increase from 1991 to 1994 of 50 micrograms per cubic meter in PM_{10} concentrations averaged over eight days was, however, associated with an increase of 21.0% in the number of asthma admissions. An even stronger increase--27.4%--was noted among MediCal asthma admissions. The authors conclude that low family income, as indicated by MediCal coverage, is a useful predictor of strength of asthma associations with air pollution. Similarly, Gwynn and Thurston (2000) have recently found that air pollution effects are worse in the poor and working poor than in other groups, and that these differences account for apparent racial differences in air pollution effects in New York City. These studies' results both indicate that children are especially at risk from air pollution, as they more often live in poverty than any other age group (e.g., in 1989, 27.3% of children in LA lived in poverty, as compared to 18.9% overall, and 10.5% for those 65+ years of age) (U.S. Census, 1994).

D.4. Infant and Child Mortality Associated with Acute PM Exposures

Table 8 shows the results of recent studies in which excess mortality was associated with PM. Significant mortality was reported in three of the four studies, using $PM_{2.5}$ exposure for infants in Mexico City (Loomis et al., 1999), TSP exposure for school- age children (but not younger children) in Delhi (Cropper et al., 1997), and PM_{10} exposure for a composite group of children 0-5 years in Bangkok (Ostro et al., 1998). Pereira et al. (1998) did not find excess stillbirths associated with PM_{10} in Sao Paulo. These studies are highly diverse in terms of age group, location, and environment. As with adult mortality, we do not now know the exact biological mechanisms that specifically account for excess child mortality from short exposures to PM at levels found in these Latin American and Asian countries. However, the available studies suggest that short-term PM exposure in general may cause deaths of some children in urban environments. The mortality findings are consistent with findings noted above of less

serious health effects from short-term PM exposure, including lung function decreases, respiratory symptoms, asthma attacks and medical visits that may affect substantial numbers of children.

Table 8. Neonatal, Infant, And Child Mortality Attributable To Short-Term PM Exposure

Study	Mortality	Ages	PM Effects	Pollutants	Remarks (N)
Loomis et al. (1999) Mexico City	Total	0-11 mo.	$PM_{2.5}$ signif. w and w/o co-pollutant	$PM_{2.5}$, O_3, NO_2	
Pereira et al. (1998) São Paulo, Brazil	Intrauterine	0 d	PM_{10} N.S.	PM_{10}, O_3, SO_2, NO_2, CO	
Cropper et al. (1997) Delhi, India	Total, cardiovascular, respiratory	0-4 yr. 5-14 yr.	TSP N.S. for total mort. TSP signif. for total mort	TSP, SO_2, NO_x	Similar RR in both age groups
Ostro et al. (1999) Bangkok, Thailand	Total, cardiovascular, respiratory	0-5 yr.	PM_{10} signif. all	PM_{10}, $PM_{2.5}$	

Source: Adapted from US EPA (1998)

D.5. Increased Infant and Child Mortality Associated with Long-Term PM Exposures

A number of studies suggest that the very young represent an especially susceptible sub-population, although the precise magnitude of the effects of specific levels of air pollution can be expected to vary with other underlying conditions. Lave and Seskin (1977) found mortality among those 0-14 years of age to be significantly associated with TSP. More recently, Bobak and Leon (1992) studied neonatal (ages less than one month) and post-neonatal mortality (ages 1-12 months) in the Czech Republic, finding significant and robust associations between post-neonatal mortality and PM_{10}, even after considering other pollutants. Post-neonatal respiratory mortality showed highly significant associations for all pollutants considered, but only PM_{10} remained significant in simultaneous regressions. Woodruff et al. (1997) used cross-sectional methods to follow-up on the reported post-neonatal mortality association with outdoor PM_{10} pollution in a U.S. population. This study involved an analysis of a cohort consisting of approximately 4 million infants born between 1989 and 1991 in 86 U.S. metropolitan statistical areas (MSA's). After adjustment for other covariates, the odds ratio (OR)

and 95% confidence intervals for total post-neonatal mortality for the high exposure versus the low exposure group was 1.10 (CI=1.04-1.16). In normal birth weight infants, high PM_{10} exposure was associated with mortality for respiratory causes (OR = 1.40, CI=1.05-1.85) and also with sudden infant death syndrome (OR = 1.26, CI=1.14-1.39). Among low birth weight babies, which are lower in counts (and therefore with greater uncertainty and power) high PM_{10} exposure was associated, but not significantly, with mortality from respiratory causes (OR = 1.18, CI=0.86-1.61).

The Woodruff et al. (1997) study was recently corroborated by a more elegant follow-up study by Bobak and Leon (1999), who conducted a matched population-based case-control study covering all births registered in the Czech Republic from 1989 to 1991 that were linked to death records. They used conditional logistic regression to estimate the effects of suspended particles, sulfur dioxide, and nitrogen oxides on risk of death in the neonatal and post-neonatal period, controlling for maternal socioeconomic status and birth weight, birth length, and gestational age. The effects of all pollutants were strongest in the post-neonatal period and were specific for respiratory causes. Only particulate matter showed a consistent association when all pollutants were entered in one model. Thus, it appears that PM is the air pollutant metric most strongly associated with excess post-neonatal deaths.

Collectively, all the recent studies of children less than one year old presented in Table 9 indicate severe adverse consequences to the mother, fetus, and infant from prolonged PM exposure during and shortly after pregnancy. There appears to be a possible relationship between preterm birth (< 37 weeks gestational age) or low birth weight (< 2,500 g) and PM exposure in several locations. A significant relationship with PM_{10} and $PM_{2.5}$ was found in Teplice, Czech Republic (Dejmek et al., 1999), but not with PM_{10} in Los Angeles (Ritz and Yu, 1999). In the case of Ritz and Yu, CO was significant, which might well be serving as an index of traffic-related pollution effects, and therefore possibly related to diesel particulate matter (DPM), but this is not evaluated. Bobak and Leon (1999) did not find a relationship of low birth weight to TSP. There was a significant risk of low birth weight and pre-term delivery in Beijing

(Xu et al., 1995; Wang et al., 1997) associated with TSP, but SO_2 was the only co-pollutant considered. However, low birth weight is known to be an important risk factor for infant mortality, so that the findings of excess mortality in U.S. and Czech infants (Woodruff et al., 1997; Bobak and Leon, 1999) are consistent with many of the other findings on intrauterine growth reduction (IUGR), which is supportive of a causal relationship between PM exposure and adverse health effects in this age group.

Several methodological differences across studies make generalized conclusions more difficult to make. Dejmek et al. (1999) characterize IUGR as low-weight-for-gestational-age, whereas others use a fixed weight for full-term infants (37 to 44 weeks) without adjusting for gestational age. Dejmek et al. (1999) also find the average PM during the first month of pregnancy as the index of fetal exposure, whereas Xu et al. (1995), Wang et al. (1997), and Ritz and Yu (1999) use final trimester averages. Despite these methodological differences, there appears to be an identifiable PM risk to the fetus and infant.

A very recent study of infant mortality in U.S. counties indicates that these effects can occur in the U.S., as well (Chay and Greenstone, 1999). This study uses sharp, differential air quality changes across sites attributable to geographic variation in the effects of the 1981-82 recession to estimate the relationship between infant mortality and particulate matter air pollution. It is shown that, in the narrow period of 1980-82, there was substantial variation across counties in changes in particulate (TSP) pollution, and that these differential pollution reductions appear to be independent of changes in a multitude of other socio-economic and health care factors that may be related to infant mortality. The authors find that a 1 ug/m^3 reduction in TSP resulted in about 4-8 fewer infant deaths per 100,000 live births at the county level of the roughly 1,300 U.S. infant deaths in the first year of life per 100,000 live births (a 0.35-0.45 elasticity). The estimates are remarkably stable across a variety of specifications. The estimated effects are driven almost entirely by fewer deaths occurring within one month and one day of birth (i.e., neonatal), suggesting that fetal exposure to pollution may have adverse health consequences. The estimated effects of the pollution reductions on infant birth weight in

this study provide evidence consistent with the infant mortality effects found, suggesting a causal relationship between PM exposure and infant mortality, especially in the first month of life.

Table 9. Adverse Infant Health Effects Associated With Long-Term PM Exposure

Study	Effects	Ages	PM Effects	Pollutants	Remarks (N)
Bobak and Leon (1992) Czech. Repub.	Total infant mortality, respir. mort.	0+ d neonatal post-neonatal post, respir.	TSP-10 N.S. TSP signif. TSP signif.	TSP-10, SO_2, NO_x	Ecologic study; TSP indexed as 90th percentile
Bobak and Leon (1999) Czech. Rep.	Low birth wt. Stillbirth	0 d	TSP N.S.	TSP, SO_2, NO_x	
Chay and Greenstone (1999) California Counties	Infant mortality	0-1 yr.	TSP Signif.	TSP	1 ug/m^3 reduction associated with 4-8 fewer deaths per 100k live births
Dejmek et al. (1999) Teplice, Czech. Rep.	Intrauterine growth reduction	0 d	First month $PM_{2.5}$ > 37, PM_{10} > 40 signif.	PM_{10}, $PM_{2.5}$, SO_2, NO_x, PAH	30-d avg. PM per month of pregnancy
Ritz and Yu (1999) Los Angeles, CA	Low birth weight (adj. Gest age)	0 d	Last trimester PM_{10} N.S.	PM_{10}, O_3, NO_2, CO	CO signif., may be index of traffic air poll., e.g. DPM
Wang et al. (1997) Beijing, PRC	Low birth weight	0 d.	TSP signif. increases risk of LBW	TSP, SO_2 in third trimester	SO_2 also signif. Small reduc. mn.wt.
Woodruff et al. (1997)	Total infant mortality, SIDS, resp.	1-11 mo.	PM_{10} signif. total, SIDS, respir. NBW	PM_{10}	PM_{10} avg. over 2 mos.
Xu et al. (1995) Beijing, PRC	Preterm gestational age	0 d	TSP signif. lag 5-10 days	TSP, SO_2	SO_2 also signif.

Source: Adapted from US EPA (1998)

D.6. Evidence for a Role of Sulfates in PM Health Effects

The characteristics of particles responsible for the adverse health effect associations of PM are not yet known. However, lung injury has been postulated to be mediated by ultrafine particles, biological agents (e.g., endotoxin), acid aerosols, organic fraction of PM and oxidant generation catalyzed by transition metals associated with particles. Of these, the role of acidic combustion aerosols and their possible mechanisms for effects are among the best documented.

While significant associations are sometimes reported between total suspended particulate (TSP) and health effects in large populations, the degree of association in studies comparing various PM indices (e.g., Ozkaynak and Thurston, 1987; Dockery et al., 1993; Thurston et al., 1994) is as follows:

$$TSP < PM_{10} < PM_{2.5} < SO_4^{=}$$

Each metric is essentially a subset of the one to its left, implying that $SO_4^{=}$, or something in the mixture closely associated with it, is a likely causal factor in the effects reported.

The sulfate ion itself is an unlikely causal factor if it is in a neutralized state. It is already present in body fluids at relatively high concentrations, and controlled inhalation studies in humans and laboratory animals of pH neutral or nearly neutral sulfate salts, such as ammonium sulfate [$(NH_4)_2SO_4$], even at relatively high concentrations, produce none of the effects reported from the epidemiologic studies (Utell et al., 1983; Lippmann et al., 1987; Schlesinger, 1989; Schlesinger et al., 1990). What these controlled exposure studies do show is that sulfate aerosols containing strong acids, such as sulfuric acid (H_2SO_4) and, to a lesser extent, ammonium bisulfate (NH_4HSO_4), do produce functional and structural changes in healthy subjects consistent with those observed in epidemiological studies, and do so at exposures within the upper bounds of current H^+ ambient levels. Furthermore, it is reasonable to speculate that the effects seen in the epidemiological studies are occurring in hyper-susceptible segments of the population, and that controlled exposure studies in susceptible human and animal cohorts, if they could be ethically performed, might well produce comparable effects at low ambient levels of H^+. A working hypothesis, therefore, is that H^+ is a causal factor for human health effects (e.g., see Lippmann and Thurston, 1996) and that, among the commonly measured PM indices, $SO_4^{=}$ is the best surrogate metric for H^+.

Historical and present-day evidence suggest that there can be both acute and chronic effects by acidic sulfates on human health. Evidence from historical pollution for episodes, notably the London Fog episodes of the 1950's and early 1960's, indicate that extremely elevated daily acid aerosol concentrations (on the order of 400 ug/m^3 as H_2SO_4, or roughly 8,000 nmoles/m^3 H^+) may be associated with excess acute human mortality when present as a co-pollutant with elevated concentrations of PM and SO_2 (Ministry of Health of Great Britain, 1954). In addition, Thurston et al. (1989) and Ito et al. (1993) both found significant

associations between acid aerosols and mortality in London during non-episode pollution levels (30 ug/m^3 as H_2SO_4, or approximately 600 nmoles/m^3 H^+), though these associations could not be separated from those for BS or SO_2.

Attempts to date to associate present-day levels of acidic aerosols in the U.S. with acute and chronic mortality (Dockery et al., 1992; Dockery et al., 1993, Schwartz et al., 1996, and Gwynn, et al., 2000) have had more mixed results, but there may not have been a sufficiently long series of H^+ measurements to detect H^+ associations in many of these studies. In the Utah Valley studies (Pope et al. 1991, 1992), PM_{10}-health effects association were found, despite limited H^+ sampling indicating low acid aerosol levels. This is not inconsistent with adverse health effects from H^+, however, when it is considered that PM can contain numerous toxic agents other than H^+. The more recent work of Gwynn et al. (2000) reported significant pollutant-health effect associations in Buffalo, NY--most strongly between $SO_4^=$ and respiratory hospital admissions (as indicated by its t-statistic). Additionally, H^+ and $SO_4^=$ demonstrated the most coherent associations with both respiratory hospital admissions and respiratory mortality. The authors concluded that "acidic sulfate aerosols represent a component of PM air pollution that may contribute to the previously noted adverse effects of PM mass on human health."

Pope et al. (1995) linked ambient air pollution data from 151 U.S. metropolitan areas in 1980 with individual risk factor on 552,138 adults who resided in these areas when enrolled in a prospective study in 1982. Deaths were ascertained through December 1989. Exposure to $SO_4^=$ and $PM_{2.5}$ pollution was estimated from national databases. The relationships of air pollution to all-cause, lung cancer, and cardiopulmonary mortality were examined using multivariate analysis that controlled for smoking, education, and other risk factors at the individual level. An association between mortality and particulate air pollution was observed. Figure 7 shows the range of values for the adjusted mortality rates in the various communities versus annual average $SO_4^=$ concentrations. The Pope et al. (1995) results thus indicate that the concerns raised about the credibility of the earlier results, due to their inability to control for potentially confounding factors such as smoking and socioeconomic variables on an individual

level, can be eased, and these findings are consistent with the prior findings of Ozkaynak and Thurston (1987) and Lave and Seskin (1970, 1977). Adjusted relative risk ratios (and 95% confidence intervals) of all-cause mortality for the most polluted areas compared with the least polluted were RR($SO_4^=$) =1.15 (1.09 to 1.22) and RR($PM_{2.5}$) = 1.17 (1.09 to 1.26). The findings of Dockery et al. (1993) and Pope et al. (1995) in prospective cohort studies also indicate that mean lifespan shortening of long-term exposures to PM is of the order of two years (Brunekreef, 1997). This implies that some individuals in the population have lives shortened by many years, and that there is excess mortality associated with long-term fine particle exposure that is greater than that indicated by an accumulation of acute effect estimates provided by the time-series studies of daily mortality.

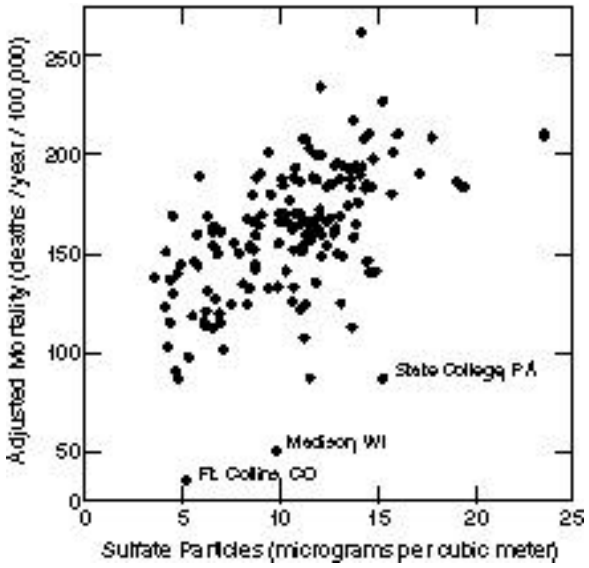


Figure 7. Age-, sex-, and race-adjusted population-based mortality rates versus mean sulfate air pollution levels for 1980. (Adapted from Pope, C.A. et al., Am. J. Respir. Crit. Care Med. 151:669-674 (1995).

Increased hospital admissions for respiratory causes were also documented during the London Fog episode of 1952, and this association has also been observed under present-day conditions. Thurston et al. (1992) and Thurston et al. (1994) have noted associations between ambient acidic aerosols and summertime respiratory hospital admissions in both New York State and Toronto, Canada, respectively, even after controlling for potentially confounding

temperature effects. In the latter of these studies, significant independent H^+ effects remained even after simultaneously considering the other major co-pollutant, O_3, in the regression model. While the New York State study considered only ozone as a possible confounder, the Toronto study also considered NO_2 and SO_2, but found them to be non-significant. In the Toronto analysis, the increase in respiratory hospital admissions associated with H^+ was indicated to be roughly six times that for non-acidic PM_{10} (per unit mass). In these studies, H^+ effects were estimated to be the largest during acid aerosol episodes (H^+ > 10 ug/m^3 as H_2SO_4, or 200 nmoles/m^3 H^+). These studies provide evidence that present-day strongly acidic aerosols can represent a portion of PM which is particularly associated with significant acute respiratory disease health effects in the general public.

Burnett et al. (1994) has related the number of emergency or urgent daily respiratory admissions at 168 acute care hospitals in all of Ontario during 1983 to 1988 to estimates of ozone and sulfates in the vicinity of each hospital. The authors reported that SO_2 and NO_2 were only weakly correlated with SO_4 in these data (r = 0.3), so these pollutants were unlikely to be confounders. Long-wave cycles in the admissions data were removed using a 19-day moving average equivalent high pass filter. A random effects model (wherein hospital effects were assumed to be random) was employed, using the generalized estimating equations (GEE). After adjusting admissions data for seasonal patterns, day of week effects, and individual hospital effects, positive and statistically significant associations were found between hospital admissions and both ozone and sulfates lagged 0 to 3 days. Positive associations were found in all age groups (0 to 1, 2 to 34, 35 to 64, 65+). The bivariate relationship found between adjusted admissions and sulfates in these data are shown in Figure 8. Positive and significant air pollution associations were found for asthma, chronic obstructive pulmonary disease (COPD), and infections, but not for nonrespiratory (control) admissions, nor for respiratory admissions in the winter months (when people are indoors and levels of these pollutants are low). While these analyses employed much more sophisticated statistical methods, the results generally consistent with Bates and Sizto's prior work in this region, though ozone was found to

yield a larger effect than sulfates in this study. The authors point out that $PM_{2.5}$ and H^+ are highly intercorrelated with sulfates in the summer months ($r > 0.8$), and that one of these agents may be responsible for the health effects relationships found with sulfates in this work.

Ostro (1988) also conducted a cross-sectional analysis of the U.S. Inhalable Particle Monitoring Network airborne particulate matter dataset, but analyzed the 1979-1981 annual Health Interview Surveys (HIS) to test if there were morbidity associations coherent with those found for mortality by Ozkaynak and Thurston during this period. Ostro reported a stronger association between several measures of morbidity (work loss days, restricted activity days, etc.) and lagged fine particle estimates than found with prior 2-week average TSP levels in 84 U.S. cities. In this analysis, a Poisson model was employed, due to the large number of days with zero cases in the dependent variables, and the analyses focused on adults aged 18 to 65. Smoking was not considered in the model, since not all metropolitan areas had data, but the correlation between smoking and any of the pollutants was less than 0.03 and non-significant in the one-third of the HIS sample for which smoking data were available. This indicates that, while presumably important to morbidity, smoking is not a confounder to pollutants in such cross-sectional analyses. Ostro concluded that his findings were consistent with the results of prior cross-sectional analyses reporting an association between mortality and exposures to fine particles and sulfates.

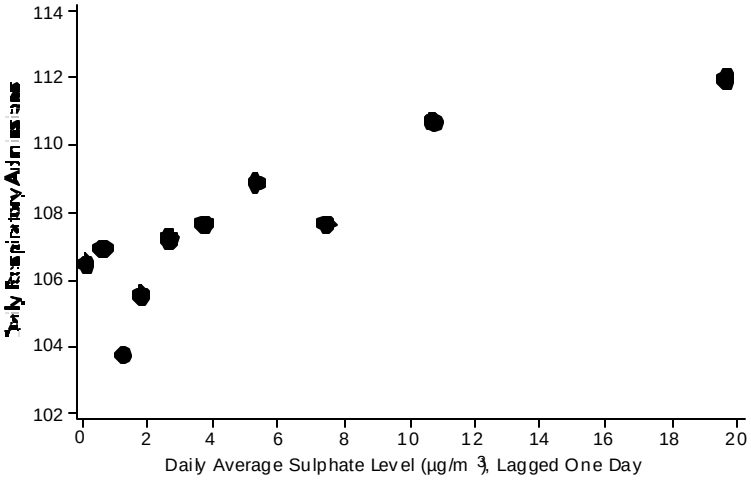


Figure 8. Average number of respiratory admissions Ontario hospitals by decile of the daily average sulfate level (ug/m^3), 1 day lag. (Adapted from Burnett et al., 1994).

Taken as a whole, these analyses are suggestive of mortality and morbidity associations with the sulfate fraction of fine particles found in contemporary American urban airsheds. Without nationwide measurements of airborne acidity, however, it is not now possible to evaluate the relative contribution of acid aerosols within these fine particle sulfates to the reported health effects.

Results from recent acute symptoms and lung function studies of healthy children indicate the potential for acute acidic sulfate effects in this population. While the 6-City study of diaries kept by parents of children's respiratory and other illness did not demonstrate H^+ associations with lower respiratory symptoms, except at H^+ above 110 moles/m_3 (Schwartz et al., 1994), upper respiratory symptoms in two of the cities were found to be most strongly associated with daily measurements of H_2SO_4 (Schwartz, et al., 1991b). Some, but not all, recent summer camp and school children studies of lung function have also indicated significant associations between acute exposures to acidic PM and decreases in the lung function of children independent of those associated with O_3 (Studnicka et al., 1995; Neas et al., 1995).

Studies of the effects of chronic H^+ exposures on children's respiratory health and lung function are generally consistent with effects as a result of long-term H^+ exposure. Preliminary analyses of bronchitis prevalence rates as reported across the 6-City study locales were found to be more closely associated with average H^+ concentrations than with PM in general (Speizer, 1989). A follow-up analysis of these cities and a seventh locality which controlled the analysis for maternal smoking and education and for race, suggested associations between summertime average H^+ and chronic bronchitic and related symptoms (Damokosh et al., 1993). The relative odds of bronchitic symptoms with the highest acid concentration (58 nmoles/m^3 H^+) versus the lowest concentration (16 nmoles/m^3) was 2.4 (95% CI: 1.9 to 3.2). Furthermore, in a follow-up study of children in 24 U.S. and Canadian communities (Dockery et al., 1996) in which the analysis was adjusted for the effects of gender, age, parental asthma, parental education, and parental allergies, bronchitic symptoms were confirmed to be significantly associated with

strongly acidic PM (relative odds = 1.66, 95% CI: 1.11 to 2.48). It was also found that mean FVC and $FEV_{1.0}$ were lower in locales having high particle strong acidity (Raizenne et al., 1996). Thus, epidemiological evidence indicates that chronic exposures to strongly acidic PM can have effects on measures of respiratory health in children.

One plausible mechanism by which acidic sulfates may act to increase the toxicity of PM is by enhancing the effects of soluble metals and reactive oxygen intermediates. PM, and especially combustion-related aerosols, contain transition metals such as iron, copper, nickel, vanadium, and cobalt that are more readily solublized at lower pH. These metals are capable of catalyzing the one-electron reductions of molecular oxygen necessary to generate reactive oxygen species (ROS) (e.g., via the iron-catalyzed Fenton Reactions. Other than Fe, several vanadium compounds have been shown to increase mRNA levels for selected cytokines in BAL cells and also to induce pulmonary inflammation (Pierce et al., 1996). $NaVO_3$ and $VOSO_4$, highly soluble forms of vanadium, tended to induce pulmonary inflammation and inflammatory cytokine mRNA expression more rapidly and more intensely than the less soluble form, V_2O_5, in rats. Neutrophil influx was greatest following exposure to $VOSO_4$ and lowest following exposure to V_2O_5, providing one plausible sulfate PM health effects mechanism.

Many studies investigating the response of animals to particle exposures have used residual oil flyash (ROFA) as a surrogate for ambient particles. ROFA has a high content of water soluble sulfate and metals. As described in the last U.S. PM Criteria Document (U.S. Environmental Protection Agency, 1995), intratracheal instillation of high doses of ROFA suspension generally produced severe inflammation, an indicator of pulmonary injury that included recruitment of neutrophils, eosinophils, and monocytes into the airway. The biological effects of ROFA have been shown to depend on aqueous leachable chemical constituents of the particles. Dreher et al. (1997) have shown that a leachate prepared from ROFA, containing predominantly Fe, Ni, V, Ca, Mg, and sulfate, produced similar lung injury to that induced by the complete ROFA suspension, indicating the potency of this sulfate-metals mixture.

E. PM and Sulfate Interactions with Other Pollutants

This section addresses any studies examining interactions between PM and sulfates and other pollutants (including noncriteria pollutants or bioaerosols).

E.1. Interaction of PM with Allergens

There is growing scientific evidence that particulate matter from fossil fuel combustion enhances the immune response to allergens, leading to an increase in allergic inflammation and allergic reactivity. Therefore, particulate air pollutants can be an important contributor to the increased morbidity of acute asthma and allergic rhinitis, as well as being a potential trigger of asthma in its own right. Furthermore, recent clinical studies and experimental studies have been able to describe the manner in which diesel particles specifically trigger a biochemical reaction which causes the type of allergic inflammation that asthma medications are aimed at preventing (e.g., see: Nel et al., 1998). Nel and colleagues (1998) have suggested that the rise in the U.S. prevalence rate for allergic rhinitis (5% in the 1950s to about 20% in the 1980s) may be related to increased diesel particulate matter (DPM), in addition to other combustion related PM. Combustion particles may also serve as carrier particles for allergens (Knox et al., 1997). These studies provide biological plausibility for the exacerbation of allergic asthma associated with episodic exposure to PM. Although DPM may make up only a fraction of the mass of urban PM, because of their small size, DPM may represent a significant fraction of the ultrafine particle mode in urban air, especially in cities that rely heavily on diesel-powered vehicles. Thus, while not themselves allergens, diesel and other combustion PM may increase an asthma patient's general responsiveness to any and all allergens and pollens to which they are already allergic, thereby increasing the chance that acute asthma problems will be experienced in a given population of persons with asthma.

Alterations in the response to a specific antigenic challenge have also been observed in animal models at high concentrations of acid sulfate aerosols (above 1,000 ug/m^3) (Pinto et al., 1979; Kitabatake et al., 1979; Fujimaki et al., 1992). Several studies have reported an enhanced response to non-specific bronchoprovocation agents, such as acetylcholine and

histamine, after exposure to inhaled particles. This non-specific airway hyperresponsiveness, a central feature of asthma, occurs in animals and human subjects exposed to sulfuric acid under controlled conditions (Gearhart and Schlesinger, 1986; Utell et al., 1983). Although its relevance to specific allergic responses in the airways of atopic individuals is unclear, it demonstrates that the airways of asthmatics may become sensitized by acidic sulfates to either specific or non-specific triggers that could result in increases in asthma severity and asthma-related hospital admissions (Peters et al., 1997; Lipsett et al., 1997).

The above noted PM-asthma interactions are of greatest significance to children because the prevalence of asthma children is higher and increasing more rapidly among children than among other age groups. Indeed, the U.S. prevalence rate of asthma in children aged <20 years rose rapidly from approximately 3.5% to 5% during the 1980's, a prevalence that was nearly double adults 20-64 years of age at that time, and higher than all other age groups (U.S. DOH, 1991). Rates for asthma prevalence, hospitalization, and death are especially high among children residing in inner cities, and important risk factors for asthma-related mortality include being poor or black (CDC, 1997a, 1997b). Thus, the above discussed PM-asthma interactions, that suggest that PM air pollution exposure makes people with asthma more reactive to all asthma triggers, mean that children will be at greater risk from PM exposure, as they have the highest prevalence and severity of this worsening disease.

E.2. Interaction of PM with Gaseous Pollutant Mixtures

Ambient PM usually co-exists in indoor and outdoor air with a number of co-pollutant gases, including ozone, sulfur dioxide, oxides of nitrogen, and carbon monoxide, and this may modify PM toxicity. The presence and nature of any interactions are not well understood at this time, but are likely to depend upon the particle size and the concentration of pollutants in the mixture, exposure duration, and the health endpoint being examined.

One of the primary particle-gas interaction mechanisms documented to-date are chemical interactions between particles and gases that occur on particle surfaces. This forms secondary products on that particle surface that may be more toxicologically active than the

primary materials, and that can then be more readily carried to a sensitive sites deeper in the lung. The hypothesis of such chemical interactions has been evaluated in the gas and particle exposure studies of SO_2 and particles by Amdur and colleagues (Amdur and Chen, 1989; Chen et al., 1992). These investigators have demonstrated that synergism occurs as secondary chemical species are produced (e.g., sulfuric acid on the surface of the particles), especially under conditions of elevated relative humidity, such as found in the human lung. Thus, these studies suggest that air quality standards set for individual air pollutants may not be fully protective of human health for exposures to mixed ambient pollutants.

Another hypothesized mechanism of gas-particle interaction may involve pollutant-induced changes in the lung, enhancing the effects of the co-pollutant. For example, Last et al. (1984) indicated that the observed synergism between ozone and acid sulfates in rats was due to a decrease in the local microenvironmental pH of the lung following deposition of acid, enhancing the effects of ozone by producing a change in the reactivity or residence time of reactants, such as radicals, involved in ozone-induced tissue injury. Kleinman et al. (1999) examined the effects of ozone plus fine H_2SO_4 coated carbon particles (MMAD = 0.26 um) for 1 or 5 days. They found the inflammatory response with the ozone-particle mixture was greater after 5 days (4 hours/day) than after day 1. This contrasted with ozone exposure alone (0.4 ppm) which caused marked inflammation on acute exposure, but no inflammation after 5 consecutive days of exposure. Thus, acids and ozone together appear to be of greater impact than either alone.

Two studies have examined interaction between carbon particles and gaseous co-pollutants. Jakab et al. (1996) challenged mice with a single 4-hour exposure to a high concentration of carbon, 10 mg/m^3, in the presence of SO_2 at low and high relative humidity. Macrophage phagocytosis was significantly depressed only in mice exposed to the combined pollutants under high relative humidity conditions. This study demonstrates that fine carbon particles can serve as an effective carrier for acidic sulfates, where chemical conversion of adsorbed SO_2 to acid sulfate species occurred. Interestingly, the depression in macrophage

function was present as late as 7 days post-exposure. Bolarin et al. (1997) exposed rats to only 50 or 100 ug/m^3 carbon particles in combination with ammonium bisulfate and ozone. Despite 4 weeks of exposure, they observed no changes in protein concentration in lavage fluid or blood prolyl 4-hydroxylase, an enzyme involved in collagen metabolism. Slight decreases in plasma fibronectin were present in animals exposed to the combined pollutants versus ozone alone. Thus, the potential for adverse effects in the lungs of animals challenged with a combined exposure to particles and gaseous pollutants is dependent on numerous factors including the gaseous co-pollutant, concentration, and time.

Linn and colleagues (1997) examined the effect of a single exposure to 60 to 140 ug/m^3 H_2SO_4, 0.1 ppm SO_2, and 0.1 ppm ozone in healthy and asthmatic children. The children performed intermittent exercise during the 4-hour exposure to increase the inhaled dose of the pollutants. An overall effect on the combined group of healthy and asthmatic children was not observed. A positive association between acid concentration and symptoms was seen, however, in the subgroup of asthmatic children. The combined pollutant exposure had no effect on spirometry in asthmatic children and no changes in symptoms or spirometry were observed in healthy children. Thus, the effect of combined exposure to PM and gaseous co-pollutants appeared to have less effect on asthmatic children exposed under controlled laboratory conditions in comparison with field studies of children attending summer camp (Thurston et al., 1997). However, prior exposure to H_2SO_4 aerosol may enhance the subsequent response to ozone exposure (Linn et al., 1994; Frampton et al., 1995); the timing and sequence of the exposures may be important. Overall, the evidence suggests that the gaseous-particle interactions of ozone and acidity indicates are more likely to enhance the effects of PM exposures in children than adults, as children playing outdoors would tend to get higher exposures to these air pollution components (as opposed to adults indoors, where acidity and ozone exposure is diminished, relative to the outdoors).

While past acid aerosol research has focused largely on acidity in a particulate form (e.g., as $H_2SO_4^=$), recent research by Peters et al. (1999) as part of the Children's Health Study

raises the possibility that the acidity-particle interaction may extend to the interaction of vapor nitric acid (HNO_3) and particles. To study possible chronic respiratory effects of air pollutants, the authors initiated a 10-yr prospective cohort study of Southern California children, with a study design focused on four pollutants: ozone, particulate matter, nitric acid vapor, and nitrogen dioxide (NO_2). Twelve demographically similar communities were selected on the basis of historic monitoring information to represent extremes of exposure to one or more pollutants. In each community, about 150 public school students in grade 4, 75 in grade 7, and 75 in grade 10 were enrolled through their classrooms. Wheeze prevalence was positively associated with levels of both nitric acid (odds ratio [OR] = 1.45; 95% confidence interval [CI], 1.14-1.83) and NO_2 (OR = 1.54; 95% CI, 1.08-2.19) in boys (who usually spend more time outdoors than girls), and only nitric acid vapor was significant overall for boys and girls. The authors conclude, based on this cross-sectional assessment of questionnaire responses, that current levels of ambient air pollution in Southern California may be associated with effects on schoolchildren's respiratory morbidity. However, it seems unlikely that the highly water soluble HNO_3 could reach deep into the lungs without interaction with particles, much the way that SO_2 has been shown to be picked up by particles entering the lung (Amdur and Chen, 1989; Chen et al., 1992). Thus, it may be that there is a nitric acid-particle interaction that is underlying the nitric acid-child health effects associations reported by Peters and colleagues.

F. Implications of Health Effects Findings to the Adequacy of PM and Sulfate Standards

The health effects studies documented in this report provide substantial evidence that PM exposures at present ambient levels are adversely affecting the health of children in places throughout the world, including in California. However, whether a PM-health effects association is present or not at a given ambient level is difficult to determine from such studies because, when an effect is not found to be significant, it may be that there is merely insufficient power (e.g., too small a population, or too short a record period) to find an effect that may really be there. Also, such studies tend to be conducted on large populations, where the power is

greatest, but where concentrations are also usually highest (i.e., in cities), so studies of low levels are difficult to find. Thus, it is more challenging to evaluate at exactly what pollution exposure concentrations these documented health effects begin to occur for groups of susceptible individuals such as infants and children with asthma.

Probably the best database available at this time for the evaluation of the levels at which pollutants show significant adverse health effects is the body of medical visits and hospital admissions studies, as: 1) they represent a health effect outcome that is clearly adverse, with only long-term illness or death being worse, and; 2) they are reported in large enough numbers to provide sufficient statistical power, and are statistics that are routinely available for analysis, so there are a large number of studies available to evaluate, as documented in the above sections and Appendix A. Therefore, these studies will be examined here for insights into the adequacy of the present California standards for the protection of children's health.

The hospital admissions study most directly relevant to the question of the U.S. EPA's $PM_{2.5}$ standard's adequacy is that by Norris and colleagues (1999). As noted in Appendix A, the estimated mean $PM_{2.5}$ level (based upon nephelometry data) in that study of asthma hospital visits by Seattle children less than 18 was $PM_{2.5}$ = 12 ug/m^3, and the PM association was still significant at these low levels, even after controlling for co-pollutants. This implies that the $PM_{2.5}$ annual average standard should be below 12 ug/m^3 if it is to protect children with asthma. The maximum $PM_{2.5}$ concentration was approximately 7 times this value, above the 65 ug/m^3 24-hr. maximum standard, but the $PM_{2.5}$ short-term standard is as a 3 year average, so that the standard may well also not have been exceeded at this location where acute effects have been documented. These results therefore indicate that the present Federal $PM_{2.5}$ annual standard is not sufficiently protective of children with asthma, and further suggest that the 24-hr maximum may also not be sufficiently protective.

However, the Morgan et al (1998) study of asthma hospital admissions in Sydney, Australia experienced a mean $PM_{2.5}$ = 9.6 ug/m^3, but was unable to detect a significant $PM_{2.5}$ association, despite having larger daily counts and a longer record than the Norris et al (1999)

study. This Australian study's results, when compared to the Norris and colleagues study results, suggests that the threshold of $PM_{2.5}$ mass effects on asthma admissions in children is approximately 10 ug/m^3 as an annual mean over several years.

Since the mean PM_{10} concentration during the Norris et al (1999) Seattle study was 21.7 ug/m^3, this study further indicates that the present California PM_{10} annual average standard (30 ug/m^3) is also not sufficiently protective. In the case of PM_{10}, this study's results are confirmed by other studies that have demonstrated significant associations at PM_{10} levels below 30 ug/m^3. As shown in Appendix A, Atkinson et al. (1999a,b) found significant associations with both children's respiratory emergency department (ED) visits and hospital admissions in London, England, where the mean PM_{10} = 28.5 ug/m^3. Similarly, Hajet confirms this result for London doctor's visits for asthma and lower respiratory disease in London, with a mean PM_{10} = 28.2 ug/m^3. Medina et al (1997) also finds significant associations between PM_{13} and doctor's house calls at PM_{13} mean = 25 ug/m^3. Since PM_{10} is a sub-component of PM_{13}, and will therefore average less than PM_{13}, this Paris study confirms the Norris et al. result that significant adverse health associations occur even at mean PM_{10} below 25 ug/m^3.

Given the results of Norris et al (1999) and confirming PM studies, it is clear that the sulfate standard of 25 ug/m^3 is far from sufficiently protective. The above sulfate health effects section made clear that sulfate is an especially potent component of $PM_{2.5}$, and it's annual average standard should therefore be even lower than that for $PM_{2.5}$. Available studies of sulfates and hospital admissions confirm this conclusion, including the above discussed Burnett (1994) study summarized in Table 6. The average Southern Ontario sulfate level (after eliminating sulfate artifact) was 5.3 ug/m^3, yet significant associations were found between sulfates and children's respiratory admissions, even after controlling for ozone. Analyses of respiratory admissions in Buffalo and New York City (Thurston et al., 1992) at mean levels of 9.3 and 8.9 ug/m^3, respectively, also find significant sulfate-respiratory associations at mean concentrations well below 25 ug/m^3. In addition, examination of the plot of the Ontario data from the Burnett et al. (1994) study (presented above in Figure 8) suggests that the sulfate threshold

of effects, if it exists, lies below 5 ug/m^3, perhaps at about 2 ug/m^3. Clearly, the existing California $SO_4^=$ standard is not now sufficiently stringent to protect public health.

G. Conclusions

Based upon the above facts and considerations, it is clear that significant adverse health effects can reasonably be expected to occur at present day ambient levels, especially among infants and children, based on the findings of published studies.

Among the factors that cause children to be especially affected by PM air pollution are:

- higher PM exposure concentrations due to greater PM personal cloud than adults;
- higher PM exposure patterns (e.g., more time spent outdoors and greater activity levels);
- higher doses per body weight and lung surface area;
- diminished pollution defenses in infants vs. older children and adults;
- PM exposures may adversely affect body (e.g., lung) development in children;
- higher prevalence of children with asthma than in other age groups,
- larger percentage of children made susceptible by poverty than other age groups; and,
- gas-particle interactions and particle-allergen interactions apparently make pollutants more toxic than they are alone, potentially making the individual pollutant standards not fully protective to susceptible populations, such as children.

Furthermore, an examination of key medical visits and hospital admissions studies conducted at relatively low ambient concentrations evaluated the adequacy of the existing Federal and California PM_{10} and $PM_{2.5}$ mass and sulfate ambient air quality standards. It was found that these standards are not presently sufficiently protective of public health, since significant adverse health impacts have been documented in published studies to occur at ambient levels averaging well below these standards.

However, to help reduce any remaining uncertainties regarding the impacts of PM and sulfates on the health of infants and children, and to determine how to most optimally control such environmental insults, additional research is needed into many aspects of the PM-health effects association among children, including:

- improved identification of the specific characteristics of PM (e.g., ultrafines, acidity, elemental composition, etc.) that are contributing most to noted PM effects, and quantification of their relative roles in PM toxicity;
- further investigation as to whether acute exposures less than one day in length (e.g., 1-hour daily maximum), or longer multi-day exposures (e.g., 2 or more day average PM), also have health importance, over and above that captured by the 24-hour PM peak PM concentration measurement;
- further investigations into particle-gas and particle-allergen interactions;
- animal studies relating increased infection following particle exposure needed, as well as more epidemiological studies of respiratory infections in infants exposed to ambient particles.
- using both experimental and epidemiological methods, conduct further investigations of apparently larger effects of acute and long-term PM exposures on children, and especially infants.

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I. Appendix

Recent Studies Evaluating PM Associations with Medical Visits or Hospital Admissions in Infants and Children

Table A-1. Summaries of Recently Published Acute PM-Medical Visits Studies of Children

Reference/Citation Location, Duration PM Index/Concentrations	Study Description:	Results and Comments	PM Index, Lag,, Excess Risk %, (95% CI=LCI-UCL), Co-Pollutants
Anderson, et al. (1998) London ('87-'92) Population = 7.2 MM BS daily mean = 14.6 ug/m^3 BS 25-75th IQR= 24-38	Poisson regression used to estimate the RR of London daily asthma hospital admissions associated with changes in O_3, SO_2, NO_2 and particles (BS) for all ages and for 0-14 (mean=19.5/d), 15-64 (mean=13.1/d) and 65+ years (mean =2.6/d).	O_3, SO_2, NO_2, and particles (BS) were all found to have associations with daily hospital admissions for asthma, but there was a lack of consistency across the age groups in the specific pollutant. The BS association was strongest in the 65+ group, especially in winter.	Asthma Admissions. BS=10 ug/m^3 BS Lag = 0-3 day average concentration All age ER= 2.3%(95%CI: 0.2-4.6%) <15yr. ER= 0.88%(95%CI: 1.8-3.7%) 15-64yr ER=0.47%(95%CI: 2.2-3.2%) 65+ yr. ER=8.6%(95%CI: 2.4-15.2%)
Atkinson et al. (1999a) London ('92-'94) Population = NR PM10 Mean = 28.5 ug/m^3 10th-90th IQR =15.8-46.5 ug/m^3 BS mean =12.7 ug/m^3 10th-90th IQR =5.5-21.6 ug/m^3	All-age Respiratory (mean=90/day), Asthma (25.9/day), and Other Respiratory (64.1/day) ED visits analyzed for associations with air pollutants using Poisson methods. Counts for ages 0-14, 15-64, and >64 also examined.	PM_{10} associated, but BS was not, for all-age/all-respiratory category. This may reflect higher toxicity by secondary particles vs. carbonaceous primary particles. PM_{10} results driven by significant children and young adult associations, while older adult visits had negative (but non-significant) PM_{10}-ED visit relationship.	PM_{10} (30.7 ug/m^3) No co-pollutant: All Respiratory ED visits All age(lag 1d)ER=3.0%(95%CI:0.8-5.2%) <15yrs(lag 2d)ER=3.9%(95%CI: 0.6-7.3%) 15-64yr(lag1d)ER=5.2%(95%CI:2.1-8.4%) Asthma ED visits All age(lag 1d)ER=5.4%(95%CI:1.8-9.0%) <15yrs (lag 2d)ER=7.4%(95%CI:2.1-13%) 15-64yr.(lg 1d)ER=7.8%(95%CI:2.8-13%)
Atkinson et al. (1999b) London ('92-'94) Population = 7.2 MM PM_{10} Mean = 28.5 ug/m^3 10th-90th IQR=15.8-46.5 ug/m^3 BS mean=12.7 ug/m^3 10th-90th IQR=5.5-21.6 ug/m^3	All-age Respiratory (mean=150.6/day), all-age Asthma (38.7/day), COPD plus Asthma in adults >64 (22.9/day), and lower Respiratory (64.1/day) in adults >64 (16.7/day) hospital admissions from London hospitals considered. Counts for ages 0-14, 15-64, and >64 also examined.	Positive associations were found between emergency hospital admissions for respiratory disease and PM_{10} and SO_2, but not for O_3 or BS. When SO_2 and PM_{10} were included simultaneously, the size and significance of each was reduced.	PM_{10} (30.7ug/m^3), no co-pollutant. All Respiratory Admissions: All age(lag 1d)ER=3.0%(95%CI:1.1-4.9%) 0-14 y (lag 1d)ER=4.9%(95%CI:2.1-7.7%) 15-64y(lag 2d)ER=4.2%(95%CI:2.6-7.3%) 65+ y.(lag 3d)ER=3.0%(95%CI:0.47-5.6%) Asthma Admissions: All age(lg 3d)ER=2.1%(95%CI: 1.1-5.4%) 0-14 y (lag 3d)ER=3.3%(95%CI: 0.7-7.5%) 15-64 y(lag 3d)ER=5.7%(95%CI:0.7-11.%) 65+ y.(lag 0d)ER=7.2%(95%CI: 1.25-16%)

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Braga et al. (2000?) Author Affiliation: Non-Profit Research Funding: Public Sao Paulo, Brazil ('92-'93) Population = NR PM_{10} mean = 66.3 ug/m^3 PM_{10} Std. Deviation = 26.1 PM_{10} Min./Max. = 26.7/165.4	Pediatric (<13 yrs.) hospital admissions (mean=67.6/day) from public hospitals serving 40% of the population were regressed (using both Poisson and maximum likelihood methods) on pollutants, controlling for month of the year, day-of-week, weather, and the daily number of non-respiratory admissions (mean=120.7/day). Pollutants considered included PM_{10}, O_3, SO_2, CO, and NO_2.	PM_{10} and O_3 were the two pollutants found by the authors to exhibit the most robust associations with respiratory HA's. SO_2 showed no correlation at any lag. Simultaneous regression of respiratory HA's on PM_{10}, O_3, and CO decreased effect estimates and their significance, suggesting that "there may not be a predominance of any one pollutant over the others". No safe threshold was found for PM_{10} or O_3. Associations are ascribed primarily to auto emissions by the authors.	PM_{10} (66.3 ug/m^3), no-co-pollutant <u>Respiratory Hospital Admissions (<13 yr.)</u> (0-5 day lg avg.)ER=12%(95%CI:6.1-18%)
Delfino et al., 1997 Montreal,Canada (6-9/92,6-9/93) Population = 3 million 1993 Means (SD): PM_{10}= 21.7 ug/m^3 (10.2) $PM_{2.5}$= 12.2 ug/m^3 (7.1) $SO_4^=$= 34.8 nmol/m^3 (33.1) H^+= 4 nmol/m^3 (5.2)	Association of daily respiratory ED visits (mean = 98/day from 25 of 31 acute care hospitals) with O_3, PM_{10}, $PM_{2.5}$, $SO_4^=$, and H^+ assessed using linear regression with controls for temporal trends, auto-correlation, and weather. Five age sub-groups considered.	No associations with ED visits in '92, but 33% of the PM data missing then. In '93, only H^+ associated for children <2, despite very low H^+ levels. H^+ effect stable in multiple pollutant models and after excluding highest values. No associations for ED visits in persons 2-64 yrs. of age. For patients >64,O_3, PM_{10}, $PM_{2.5}$, and $SO_4^=$ were all positively associated with visits ($p < 0.02$), but PM effects smaller than for O_3.	<u>Respiratory ED Visits</u> <u>Children <2 yrs:</u> (H^+ lag = 2 day) 4 nmol/m^3 H^+ ER= 5.0% (CI = 0.4-9.6%) <u>Adults >64:</u> (pollutant lags = 1 day) 21.7 ug/m^3 PM_{10} ER= 16% (CI = 4-28%) 12.2 ug/m^3 $PM_{2.5}$ ER= 12% (CI = 2-21%) 34.8 nmol.m^3 $SO_4^=$ ER= 6% (CI = 1-12%)
Gouveia et al (2000) Author Affiliation: Non-profit Research Funding: Public Study Period.:'92-'94 Sao Paulo, Brazil Population = 9.5 MM x 66% PM_{10} mean = 64.9 ug/m^3 PM_{10} IQR = 42.9-75.5 ug/m^3 PM_{10}10/90th%ile=34.5/110ug/m^3 PM_{10} 95th%ile = 131.6 ug/m^3	Daily public hospital admissions for respiratory diseases by children (mean Resp. < 5y = 56.1/d; mean Pneumonia <5y =40.8/d; mean asthma <5 y = 8.5/d; mean Pneum.<1y=24.0) and daily levels of weather and air pollutants (PM_{10}, SO_2, NO_2, O_3, and CO) were analyzed with Poisson regression. PM_{10} measured by Beta-gauge.	Children's HA's for total respiratory and pneumonia gave positive associations with O_3, NO_2, and with PM_{10}. Effects for pneumonia greater than for all respiratory diseases. Effects on infants (<1 yr. old) gave higher estimates. Similar results for asthma, but estimates higher than for other causes. Results noted to agree with prior publications, but smaller RR's. This may be an artifact of higher baseline admission rates in this poor sub-population vs. other studies, but this is not intercompared by the authors.	For PM 10th-90th %ile =75.5 ug/m^3: <u>All Respiratory HA's for children < 5yrs.</u> ER = 4.0% (95% CI = ¯1.5%, 9.9%) <u>Pneumonia HA's for children <5 yrs.</u> ER = 5.0% (95% CI = ¯1.6%, 12.1%) <u>Asthma HA's for children <5 yrs.</u> ER = 5.2% (95% CI = ¯7.7%, 19.8%) <u>Asthma HA's for children <1 yrs.</u> ER = 9.4% (95% CI = 1.3%, 18.0%)

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Hajet et al., 1999 London, England (92'-'94) Population = 282,000 PM_{10} mean = 28.2 ug/m^3 PM_{10} 10^{t}-90^{th}%=16.3-46.4 ug/m^3 BS mean = 10.1 ug/m^3 BS 10^{t}-90^{th}%=4.5-15.9 ug/m^3	Examined associations of PM_{10}, BS, NO_2, O_3, SO_2, and CO, with primary care GP asthma and "other LRD" consultations [asthma means = 35.3 (all ages); = 14.(0-14 yrs,); = 17.7 (15-64 yrs.); = 3.6 (>64 yrs.)] [LRD means = 155. (all ages); = 39.7(0-14 yrs,); = 73.8 (15-64 yrs.); = 41.1 (>64 yrs.)], Time-series analyses of daily numbers of GP consultations were performed, controlling for time trends, season factors, day of week, influenza, weather, pollen levels, and serial correlation.	Positive associations, weakly significant and consistent across lags, were observed between asthma consultations and NO_2 and CO in children, and with PM_{10} in adults, and between other LRD consultations and SO_2 in children.. Across all of the various age, cause, and season categories considered in this research, PM_{10} was the pollutant most coherent in giving positive pollutant RR estimates for both asthma and other LRD (11 of 12 categories positive) in single pollutant models considered.	<u>Asthma Doctor's Visits</u>: 30 ug/m^3 PM_{10} (10-90^{th} %ile Range) -Year-round, Single Pollutant: All ages (lg 2): ER=3.2% (CI=-0.4-6.8%) 0-14 yrs.(lg 1): ER=3.8% (CI=1.0-8.8%) 15-64 yrs.(lg 0): ER=5.4% (CI=1.6-9.2%) >64yrs.(lg 2): ER=7.1% (CI=-1.1-16%) <u>Other Lower Resp. Dis. Doctor's Visits</u>: 30 ug/m^3 PM_{10} (10-90^{th} %ile Range) -Year-round, Single Pollutant: All ages (lg 2): ER=2.1% (CI=-0.4-3.8%) 0-14 yrs.(lg 1): ER=2.5% (CI=-0.7-5.8%) 15-64 yrs.(lg 2): ER=2.2% (CI=0.0-4.5%) >64yrs.(lg 2): ER=3.7% (CI=-0.3-7.2%)
Lin CA, et al, 2000 Author Affiliation: Non-profit Research Funding: NR Sao Paulo, BR ('91-'93) Population = NR PM_{10} mean =65 ug/m^3 PM_{10} SD = 27 ug/m^3 PM_{10} range = 15-193 ug/m^3	Respiratory ED visits by children (0-12 yrs.) to a major pediatric hospital (mean = 56/day) related to PM_{10}, SO_2, NO_2, CO, and O_3 using Gaussian linear regression modeling, Poisson modeling, and a polynomial distributed lag model. Lower Respiratory (mean = 8/day) and Upper Respiratory (mean = 39/day) ED visits, and visits due to Wheezing (mean=9/day), evaluated.	PM_{10} was found to be "the pollutant that exhibited the most robust and stable association with all categories of respiratory disease". O_3 was the only other pollutant that remained associated when other pollutants were all added to the model simultaneously. However, some pollutant coefficients went negative in multiple pollutant regressions, suggesting coefficient intercorrelations in the multiple pollutant models.	For 10 ug/m^3 PM_{10} (0-5 day lag mean) <u>Respiratory ED Visits(<13 yrs.)</u> Single Pollutant Model: PM_{10} ER=4.0% (CI=3.4%-4.6%) All-Pollutant Model: PM_{10} ER=5.2% (CI=4.0%-6.5%) <u>Lower Respiratory ED Visits (<13 yrs.)</u> Single Pollutant Model: PM_{10} ER=4.2% (CI=2.4%-6.0%) All-Pollutant Model: PM_{10} ER=8.0% (CI=5.0%-11%)
Medina et al., 1997 Greater Paris '91-'95 Population = 6.5 MM Mean PM_{13} = 25 ug/m^3 PM_{13} min/max = 6/95 ug/m^3 Mean BS = 21 ug/m^3 BS min/max = 3/130 ug/m^3	Evaluated short-term relationships between PM_{13} BS air pollution and doctors' house calls (mean=8/day; 20% of city total) in Greater Paris using Poisson regression.	A relationship between all age (0-64 yrs.) asthma house calls and PM_{13}, BS, SO_2, NO_2, and O_3 air pollution, especially for children aged 0-14 (mean = 2/day). In two-pollutant models including BS with, successively, SO_2, NO_2, and O_3, only BS and O_3 effects remained stable.	<u>Doctor's Asthma House Visits</u>: 10 to 50 ug/m^3 PM_{13}:5-95^{th}%ile Increment Year-round, Single Pollutant: All ages (lg 2): ER=10% (CI=4-18%) 0-14 yrs.(lg 0-3): ER=32% (CI=16-51%) 15-64 yrs.(lg 2): ER=5% (CI=-5%-13%)

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Moolgavkar, et al (2000b) Author Affiliation: Non-profit Research Funding: Industry Study Period: 1987-1995 <u>Los Angeles (LA County), CA</u> Population = NR PM_{10} median = 44 ug/m^3 PM_{10} IQR= 33-59 ug/m^3 $PM_{2.5}$ median = 22 ug/m^3 $PM_{2.5}$ IQR = 15-31 ug/m^3	Investigated associations between air pollution and COPD HA's in LA, for children 0-19 (med.=17/d), adults 20-64 (med.=24/d), and adults 65+ (med. = 20/d). Used Poisson GAM's controlling for day-of-week, season, and splines of temperature and RH (but not their interaction) adjusted for overdispersion. Co-pollutants were O_3, SO_2, NO_2, and CO. PM data available only every 6th day, vs. every day for gases.	PM was associated with admissions in single pollutant models, but not in two pollutant models. Analysis in 3 age groups in LA yielded similar results. Author concludes that "the gases, other than ozone, were more strongly associated with COPD admissions than PM, and that there was considerable heterogeneity in the effects of individual pollutants in different geographic areas".	Most Significant Positive ER (t-statistic) Single Pollutant Models: <u>LA COPD HA's</u> (25 ug/m^3 PM_{10}, 10 ug/m^3 $PM_{2.5}/PM_{2.5-10}$) (0-19 yrs.): PM_{10} lg2=5.2% (t=3.4) (0-19 yrs.): $PM_{2.5}$ lg0=1.7% (t=1.9) (0-19 yrs.): $PM_{2.5-10}$ lg2=6.5% (t=4.3) (20-64 yrs.): PM_{10} lg2=3.2% (t=2.7) (20-64 yrs.): $PM_{2.5}$ lg2=2.2% (t=3.0) (20-64 yrs.): $PM_{2.5-10}$ lg2=3.5% (t=3.0) (>64 yrs.): $PM_{2.5-10}$ lg3=2.0% (t=1.8)
Morgan et al, 1998 Author Affiliation: Non-profit Research Funding: Public Sydney, AU ('90-'94) Population = NR $PM_{2.5}$ 24h. mean = 9.6 ug/m^3 $PM_{2.5}$ 10^{th}-90^{th}% =3.6-18 ug/m^3 $PM_{2.5}$ max-1h. mean=22.8ug/m^3 $PM_{2.5}$ 10^{th}-90^{th}%=7.5-44.4ug/m^3	A Poisson analysis, controlled for overdispersion and autocorrelation via GEE, of asthma (means: 0-14 yrs.=15.5/day; 15-64=9/day)), COPD (mean 65+yrs. =9.7/day), and heart disease HA's. $PM_{2.5}$ estimated from nephelometry. Season and weather controlled using dummy variables.	Childhood asthma was primarily associated with NO_2, while COPD was associated with both NO_2 and PM. 1-hr. max $PM_{2.5}$ more consistently positively related to respiratory HA's than 24-h avg $PM_{2.5}$. Adding all other pollutants lowered PM effect sizes, although pollutant inter-correlations makes many pollutant model interpretations difficult. No association found between asthma and O_3 or PM.	<u>Asthma HA's</u> Single Pollutant Model: For 24h $PM_{2.5}$ 10^{th}-90^{th}% =3.6-18 ug/m^3 1-14 yrs.(lag1) ER= -0.87%(CI=-4.6 - 3.0) 15-64 yrs.(lag0) ER=1.31%(CI=-2.3 - 5.1) For 1h $PM_{2.5}$ 10^{th}-90^{th}% =7.5-44.4 ug/m^3 1-14 yrs.(lag1) ER= -0.87%(CI=-4.6 - 3.0) 15-64 yrs.(lag0) ER=1.31%(CI=-2.3 - 5.1) Multiple Pollutant Model: For 24h $PM_{2.5}$ 10^{th}-90^{th}% =3.6-18 ug/m^3 1-14 yrs.(lag1) ER= -0.35%(CI=-4.3 - 3.8)
Norris et al (1999) Author Affiliation: Non-profit Research Funding: Public Seattle, WA (9/95-12/96) Pop. Of Children <18= 107,816 PM_{10} mean. =21.7 ug/m^3 PM_{10} IQR = 11.6 ug/m^3 ϑ_{sp} mean = 0.4 $m^{-1}/10^{-4}$ (12.0 ug/m^3 $PM_{2.5}$) ϑ_{sp} IQR = 0.3 $m^{-1}/10^{-4}$ (9.5 ug/m^3 $PM_{2.5}$)	The association between air pollution and childhood (<18 yrs.) ED visits for asthma from the inner city area with high asthma hospitalization rates (0.8/day, 23/day/10K persons) compared with lower hospital use areas (1.1/day, 8/day/10K persons). Daily ED counts were regressed against PM_{10}, light scattering (ϑ_{sp}), CO, SO_2, and NO_2 using a semiparametric Poisson regression model evaluated for over-dispersion and auto-correlation.	Associations found between ED visits for asthma in children and fine PM and CO. CO and PM_{10} highly correlated with each other (r=.74) and K, an indicator of woodsmoke pollution. Considering baseline risks/10K population indicates a higher PM attributable risk (AR) in the inner city. These findings were seen even though the mean estimated $PM_{2.5}$ concentration was below the newly adopted annual National Ambient Air Quality Standard of 15 ug/m^3.	<u>Children's (<18 yrs.) Asthma ED Visits</u> Single Pollutant Models: For 24h PM_{10} IQR =11.6 ug/m^3 Lag1 ER= 14% (CI= 8% - 23%) For 24h ϑ_{sp} IQR =0.3 $m^{-1}/10^{-4}$ (9.5 ug/m^3 $PM_{2.5}$) Lag1 ER= 15% (CI= 8% - 23%) Multiple Pollutant Models: For 24h PM_{10} IQR =11.6 ug/m^3 Lag1 ER= 14% (CI= 4% - 26%) For 24h ϑ_{sp} IQR=0.3 $m^{-1}/10^{-4}$ (9.5 ug/m^3 $PM_{2.5}$) Lag1 ER= 17% (CI= 8% - 26%)

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Norris et al (2000) Author Affiliation: Non-profit Research Funding: Public <u>Spokane, WA</u> (1/95—3/97) Population = 300,000 PM_{10} mean. =27.9 ug/m^3 PM_{10} Min/Max=4.7/186.4 ug/m^3 PM_{10} IQR = 21.4 ug/m^3 <u>Seattle, WA</u> (9/95—12/96) Pop. Of Children <18= 107,816 PM_{10} mean. =21.5 ug/m^3 PM_{10} Min/Max = 8/69.3 ug/m^3 PM_{10} IQR = 11.7 ug/m^3	Associations investigated between an atmospheric stagnation index (# of hours below median wind speed), a "surrogate index of pollution", and asthma ED visits for persons <65 yrs. (mean=3.2) in Spokane and for children <18 (mean=1.8) in Seattle. Poisson GAM modeling, controlled for day of week, long-wave effects, and temperature and dew point (as non-linear smooths). Factor Analysis (FA) applied to identify PM components associated with asthma HA's.	Stagnation persistence index was strongly associated with ED visits for asthma in 2 cities. FA indicated that products of incomplete combustion (especially wood-smoke related K, OC, EC, and CO) are the air pollutants driving this association. Multi-pollutant models run with Stagnation as the "co-pollutant" indicated the importance of general air pollution over any single pollutant index, but provided no indication of the importance of the various pollutants relative to each other.	<u>Asthma ED Visits</u> Single Pollutant Models Persons<65 years (Spokane) For PM_{10} IQR = 21.4 ug/m^3 Lag 3 ER = 1% (95% CI= -5% - 7%) Persons<18 years (Seattle) For PM_{10} IQR = 11.7 ug/m^3 Lag 3 ER = 11% (95% CI= 2% - 20%)
Ostro et al (1999) Author Affiliation: Non-profit Research Funding: World Bank Santiago, CI (7/92—12/93) <2 yrs. Population 20,800 3-14 yrs. Population 128,000 PM_{10} mean. =108.6 ug/m^3 PM_{10} Min/Max=18.5/380 ug/m^3 PM_{10} IQR = 70.3 – 135.5 ug/m^3	Analysis of daily visits to primary health care clinics for upper or lower respiratory symptoms by children 2-14 years of age (mean LRS=111.1/day) and < age 2 (mean LRS=104.3/day). Daily PM_{10} and O_3 and meteorological variables considered. The multiple regression GAM included controls for seasonality (LOESS smooth), temperature, day of week, and month.	Analyses indicated an association between PM_{10} and medical visits for LRS in children ages 2-14 and in children under age 2. PM_{10} was not related to non-respiratory visits (mean =208/day). Results unchanged by eliminating high PM_{10} (>235 ug/m^3) or coldest days (<8°C). Adding O_3 to the model had little effect on PM_{10}-LRS associations.	<u>Lower Resp. Symptoms Clinic Visits</u> PM_{10} IQR = 50 $^{ug/m3}$, One Poll. Model: -Children<2 years Lag 3 ER = 2.5% (95% CI= 0.2% - 4.8%) -Children 2-14 years Lag 3 ER = 3.7% (95% CI=0.8% - 6.7%) Two Pollutant Models (with O_3): -Children<2 years Lag 3 ER = 2.2% (95% CI= 0% - 4.4%) -Children 2-14 years Lag 3 ER = 3.7% (95% CI=0.9% - 6.5%)
Rosas, et al (1998) Author Affiliation: Non-profit Research Funding: public SW Mexico City ('91) Population = NR PM_{10} mean. =77 ug/m^3 PM_{10} min/max= 25/183 ug/m^3	Log-regression analysis of the relationships between emergency admissions for asthma to a hospital for children <15 years (mean=2.5/day), adults (mean=3.0/day), and older adults >59 years (mean=0.65/day) and lag 0-2 average pollen, fungal spores, air pollutants (O_3, NO_2, SO_2, and PM_{10}) and weather factors. Long wave controlled only by separating the year into two seasons: "dry" and "wet". Day-of-week not included in models.	There were few statistical associations found between asthma admissions and air pollutant. Grass pollen was associated with child and adult admissions, and fungal spores were associated with child admissions. The authors conclude that aeroallergens may be more strongly associated with asthma than air pollutants, and may act as confounding factors in epidemiologic studies. Results are limited by low power and the lack of long-wave auto-correlation controls in the models.	NR

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Sunyer et al (1997) Barcelona (‘86-‘92) BS Median: 40 ug/m^3 BS Range: 11-258 (B Helsinki (‘86-‘92) BS Median: - BS Range: - Paris (‘86-‘92) BS Median: 28 ug/m^3 BS Range: 4-186 ug/m^3 London (‘86-‘92) BS Median: 13 ug/m^3 BS Range: 3-95 ug/m^3	Daily counts of asthma HA’s and ED visits in adults [ages 15-64 years: mean/day = 3.9 (B); 0.7 (H); 13.1 (H); 7.3 (P)] and children [ages < 15 years: mean/day = 0.9 (H); 19.8 (L); 4.6 (P)] related to BS, SO_2, NO_2, and O_3 air pollution. Asthma (ICD9=493) studied in each city, but the outcome examined differed across cities:	In children, daily admissions increased significantly with SO_2 and positively (but non-significantly) with Black Smoke and NO_2, though the latter only in cold seasons. No association was observed in children for O_3. The weakness of PM in these analyses may be result of the use of the BS index, a measure of only the primary carbonaceous particles, which may be less toxic than other (i.e., secondary) aerosols.	ER per 50µg/m^3 BS (24 h Average) <u>Asthma Admissions/Visits</u>: <15 yrs.: London ER = 3.1% (lg 0d) Paris ER = 3.0% (lg 2d) Total ER = 3.0% (95%CI: ¯2.1%-8.4%) 15-64 yrs: Barcelona ER = 3.6% (lg 3d) London ER = 3.5% (lg 0d) Paris ER = 1.2% (lg 0d) Total ER = 2.1% (95%CI: ¯1.5%-5.9%)
Wong, et al (1999) Study Period.:’94-‘95 Hong Kong Population = NR PM_{10} mean = 50.1 ug/m^3 PM_{10} median = 45.0 ug/m^3 PM_{10} IQR = 30.7, 65.5 ug/m^3	Poisson regression applied to assess association of daily NO_2, SO_2, O_3, and PM_{10} with emergency HA’s for all respiratory (median = 131/day) and COPD (median = 101/day) causes. Effects by age groups (0-4, 5-64, and 65+ yrs.) also evaluated.	Positive associations were found for HA’s for all respiratory diseases and COPD with all four pollutants. PM_{10} results for lags 0-3 cumulative. Admissions for asthma, pneumonia, and influenza were associated with NO_2, O_3, and PM_{10}. Those aged > or = 65 years were at higher risk, except for PM_{10}.	PM_{10} = 10 ug/m^3 (Lags = 0-3 days) <u>Respiratory HA’s</u> All age: ER= 1.6% (95%CI: 1.0, 2.2%) 0-4yrs.: ER= 1.9% (95%CI: 1.1, 2.8%) 5-64yrs.: ER= 1.7% (95%CI: 0.9, 2.6%) 65+ yrs.: ER= 1.8% (95%CI: 1.0, 2.6%)

OZONE:
EVALUATION OF CURRENT CALIFORNIA AIR QUALITY STANDARDS WITH RESPECT TO PROTECTION OF CHILDREN

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A. Background

The existing ambient standard for ozone (O_3) for the State of California is 0.09 ppm (180 $\mu g/m^3$) for a 1-hour averaging time. The standard was set in 1987. At the time, the Department of Health Services (DHS) concluded: "*A one-hour 0.08 ppm standard provides a small, but adequate margin of safety against acute effects...*", chronic effects in animals at 0.08 ppm "...*could be expected to occur in humans at somewhat higher concentrations*..." and that 0.08 ppm "...*would provide an adequate margin of safety against the occurrence of inflammation and therefore of chronic lung disease*..." (1). On review of all of the evidence, the State of California Air Resources Board (ARB) staff recommended a standard of 0.09 ppm averaged over 1-hour. The decision to maintain a one-hour averaging time was made for "historical reasons" (1).

In July, 1997, the U.S. Environmental Protection Agency promulgated an 8-hour standard of 0.08 ppm (157 $\mu g/m^3$). However, due to a U.S. Federal Court decision (2), the previous 1-hour standard of 0.12 ppm (235 $\mu g/m^3$) remains the operative standard. The rationale for the recommendation to switch to an 8 hour standard was based on an extensive summary of health effects that indicated "...*an array of health effects has been attributed to short-term (1 to 3 hours), prolonged (6-8 hours) and long-term (months to years) exposures to* O_3" (3). In its summary statement, the E.P.A. concluded that "...*longer exposure periods are of greater concern at lower* O_3 *concentrations*..." (3).

B. Principal Sources and Exposure Assessment:

The major source for O_3 exposure, for the vast majority of people, is from the outside air. Therefore, for practical purposes, understanding exposure patterns of infants and children to ambient O_3 is tied to an understanding of patterns of activities relative to the outdoors.

In an ARB study (4), children ages 11 and under spent nearly twice as much time outdoors per day (10% of a 24-hour period) versus only 5.1% for Californians ages 12 and over (Table 4.41; 4). Compared to a national sample, these young children spent more than 3-times as much time involved in sports and outdoor activities (Table 4.15 & p. 67; 4). For teenagers (ages 12-17),

overall time differences compared to older adults was less striking (Table 3-5; 5). However, when time spent in active sports and outdoor recreation was considered, teenagers spent more than twice as much time engaged in active sports and outdoor activities than did older persons (Table 3-8; 5).

In addition to the greater amounts of time spent outdoors, young children (≤10 years) have higher minute ventilation, expressed as L/minute/kg body weight, than do adults (Figure 1) (6). Thus, on a weight basis, the respiratory tract of young children can be expected to be exposed to a larger "dose" of O_3 for any given level of activity. Moreover, given the greater propensity of children to be outside and to engage in activities with ventilatory demands above the resting state (4; 5), it is to be expected over the short and long-term children will have greater exposures to ambient ozone that will adults.

C. Controlled Human Exposure Studies

The 1987 ARB Staff Report on Health and Welfare Effects (1) supporting the current ambient air quality standard for ozone (0.9 ppm or 180 mcg/m^3 for 1 hour) stated the following: "*The major evidence directly related to the need for a one-hour ozone standard comes from brief exposures of human subjects in clinical studies. Evidence of ozone-induced dysfunction in humans is provided by research showing that alterations in pulmonary airflow tests (pulmonary function decrements) occur in healthy exercising adults and children exposed to ozone concentrations as low as 0.12 ppm for one or two hours. The subjects in these tests (sic) also experience respiratory symptoms. In similar studies at 0.10 ppm, such pulmonary function changes were not demonstrated although effects could occur at levels between 0.10 ppm and 0.12 ppm.*" Thus, 0.12 ppm was determined to be the lowest level of ozone for which adverse effects had been clearly demonstrated in humans. The Staff Report recommended that a standard of 0.09 ppm, averaged over 1 hour, would protect the public health from ozone exposure with an adequate margin of safety relative to the level at which acute pulmonary effects occur.

C.1. Controlled Exposure Studies in Children

Although controlled human exposure studies of the effects of ozone are rarely performed with children as subjects, several studies involving healthy and asthmatic adolescents have been published, including two since the last revision of the California ambient air quality standard. McDonnell *et al*. (7) reported small (mean=3.4%) decrements in forced expiratory volume in 1 second (FEV_1) in 23 boys (ages 8-11 years). Koenig *et al*. (8) exposed 22 adolescents (both genders, ages 14-19 years) to 0.12 ppm or 0.18 ppm ozone through a mouthpiece. Not all subjects were exposed to both concentrations. The exposure protocol was a 30-minute resting exposure followed by a 5-7 minute break for pulmonary function testing followed by a 10-minute exposure during moderate exercise. There were no significant decrements in FEV_1 with exposure to either concentration of ozone and no consistent differences between normal and asthmatic subjects. The same group of investigators (9) exposed another group of 12 non-asthmatic and 12 asthmatic adolescents (both genders, ages 12-17 years) to air or 0.12 ppm ozone for 1-hour with alternating 15-minute periods of rest and exercise. Healthy subjects had no significant decrements in pulmonary function after the ozone exposure, but there was a significant decrease in maximal expiratory flow at 50% of forced vital capacity (FEF_{25-75}) in the asthmatic subjects after ozone exposure compared to after filtered air.

The 1996 U.S. Environmental Protection Agency (EPA) criteria document on ozone reviews the studies described above and states that “the limited existing data do not identify adolescents as being either more or less responsive than adults” (10).

C.2. Controlled Exposure Studies in Adults – Pulmonary Function.

Since the 1987 ARB review of the California ambient air quality standard for ozone, several controlled human exposure studies by U.S. EPA investigators have documented short-term decrements in pulmonary function in adult subjects with multi-hour exposures to concentrations of ozone below 0.12 ppm (11-13). In addition, one study also demonstrated evidence of acute airway

epithelial injury and inflammation with such exposures (13). Folinsbee *et al*. (11) reported the results of a study of 10 male adults (ages 18-33 years) exposed to 0.12 ppm ozone for a total of 6.6 hours (moderate exercise for 50 minutes of each of 6 hours with a 35-minute lunch break after 3 hours). Hourly pulmonary function measurements showed that FEV_1 decreased in a roughly linear fashion throughout the exposure and had fallen by a mean of 13% by the end of exposure (three subjects had FEV_1 decrements of ≥25%). Symptoms of cough and chest discomfort were increased after ozone as compared to after filtered air. Airway responsiveness to methacholine (a measure of non-specific airway hyperresponsiveness to inhaled noxious stimuli) was also significantly increased (approximately doubled) after ozone exposure.

Using the same 6.6-hour protocol, these investigators (12) then compared the effects of three different ozone concentrations (0.08 ppm, 0.10 ppm, and 0.12 ppm) in a group of 22 males (ages 18-33 years). With 0.12 ppm, the responses were similar to those of the previous study. With the two lower concentrations, the responses to ozone were of lesser magnitude but still significant. The FEV_1 decrements after 0.08 ppm, 0.10 ppm, and 0.12 ppm exposures were 7%, 5%, and 13%, respectively (Figure 2). The methacholine responsiveness increased by 56%, 89%, and 121%, respectively. In yet another study using the 6.6-hour protocol by the same group of investigators (13), designed to look at airway injury and inflammatory responses in 38 males (mean age=25 years), there was a 8% decrease in FEV_1 after 0.08 ppm ozone and a 11% decrease after 0.10 ppm. In a paper summarizing the results of the 6.6-hour EPA exposures to these low-level concentrations of ozone, Folinsbee *et al*. (14) reported that 26% of subjects after 0.08 ppm, 31% after 0.10 ppm, and 46% after 0.12 ppm had decreases in FEV_1 >10%, with some decreases as great as 50%.

Given that children's pulmonary function responses to ozone are likely to be at least as great as those of young adults, it follows that a substantial proportion of healthy children will have symptoms and decrements in lung function with multi-hour exposures to ozone at concentrations allowable under the current California ambient air quality standard.

Repeated daily exposures to ozone have been shown to lead to attenuation of decrements in lung function and symptom responses in multiple controlled exposure studies. In two recent studies with 4 and 5 days of consecutive exposures to ozone, the cross-exposure decrement in FEV1 was greatest on the second day and greatly diminished by the fourth or fifth day (14a, 14b). Folinsbee at al. (14c) exposed 17 subjects to 0.12 ppm ozone for 6.6 hours on 5 consecutive days. While cross-exposure decrements in FEV1 declined progressively with each day of exposure, ozone-induced changes in methacholine responsiveness did not markedly attenuate across the 5 consecutive days of exposure. This result suggests that repeated exposure to ambient levels of ozone is not without hazard, despite the attenuation of symptom and spirometric responses.

There is considerable inter-subject variability in symptom and lung function responses to ozone, and some individuals do not respond at all to moderate levels of ozone in controlled exposure studies (14 d). The mechanism(s) underlying this variability in responsiveness to ozone is unknown. The higher the effective dose of ozone, the greater the number of subjects that will have respiratory symptoms and decrements in lung function in controlled human exposure studies.

C.3. Controlled Exposure Studies in Adults – Airway Inflammation.

Since the 1987 ARB review, the results of multiple controlled human exposure studies on the airway inflammatory effects of ozone have been reported (15-17). It is now clear that short-term exposure of humans to ozone can cause acute inflammation of the respiratory tract. To date, no controlled exposure study of ozone-induced inflammation has involved children. The study most relevant to the issue of whether the current California standard is adequately protective of the health of children was conducted by Devlin *et al*. (18). In this study, 18 males (ages 18-35 years) were exposed to 0.08 ppm ozone using the 6.6-hour EPA protocol described above. Ten of these subjects were also exposed to 0.10 ppm. Bronchoscopy to obtain bronchoalveolar lavage (BAL) fluid for cellular and biochemical analyses was performed 18 hours after the exposures. Significant increases in polymorphonuclear cells (PMNs), interleukin (IL-6), lactate dehydrogenase, prostaglandin E2 (PGE2), and α-1 antiprotease were found in BAL fluid after both concentrations of

ozone. In addition, increased total protein and fibronectin levels were found in BAL fluid after 0.10 ppm and decreased phagocytosis of opsonized *Candida albicans* by alveolar macrophages recovered from BAL was observed after both concentrations of ozone. Although the mean changes in PMNs, IL-6, and PGE2 were not large, there were some subjects who had large responses. These data indicate that multi-hour exposures with exercise to concentrations of ozone allowable under the current California ambient air quality standard can cause acute airway injury and inflammation. The relationship between recurrent acute episodes of acute injury and inflammation in humans and the development of chronic respiratory disease is unknown, but given the potentially increased susceptibility of the developing respiratory tract of children to oxidant-induced injury, there is greater cause for concern about the long-term sequelae of such episodes.

Several recent studies have addressed the issue of whether repeated daily exposures to ozone on consecutive days leads to attenuation of airway injury/inflammation. Although 4-hour exposures to 0.2 ppm ozone during intermittent exercise for four consecutive days led to attenuation of the neutrophilic influx into BAL in two such studies (14a, 14b), evidence of persistent ozone-induced injury and/or inflammation was present after the 4-day exposures in both studies.

One controlled human exposure study that was designed to study the earliest events involved in ozone-induced inflammatory cell recruitment to the airways has some relevance to the margin of safety of the current California air quality standard. Krishna *et al*. (19) exposed 12 healthy adults (both genders, mean age=28 years) to 0.12 ppm ozone during intermittent light exercise. The subjects underwent bronchoscopy at 1.5 hours after exposure. While there were no significant differences seen in inflammatory cell numbers in either BAL fluid or bronchial biopsies between ozone and filtered air exposures, there was a significant increase in the percentage of bronchial mucosal blood vessels expressing P-selectin after ozone. P-selectin is an adhesion molecule that is involved in the margination and rolling of PMNs on blood vessel walls prior to transendothelial migration (diapedesis). This ozone-induced upregulation of P-selectin is early

evidence of an inflammatory response following exposure to a concentration that is still regularly attained during the summer smog season in the Los Angeles basin.

As reviewed subsequently in this document, there are multiple epidemiological studies that have demonstrated an association between high ambient levels of ozone and exacerbations of asthma. The mechanism by which ozone induces asthma exacerbations is not entirely clear, but there have been several reports since 1987 of controlled human exposure studies in adults that have shed some light in this area. Two studies, Basha *et al*. (20) and Scannell *et al*. (21), showed enhanced inflammatory responses of asthmatic subjects as compared to healthy controls after a multi-hour exposure to 0.2 ppm ozone with moderate exercise. Another study by Molfino *et al*. (22) examined the effects of a 1-hour resting exposure to 0.12 ppm on the response to a subsequent ragweed or grass allergen challenge in seven allergic asthmatics (both genders, ages 21-64 years). The provocative concentration of allergen that caused a 15% decrease in FEV_1 was significantly lower after ozone than after filtered air, suggesting that allergen-specific airway responsiveness is increased after ozone exposure. The number of subjects studied was small and the findings could not be replicated in a study by another group of investigators (23). Nevertheless, several subsequent studies have demonstrated ozone-induced enhancement of the bronchoconstrictor response to allergen with higher doses of ozone. It is likely that there is at least a subset of allergic asthmatic individuals, including children, who will experience enhanced airway responses to allergen following high ambient ozone exposures.

C.4. Field Studies in Adults – Airway Inflammation

Although properly categorized as epidemiological rather than controlled human exposure research, two studies of ozone-associated airway inflammation in children involving ambient exposures to ozone are discussed here because of the use of nasal lavage, a technique that provides similar information to what is generated with BAL. Frischer *et al*. (24) performed multiple (five to eight) nasal lavages in 44 German children (both genders) during the 1991 summer ozone season (May to October). Comparing “high-ozone” (daily half-hour maximum ≥ 0.09 ppm) to “low-

ozone" (daily half-hour maximum $\leq$ 0.07) days, significant increases in PMNs and eosinophilic cationic protein (ECP) in nasal lavage were observed on the high-ozone days. A follow-up study by the same group of investigators (25) during the 1994 summer ozone season (when the daily half-hour maximum exceeded 0.12 ppm on only one day) confirmed these findings in 170 school children (both genders, mean age=9 years).

Another study designed to investigate the inflammatory effects of ambient exposures to ozone was performed by Kinney *et al*. (26). In this study, 15 male subjects (ages 23-38 years) who jogged regularly on Governors Island in New York City underwent at least two bronchoscopies, one during the 1992 summer ozone season and one during the following winter; six subjects also had a third bronchoscopy during the 1993 summer ozone season. The maximum ozone concentration in summer 1992 was 0.11 ppm (mean=0.58); the maximum concentration in the following winter was 0.64 (mean=0.32); the maximum concentration in summer 1993 was 0.14 (mean=0.69). Lactate dehydrogenase (LDH), a marker of cell injury, was significantly higher in BAL during the 1992 summer than during the following winter. There were non-significant trends for increases in IL-8, a cytokine that is a potent chemoattractant for PMNs, and PGE2 during the 1992 summer. For the six subjects with a second summer bronchoscopy, IL-8 was significantly higher than compared to the previous winter. The results of this study also suggest that ambient exposure to concentrations allowable by the current California air quality standard can cause airway injury and inflammation.

C.5. Interactions

Since the 1987 ARB review, the results of several controlled human exposure studies on the combined effects of relatively low concentrations of ozone and one or more other pollutants have been reported. In addition to the fact that ozone is rarely the only pollutant of concern in a given air shed, the steeper dose-response for ambient ozone and lung function decrements observed in multiple field studies as compared to controlled laboratory studies has been thought to be due to the effects of co-pollutants in summer "acid haze" (27).

Koenig *et al.* (28) exposed 13 allergic asthmatic adolescents (both genders, ages 12-18 years) to three different exposure sequences (air for 45 min followed by 0.10 ppm sulfur dioxide for 15 min ; 0.12 ppm ozone for 1 hour; and 0.12 ppm ozone for 45 min followed by 0.10 ppm sulfur dioxide for 15 min). Only the ozone-sulfur dioxide sequence was associated with a significant decline in FEV_1 (-8%) across the exposure.

Koenig *et al.* (9) exposed 12 non-asthmatic and 12 asthmatic adolescents (both genders, ages 12-17 years) to four atmospheres (filtered air, 0.12 ppm ozone, 0.3 ppm nitrogen dioxide, and a mixture of the two pollutants) for 1 hour with intermittent moderate exercise. No decrements in pulmonary function were observed after any of the exposures. A similar study of asthmatic adolescents by the same investigators (29) involving four different exposure atmospheres (filtered air, 0.12 ppm ozone and 0.3 ppm nitrogen dioxide, 0.12 ppm ozone and 0.3 ppm nitrogen dioxide and 70 $\mu g/m^3$ sulfuric acid, and 0.12 ppm ozone and 0.3 ppm nitrogen dioxide and 0.05 ppm nitric acid vapor) again found no significant decrements in pulmonary function after any exposure.

Linn *et al.* (30) exposed 24 asthmatic adolescents (both genders, ages 11-18 years) to three atmospheres (filtered air, 0.2 ppm ozone and 0.3 ppm nitrogen dioxide, and 0.2 ppm ozone and 0.3 ppm nitrogen dioxide and 127 $\mu g/m^3$ sulfuric acid). Although there were no statistically significant mean differences among the exposures, a few subjects had relatively large decrements in FEV_1 after the exposure containing acid as compared to filtered air suggesting the possibility of susceptible sub-group. The same group of investigators (31) evaluated the pulmonary function and symptom responses of 41 children (both genders, ages 9-12 years, 26 with allergies or asthma) to a mixture of 0.10 ppm ozone, 0.10 ppm sulfur dioxide, and 100 $\mu g/m3$ sulfuric acid. There were no significant decrements in pulmonary function after the exposure compared to after filtered air, but subjects with allergies and/or asthma had an exposure-related increase in respiratory symptoms.

Another interesting study by this group of investigators (32) involved exposure of 59 adolescents (both genders, ages 12-15 years) to smoggy Los Angeles air in a mobile laboratory during summer 1993. Ambient air during the exposures contained a mean ozone concentration of

0.144 ppm and a mean total suspended particulate concentration of 153 $\mu g/m^3$. Exposures were for 1 hour and 20 minutes with a 10-minute warm-up period, 1 hour of continuous moderate exercise, and a 10-minute post-exercise cool-down period. There was a significant decline in FEV_1 after the exposure to smoggy air as compared to after a filtered air control. Of note, unlike adults, the adolescents in this study did not report increased respiratory symptoms in association with decrements in FEV_1, suggesting that they are less aware of irritation and thus more at risk from ambient air pollution. Avol *et al*. (33) also studied 66 younger children (both genders, ages 8-11) using the same protocol and found a "similar reactivity to ambient oxidants" as for older children and adults. The ambient air during the exposures contained a mean ozone concentration of 0.113 ppm and a mean total suspended particulate concentration of 188 $\mu g/m^3$.

D. Epidemiological Studies of Acute and Chronic Health Effects:

The 1996 EPA criteria document for ozone provided an exhaustive review of the health effects of O_3 (10, vol. III). These will be summarized briefly, particularly those parts of the report that are relevant to children. Selected studies published since the release of the criteria document will be given a more detailed presentation.

The results of the EPA Criteria document are summarized in Table 1, which focuses particularly on those studies that include children exclusively or as part of a larger sample. Based on the types of data presented in Table 1, the EPA report came to a set of overall conclusions presented in Table 2. The summary statement from the Criteria Document did not provide a specific identification of children as particularly susceptible. However, the "Proposed Decision" document of November, 1996 (3) reported the results of an exposure assessment based on a variety of possible standards and identified the following as one of the "key observations" related to alternative standards: "Children who are active outdoors... appear to be the at-risk population group examined with the highest percentage and number of individuals exposed to O_3 concentrations at and above which there is evidence of health effects, particularly for 8-hour average exposures at moderate O_3 concentrations 0.080 ppm." (3, Section IIB).

The remainder of the section on epidemiological studies is devoted to studies published largely, but not exclusively, since the issuance of the "Decision" paper and which focus specifically on effects in children or present data on children in the context of general population surveys.

From the point of view of relevance to the State of California, five recent publications are presented in some detail. Four of these are from the ARB/University of Southern California (USC) Children's Health Study (CHS) (34-37). Samples of 4th graders (9-10 years), 7th graders (12-13 years) and 10th graders (15-16 years) were enrolled from 12 southern California communities which were selected to maximize differences in ambient pollutant profiles between them (36). The initial sample size was 3,676 (36). The last study is one related to effects of long-term O_3 exposure carried out in a small sample of adolescents who were lifelong California residents (38)

A random sample of 10-12 year-old CHS subjects participated in a 2 season study of the effects O_3 on symptoms and lung function in healthy children and children with asthma or wheezing (34). Exposure assessment was based on ambient monitoring and personal passive sampler data. Exposure, symptoms and forced expiratory volumes and flows were assessed daily for 4 days for each child during mid-spring and mid-summer. Summary data for the distribution of ambient and personal ozone exposure were not given. Exposure to ozone was categorized as "low" and "high" for ambient data based on a cut-point of a 1-hour peak O_3 concentration above and below 100ppb. Personal monitoring data were valuated as "low" and "high" based on a lowest value for the "high" group that was at least 35% greater than the highest value of the low group. The results from this study are very difficult to interpret and not informative for several reasons: 1) All O_3 exposures are presented as dichotomous; 2) The principal lung function outcomes are presented as the difference between evening and morning function with no account taken of possible lagged effects on morning function (39)–a fact which makes the interpretation of any difference somewhat ambiguous; and 3) The estimation of ozone effects on symptoms in children with asthma appears counter-intuitive and is likely due to increasing symptoms in the "healthy" group with increased O_3 concentrations. Therefore, no specific results are presented.

Data on the relationship between respiratory morbidity at baseline and air pollution have been reported for the CHS (36). Average daily 1-hour maximum and 24-hour average O_3 for the 12 communities in 1994 ranged between 41.3-97.5 ppb (mean=64.5 ppb) and 13.0-70.7 ppb (mean=34.9 ppb), respectively. A two-stage regression analysis provided estimates of the effect of community levels of ambient pollutants after adjustment for individual-level covariates. Average levels of NO_2 and acid (HNO_3+HCL) were associated with wheeze prevalence in males only–odds ratio (OR) and 95% confidence intervals (CI): 1.47 (CI, 1.08-2.02); 1.55 (CI, 1.09-2.21), respectively. No significant O_3 effects were observed. Similar results were obtained when the 1994 air pollution data were used.

Relationships between baseline lung function and air pollution also have been reported for CHS (37). Based on average 1986-1990 ambient pollutant data, significant O_3 effects were observed only for females. In single pollutant models, peak 1-hour daily ozone (5-year average of the 1 year daily averages) was associated with decrements in peak expiratory flow (PEFR) and maximum mid-expiratory flow (FEF_{25-75}) only. Somewhat larger effects for the same function measures were observed when the 1994 pollutant data were used. The only function measure on which 1-hour maximum O_3 had the largest effect was PEFR. Twenty-four hour O_3 was not related to any measure of lung function in either sex. For forced vital capacity (FVC), FEV_1 and PEFR, no 2-pollutant model fit the data better than single-pollutant models. For FEF_{25-75}, O_3 in combination with PM_{10} or NO_2 fit the data better than any single-pollutant model. When the data were stratified by time spent outdoors, the effects of O_3 on FEF_{25-75} were increased and those on PEFR decreased in girls. Effects were greater in girls with asthma compared to those without only for PEFR. All regression coefficients are presented in terms of the effect of an interquartile change in pollutant concentrations between communities (40 ppb in the case of 1-hour peak O_3). Unfortunately, insufficient data are given in the publications (36; 37) to estimate a percentage reduction in average PEFR and FEF_{25-75} in two typical girls each of whom resides in 2 communities with average 1-hour

peak O_3 concentrations that differ by ~40 ppb and whose distribution of 1-hour and 24-average O_3 concentration do or do not exceed the current California standard for O_3.

The last of the four CHS publications focused on children in the sample who reported doctor-diagnosed asthma (35). In this study, O_3 concentrations were not associated with the occurrence of either bronchitis or phlegm. The strongest associations were seen with NO_2 in children with a history of asthma. No effects for either NO_2 or PM_{10} were observed in children who did not report a history of asthma.

Künzli and colleagues conducted a study of effects lifetime exposure to ambient O_3 on lung function in a group of 130 UC, Berkeley freshman, all of whom were life long residents of either the San Francisco Bay Area (SFBA) or the Los Angeles Basin (LAB) (38). Estimates of lifetime exposure to ambient O_3 were based on detailed residential histories, typical time activity patterns over the lives of the students and monthly average ambient O_3 based on the extant ARB monitoring network (inverse distance squared weighting). The reproducibility of the estimates of lifetime exposure were found to be comparable to that for laboratory and other health-related outcomes routinely used in epidemiological studies (40). Relationships between lifetime exposure and lung function were not sensitive to any of the several O_3 metrics that were evaluated. The median lifetime 10 AM to 6 PM average O_3 concentrations based solely on residence-specific ambient monitoring data were 22.5 ppb (interquartile range: 17-28) and 51.5 ppb (IQR: 40-60) for the SFBA and LAB, respectively. Analyses demonstrated consistent and negative associations between lifetime exposure and measures of small airways function. No such relationships were found for FVC or $FEV_{1.}$ (Table 3) (38). The results were not altered by the inclusion of lifetime estimates of average 24-hourPM_{10} and NO_2 exposures. Of particular note is the fact the estimated coefficient based on the first 6 years of exposure is nearly identical to that for the total lifetime (up to 19 years). The relationship was found to be similar across both the SFBA and LAB (38, Figure 2). The authors estimated that a 20 ppb difference in average annual 8 hour exposure to O_3 over the first 19

years of life would result in a mean decrease of 14% (95% CI: -1% to -28%) in FEF_{75} compared to the population mean and a 7.2% (95% CI: +1% to -21%) for FEV_1.

The results of the above study are support by a study of similar design by Galizia and Kinney in 520 Yale freshman (41). Students who spent 10-years in residential locations with monthly average 1-hour peak O_3 concentrations greater >80 ppb (95^{th} percentile of exposure distribution for study subjects) had 10% (95% CI: 1.3% to -21.3%) 13% (95% CI: -4.9% to -21.2%) reductions in FEF_{75} and FEF_{25-75}, respectively, compared to students in the lower 95% of the distribution. The reduction for FEV_1 was substantially smaller (-4.7%; 95% CI: 0.7% to -8.8%). Report of respiratory symptoms also was more common in adolescents from areas with O_3 > 80 ppb. Taken together this study and that of Künzli *et al*. (38) provide evidence that long-term exposure to increased concentrations ambient ozone may have detrimental effects on lung function. Moreover, they support studies on O_3 dosimetry in humans (10, Section 8.2.4.2) and animal toxicology data (42; 43) which predict that the maximum site of effect of O_3 in the human lung will be at the level of small airways (reflected by levels of FEF_{75} and to a lesser extent FEF_{25-75}).

Several recent studies provide some insight either into the shape of an O_3 exposure response function for population data. Castillejos and colleagues studied 40 children ages 7.5-11 years in Mexico City (44). Children with asthma or difficulty breathing with wheeze or FEV_1 < 80% predicted were excluded. Forced expiratory flows were assessed during 1-hour of treadmill exercise. Average hourly O_3 during the test but not $PM_{2.5}$ on the day of test was associated with decrements in FEV_1 and FEF_{25-75}, with the percentage decrements in the later measure being 2- 3 times greater than the former. Results were not affected by the symptom status of the children. Plots of the average 1-hour O_3 concentration during exercise versus % change in FEV_1 (Figure 3) suggest a threshold for effects at ~50 ppb. The authors interpreted this figure to indicate that "...on average the response to O_3 is not detectable until a certain cumulative dose is attained....". Another study conducted in the same group of children (39) measured morning and afternoon PEFR for approximately 1 month during each of three periods (winter: Jan. 23-Feb. 22, 1991; spring: April 22-

May 27, 1991; fall: Oct. 11-Nov. 8, 1991). Hourly average O_3 was measured at the children's school as was 24-hour PM_{10} and $PM_{2.5}$. Early afternoon O_3 concentrations ranged between 17-319 ppb. A polynomial distributed lag model suggested a linear decline relation between 24-hour mean O_3 concentrations and morning peak flow (3.8% for each 25 ppb in 10 day exposure). The effect of O_3 on morning PEFR was independent of effects of $PM_{2.5}$. In the case of afternoon PEFR, "Exposures to O_3 briefer than 6 hours were not associated with reduced afternoon PEF." Moreover, O_3 had a predominant effect over particles on afternoon PEFR.

A study of 941 primary school children (mean age 9.8±1.6 years) in Taiwan compared lung function across three different areas (45). One-hour peak O_3 ranged from 20-110 ppb. In multi-pollutant models (O_3, SO_2, CO, NO_2, PM_{10}), only O_3 (with 1-day lag) had an effect on both FVC and FEV_1. However, the O_3 effects did not appear to occur until 1-hour peaks exceeded ~60 ppb (Figure 4).

Two studies in adults also provide some useful data on the possible shape of the population O_3 response curve for lung function (46) and emergency department visits for asthma (47). Korrick, *et al*. studied 595 volunteers (age range 18-64 years, mean 35 years) who were performing a day hike on Mt. Washington, NH (46). Data on hourly O_3, 24-hour $PM_{2.5}$ and 24-hour strong aerosol acidity (sulfate equivalents) were available. Mean hourly O_3 (mean of base and summit 1-hour values) ranged between 21-74 ppb (mean 40 ppb). There was an inverse relation between hourly O_3 and FEV_1 (2.6% – in FEV_1 per 50 ppb – in O_3; 95% CI: 0.4-4.7%) which was not altered by adjustment for $PM_{2.5}$ and strong aerosol acidity. Decrements in subjects with self-reported asthma were approximately 3-fold greater. No effects were observed for PEFR or FEF_{25-75} with or without adjustment for $PM_{2.5}$ and acidity, although O_3 was associated with the frequency of >10% declines in FEF_{25-75}. Three methods were used to fit the O_3 FEV_1 exposure relationship. A threshold model with an inflection point near 40 ppb seemed to fit the data best (Figure 5).

Stieb and colleagues studied emergency department visits for asthma in St. John, New Brunswick, Canada from 1984-1992 (May-Sept. only) (47). Forty-nine percent of subjects were 15

years of age or younger. One-hour maximum O_3 ranged between 0-160 ppb (mean: 42 ppb; 95th %tile: 75 ppb), and a level of 80 ppb only was exceeded on 3.7% of study days. One-hour maximum O_3 was not highly correlated with SO_2, NO_2, SO_4^{2-} or TSP (all correlations $\leq$0.30). Only O_3 "exhibited a consistently positive association with asthma visit rates..."(47). Moreover, non-linear models revealed stronger associations both with 1-hour maximum and 24-hour average O_3. Only when values above the 75 ppb (95th %tile) were included was there an effect of 1-hour maximum O_3 on emergency department visits for asthma. The results were identical for subjects ages 0-15 and $\geq$15 years (Figure 6) (47) in terms of the shape of the response curve. However, at all O_3 concentrations, visits per day were higher in the older age group and, in regression models, were only significant in this latter group.

Finally, a daily time series study of women in Virginia which had data on multiple pollutants indicated that O_3 effects on declines in PEFR were not observed with 5-day average O_3 until values exceeded 35 ppb when 5-day average values were grouped as quartiles (48, see below and Table 4).

There are a number of studies which, although they do not necessarily permit any inference on the shape of the population O_3 response curve, do permit inferences on either the lower levels at which exposures to O_3 result in health effects and/or the contribution of O_3 to health effects relative to other ambient pollutants. These are summarized in Table 4. Only 2 of these studies were performed in the United States, and these were in the Eastern portion of the country.

The study of Neas et al. in Uniontown, PA is most relevant (Table 4) (49). In this daily time series study, O_3 was most strongly associated with daily cough episodes then any other of the other pollutants evaluated. Daily maximum 12-hour average O_3 never exceeded 80 ppb. Although O_3 also was strongly associated with decrements in PEFR, its effect was dependent on proper adjustment for temperature. In a 2- pollutant model with particle strong acid, the effect of O_3 on PEFR decrements was eliminated, despite only a modest correlation (r=0.48) between the 2 pollutants.

A times series study of non-smoking women in Virginia (Table 4) (48), while it did not include children, does, nonetheless, provide useful data. O_3 exceeded the proposed EPA 8-hour standard of 80 ppb on only 2 days and PM concentrations were all below E.P.A. and WHO standards (Table 4). O_3 showed the strongest association of any pollutant with evening decrements in PEFR. Averages of 1-hour values seemed to have a larger effect than the maximum daily 8-hour average. When O_3 was expressed as quartiles of a 5-day moving average, effects appeared only at average O_3 concentrations >35 ppb (Figure 7) (48). Unfortunately, no multi-pollutant models were presented. However, correlations between O_3 and the other pollutants were modest (range 0.22 - 0.46, see Table 4).

Two studies conducted in Canada (50; 51) provide somewhat conflicting results. A study of berry pickers in British Columbia (Table 4), all of whom were age 44 years, found associations of daily 1-hour maximum O_3 on decrements in FVC and FEV_1 that were independent of a number of other pollutants. One-hour maximum O_3 concentrations never exceeded 84 ppb (mean 44 ppb), and the concentration of other pollutants was low. In contrast, a daily time series study of hospital admissions in Montreal (51) found associations between ambient O_3 with emergency room visits for respiratory illness only in people aged 64 and older. These associations were observed for only 1 of the 2 years studied. Mean 8-hour maximum concentrations averaged 29 ppb, and 1-hour maximum values averaged 33 ppb. To what extent the differences in the two studies relates to different endpoint and different pollutant mixtures cannot be determined.

The studies from European countries represent a mixture of designs, endpoints and ambient exposure profiles (Table 4). A study of daily hospital admission for asthma from 4 cities in the APHEA project (52) failed to show any associations with O_3 in children. However, a daily time series study of visits to a clinic in Santiago, Chile (53) did show an association between daily 1-hour maximum O_3 and respiratory visits for children between the ages of 2-14 years. No effects were seen for younger children. Effects of O_3 were independent of and greater than those for PM_{10} (the only other pollutant studied) in 2 pollutant models. A Dutch daily time series study of PEFR

decrements and respiratory found associations between ambient O_3 and PEFR decrements and upper respiratory symptoms. The effects of black smoke on PEFR were greater (per IQR change) than those for O_3. No multi-pollutant models were presented.

Two of the European studies evaluated the effects of long-term pollutant exposures on respiratory health in children (Table 4) (54; 55). A 10-community Swiss study (54) in which average annual O_3 levels were very low and showed relatively little variation across communities, observed associations between annual O_3 concentrations and asthma and wheeze only in children without a family history of allergy and only when the communities with the highest and lowest O_3 concentrations were compared. A 9 community Austrian study (55) attributed both short-term and medium term decrements in forced expiratory volumes and flow to ambient O_3 concentrations that were independent of the other pollutants measured. An accompanying editorial suggested that the effects could not be ascribed solely to O_3 and might have an important component related to PM/NO_2 (56).

None of the epidemiological studies that were reviewed provide any data on interactions between various pollutant mixtures on human health effects.

E. Conclusions:

E.1. Controlled Exposure Studies

Controlled human exposure studies of the effects of ozone involving children and adolescents have generally not shown greater decrements in pulmonary function than in adults. Children do appear to report less respiratory symptoms for a given magnitude of decrement in FEV1, suggesting that they are less likely to avoid high ambient exposures. Multi-hour exposures of adults during exercise to concentrations of ozone allowable under the current California air quality standard have been demonstrated to induce substantial pulmonary function decrements as well as airway inflammation. Persons with asthma appear to have enhanced airway inflammatory responses to ozone, and asthmatic responses to specific allergen appear to be enhanced by ozone. Field studies involving assessment of airway inflammation provide evidence of ozone-induced

airway injury and inflammation from real-world exposures. Finally, controlled human exposure studies of ozone mixed with other pollutants have not tended to show greatly amplified effects over what exposure to ozone alone would be expected to have caused.

E.2. Epidemiological Studies

Inspection of the data in figures 3-5 and 7 provides some basis on which to address the question of whether or not significant adverse health effects might be expected to occur in children. The various measures of lung function can be taken as a meaningful health outcome. Lowered lung function is associated with increased airway reactivity in children (57) and airway reactivity is associated with more rapid rates of lung function decline (58). Moreover, numerous studies in adults have indicated that level of lung function in adult life, especially FEV_1, is linked to the risk of respiratory illness and all-cause mortality (59-62). In 4 or the 5 sets of data quoted (Figures 3-5, 7), it appears that effects on measures lung function can be detected at levels below the current State standard of 90 ppb for a 1-hour maximum value. It is interesting to note that Schwartz (63) in a cross-sectional study of NHANES II data suggested that O_3 effects on FVC had a threshold at about 40 ppb. This value is not too different from that observed in several of the newer studies. Unfortunately, the California-specific, CHS studies cited do not provide useful data in this regard. Presumably the CHS will have relevant data in the future. However, the study of Künzli, *et al*. (38) and, to a lesser extent, that of Kinney, *et al.* (64) do provide evidence that long-term exposure at relatively low levels may have important effects on lung function. Finally, it should be noted that the issue that cannot be satisfactorily resolved is whether children indeed are at greater risk for functional and or discrete health outcomes than are adults at any given level of ambient O_3. The data from Stieb and colleagues (47) are not supportive in this regard.

In contrast to the relative certainty about the levels at which O_3-related health effects may be seen, it is more difficult to be certain to what extent the observed effects are due to O_3 itself or O_3 in the context of the various pollutant mixtures in which it is found. No epidemiological data on true interactions with other pollutants were found, and such data would be expected to be very difficult to

obtain. The most compelling data cited are those from studies where a number of other pollutants have been studied in low concentration and where O_3-related effects are observed (50). Unfortunately, such data are few. Nonetheless, the number of studies which have identified important O_3-related health effects in the presence of other pollutants, either as the only association or the strongest association, clearly indicates that ambient O_3 concentrations are, at a minimum, an important marker for adverse health effects in children that are related to ambient air pollution.

Table 1: Summary of Ozone-Related Health Effects from Field and Epidemiological Studies, 1996 U.S. E.P.A Criteria Document for Ozone

Type of Study	Outcome Measure	Range of O_3 Concentrations	Major Findings
"Camp Studies" of children ages 7-17*	FEV_1–regression slopes	1-hour peak: 100-160 ppb Minimum levels: 10-60 ppb	· Meta-analysis of 6 studies shows relationship between previous hour's O_3 concentration and FEV_1 of -0.50ml/ppb ±0.07 (27); · No evidence for response threshold
"Daily life" studies+ : repeated measurement of lung function in children mostly in elementary school ages	$FEV_{0.75}$;	· 1-hour peak: 3-63 ppb	· mean slope for $FEV_{0.75}$ -99ml/pbb ±0.36; no negative slopes for SO_4 or fine particles
	FVC, FEV_1 FEF_{25-75}	· 1-hour mean: 14-287 ppb	· only FVC with statistically significant slope in relation to previous hour's O_3 in contrast to "Camp Studies"; however, significant slopes for FEV_1 and FEF_{25-75} with 24, 48 168 hour average O_3–suggest sub-acute effects
	FVC, FEV_1 FEF_{25-75} PEFR	· 1-hour peak: 3.5-103 ppb	· Significantly negative slopes for FVC, FEV_1, FEF_{25-75}; not affected by SO_2, NO_2, PM_{10}
	PEFR	· 1-hour peak: 0.0-66 ppb	· No association between O_3, SO_2, NO_2, and COH with respiratory symptoms or PEFR

Type of Study	Outcome Measure	Range of O_3 Concentrations	Major Findings
Aggravation of existing respiratory			

disease[†]			
· asthmatic/non-asthmatic children	PEFR	· average 1-hour peak: 0.55±0.14 ppm; moving average 8-hour O_3: 0.46±0.13 ppm	· PEFR slopes: non-asthmatic children: -11.9L/min/0.1 ppm asthmatic children: -31.0L/min/0.1 ppm interaction between O_3. PM_{10}, temperature
· children attending camp for asthmatic children	PEFR, daily symptoms and treatment	· 1991 1-hour peaks: 0.154 ppm 1992 1-hour peaks: 0.063 ppm	· 1991 daily treatments correlated with daily O_3, SO_4 H^+, but not pollen; no associations in 1992 afternoon symptoms and PEFR variability correlated with O_3 and H^+

Type of Study	Outcome Measure	Range of O_3 Concentrations	Major Findings
Studies on effects of chronic exposure; 13 studies reported§	Pathology allergic responses FEV_1, FVC, PEFR FEF_{25-75}	(only 5/7 give ranges for studies with children)	
· 6 studies include children or restricted to children; 7th study restricted to teenagers and young adults		· median average 1-hour value: 0.03 ppm	· non-linear relation between average annual O_3 with threshold ~0.40 ppm; data consistent with effects on forced flows at concentrations <0.120 ppm; no control for other pollutants
		· 90th %tile average annual 1-hour peak: 0.34-0.50 ppm	· small decrements (<2%) in FEV_1 and FVC; results likely confounded by SO_4
		· average annual 1-hour peak: 0.024-0.031 ppm	· no effect on lung function, except for FEF_{25-75} in asthmatic children; results potentially confounded by SO_4
		· average ½-hour peak: 0.015-0.052 ppm	· increased asthma prevalence, no effects on forced volumes
		· 3 month average 1-hour peak: 0.100-0.200 ppm	· no effect on respiratory symptoms; effect on slope of Phase III of N_2 washout in all age groups, effect on forced volumes limited to subjects >14 years

* (Adapted from reference 10, vol. III—Table 7-15)
+ (Adapted from reference 10, vol. III—Table 7-18)
† (Adapted from reference 10, vol. III—Table 7-20)
¶ (Adapted from reference 10, vol. III—Tables 7-21 & 7-23)
§ (Adapted from reference 10, vol. III—Tables 7-25 & 7-26)

Table 2: Summary of U.S. E.P.A Conclusions Based on Data Summarized in Table 1 With Particular Reference to Children*

Effects of Short-Term Exposures to O_3

Respiratory Symptoms

- Association between O_3 exposure and presence of symptoms shown in human clinical, field and epidemiological studies
  - Most common respiratory symptoms have higher incidence in young adults...and generally not reported in children
- Symptom responses follow a monotonic exposure-response relationship

Lung Function Responses

- Acute exposure to O_3 results in decreased forced expiratory volumes and flows
- Responses in healthy children are similar to those seen in adults

Exacerbation of Respiratory Disease

- Small decreases in forced expiratory volumes, increased respiratory symptoms and exacerbations of asthma occur with increasing ambient O_3, especially in children
- based on camp studies, estimate for pre-adolescent children exposed to 0.120 ppm, decrement is ~2.4%-3.0% FEV_1
- Increases in visits and hospitalization for respiratory disease seen with O_3 <0.12 ppm

Individuals and Populations Susceptible to Ozone+

Effects of Long-Term Ozone Exposures

- Findings suggest small, but consistent decrements in lung function
  - findings difficult to interpret due to uncontrolled effects of co-pollutants

* (Adapted from reference 10, vol. III—Section 9)

+ No specific statement made with regard to children or adolescents; NB: McDonnell, et al. modeled ozone responses in chamber studies with subjects as young as 18 and found that decrements in FEV_1 in response to increasing O_3 decreased with age (65; 66).

Table 3: Effective of Estimated Lifetime Exposure to Ambient Ozone on Various Measures of Lung Function*

Lifetime Average 10 AM - 6 PM O_3 Concentration+	1 Standard Deviation of Exposure Distribution in ppb (min/max concentration)	Parameter Estimates for Effect of 1 Standard Deviation Difference in Estimated Lifetime O_3 Exposure (±SE)†		
		FEV_1	FEF_{25-75}	FEF_{75}‡
Total Lifetime	14.8 (16/74)	-0.092 (0.089)	-0.331 (0.176)	-0.247 (0.122)
Age <6 years	18.1 (14/75)	-0.115 (0.091)	-0360 (0.180)	-0.260 (0.125)

***** (Adapted from reference 38, Table 5)

+ Based on inverse distance squared interpolation to residences

† None of the results for FEV_1 statistically significant; all results for FEF_{75} $0.05<p<0.10$; all results FEF_{25-75} statistically significant

‡ Forced expiratory flow after 75% of volume has been expired–measure of small airways

Table 4: **Selected Studies on Health Effects of Ozone Levels at Which Effects are Observed and Effects Relative to Other Pollutants**

Study Population	Outcome Measures	Ozone Concentrations	Other Pollutants	Results and Comments
83 4^{th} and 5^{th} grade children Uniontown, PA (49)	PEFR, symptoms	12-hour average; daytime mean=50 ppb; max.=88 ppb	SO_2, PM_{10}, $PM_{2.5}$, total SO_4, particle strong acid	· O_3 most strongly associated with evening cough in 1 pollutant models · O_3 and total SO_4 similar effect on PEFR and > than that for other pollutants (O_3 effect highly temperature dependent) · in 2-pollutant model with strong acid, O_3 effect on PEFR eliminated (correlation between O_3 & acid=.48) · widely variable individual-specific regressions
58 berry pickers ages 10-44, British Columbia, Canada (50)	forced expiratory flows	1-hour maximum range 13-84 ppb (mean=44)	Aerosol acidity, $PM_{2.5}$, SO_4^{2-}, NO_3^-, NH_4^+ and elements Concentrations all low	· both FVC and FEV_1 negatively associated with daily max. O_3 · O_3 effect independent of other pollutants and strongest

Study Population	Outcome Measures	Ozone Concentrations	Other Pollutants	Results and Comments
Population of Montreal, Canada 1992-1993(51)	Emergency room visits for respiratory illness,	8 hour max.(1992): mean=29 ppb; max/90th %tile =65/43 ppb 1 hour max (1992): mean=33 ppb; max/90th %tile=79/49 ppb	PM_{10}, $PM_{2.5}$, SO_4 H^+ all PM_{10} <100 /m^3; all $PM_{2.5}$ <71 /m^3	· No relationships significant for 1992 data; focus on 1993 (generally lower pollutant concentrations) · Only positive association-children <2 years and H^+ · authors raise question of spurious result · O_3 effects confined to persons > age 64 years · O_3-acid correlations ~.46
Populations of 4 Western European Cities, 1986-92 (52)	Daily hospital admissions for asthma; stratified by age <15 years, 15-64 years	1-hour max: medians 27-72 ppb ranges 1-78, 7-283	NO_2, SO_2	· Over all cities, no effect for O_3 in children; suggestive effect in older people
Children 7-13 in Netherlands, 1995 (67)	PEFR, respiratory symptoms	8-hour max: range: 28-111 ppb (mean=67) 1-hour max: range 33-130 ppb (mean=77)	PM_{10}, black smoke, NO_2, grass pollen	· Significant association between O_3 and PEFR with 2-day lag · Association with upper resp. symptoms · Black smoke effects on PEFR somewhat > O3 · No multi-pollutant models

Study Population	Outcome Measures	Ozone Concentrations	Other Pollutants	Results and Comments

Children ≤14 years attending sentinel clinics in Santiago, Chile, 1992-93 (53)	total and respiratory visits	1-hour max: mean=56 ppb range=10-176 ppb IQR=31-77 ppb	PM_{10}	· No O_3 effects for children < 2-years in single or 2 pollutant model · In single and 2-pollutant models, children 2-14 showed O_3 associations with upper and lower resp. visits; O_3 >> PM_{10}
473 non-smoking women in Virginia, 1995-96, 30% < age 27 years, summertime time series (48)	PEFR	1-hour: range=9-57 ppb mean=35 ppb daily max 8-hour mean: range=17-88 ppb, mean=54 ppb; Proposed EPA 8-hour standard of 80 ppb exceeded only on 2 days	PM_{10}, $PM_{2.5}$, $PM_{10-2.5}$ SO_4^{2-}, H^+, SO_2, NH_4^+ Proposed EPA 24 hour $PM_{2.5}$ standard of 65 $/m^3$ not exceeded on any day, nor was WHO 24-hr PM_{10} standard (110 $/m^3$)	· Modest association between 3-day average 1-hr O_3 and a.m. PEFR · Strong association with evening PEFR, larger than all other pollutants except $PM_{10-2.5}$ · 3-day mean of 1-hr > max. 8-hour average · O_3 correlations with other pollutants ranged from 0.22 ($PM_{10-2.5}$) to 0.46 ($PM_{2.5}$) · Ozone effects apparent with 5-day average >35 ppb · no multi-pollutant models

Study Population	Outcome Measures	Ozone Concentrations	Other Pollutants	Results and Comments
Cross-section of children 6-15 years in 10 Swiss communities, 1992/1993 (54)	respiratory symptoms	1992 annual mean: range over 10 communities 9 ppb - 38 ppb # of hours/year >81 ppb: range 0-195 (7/10 <20 hours/yr)	PM_{10}, NO_2, SO_2	· Only association for O_3 was observed for wheeze and asthma in children from cities with lowest and highest O_3 concentrations compared · observed only in children without an allergic family history
1060 1st and 2nd grade children in 9 communities in Austria, 1994-1996 (55)	cross-sectional and longitudinal change in forced expiratory flows	1994-96 annual ½ hour mean: range 18-41 ppb; max. values 24 hr prior to lung function 51-59 ppb Spring, 34-40 ppb Fall	PM_{10}, SO_2, NO_2	· Short-term effects on FEV_1 and FEF_{25-75} (largest effects) · somewhat inconsistent by season · Adverse effects on longitudinal change for FEV_1 in 1994, 1995, but not 1996 · Adverse effects on longitudinal change in FEF_{25-75} only in 1995 · Unclear that effects are due solely to O_3 · question of effects related to PM_{10} and/or NO_2 (56)

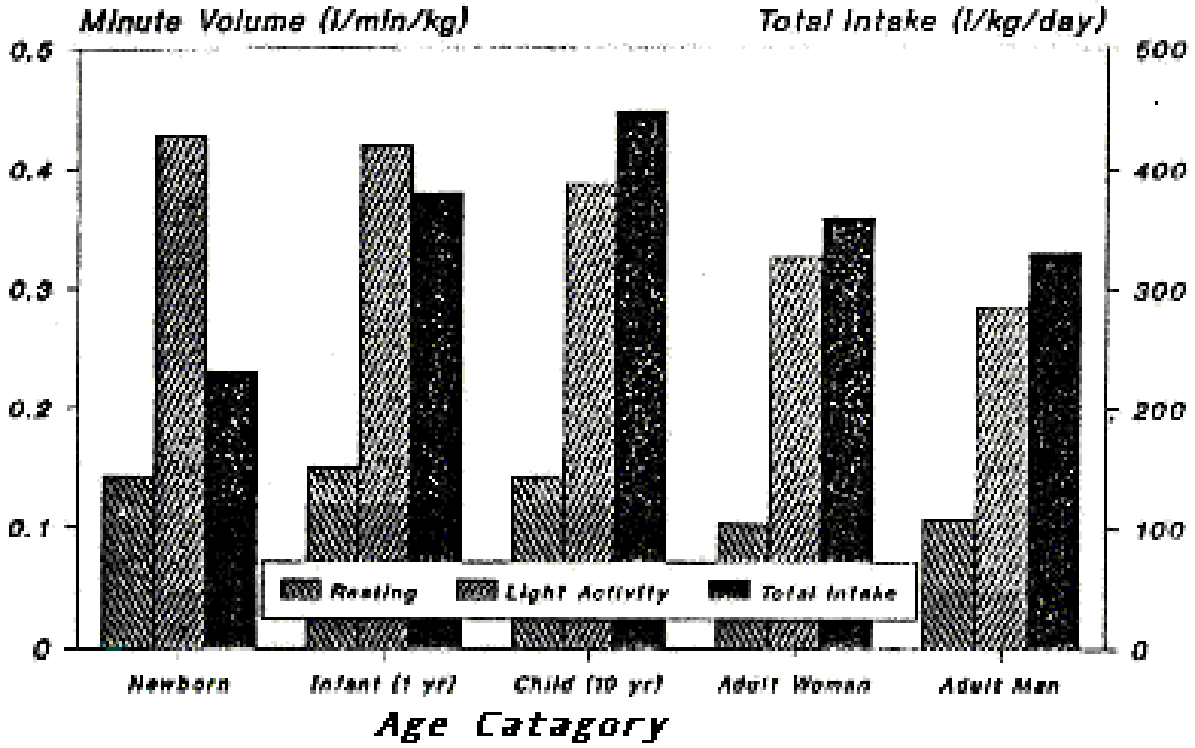


Figure 1: Minute ventilation as a function of age and levels of physical activity (Adapted from Reference 6)

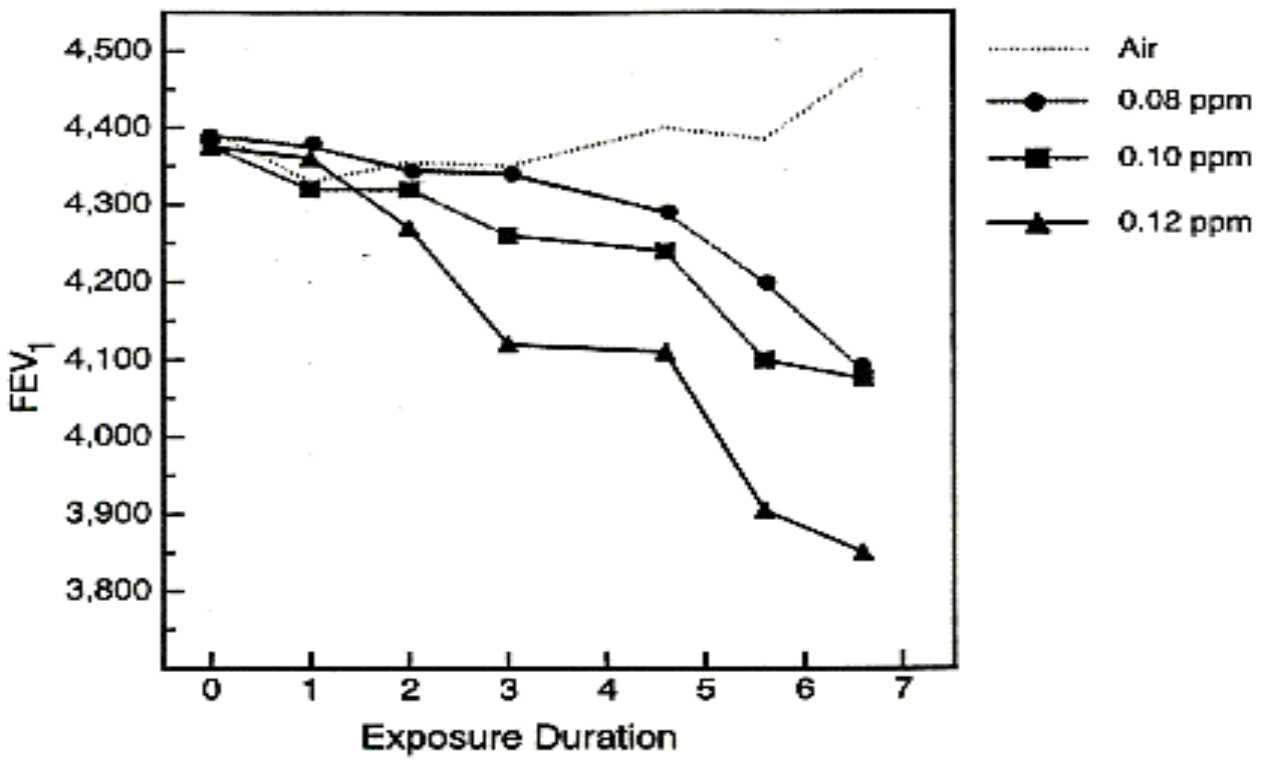


Figure 2: FEV_1 (in mL) in relation to exposure at different O_3 levels. Total exposure duration was 6.6 hours (Adapted from Reference 12)

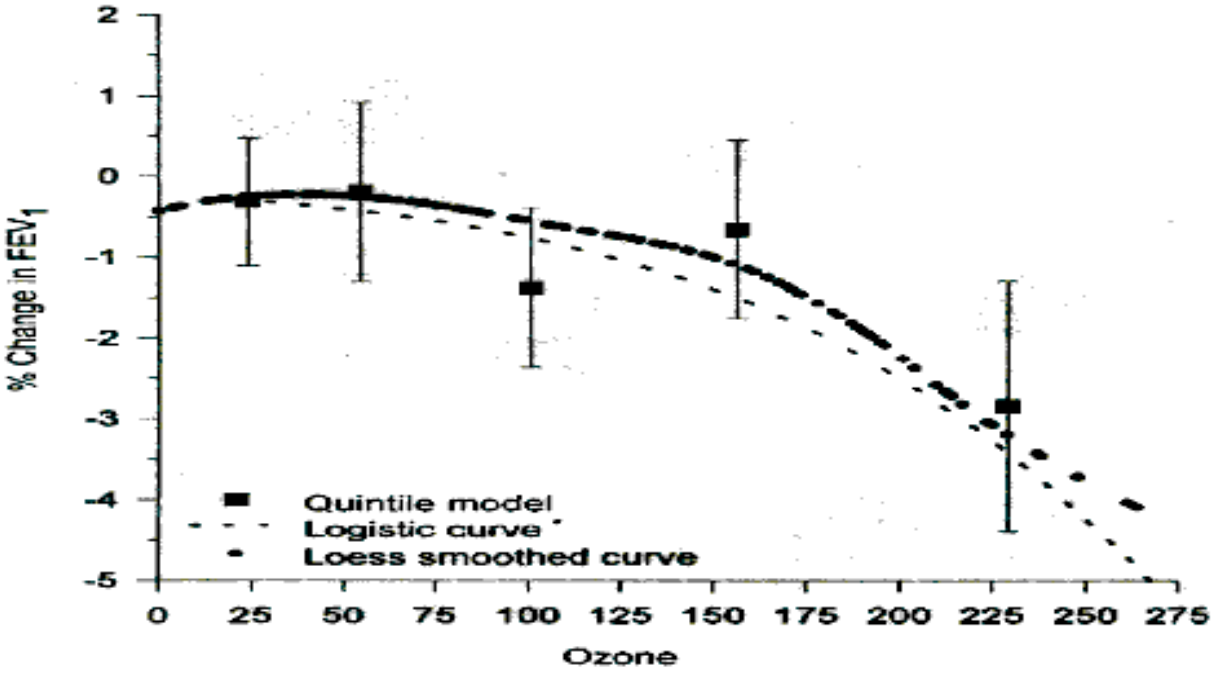


Figure 3: Percent change in FEV_1 based on 3 methods from (Reference 44). O_3 concentrations (in ppb) are averages of 1-hour maximum. (Adaped from Reference 44).

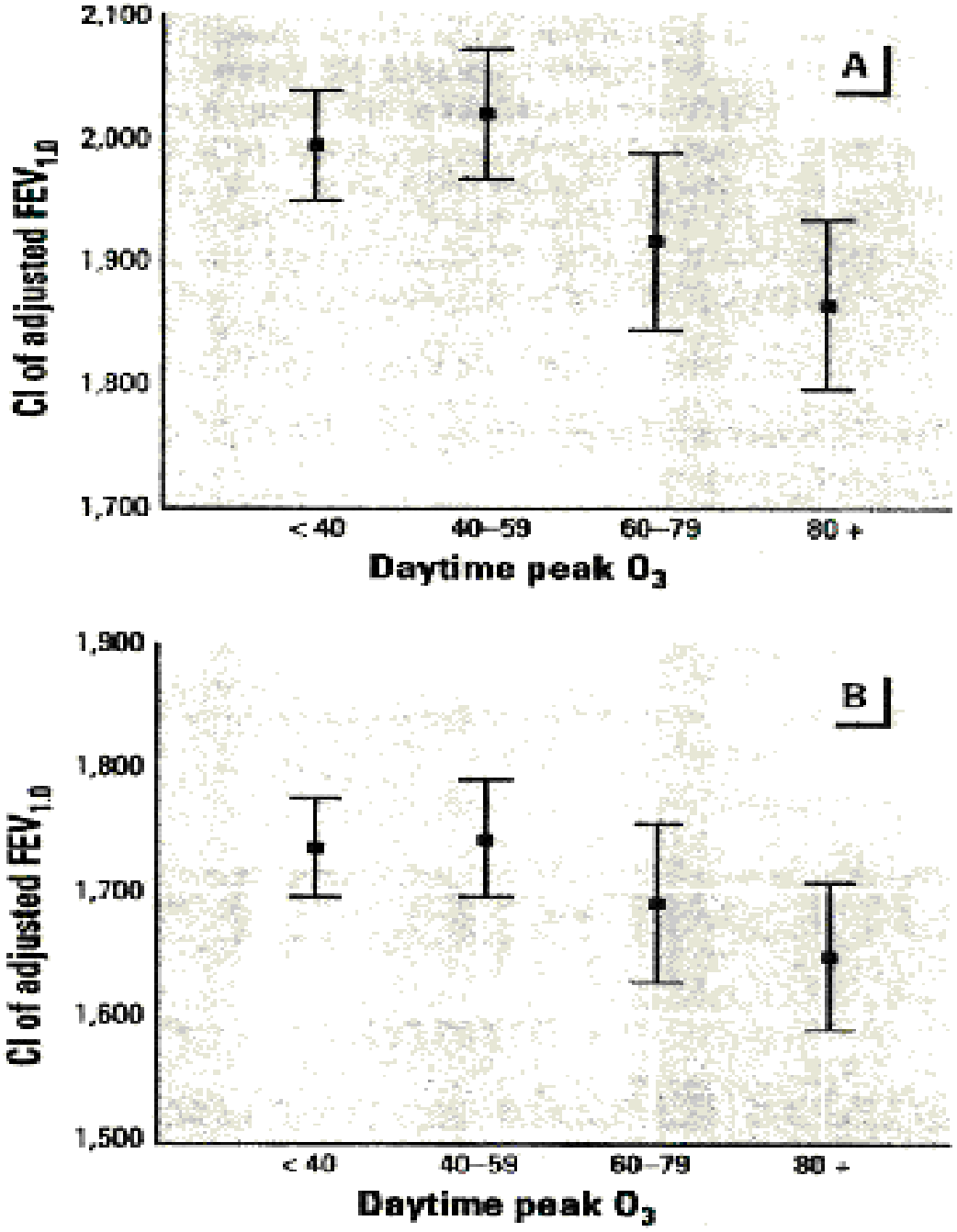


Figure 4: Relation between daily peak O_3 concentrations (in ppb)and FVC (in mL) and FEV_1 (in mL) in 941 primary school children (Adapted from Reference 45)

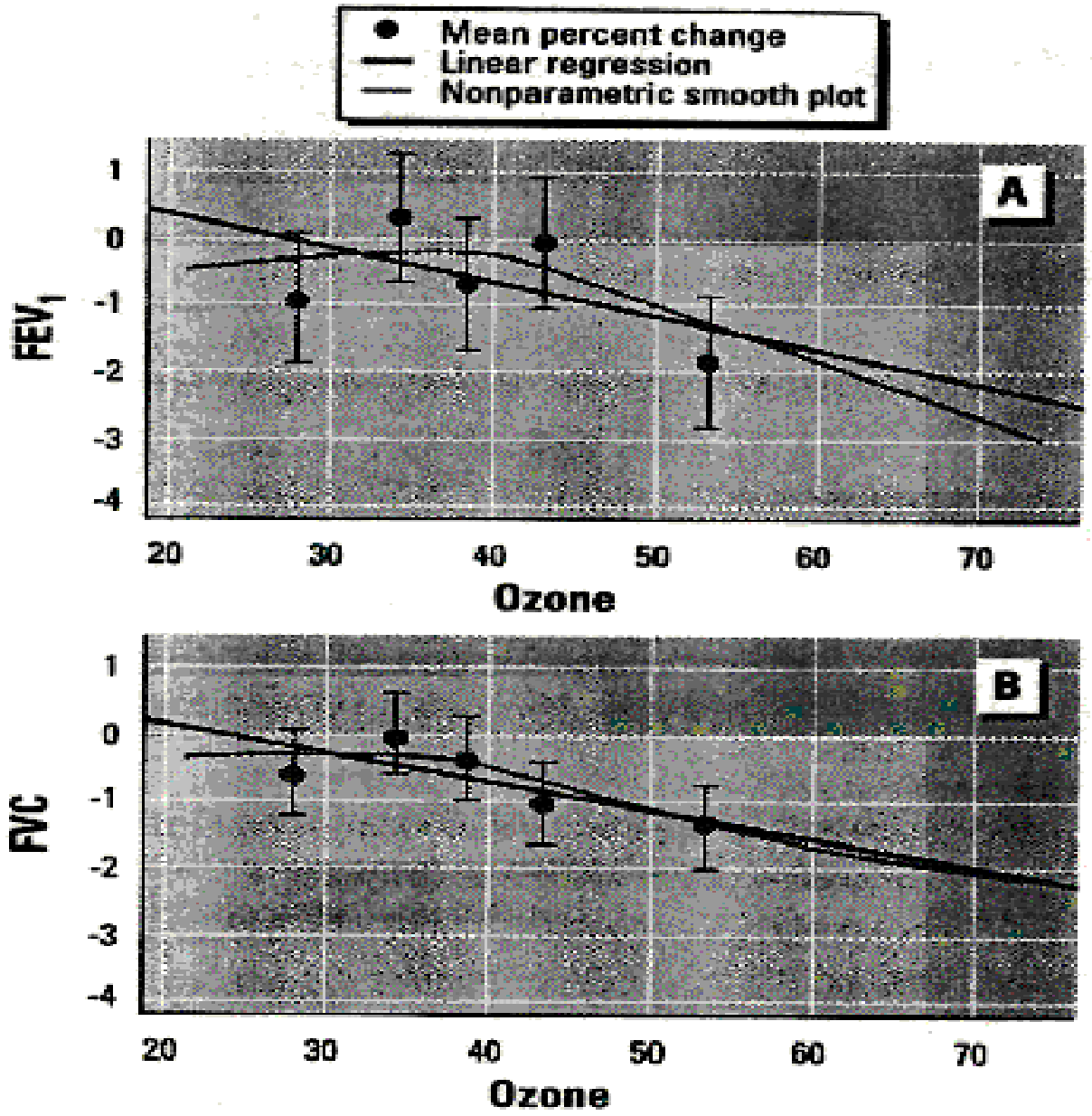


Figure 5: Relationships between maximum 1-hour O_3 (in ppb) and FEV_1 and FVC in 595 hikers evaluated by 3 different models (Adapted from Reference 46).

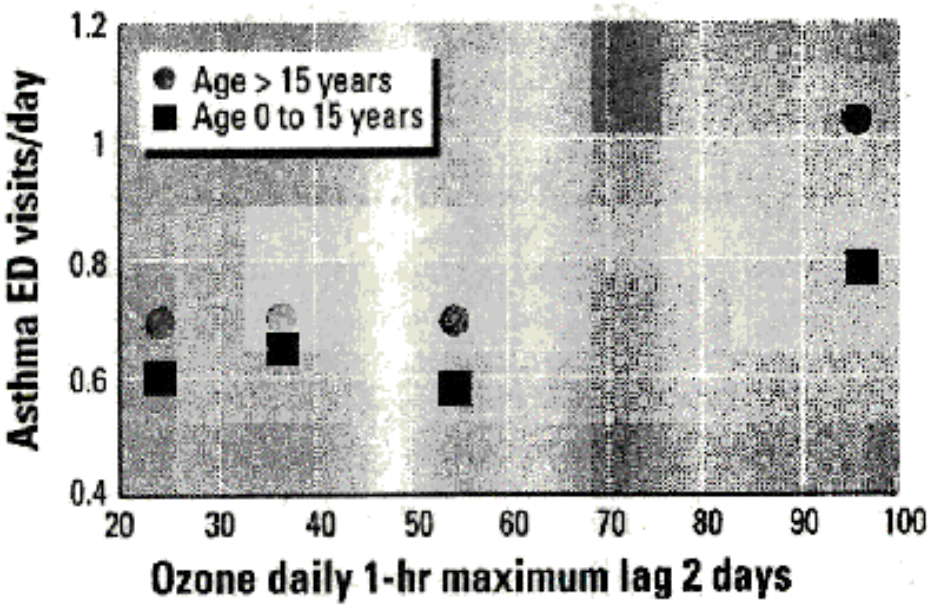


Figure 6: Relationship between emergency department visits for asthma and 1-hour maximum O_3 concentrations (in ppb) in St John, New Brunswick, Canada, 1984-1992 (Adapted from Reference 47).

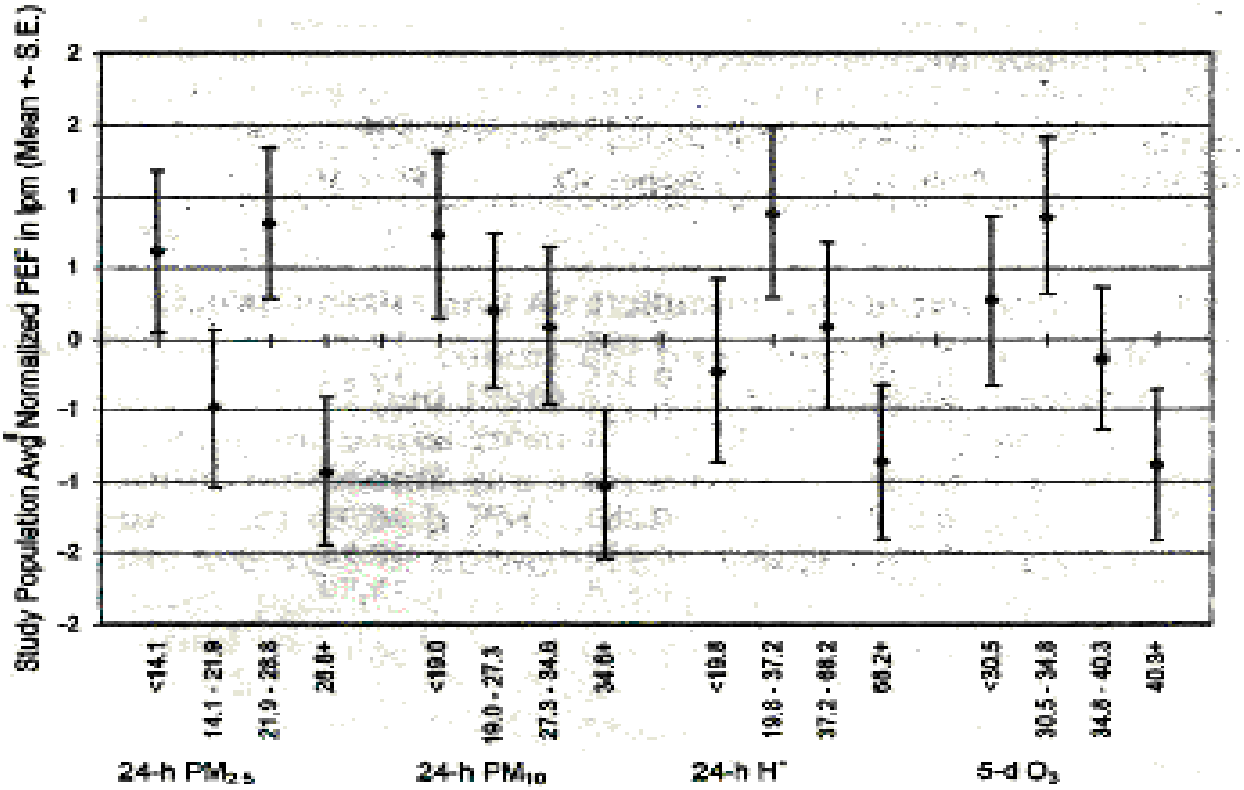


Figure 7: Normalized deviations in PEFR using the method of Neas, *et al*. (49) in 473 non-smoking women in relation to quartiles of ambient pollutants. "5-d O_3" refers to a 5-day average of 1 hour O_3. PM2.5 and PM10 measured in $\mu g/m^3$; H+ measured in $nmol/m^3$; O_3 in ppb. (Adapted from Reference 48).

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NITROGEN DIOXIDE:
EVALUATION OF CURRENT CALIFORNIA AIR QUALITY STANDARDS WITH RESPECT TO PROTECTION OF CHILDREN

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1. EXTENDED ABSTRACT

Nitrogen dioxide (NO_2) is the most abundant and toxic of the nitrogen oxides formed from combustion of fossil fuels, and ambient concentrations are related to traffic density as well as point sources. Indoor NO_2 levels may exceed those found outdoors. When inhaled, NO_2 persists to the lung periphery because of its relatively low solubility. Greater than 60% of inhaled NO_2 is deposited, predominantly in the centri-acinar region, and the fraction deposited increases with exercise. Epidemiological studies have found relationships between both outdoor and indoor NO_2 levels and respiratory illness, decrements in lung function, and exacerbation of asthma, especially in children. Outdoor NO_2 was associated with increased infant mortality and intrauterine mortality in Sao Paulo, Brazil. However, these studies are subject to exposure misclassification, and generally fail to consider a possible role of indoor and outdoor particle exposure as a confounding factor. NO_2 may represent a marker for exposure to traffic- or combustion-related pollution in these epidemiological studies. Human clinical studies generally fail to show effects of exposure concentrations at or below the current California standard of 0.25 ppm, which supports the concept that NO_2 is a marker of pollution rather than a cause of direct effects at ambient levels. However, exposure to NO_2 at concentrations only slightly above 0.25 ppm appear to enhance responsiveness to allergen challenge in subjects with asthma.

2. BACKGROUND

Combustion of fossil fuels results in the oxidation of nitrogen-containing compounds and the formation of nitrogen oxides. There are at least 7 species of nitrogen oxide compounds: nitric oxide (NO), nitrogen dioxide (NO_2), nitrous oxide (N_2O), nitrogen trioxide (NO_3), dinitrogen trioxide (N_2O_3), dinitrogen tetroxide (N_2O_4), and dinitrogen pentoxide (N_2O_5). These species are largely interconvertible, and therefore referred to collectively as NO_x. Nitrogen dioxide is the most abundant in the atmosphere, and represents the greatest risk to human health. The U.S. Environmental Protection Agency has established a National Ambient Air Quality Standard (NAAQS) for NO_2 of 0.053 ppm (100 $\mu g/m^3$), measured as an annual arithmetic mean. The State of California has established only a short-term (1 hour) standard for NO_2 of 0.25 ppm (470 $\mu g/m^3$).

Nitrogen dioxide is considered an important outdoor pollutant not only because of potential health effects, but because it is an essential precursor in the formation of tropospheric ozone via photochemical reactions, and contributes to the formation of atmospheric acids and secondary particles. These issues will not be discussed in this review, which will focus on the health effects of exposure to NO_2 itself.

This review will not address the role of NO_2 in ozone or acid formation via photochemical reactions, and will only briefly discuss the chemistry, sources, and dosimetry of NO_2. A number of reviews of these topics are available.

3. PRINCIPAL SOURCES AND EXPOSURE ASSESSMENT

The primary sources for NO_2 are internal combustion engines, both gasoline and diesel powered, as well as point sources, especially power plants. U.S. emissions of NO_x in 1996-1997 were approximately 23,000 short tons per year, with roughly 11,000 tons contributed by fuel combustion from non-transportation sources (Office of Air and Radiation, 1998). In 1991, 8.9 million people resided in counties that exceeded the NAAQS for NO_2, with the highest annual concentrations occurring in Southern California (Bascom et al., 1996). National mean concentrations of NO_2 decreased 14% from 1988 to 1997, to about 20 ppb, although NO_x emissions decreased little during that time period, and increased 1% in 1996-1997 (Office of Air and Radiation, 1998). Since 1970, total NO_x emissions have increased 11% and emissions

from coal-fired power plants have increased 44%. During the past 5 years, all U.S. counties have been in compliance with the Federal NO_2 standard.

Compliance with the Federal NAAQS for NO_2 does not preclude substantial short-term peak concentrations, and the California standard of 0.25 ppm for 1 hour continues to be exceeded, although with less frequency. In 1999, maximum one-hour values for NO_2 were highest in the counties of Riverside (0.307 ppm) and Imperial (0.286), with annual mean concentrations of 0.022 and 0.035, respectively (Office of Air and Radiation, 1998).

Because NO_2 concentrations are related to traffic density, commuters in heavy traffic may be exposed to higher concentrations of NO_2 than those indicated by regional monitors. In one study of personal exposures by Los Angeles commuters (Baker et al., 1990), in-vehicle NO_2 concentrations, averaged over 1 week of travel, ranged from 0.028 to 0.170 ppm, with a mean of 0.078 ppm. This was 50% higher than ambient concentrations measured at local monitoring sites.

Indoor NO_2 levels, in the presence of an unvented combustion source, may exceed those found outdoors. Natural gas or propane cooking stoves release NO_2, as do kerosene heaters. Peak levels exceeding 2.0 ppm have been measured in homes with gas stoves (Leaderer et al., 1984), and exposures during cooking have been measured as high as 0.6 ppm for up to 45 minutes (Goldstein et al., 1988). It is important to recognize that outdoor NO_2 levels provide a “background” for the higher peaks that may occur indoors; thus higher outdoor levels may drive higher peaks indoors, with outdoor levels contributing approximately 50% to indoor levels (Marbury et al., 1988).

Distance of residences from roadways appears to influence indoor NO_2 levels. In Tokyo, Japan, NO_2 exposure among adult women, age 40-60 years, was determined at varying distances from the roadside, using personal monitoring and monitoring inside and outside the home (Nakai et al., 1995). The highest mean personal exposure levels were found in women living closest to the roadway at 63.4 ppb, compared with 55.3 ppb farthest from the roadway. Personal monitoring in homes with unvented combustion sources were less clearly correlated to distance from the roadway than homes without combustion sources. In another study in the Netherlands (Roorda-Knape et al., 1999), NO_2 levels in school classrooms were found to be significantly correlated with traffic density and distance of the school from the roadway.

Concentrations of NO_2 as high as 4 to 5 ppm have been measured inside ice hockey arenas, from operation of natural gas-fueled ice resurfacing machines in the presence of inadequate ventilation (Hedberg et al., 1989). These exposures have been associated with "epidemics" of acute respiratory illness in exposed players and fans.

3.1 Dosimetry

Nitrogen dioxide is an oxidant gas that dissolves in water to form nitric acid, and also reacts with lipids and proteins in cells. It likely reacts either within the lung epithelial lining fluid or in the epithelial cell membrane, and probably does not penetrate beyond the epithelium as an intact molecule (Postlethwait et al., 1990). Toxic effects are presumably related to the effects of NO_2 and its reaction products on lung cells.

Nitrogen dioxide is less reactive than ozone, and is relatively insoluble; therefore, removal of inhaled NO_2 in the upper airway is limited. Dosimetric studies indicate that most inhaled NO_2 is retained in the lungs and deposited primarily in peripheral airways, particularly the terminal bronchiolar region. Miller et al. (Miller et al., 1982) developed a dosimetric model for NO_2 in the human which indicated that the NO_2 dose to the transitional airways increased three- to four-fold compared with the more proximal airways, and then decreased again in the alveolar region. Using this model, increases in tidal volume from 500 to 1500 mL would increase lung uptake from 60% to 90%, primarily attributable to increased alveolar uptake. Approximately 15 times more NO_2 would be delivered to pulmonary tissue at maximum tidal volume, as would occur during heavy exercise, than during rest. Data from a clinical study (Bauer et al., 1986) were supportive of these predictions. Fifteen asthmatic subjects were exposed to 0.3 ppm NO_2 via mouthpiece for 20 minutes at rest, followed by 10 minutes of exercise. Expired NO_2 concentrations were measured continuously. NO_2 deposition was 72±2% at rest, increasing to 87±1% with moderate exercise. These findings indicate that the NO_2 dose to the distal airways and alveolar space, and therefore toxic effects in this region, would be substantially increased by exercise.

4. DESCRIPTION OF KEY STUDIES

The assessment of health risks of exposure to NO_2 and other ambient pollutants depends on three types of investigations: epidemiological studies, human clinical studies, and

animal exposure and toxicology studies. In addition, in vitro exposure of cells and tissues assist with determining mechanisms of effects. Traditionally, epidemiological studies have focused on symptoms, doctor visits, hospitalizations, medication use, pulmonary function measures, and mortality as health outcomes. Clinical studies have focused on symptoms, changes in pulmonary function (principally spirometry), and occasionally assessment of non-specific airways responsiveness, in part because these measurements are relatively simple, safe, and reproducible. More recently, innovative approaches have been used to examine pollutant effects on respiratory host defense, airway inflammation, cardiac effects, and systemic effects. This review will first summarize findings from epidemiological studies, followed by human clinical studies. Although animal and in vitro exposure studies *per se* will not be addressed in detail in this review, particularly relevant data from these approaches will be addressed in the appropriate context. Emphasis will be placed on relevant studies within the past 5 years, particularly those dealing with the health of children.

4.1 Epidemiological Studies

4.1.1 Outdoor

A number of epidemiological studies have sought evidence for health effects of exposure NO_2 outdoors, along with other pollutants, in both adults and children. A selection of studies published since 1995 are summarized in Table 1. Several studies show significant relationships between ambient NO_2 levels and health effects, including respiratory symptoms, episodes of respiratory illness, lung function, and even mortality. However, because NO_2 shares sources with other pollutants, especially fine particles, epidemiological studies are often unable to distinguish the relative importance of NO_2 in causing health effects. Particular caution is needed in interpreting the results of studies measuring ambient concentrations of NO_2, but not particles. Indeed, many studies conducted over the past 10 years in a variety of locations around the world have observed a strong relationship between fine particle levels and both mortality and morbidity. That NO_2 appears strongly correlated with health outcomes in a few of these studies is perhaps not surprising, given the close correlation between NO_2 and particles.

Beginning in the 1970s, epidemiological studies in Chattanooga, Tennessee examined the relation between respiratory illnesses and ambient levels of NO_2. Shy and colleagues (Shy

et al., 1970) tracked the respiratory symptoms of 871 families (4,043 individuals) selected from five schools situated near a munitions factory in Chattanooga. This factory emitted NO_2 into surrounding areas. The ambient 24-hr mean NO_2 levels were 0.083 ppm in the high exposure area, 0.063 ppm in the intermediate area, and 0.043 ppm in the low area. Total suspended particulate and sulfate concentrations were similar across the three areas. Biweekly questionnaires indicated that the rates of acute respiratory illness were higher among the families living in the relatively high exposure area, although the rates were not consistently associated with the exposure gradient among the three schools in the high exposure area. Differences in family size, income, or education did not explain the observed associations. Parental smoking habits did not appear to influence the illness rates among children.

A subsequent study in the same Chattanooga community (Pearlman et al., 1971) studied lower respiratory tract infections in 3,217 school children and infants. Physician's office records were used to validate the parental reports of illness. Episodes of bronchitis were reported more often for school children living two and three years in the high and intermediate ambient NO_2 areas. This pattern was not observed in the infants, and no significant difference in incidence was observed between the high and intermediate areas. The incidence of croup and pneumonia did not differ significantly among the three exposure areas. Control for socioeconomic status and for parental smoking was not mentioned.

In further collection and analyses of data and from the Chattanooga studies (Love et al., 1982), including improved estimates of environmental exposures data, there was an apparent increase in lower respiratory illness in children who resided in an area previously defined as having high exposure to NO_2, although exposure levels at the time of the illnesses were comparable across the study region. The authors noted that the increased illnesses could not be attributed unequivocally to the atmospheric NO_2.

In analyses of another EPA database from Chattanooga, Harrington and Krupnick (Harrington & Krupnick, 1985) found a statistically significant relationship between NO_2 and reports of acute respiratory illness for children 12 years of age and younger. However, there was no clear exposure-response relationship.

Braun-Fahrlander and colleagues (Braun-Fahrlander et al., 1992) followed respiratory symptoms of 625 Swiss children in two cities using a daily symptom diary. Exposures to NO_2

were estimated using passive samplers placed outside the residence location and inside in the room where the child spent the most time. The concentrations of NO_2 indoors and outdoors were not associated with symptom incidence rates. The duration of symptom episodes was associated with outdoor but not indoor NO_2 concentration.

The Swiss Study on Air Pollution and Lung Disease in Adults (SAPALDIA) (Zemp et al., 1999; Schindler et al., 1998; Ackermann-Liebrich et al., 1997) examined the long-term effects of air pollution exposure in a cross-sectional and longitudinal study of 8 areas in Switzerland. Significant associations were observed between symptoms (chronic phlegm, chronic cough, breathlessness at rest, dyspnea on exertion) and both NO_2 and particles (Zemp et al., 1999). In the cross-sectional component of the study (Schindler et al., 1998), a significant negative correlation was observed between NO_2 and both FVC (β = -0.0123, $p<0.001$) and FEV_1 (β = -0.0070, $p<0.001$). NO_2 levels correlated strongly with PM_{10} levels ($r = 0.91$), making it impossible to determine the role of specific pollutants in the observed associations.

Frischer et al. (Frischer et al., 1993) studied 423 Austrian school children living in 4 small towns with varying levels of outdoor NO_2 levels. The children were assessed with spirometry and cold air inhalation challenge on two occasions 6 months apart. Lung function increased for the children coincident with an overall decrease in NO_2 levels, and NO_2 levels were found to be predictive for an increase in FVC. However, the study does not provide convincing evidence for causality in the relationship; the amount of lung function increase was consistent with that expected from increase in height during the interval. No measurements of ambient particles were reported.

A population-based study in the Netherlands (Boezen et al., 1998) suggested that, in adults, airways hyperresponsiveness at baseline increased risk for respiratory symptoms from air pollution. Relationships were observed between exposure to NO_2 and to PM_{10} with respiratory symptoms, only in the group with some measure of airway lability.

Associations have also been observed between NO_2 levels and emergency visits for asthma in Valencia, Spain (Tenias et al., 1998), in Barcelona (Castellsague et al., 1995), in Israel (Garty et al., 1998), and in Santa Clara County, California (Lipsett et al., 1997). In these studies, NO_2 effects may have been reflective of the pollutant mix rather than NO_2 alone.

Children with asthma appear to be more susceptible to the health effects of air pollution in general, although the specific role of NO_2 exposure remains in question. McConnell et al (McConnell et al., 1999), reporting data from the Southern California Children's Health Study, found positive associations between indices of air pollution, including NO_2, PM_{10}, and $PM_{2.5}$, and respiratory symptoms in children with asthma. The strongest association was with NO_2 (Figure 1). No association was seen for children without asthma. Particles, NO_2, and acids were too highly correlated to allow estimation of individual pollutant effects. Krämer et al. (Krämer et al., 2000) examined the relationship between NO_2 exposure, as assessed by outdoor and personal monitors, and the prevalence of atopy and rhinitis in 9 year old children. Interestingly, a significant relationship for both endpoints was observed with outdoor NO_2 levels, but not with levels obtained from personal monitoring. This suggests that a factor associated with outdoor air pollution, other than NO_2, may be playing a causative role.

A large study of visits to doctors' offices in London for respiratory complaints (Hajat et al., 1999) found different pollutant associations for children than for adults. Among children, positive associations were found between asthma visits and both NO_2 and CO. The strongest relationship was during the summer, when the percentage change in asthma visits for a 10 to 90^{th} percentile increase in 24-hour NO_2, lagged by one day, was 13.2% (CI: 5.6-21.3%). For adults, the only significant association was for PM_{10}. This finding suggests that children and adults may differ in their susceptibilities to components of the ambient pollutant mix.

Associations between NO_2 levels and mortality have been observed. A very brief report (Garcia-Aymerich et al., 2000) examined mortality in a cohort of patients with chronic obstructive pulmonary disease in Barcelona. Significant relationships were found between mortality and increases in SO_2, 1 hour maximum NO_2, and 24 hour average NO_2, but not black smoke. However, data for black smoke nearly missed significance, and it is likely that NO_2 represents a surrogate for pollution in general in this study. Saldiva et al. (Saldiva et al., 1994) studied mortality among children under age 5 in Sao Paulo, Brazil, a city with dense traffic, high pollution levels, and high infant mortality. Mortality due to congenital malformations, neonatal events, or prematurity was excluded. Mean NO_2 (NO_x) levels were 0.127 ppm. Only NO_2, and not PM_{10}, ozone, SO_2, or CO, was associated with mortality in this study, with an estimated odds of 1.30, 95% CI: 1.17-1.43.

The Sao Paulo group subsequently examined the influence of pollutant exposure on intrauterine mortality (Pereira et al., 1998). Again, the strongest single-pollutant coefficient was for NO_2 (0.0013/μg/m^3, $p<0.01$, Figure 2), with lesser coefficients for SO_2 and CO. No significant relationship was seen for PM_{10} or ozone. An index combining the effects of NO_2, SO_2, and CO associated most strongly with fetal mortality. The authors postulated one mechanism may be formation of methemoglobin in the fetus; fetal hemoglobin is more easily oxidized than that in adults.

Exposure to ambient fine particulate matter has been associated with increases in cardiovascular mortality. Peters and colleagues (Peters et al., 2000) used a novel approach to determine whether ambient pollution levels were associated with cardiac arrhythmias. The investigators obtained data from patients with implantable cardiac defibrillators, determining the number of times the defibrillator was activated in response to an arrhythmia, and correlating this with ambient concentrations of particles and gases. The strongest association was with NO_2 , with a 1 to 2-day lag. For example, the odds ratio for having at least 10 defibrillator events in association with a 26 ppb increase in NO_2 was 2.79, with 95% confidence intervals of 1.53-5.10. The concentration-response relationship was steeper for NO_2 than for $PM_{2.5}$ or black carbon (Figure 3). This is a potentially instructive study because NO_2 levels were highest in the winter, and $PM_{2.5}$ levels were highest in the summer. Correlation between NO_2 and $PM_{2.5}$ measurements were lower ($r=0.57$) than in many epidemiological studies, allowing some ability to attribute effects. The authors hypothesized that NO_2 may be a marker for the more toxic emissions associated with local traffic-related pollution, rather than PM alone, which is a mixture of combustion and transported particles. The data are also consistent with toxicity related to NO_2 as a component of the ambient pollutant mixture.

4.1.2 Indoor

The indoor setting provides the potential for discrimination between NO_2 and particle effects, because stoves burning natural gas emit primarily NO_x. Many studies have examined the potential for health effects of indoor NO_2 exposure, especially in children; many of these studies, and their methodological problems, have been reviewed (Samet & Utell, 1990; Samet & Spengler,1991; Frampton et al., 1991b), and only selected studies will be mentioned here. Key studies published since 1995 are summarized in Table 2.

Reports during the 1970's, from the United Kingdom (Melia et al., 1977)and the U.S. (Speizer et al., 1980), suggested that residence in a home with a gas stove increased the frequency of respiratory symptoms and of respiratory illness among children less than 2 years of age. Small sample size, inadequate control of potential confounding factors (e.g., presence of other children in the household, day care attendance, exposure to environmental tobacco smoke, and socioeconomic status) and potential misclassification of exposure and outcome limit the validity of these investigations. In particular, misclassification of exposure by using gas stoves as a surrogate for NO_2 exposure, and small sample sizes, may tend to bias many of the studies toward no effect.

In a pilot study, Goldstein and associates (Goldstein et al., 1988) monitored NO_2 exposures for 5 days in asthmatic subjects with a portable continuous monitoring instrument held at breathing level before, during, and after they used a gas stove for cooking. The limited data suggested that at average NO_2 levels below 0.3 ppm there were no consistent effects on lung function, while at concentrations above 0.3 ppm most of the asthmatic subjects showed a drop in forced vital capacity (FVC).

To reduce the problem of small sample size, Hasselblad et al. (Hasselblad et al., 1992) reported a meta-analysis of 11 epidemiological studies of respiratory illness in children and residential NO_2 exposure. The authors found an estimated 20% increase in risk of respiratory illness in children per 15 ppb increment in indoor NO_2 exposure.

A number of additional studies have been published since 1990, with continued mixed results. A prospective cohort study of infants conducted in Albuquerque, New Mexico (Samet et al., 1993) attempted to address many of the issues of previous studies related to sample size and exposure misclassification. Exposures to NO_2 and respiratory illnesses were monitored prospectively from birth to 18 months of age in a cohort of 1,205 infants living in homes with gas and electric cooking stoves, without smoking. NO_2 exposures were estimated from serial measurements of bedroom NO_2 concentrations. Respiratory illnesses were quantified from reports of symptoms and illnesses from mothers and validated by home visits. No consistent trends in incidence or duration of illness were observed by level of NO_2 exposure at the time of illness or during the prior month, or by type of stove. However, indoor NO_2 levels were very low in this study.

Neas et al. (Neas et al., 1991) reported that a composite measure of respiratory symptoms increased monotonically with measured annual average NO_2 concentrations within the home, among children in the Harvard Six Cities study. Symptoms included shortness of breath with wheeze, chronic wheezes, chronic cough, phlegm, or bronchitis. Residential NO_2 levels were not associated with pulmonary function. On the other hand, Dijkstra et al. (Dijkstra et al., 1990) found no associations between chronic cough, persistent wheeze, or shortness of breath with wheeze with indoor NO_2 measurements in the homes of children in the Netherlands.

More recent studies have utilized personal monitoring methods in an attempt to improve exposure classification. Mukala et al. (Mukala et al., 1999) prospectively studied personal exposure to NO_2 for periods of 13 weeks among 163 preschool children in Helsinki, using individual passive diffusion monitors. Daily diaries of symptoms were kept by the parents, and in a subset of 53 children, peak expiratory flow rates were measured in the morning and evening. Co-variates considered in the model included allergy, education, smoking, stove type, and outdoor pollutant concentrations (NO, NO_2, O_3, SO_2, and total suspended particles). The median personal NO_2 exposure was 21.1 $\mu g/m^3$ (0.011 ppm), with a maximum of 99 $\mu g/m^3$ (0.05 ppm). An increased risk of cough was associated with increasing NO_2 exposure (risk ratio = 1.52; 95% confidence interval 1.00-2.31). There were no significant effects on other respiratory symptoms or peak flow.

In Australia, where unvented natural gas cooking and heating are common, Pilotto et al. (Pilotto et al., 1997) queried respiratory symptoms and school absences among 388 children from 6 to 11 years of age, and monitored indoor NO_2 levels at their schools, which were chosen for having either unvented gas heating or electric heating. Classroom monitoring of NO_2 levels was conducted intermittently over several months. A significant increase in sore throat, colds, and absences from school were found for children in environments with hourly peak levels 80 ppb, compared with background levels of 20 ppb. Exposure-response relationships were evident for each outcome. However, no measurements of other pollutants, either indoor or outdoor, were provided. Caution must be used in interpreting the findings from cross-sectional studies, because many factors other than pollutant levels may influence differences between populations.

In the Latrobe Valley of Australia (Garrett et al., 1998), NO_2 levels were monitored in eighty homes, on 5 separate occasions for 4 days each, and health questionnaires administered to the 148 children residing in those homes. 58 of the children were asthmatic, although the diagnostic criteria were not provided. Children underwent allergy prick testing and monitored their peak flow rates for a 2-week period in the winter and spring. The indoor median NO_2 concentration was 6.0 ppb, with a maximum of 128 ppb. Respiratory symptoms were more common in children exposed to a gas stove (odds ratio 2.3, CI 1.00-5.2), even after adjusting for NO_2 levels (odds ratio 2.2, CI 1.0-4.8). Atopic children tended to have a greater risk than non-atopic children. NO_2 concentration was not a significant risk factor for symptoms. The authors conclude that gas stoves may pose a risk apart from NO_2. However, the relative paucity of NO_2 monitoring data for each home may have provided insufficient statistical power to demonstrate an association. More important weaknesses in the study are the inclusion of homes with cigarette smokers, and the failure to monitor other pollutants, either inside or outside the home. These factors may have confounded the findings.

Jarvis et al. (Jarvis et al., 1996) studied symptoms, lung function, and atopy in 15,000 adults aged 20-44 years in Britain, as part of the European Community Respiratory Health Survey. Women, but not men, who reported cooking with gas had an increased risk for symptoms consistent with asthma, such as wheezing (odds ratio (OR) 2.07, CI 1.41-3.05), waking with shortness of breath (OR 2.32, CI 1.25-4.34), and “asthma attacks” (OR 2.60, CI 1.20-5.65). Lung function was measured in a subset of subjects, and FEV_1 was reduced 3.1% of predicted for women cooking with gas compared to those using other means, after adjusting for age, smoking, and town of residence. Total and specific IgE levels were not associated with gas stove use. There was no protective effect associated with use of an exhaust fan. The authors boldly concluded from their estimate of the population attributable risk fraction that “the prevalence of wheeze with breathlessness in young women would be reduced by between 8% and 48% if cooking with gas were abandoned.” Although studies such as this are limited by the potential for exposure misclassification and the influence of other environmental and biological factors, the findings are consistent with women spending more time at cooking than men, and with reports of increased responsiveness to allergen challenge following NO_2 exposure (see below).

Taken together, studies of the health effects of exposure to NO_2 indoors fail to make a convincing case for association with respiratory illness in either children or adults. The findings of the Hasselblad meta-analysis (Hasselblad et al., 1992) must be interpreted with caution because the 11 studies used in the analysis employed varying methodologies and study populations. Small sample size, potential for misclassification, inclusion of smokers in many of the studies, and failure to consider potential effects of outdoor pollution, or other indoor pollutants, may bias many of the studies. For example, burning of natural gas in gas stoves emits ultrafine particles in addition to NO_2, and the cooking process is also a source of particles. It is possible that observed health effects associated with gas stove use may represent health effects of particle exposure, or of particles combined with NO_2. This may explain why Garrett et al. (Garrett et al., 1998), found a significant relationship between respiratory symptoms in children and gas stove use, but not indoor NO_2 levels. The Samet et al. study of infants in Albuquerque (Samet et al., 1993) provides convincing evidence that indoor NO_2, at the very low concentrations found in that study, are not associated with respiratory illnesses in children under 18 months of age.

4.2 Clinical Studies

4.2.1 Studies with Healthy Subjects

Effects on Pulmonary Function: Studies examining responses of healthy volunteers to acute exposure to NO_2 have generally failed to show alterations in lung mechanics of healthy volunteers (Hackney et al., 1978; Kerr et al., 1979; Frampton et al., 1991a; Azadniv et al., 1998). Exposures ranging from 75 minutes to 3 hours at concentrations up to 4.0 ppm NO_2 (Linn et al., 1985b; Mohsenin, 1987b; Mohsenin, 1988) did not alter pulmonary function. Curiously, Bylin and associates (Bylin et al., 1985) found increased airway resistance after a 20-minute exposure to 0.25 ppm NO_2 and decreased airway resistance after a 20-minute exposure to 0.5 ppm NO_2, but no change in airway responsiveness to aerosolized histamine challenge in the same subjects. Overall, there is little convincing evidence that exposure of healthy volunteers to NO_2 at levels as high as 4.0 ppm alters airway mechanics, as measured by spirometry or flow resistance.

Several observations indicate that NO_2 exposures in the range of 1.5-2.0 ppm cause small but significant increases in airway responsiveness. Mohsenin (Mohsenin, 1988) found that a 1-hour exposure to 2 ppm NO_2 increased responsiveness to methacholine, as measured by changes in specific airway conductance, without directly affecting lung function. Furthermore, pretreatment with ascorbic acid prevented the NO_2-induced increase in airway responsiveness (Mohsenin, 1987b). A mild increase in responsiveness to carbachol was observed following a 3-hour exposure to 1.5 ppm NO_2, but not to intermittent peaks of 2.0 ppm (Frampton et al., 1991a).

Few human clinical studies of NO_2 have included elderly subjects. Morrow et al. (Morrow et al., 1992) studied the responses of 20 healthy volunteers, 13 smokers and 7 nonsmokers of mean age 61 years, following exposure to 0.3 ppm NO_2 for 4 hours with light exercise. There was no significant change in lung function related to NO_2 exposure for the group as a whole. However, the 13 smokers experienced a slight decrease in FEV_1 during exposure, and their responses were significantly different from the 7 nonsmokers (% change in FEV_1 at end of exposure: -2.25 vs. +1.25%, $p = 0.01$).

Effects on Host Defense: Clinical studies have attempted to address the question of whether NO_2 exposure increases susceptibility to infection. Goings et al. (Goings et al., 1989) exposed healthy volunteers to either 1-3 ppm NO_2 or to air for 2 hours per day for 3 consecutive days. A live, genetically engineered influenza A vaccine virus was administered intranasally to all subjects after exposure on day 2. Infection was determined by virus recovery from nasal washings, a 4-fold or greater increase in antibody titer, or both. The findings of this study were inconclusive, in part because of limitations in sample size. In addition, the attenuated, cold-adapted virus used in the study was incapable of infecting the lower respiratory tract, where NO_2 may have its greatest impact on host defense.

Another approach has been to obtain lavaged cells from NO_2-exposed individuals and examine their handling of infectious virus *in vitro*. Several NO_2 exposure scenarios, including continuous low-level exposure or intermittent peak exposures have been examined (Frampton et al., 1989). Alveolar macrophages obtained by BAL 3 1/2 hours after a 3-hour continuous exposure to 0.60 ppm NO_2 tended to inactivate influenza *in vitro* less effectively than cells collected after air exposure. The effect was observed in cells from 4 of the 9 subjects studied;

alveolar macrophages from these 4 subjects increased release of interleukin-1 after exposure to NO_2, whereas cells from the remaining 5 subjects decreased release of interleukin-1 following exposure. However, in a subsequent study (Azadniv et al., 1998) involving 2.0 ppm NO_2 exposures for 6 hours with intermittent exercise, no effect on alveolar macrophage function or inactivation of influenza virus was observed, either immediately or 18 hours after exposure.

Airway Inflammation: Unlike ozone exposure, NO_2 exposure at near-ambient levels (i.e., less than 2.0 ppm) does not cause a significant influx of polymorphonuclear leukocytes (PMN) into the airways and alveoli (Frampton et al., 1989). NO_2 appears to be much less potent than ozone in eliciting a neutrophilic inflammatory response.

However, prolonged exposure to NO_2 at concentrations only slightly above peak levels occurring indoors can cause mild airway inflammation. Healthy volunteers exposed to 2.0 ppm NO_2 for 6 hours with intermittent exercise (Azadniv et al., 1998) showed a slight increase in the percentage of PMN obtained in bronchoalveolar lavage fluid 18 hours after exposure (air: 2.2±0.3%; NO_2: 3.1±0.4%). In a separate group of subjects, no effects of this exposure protocol were found on alveolar macrophage phenotype or expression of the adhesion molecule CD11b or receptors for IgG when assessed immediately after exposure (Gavras et al., 1994). Blomberg et al. (Blomberg et al., 1997) reported that 4-hour exposures to 2.0 ppm NO_2 resulted in an increase in interleukin-8 and PMN in the proximal airways of healthy subjects, although no changes were seen in bronchial biopsies. This group also studied the effects of repeated 4-hour exposures to 2 ppm NO_2 on 4 consecutive days, with BAL, bronchial biopsies, and BAL fluid antioxidant levels assessed 1.5 hours after the last exposure (Blomberg et al., 1999). The bronchial wash fraction of BAL fluid showed a two-fold increase in PMN and a 1.5-fold increase in myeloperoxidase, indicating persistent mild airway inflammation with repeated NO_2 exposure. Interestingly, small but significant decrements in FVC and FEV_1 were observed after the first exposure, which returned to baseline following subsequent exposures.

There is evidence from both animal and human studies that exposure to NO_2 may alter lymphocyte subsets in the lung and possibly in the blood. Lymphocytes, particularly cytotoxic T cells and NK cells, play a key role in host defense against respiratory viruses by eliminating infected host cells. Richters and colleagues (Damji & Richters, 1989) (Richters & Damji, 1988; Richters & Richters, 1989; Kuraitis & Richters, 1989) showed that mice exposed to NO_2 at

levels as low as 4 ppm for eight hours demonstrate reductions in populations of $CD8^+$ (cytotoxic/suppressor) lymphocytes in the spleen. In humans, Sandstrom et al. (Sandstrom et al., 1991) observed a significant, dose-related increase in lymphocytes and mast cells recovered by BAL 24 hours after a 20-minute exposure to NO_2 at 2.25 - 5.5 ppm. Rubinstein et al. (Rubinstein et al., 1991) found that a series of 4 daily 2-hour exposures to 0.60 ppm NO_2 resulted in a small increase in NK cells recovered by BAL. In contrast, repeated exposures to 1.5 or 4 ppm NO_2 for 20 minutes every 2^{nd} day on six occasions resulted in decreased $CD16^+56^+$ and $CD19^+$ cells in BAL fluid, 24 hours after the final exposure (Sandstrom et al., 1992b; Sandstrom et al., 1992a). No effects were seen on PMN or total lymphocytes. Finally, Azadniv et al. (Azadniv et al., 1998) observed a small but significant reduction in $CD8^+$ T lymphocytes in peripheral blood, but not BAL, 18 hr following single 6 hour exposures to 2.0 ppm NO_2.

Differing exposure protocols and small numbers of subjects among these studies may explain the varying and conflicting findings. Furthermore, the clinical significance of transient, small changes in lymphocyte subsets is unclear. However, even small changes in susceptibility to respiratory viruses resulting from exposure to NO_2 may have a significant public health impact because of the large number of individuals exposed in the home, both to NO_2 and to respiratory viruses. However, clinical studies provide little evidence for effects on lung function, airway inflammation, or host defense impairment in healthy subjects at outdoor ambient exposure concentrations.

Induction of Emphysema: Clinical emphysema in humans has been linked with deficient proteinase inhibitor activity in the lung, presumably via inactivation by cigarette smoke. One mechanism by which chronic NO_2 exposure may result in structural lung injury is through inactivation of lung proteinase inhibitors. Animal models involving prolonged exposure to relatively high levels of NO_2 have found pathological changes of emphysema (Evans et al., 1976; Lafuma et al., 1987). Mohsenin and Gee (Mohsenin and Gee, 1987) exposed healthy volunteers to 3 or 4 ppm NO_2 for 3 hours and observed a 45% decrease in the functional activity of α_1-proteinase inhibitor in BAL fluid. Supplementation with vitamins C and E prior to exposure abrogated the effect of 4.0 ppm NO_2 on elastase inhibitory capacity of the alveolar lining fluid (Mohsenin, 1991). In contrast, Johnson et al. (Johnson et al., 1990) found no effect of

exposure for 3 hours to continuous 1.5 ppm or intermittent peaks of 2.0 ppm NO_2 on either the concentration (immunoassay) or functional activity of α_1-proteinase inhibitor in BAL fluid. The absence of an effect in the Johnson study may reflect the lower exposure levels used.

Frampton et al. (Frampton et al., 1989) observed a 47% increase in α_2-macroglobulin, a metalloproteinase inhibitor released by alveolar macrophages, in BAL fluid 3 and 1/2 hours following 3-hour exposures to 0.60 ppm NO_2. This protein may have local immunoregulatory effects as well as provide local protection against proteinases. Its increase following NO_2 exposure suggests a protective response. However, no change in BAL fluid levels of α_2-macroglobulin were observed following similar exposures to 1.5 ppm NO_2 (Frampton et al., 1989).

4.2.2 Studies of People with Asthma

Orehek and colleagues (Orehek et al., 1976) were the first to report that relatively brief exposures of asthmatics to low-level NO_2 (0.1 ppm) might enhance subsequent responsiveness to challenge with a broncho-constricting drug. Although NO_2 alone caused an increase in airway resistance in only 3 of 20 asthmatics, bronchial responsiveness to carbachol increased in 13 of these 20 subjects. However, this report was challenged because of the retrospective separation of responding from non-responding subjects. Hazucha and colleagues (Hazucha et al., 1983) failed to confirm these results in a study of 15 asthmatic subjects. Although there were some differences in techniques and patient selection between the Orehek and Hazucha studies, it seems likely that the findings of Orehek and coworkers reflect a retrospective stratification of subjects into “responder” and “non-responder” groups that was not justified *a priori*. Other investigators have also been unable to confirm effects of 0.1-0.2 ppm NO_2 on lung function in either asthmatic adolescents (Koenig et al., 1985; Koenig et al., 1988) or in mildly asthmatic adults (Koenig et al., 1985; Bauer et al., 1986; Orehek et al., 1976; Bylin et al., 1985; Hazucha et al., 1983; Koenig et al., 1988; Kleinman et al., 1983; Linn et al., 1986; Mohsenin & Gee, 1987; Morrow & Utell, 1989; Roger et al., 1990)**.**

Kleinman and colleagues (Kleinman et al., 1983) evaluated the response of lightly exercising asthmatic subjects to inhalation of 0.2 ppm NO_2 for 2 hours, during which resting minute ventilation was doubled. Although NO_2 did not cause alterations in flow rates or airways resistance, approximately two-thirds of the subjects experienced increased responsiveness to

methacholine after inhalation of NO_2 compared with clean air, as assessed by specific airway resistance.

In view of the inconclusive findings at 0.1 and 0.2 ppm NO_2, Bauer and colleagues (Bauer et al., 1986) studied the effects of mouthpiece exposure to 0.3 ppm NO_2 for 30 minutes (20 minutes at rest followed by 10 minutes of exercise at approximately 40 L/min) in 15 asthmatics. At this level, NO_2 inhalation produced significant decrements in forced expiratory flow rates after exercise, but not at rest. Furthermore, after airway function was allowed to return to baseline during a 1-hour recovery period, isocapneic cold-air hyperventilation elicited increased airway responsiveness in the asthmatics who had earlier been exposed to NO_2.

Roger and coworkers (Roger et al., 1990), in a comprehensive, concentration-response experiment, were unable to confirm the results of a previous pilot study suggesting airway responses in asthmatic subjects. Twenty-one male asthmatics exposed to NO_2 at 0.15, 0.30, and 0.60 ppm for 75 minutes did not experience significant effects on lung function or airway responsiveness compared with air exposure. Bylin and coworkers (Bylin et al., 1985) found significantly increased bronchial responsiveness to histamine challenge compared with sham exposure in 8 atopic asthmatics exposed to 0.30 ppm NO_2 for 20 minutes. Five of 8 asthmatics demonstrated increased reactivity, while 3 subjects showed no change, as assessed by specific airway resistance. Mohsenin (Mohsenin, 1987a) reported enhanced responsiveness to methacholine in eight asthmatic subjects exposed to 0.50 ppm NO_2 at rest for 1 hour; airway responsiveness was measured by partial expiratory flow rates at 40% vital capacity, which may have increased the sensitivity for detecting small changes in airway responsiveness. Strand et al. (Strand et al., 1996) found increased responsiveness to histamine among 19 asthmatic subjects 5 hours after a 30 minute exposure to 0.26 ppm NO_2, with intermittent exercise.

The inconsistent results of these studies have not been satisfactorily explained. It is evident that a wide range of responses occur among asthmatics exposed to NO_2. This variation may in part reflect differences in subjects and exposure protocols: mouthpiece vs. chamber, obstructed vs. non-obstructed asthmatics, sedentary vs. exercise, and requirements for medication. Identification of factors that predispose to NO_2 responsiveness requires further investigation. These studies have typically involved volunteers with mild asthma; data are

needed from more severely affected asthmatics who may be more susceptible. Overall, there is little convincing evidence that short-term exposures to NO_2 at outdoor ambient concentrations significantly alter lung function or non-specific airway responsiveness in most people with mild asthma. However, outdoor levels influence indoor concentrations, which may reach peak levels that are clinically important for some adults and children with asthma.

Effects on Allergen Responsiveness: The potential for NO_2 exposure to enhance responsiveness to allergen challenge in asthmatics deserves special mention. Several recent studies, summarized in Table 3, have reported that low-level exposures to NO_2 ,both at rest and with exercise, enhance the response to specific allergen challenge in mild asthmatics. Tunnicliffe et al. (Tunnicliffe et al., 1994) reported exposures of 8 subjects with asthma to 400 ppb NO_2 for only 1 hour at rest, and found increased responsiveness to a fixed dose of allergen, both during the early and late phases of the response. No significant effect was seen at 100 ppb, but the data suggested an exposure-response relationship. Davies' group from the U.K., in two reports (Devalia et al., 1994; Rusznak et al., 1996), described an effect of exposure to the combination of 400 ppb NO_2 and 200 ppb SO_2, but not either pollutant alone, on subsequent allergen challenge in mild asthmatics. Strand and colleagues (Strand et al., 1998) from Sweden demonstrated increases in both the early and late phase responses to allergen following 4 daily repeated exposures to 260 ppb NO_2 for 30 minutes, at rest. Finally, Jenkins et al. (Jenkins et al., 1999) exposed asthmatic subjects to NO_2, ozone, and their combination using two different protocols that varied time of exposure and gas concentration, but kept the total exposure constant. All three exposures of the high concentration regimen (200 ppb ozone, 400 ppb NO_2, and the combination for 3 hours), but not the low concentration regimen, enhanced subsequent responsiveness to allergen.

Additional data from both animal exposure and in vitro exposure studies provide support for enhancement of allergen responsiveness by NO_2 exposure. Gilmour (Gilmour, 1995) has reviewed the evidence in animal models. Of particular interest is a rat model of house-dust-mite sensitivity in which a 3-hour exposure to 5 ppm NO_2, after a priming injection and pulmonary challenge with antigen, increased the specific immune response and immune-mediated pulmonary inflammation. NO_2 exposure also enhanced lymphocyte proliferation responses to allergen in both the spleen and mediastinal lymph nodes. Schierhorn et al.

(Schierhorn et al., 1999) observed increased histamine release by cultured human nasal mucosa from surgical resections in response to exposure to NO_2 at 200 and 800 $\mu g/m^3$ (106 and 424 ppb) for 24 hours. The magnitude of the effect was more pronounced than for ozone.

These recent studies involving allergen challenge appear relatively consistent in demonstrating effects at concentrations that occur indoors, and suggest that NO_2 may enhance both allergen sensitization and its associated inflammatory response. Confirmation of these findings is needed from other centers. However, the rising incidence, prevalence, and mortality from asthma makes these observations particularly important and timely. Additional work is needed in understand more completely the exposure-response characteristics, effects of exercise, relationship to severity of asthma, role of asthma medications, and other clinical factors. Animal and in vitro studies are needed to establish the precise mechanisms involved.

4.2.3 Chronic Obstructive Pulmonary Disease

Few studies have examined responses to NO_2 in subjects with chronic obstructive pulmonary disease (COPD). In a group of 22 subjects with moderate COPD, Linn and associates (Linn et al., 1985a) found no pulmonary effects of 1-hour exposures to 0.5, 1.0, and 2.0 ppm NO_2. In a study by Morrow and colleagues (Morrow et al., 1992), 20 subjects with COPD were exposed for 4 hours to 0.3 ppm NO_2 in an environmental chamber, with intermittent exercise. Although progressive decrements in lung function occurred during the exposure, significant decreases were not found for FVC until the end of the exposure. The decrement in lung volume occurred without changes in flow rates. The difference in results between the Linn and Morrow studies may reflect the difference in duration of exposure. It is worth noting that changes in lung function were typical of the “restrictive” pattern seen with ozone rather than the obstructive changes described by some with NO_2 exposure in asthmatics.

5. INTERACTIONS

Environmental exposures to NO_2 do not occur singly, but rather as a complex mixture of pollutants, and failure to consider the presence of other pollutants may confuse interpretation of the observed effects. Recent data suggest exposure to low concentrations of NO_2 at rest may enhance the response to allergen inhalation in subjects with asthma (see section 4.2.2). When

considering mixtures of anthropogenic pollutants, It may be impossible to separate the effects of one component from those of other components, particularly with the possibilities of synergistic or antagonistic interactions. In considering the health effects of mixtures, potential causal pathways should be carefully delineated. For example, some reports have suggested that HONO may contribute to the health effects attributed to indoor NO_2 (Spengler et al., 1990).

Efforts have been made to study effects of NO_2-ozone mixtures on pulmonary function. These studies have generally revealed no interactive effects; the observed pulmonary function decrements appear to reflect the ozone component of the mixtures. Hazucha et al., (Hazucha et al., 1994) found that pre-exposure of healthy women to 0.6 ppm NO_2 for 2 hours enhanced the development of nonspecific airway responsiveness induced by a subsequent 2-hour exposure to 0.3 ppm ozone, with intermittent exercise.

Relatively high-level, prolonged (6 hours/day, up to 90 days) exposure to NO_2 (14.4 ppm) and ozone (0.8 ppm) results in a syndrome of progressive pulmonary fibrosis in rats (Rajini et al., 1993), associated with a sustained increase in procollagen gene expression in the central acini (Farman et al., 1999). This does not occur with either gas alone, indicating a true synergistic effect. The relevance of this observation for human ambient exposures is not clear, given the high exposure concentrations used in the study, and absence of evidence for alveolar fibrosis or restrictive lung disease in epidemiological studies.

Bermudez et al. (Bermudez et al., 1999) examined DNA strand breaks in BAL cells from rats exposed to ozone (0.3 ppm), to NO_2 (1.2 ppm), and the combination. Ozone and the combination exposure increased DNA strand breaks to a similar degree compared with air exposure, but NO_2 alone had no effect.

The effects of NO_2 exposure on SO_2-induced bronchoconstriction have been examined, but with inconsistent results. Jorres and Magnussen (Jorres & Magnussen, 1991) found an increase in airways responsiveness to SO_2 in asthmatic subjects following exposure to 0.25 ppm NO_2 for 30 minutes, yet Rubinstein et al. (Rubinstein et al., 1990) found no change in responsiveness to SO_2 inhalation following exposure of asthmatics to 0.30 ppm NO_2 for 30 minutes.

Overall, there are little definitive data suggesting that NO_2 interacts with other pollutants in causing human health effects. However, human clinical studies have not systematically

addressed the effects of pollutant combinations containing NO_2, in part because of the complexity of the experimental design and the difficulty in studying the most susceptible subjects.

6. CONCLUSIONS

Evidence for human health effects of exposure to ambient NO_2 derives from epidemiological, human clinical, and animal exposure studies. This review has focused primarily on epidemiological and human exposure studies; those studies published since 1995 that appear most relevant to the current re-evaluation of the California air quality standard for NO_2 are indicated with an asterisk in the first column of Tables 1-3.

Many studies have found an increased incidence of respiratory illness in children associated with indoor NO_2 exposure, and a meta-analysis indicates that a long-term increase in exposure to NO_2 of 15 ppb is associated with an increase in illness odds of approximately 20% in children but not in adults. However, these studies are subject to exposure misclassification, and generally fail to consider a possible role of indoor and outdoor particle exposure as a confounder.

Several recent epidemiological studies examining health outcomes related to outdoor pollutant exposure have found the strongest indicator of health effects to be NO_2. Because outdoor NO_2 concentrations correlate strongly with fine particles, and because a substantial body of evidence now exists associating exposure to fine particles with increased morbidity and mortality, NO_2 is presumed to be a marker for traffic-related pollution, rather than a direct cause of the observed effects. Epidemics of respiratory illness described in ice hockey arenas with a poorly functioning Zamboni, which emit NO_2, would suggest that exposure to NO_2 at levels of 4 to 5 ppm, with exercise, can cause significant acute respiratory illness in some people. However, natural gas combustion also emits ultrafine particles (less than 100 nm in diameter), and it is possible that these particles were present and contributed in causing the observed episodes of respiratory illness. Taken together, the epidemiological evidence would indicate that traffic- and combustion-related pollutant exposure has adverse health effects, and that NO_2 is an important atmospheric marker of exposure. We cannot exclude the possibility that NO_2, as part of that ambient mixture, plays an important role in causing the observed health effects.

Responses to NO_2 exposure in clinical studies are characterized by marked variability, which directs attention toward identifying determinants of susceptibility, including the pattern of exposure, age of subjects, underlying diseases, antioxidants in the diet, and presence of other pollutants in the atmosphere. Most human clinical studies do not show effects with concentrations at or below the current California standard of 0.25 ppm. Recent studies from the UK and Sweden suggest that exposure to NO_2 at concentrations as low as 0.26 to 0.4 ppm, at rest, enhances responsiveness to allergen challenge in subjects with asthma. Animal models of allergic asthma support the observation, and in vitro studies using human nasal epithelium suggest the mechanism may involve enhanced mast cell degranulation and histamine release.

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8. FIGURE LEGENDS

Figure 1. Association between ambient NO_2 concentrations in (ppb) and production of phlegm in the Children's Health Study. A concentration-response relationship was seen for children with asthma. Adapted from Figure 2 in McConnell et al., 1999.

Figure 2. Relative risk of intrauterine mortality for increasing concentrations of NO_2 (quintiles of the 5-day moving average, in μ/m^3). Adapted from Figure 4 in Pereira et al., 1998.

Figure 3. Associations between defibrillator discharges and quintiles of 2-day lagged values of $PM_{2.5}$, black carbon, and NO_2, adjusted for season, minimum temperature, humidity, trend, and day of the week. Adapted from Figure 2 in Peters et al., 2000.

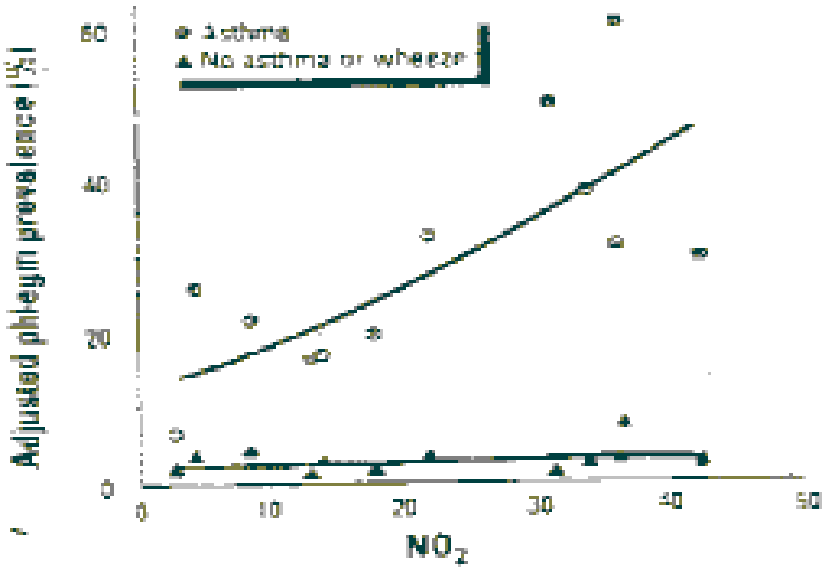


Figure 1

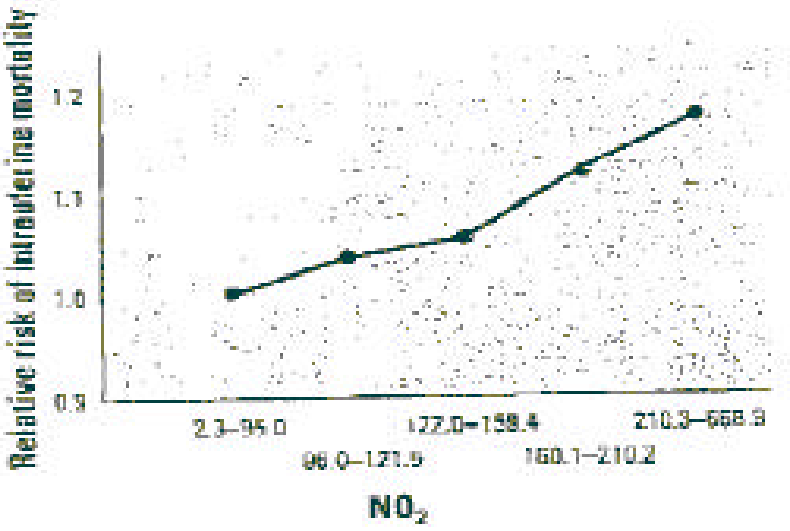


Figure 2

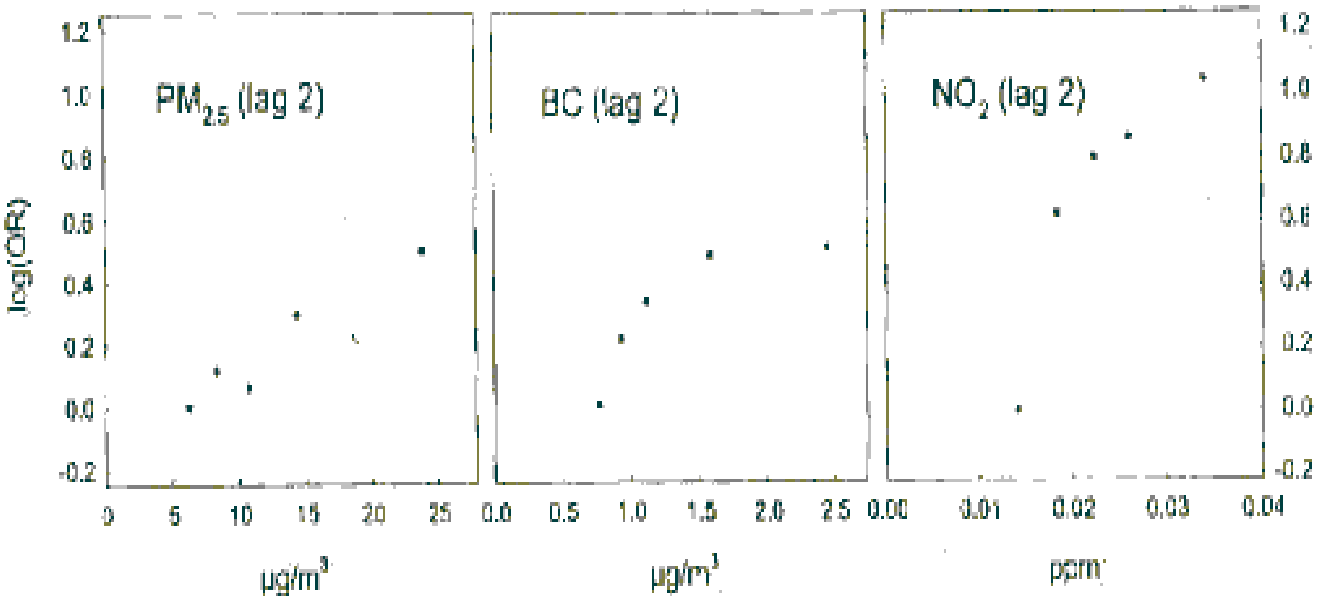

PM2.5 (lag 2)
BC (lag 2)
NO2 (lag 2)
log(OR)
1.2
1.0
0.8
0.6
0.4
0.2
0.0
-0.2
0
5
10
15
20
25
0.0
0.5
1.0
1.5
2.0
2.5
0.00
0.01
0.02
0.03
0.04
µg/m3
µg/m3
ppm

Figure 3

Table 1. Epidemiological studies of outdoor NO_2 exposure (since 1995). ***** Indicates particular relevance to Standard.

Reference	Location	Participants	Approach & Methods	Exposure Levels (ppb)	Findings
(Boezen et al., 1998)	Netherlands	288 adults age 48-73 yrs, with and without respiratory symptoms.	Time series, respiratory symptoms	24-h means: Urban, 46; Rural, 27	Group with airways hyperresponsiveness or peak flow lability experienced increased symptoms with exposure to NO_2 or PM_{10}
(Castellsague et al., 1995)	Barcelona	Asthmatics age >14 visiting emergency departments	Time series	24-h means: Summer, 55; Winter, 53	Relative risk for asthma visits associated with both black smoke and NO_2.
(Garcia-Aymerich et al., 2000)	Barcelona	Patients with COPD	Time series mortality	Not given	Associations between mortality and NO_2, but black smoke not significant.
(Garty et al., 1998)	Israel	1076 Children age 1-18 yrs presenting to ED with asthma attack	Time series	Weekly means ~50-250	Emergency department visits correlated with concentrations of NO_2 and SO_2.
*****(Hajat et al., 1999)	London, UK	Patients with respiratory complaints visiting physicians' offices	Time series analysis of Dr visits for asthma and lower respiratory diseases	Annual Mean 33.6, SD 10.5	Significant associations between asthma consultations and NO_2 for children, PM_{10} for adults
(Krämer et al., 2000)	Germany	317 children age 9 yrs	Time series, with both outdoor and personal monitoring	Weekly means: Outdoors, 84-116; Personal, 43-50	Atopy related to outdoor NO_2 levels (OR=1.81) but not personal NO_2 exposure. No measurements of other pollutants.
*****(Lipsett et al., 1997)	Santa Clara County, California	Asthmatics making visits to ED.	Time series, ED visits for asthma at 3 hospitals. ED visits for gastroenteritis were control population.	Mean 1-h peak, 69, SD 28	Significant PM_{10} risk, dependent on temperature. NO_2 also significant but not when PM_{10} factored in.
*****(McConnell et al., 1999)	Southern California	4^{th}, 7^{th}, and 10^{th} grade children with or without asthma in 12 suburban communities	Cross-sectional	24 h means: 21.9, range 2.7-42.6	"Bronchitis" symptoms in children with asthma associated with NO_2 and PM_{10} levels. Effects of PM_{10}, NO_2, and acid inseparable because all were closely correlated.

Table 1 (continued)

Reference	Location	Participants	Approach & Methods	Exposure Levels (ppb)	Findings
*(Moolgavkar et al., 1997)	Minneapolis-St. Paul & Birmingham	Elderly adults hospitalized for pneumonia and chronic obstructive pulmonary disease	Time series	24 h means: 16.3; 10-90th percentile, 7.9-25.3	NO_2 associated with hospital admissions in Minneapolis-St. Paul, but ozone gave strongest association, and other pollutants were inseparable.
*(Pereira et al., 1998)	Sao Paulo, Brazil	Unborn children	Time series, intrauterine mortality	24-h means 296, SD 153	NO_2 showed strongest association with fetal mortality
*(Peters et al., 2000)	Boston, MA	Patients with implantable cardiac defibrillators	Time series	24 h means 23; 5-95th percentile, 11-37	Increased risk of defibrillator discharge associated with 1-2 day lagged NO_2 levels
(Pershagen et al., 1995)	Stockholm, Sweden	204 infants age 4-48 mos. hospitalized for "wheezing bronchitis" (cases), 409 controls.	Case-control study; model estimates of outdoor NO_2 concentrations at home address	1-h values, mean ~100, range 38-660	Increased risk of hospitalization related to NO_2 exposure in girls, RR = 2.7 (p=0.02), but not boys. NO_2 levels considered a surrogate for air pollution in general.
(Schindler et al., 1998)	Switzerland (SAPALDIA)	Children	Cross-sectional, pulmonary function	Annual means 17-109. Estimated average personal exposure: 24-93	Negative correlation between NO_2 and both FVC and FEV_1. NO_2 levels correlated strongly with PM_{10} levels (r=0.91),
(Studnicka et al., 1997)	Austria	Children age 7 yrs	Cross-sectional, 8 non-urban communities with varying pollution from traffic.	Overall means: 6-17	Prevalence of asthma significantly associated with long-term NO_2 exposure. No particle measurements
(Tenias et al., 1998)	Valencia, Spain	Asthmatics age >14 identified from emergency department (ED) visits	Ecological time series, ED visits	1 h means 189, 5-95th percentiles 134-288	Relative risk for ED visit significant for NO_2 24 hour mean, NO_2 1 hour maximum, and ozone 1 hour maximum. Not significant for SO_2 or black smoke.
(Zemp et al., 1999)	Switzerland	9,651 adults age 18-60 yrs (SAPALDIA study)	Time series, respiratory symptoms	Annual mean 67, range 17-109	Significant associations between symptoms (chronic phlegm, chronic cough, breathlessness at rest, dyspnea on exertion) and both NO_2 and particles. Effects of NO_2 and particles could not be distinguished.

Table 2. Epidemiological studies of indoor NO_2 exposure (since 1995). ***** Indicates particular relevance to Standard.

Reference	Location	Participants	Approach & Methods	Findings
(Garrett et al., 1998)	Australia	Healthy and asthmatic children 7-14 yr.	Prospective. Intermittent monitoring in homes with and without gas stoves. Respiratory symptoms, peak flow, skin prick testing. Smoking homes included, no measurements of other pollutants.	Relationship between gas stove, but not NO_2 levels, and respiratory symptoms.
*****(Jarvis et al., 1996)	East Anglia, UK	Adults age 20-44 yrs	Cross-sectional, questionnaire, lung function and IgE levels on a subset	Gas stove use associated with Increased symptoms and decreased lung function in women, but not men
(Magnus et al., 1998)	Oslo, Norway	Oslo birth cohort: Children age <2 yrs who developed 2 episodes of bronchial obstruction or 1 episode lasting >4 months.	Case-control study; personal and home monitoring	No effect of NO_2
(Moran et al., 1999)	U.K.	National Child Development Study, cohort born in 1958 (age 34-35 yrs at time of study). 1449 examined, 1119 with "chest disease" and 330 controls.	Retrospective cohort study. Gas or electric cooking, health status, lung function, skin tests.	No association between gas cooking in childhood or adulthood and incidence of asthma, respiratory symptoms, or allergic sensitization. Slightly lower FEV_1 associated with gas cooking in men only.
*****(Mukala et al., 1999)	Helsinki	Pre-school children in day care, 3-6 yr. No information on baseline health status.	Prospective. Personal monitoring of NO_2 exposure and respiratory symptoms, peak flow in a subset of subjects.	Relationship between NO_2 exposure and cough
*****(Pilotto et al., 1997)	Australia	School children 6-11 yr. No information on baseline health status.	Prospective. Fixed monitoring in homes and schools with electric versus gas heating. Respiratory symptoms and school absences. No measurements of other pollutants.	Hourly peak levels 80 ppb associated with increased sore throat, colds, and absences

Table 3. Effects of NO_2 exposure on response to inhaled allergen. ***** Indicates particular relevance to Standard.

Reference	Location	Participants	Approach & Methods	Findings
*****(Devalia et al., 1994; Rusznak et al., 1996)	United Kingdom	Mild asthmatics	6 h exposures to combination of 400 ppb NO_2 and 200 ppb SO_2.	Increased allergen responsiveness to combination of NO_2 and SO_2, but not to individual gases. Effect persists 48 h, maximal at 24 h.
*****(Jenkins et al., 1999)	United Kingdom	11 patients with mild asthma	1) 6-h exposures to air, 100 ppb ozone, 200 ppb NO_2, and combination followed by allergen challenge; 2) 3-h exposures to air, 200 ppb ozone, 400 ppb NO_2, and combination; all with intermittent exercise.	All of the second exposure scenarios (ozone, NO_2, and combination), but none of the first exposure scenarios, resulted in enhanced responsiveness to allergen. Authors conclude that response may have a concentration threshold.
*****(Strand et al., 1997)	Sweden	18 patients with mild asthma, age 18-50 yrs	Exposure to 490 $\mu g/m^3$ NO_2 (260 ppb) for 30 min at rest	Late phase, but not early phase, response to allergen enhanced by NO_2.
*****(Strand et al., 1998)	Sweden	16 patients with mild to moderate asthma, age 21-52 yrs	4 daily repeated exposures to 260 ppb NO_2 for 30 min at rest	Significant increases in both early and late phase response to allergen after 4^{th} day of exposure.
*****(Tunnicliffe et al., 1994)	United Kingdom	10 nonsmoking mild asthmatics age 16-60 yrs. 8 subjects completed.	Exposure to air, 100 ppb, and 400 ppb NO_2 for 1 hr at rest, separated by at least 1 week, followed by allergen challenge.	Post-challenge reduction in FEV_1 after 400 ppb NO_2 was greater than after air, for both the early ($p<0.009$) and late ($p<0.02$) responses. No difference in nonspecific airway responsiveness.
(Wang et al., 1995b; Wang et al., 1995a)	United Kingdom	2 groups of 8 subjects with allergic rhinitis	Exposure to 400 ppb NO_2 (at rest?) for 6 h followed by nasal allergen challenge and nasal lavage	Increase in myeloperoxidase and eosinophil cationic protein in nasal lavage fluid following allergen challenge.

CARBON MONOXIDE:
EVALUATION OF CURRENT CALIFORNIA AIR QUALITY STANDARDS WITH RESPECT TO PROTECTION OF CHILDREN

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A. INTRODUCTION

Carbon monoxide (CO) is a toxic gas to which children are exposed in a many different types of environment, including the home, in vehicles, while out-of-doors and in their schools. This report will first examine studies that have been part of the scientific basis for the establishment of California's CO air quality standard. Although many of these articles deal with adults rather than children, the mechanisms of action and injury are by and large similar. Next, recently published articles that examine the issue of whether children's exposures or their health responses to CO are different from those of adults will be examined. Finally, these data will be integrated to provide an appraisal of possible differences in responses between children and adults at given environmental levels of CO.

A.1. Background

CO competes with oxygen (O2) for binding sites on the heme portion of the hemoglobin (Hb) molecules in red blood cells to form carboxyhemoglobin (COHb). Most of the documented health effects of CO derive from its ability to reduce oxygen delivery to metabolizing tissues, most notably the heart and the central nervous system (CNS).

A.1.1. State Standards: The Air Resources Board (ARB) is required by Section 3906(b) of the Health and Safety Code to adopt ambient air quality standards to protect public health and welfare. The health-based ambient air standards specify concentrations and averaging times chosen to prevent adverse effects with consideration to providing protection to sensitive population groups. The ARB adopted a standard of 20 ppm averaged over 8 hours in 1969. The standard was revised in 1970 to 10 ppm averaged over 12 hours and 40 ppm averaged over 1 hour. When the U.S. EPA, in 1971, promulgated national health standards of 9 ppm averaged over 8 hours and 35 ppm averaged over 1 hour, ARB staff proposed changing the state ambient air quality standards to match. In 1975 the ARB requested that the California Department of Health

Services (DHS) consider the potential increased health risks of exposure to CO at high altitude. DHS responded by recommending a more stringent standard (6 ppm CO averaged over 8 hours) for regions of the state 4,000 or more feet above sea level. In 1982, the DHS developed ambient air quality standards for CO based on its recommendation that "a target concentration of 2.5% COHb serve as a basis for the air quality standard for CO." A mathematical model was used to estimate the ambient concentrations to which individuals might be exposed that would lead to the target 2.5% COHb. The model calculations lead to the adoption of the current standards (9 ppm CO averaged over 8 hours and 20 ppm averaged over 1 hour). The current California ambient air CO standards are more stringent than the national standards, and California is unique in the US in having a more stringent standard for high altitude areas.

A.1.2. U.S. Federal Standards: The National Ambient Air Quality Standards (NAAQS) for CO were promulgated by the Environmental Protection Agency (EPA) in 1971 at levels of 9 ppm (10 mg/m^3) for an 8 h average and 35 ppm (40 mg/m^3) for a 1 h average, not to be exceeded more than once per year. (Primary and secondary standards were established at identical levels). The 1970 CO criteria document (National Air Pollution Control Administration, 1970) cited as the standard's scientific basis a study which indicated that subjects exposed to low levels of CO, resulting in COHb concentrations of 2 to 3% of saturation exhibited neurobehavioral effects (Beard and Wertheim, 1967). A revised CO criteria document (U.S. Environmental Protection Agency, 1979) concluded that it was unlikely that significant, and repeatable, neurobehavioral effects occurred at COHb concentrations below 5%. However, reports that aggravation of angina pectoris, and other symptoms of myocardial ischemia, occurred in men with chronic cardiovascular disease, exposed to low levels of CO resulting in COHb concentrations of about 2.7% (Aronow and Isbell, 1973; Aronow et al., 1972; Anderson et al., 1973), lead EPA to retain the 8 h 9 ppm primary standard level and to reduce the 1 h primary

standard from 35 to 25 ppm. (EPA also revoked the secondary CO standards because no adverse welfare effects had been reported at near-ambient levels). Later, concerns regarding the validity of data on which the proposed reduction in the 1 h standard was based caused EPA to decide to retain the 1 h 35 ppm standard.

The l984 addendum to the 1979 CO criteria document (U.S. Environmental Protection Agency, 1984) reviewed four effects associated with low level CO exposure: cardiovascular, neurobehavioral, fibrinolytic, and perinatal. Dose response data provided by controlled human studies allowed the following conclusions to be drawn:

a) Cardiovascular effects. Among those with chronic cardiovascular disease, a shortening of time to onset of angina was observed at COHb concentrations of 2.9-4.5%. A decrement in maximum aerobic capacity was observed in healthy adults at COHb concentrations at and above 5%. Patients with chronic lung disease demonstrated a decrease in walking distance when COHb concentrations were increased from 1.1-5.4% to 9.6-14/9%.

b) Neurobehavioral effects. Decrements in vigilance, visual perception, manual dexterity, and performance of complex sensorimotor tasks were observed at, and above, 5% COHb.

c) Effects on Fibrinolysis. Although evidence existed linking CO exposure to fibrinolytic mechanisms, controlled human studies did not demonstrate consistent effects of carbon monoxide exposure on coagulation parameters.

d) Perinatal effects. While there were some epidemiological associations between CO exposure and perinatal effects, such as low birth weight, slowed post-natal development and incidences of sudden infant death

syndrome (SIDS), the available data were not sufficient to establish causal relationships.

In September 1985, EPA issued a final notice that announced the retention of the existing 8 h 9 ppm and 1 h 35 ppm primary NAAQS for CO and the rescinding of the secondary NAAQS for CO.

The EPA completed the most recent CO criteria document in 1991 and this chapter reviews the health-based literature that has been published since the December 1991 criteria document. Addendum (U.S. Environmental Protection Agency, 1991) including controlled human clinical exposures and population based studies. There have also been inhalation studies using laboratory animal models. These studies have provided important insights into the possible mechanisms of toxic action of CO, in addition to those related to hypoxia, and illuminate effects not currently identified in human studies, or which might not be amenable to controlled human experimentation, such as perinatal and developmental effects. The existing NAAQS for CO were retained, and are the current US standards.

A.2. Principle Sources and Exposure Assessment

A.2.1. Sources: Carbon monoxide is essentially ubiquitous in our environment. It is emitted from virtually all sources of incomplete combustion. Outdoor sources include gasoline and diesel engines and other combustion activities. Indoor sources include improperly adjusted gas and oil appliances (e.g. space heaters, water heaters, stoves, clothes dryers and ovens); and tobacco smoking (Darbool, et al., 1997; Clifford, et al., 1997; Hampson and Norkool, 1992). Because ambient CO concentrations show large temporal and spatial variations, the exposure of individuals to CO is, therefore, also quite variable, and will depend upon the types of activities in which that individual is engaged and how long he or she is engaged in those activities (time - activity profiles). Other factors that are of importance are related to where the activity takes place (microenvironments e.g. indoors, at a shopping mall, outdoors, in a vehicle, at work or school, in a parking garage or even in a skating rink), (Viala, 1994; Levesque, et al., 1990; Dor, et al., 1995;

Koushki, et al., 1992) and the proximity to CO sources.

A.2.2. Exposure assessment and dosimetry: In adults, the affinity of Hb for CO is about 220 to 250 times that for O_2 (Roughton, 1970). The formation of COHb by the binding of CO to circulating Hb thus reduces the oxygen-carrying capacity of blood. In addition, binding of CO to one of the four hemoglobin binding sites increases the O_2 affinity of the remaining binding sites, thus interfering with the release of O_2 at the tissue level. When O_2 content of blood [mL O_2 / mL blood] is plotted vs. O_2 partial pressure [mm Hg] in blood, the increased O_2 affinity is seen as the so-called leftward shift in the curve for blood partially loaded with CO (Longo, 1976). CO-induced tissue hypoxia is therefore a joint effect of the reduction in O_2 carrying capacity and the reduction of O_2 release at the tissue level. The brain and heart, under normal conditions, utilize larger fractions of the arterially delivered O_2 (about 75%) than do peripheral tissues and other organs (Ayers, et al., 1970), and are therefore the most sensitive targets for hypoxic effects following CO exposures. The potential for adverse health effects is increased under conditions of stress, such as increased activity levels, which increase O_2 demands at the tissue level. CO may also have a neurotransmitter function and may mediate changes in blood pressure. Children, acutely exposed to CO, present with acidosis and hypertension, among other symptoms (Meert et al., 1998).

The measure of biological dose that relates best to observed biological responses and deleterious health effects is the concentration of COHb expressed as a percentage of available, active Hb, thus representing the percent of potential saturation of Hb. COHb can be measured directly in blood or estimated from the CO content of expired breath (Lambert, et al., 1988; Lee et al., 1994). When direct measurements cannot be made, COHb can be estimated from ambient air CO concentrations (Ott et al., 1988), indoor air CO concentrations and personal CO monitoring data (Wallace and Ott, 1982). This requires using pharmacokinetic and other models (Wallace and Ott, 1982; Forbes et al., 1945; Pace et al., 1946; Goldsmith et al.,

1963; Coburn et al., 1965) that compute COHb from the concentration of inhaled CO, breathing rate and volume, blood volume, metabolic production of endogenous CO and rate of removal of CO. The Coburn-Forster-Kane (CFK) model (Coburn et al., 1965) has been widely used for this purpose. The CFK model has been experimentally verified for exposures at 25 to 5000 ppm, during rest and exercise (Peterson and Stewart, 1975; Tikuisis et al., 1987).

A.3. CO Toxicity and sensitive populations

A.3.1. Toxicology: CO affects health by interfering with the systemic transport of oxygen to tissues (especially the heart and other muscles and brain tissue) (Costa and Amdur, 1996). The resulting impairment of O_2 delivery cause tissue hypoxia and interferes with cellular respiration. Direct intracellular uptake of CO could permit interactions with hemoproteins such as myoglobin, cytochrome oxidase and cytochrome P-450, and therefore interfere with electron transport processes and energy production at the cellular level (Brown and Piantidosi, 1992). Thus, in addition to observed physiological effects and cardiovascular effects, CO can modify electron transport in nerve cells resulting in behavioral, neurological and developmental toxicological consequences, and may itself play a role in neurotransmission.

Some data suggest a possible role of CO as an etiologic factor in development of atherosclerosis (Ramos et al., 1996) and can contribute to cardiac ischemia. Cardiac ishemia is a causative factor in cardiac arrhythmias, which can lead to sudden cardiac arrest and myocardial infarctions. Thus, chronic exposure to elevated CO levels could potentially have long term consequences for the developing child.

The hemodynamic responses to CO have been reviewed by Penney (1988). Chronic CO exposures, at levels sufficient to raise COHb concentrations to greater than 10% can produce increased numbers of red blood cells (polycythemia), increased blood volume, and increased heart size (cardiomegaly). In addition, heart rate, stroke volume, and systolic blood pressure may be increased. Some of these effects have been seen in smokers. Other environmental factors, such as effects of other pollutants (both from conventional air pollution

sources and from environmental tobacco smoke), interactions with drugs and medications, health and related factors (e.g. cardiovascular and respiratory diseases, anemia, or pregnancy), and exposures at high altitude are possible risk modifiers for the health effects of CO.

A.3.2. Mechanisms and human characterisitics that increase risk

(i) Heart diseases

Ischemic heart disease, or coronary artery disease, which is a leading cause of disability and death in industrialized nations (Levy and Feinleib, 1984), is a clinical disorder of the heart resulting from an imbalance between oxygen demand of myocardial tissue and oxygen delivery via the bloodstream. The ability of the heart to adjust to increases in myocardial O_2 demands resulting from increased activity, or to reductions in O_2 delivery by arterial blood due, for example, to COHb or reduced partial pressure in O_2 in inspired air, by increasing O_2 extraction, is limited, because the extraction rate in myocardial tissue is already high. Normally, coronary circulation responds to such increased O_2 demands by increasing blood flow. Individuals, including children, with blood flow insufficiencies may be at increased risk of CO effects, especially when exercising. If impedance of local coronary blood flow occurs during exercise, exercise-induced increased O_2 demands can force the myocardium to extract more O_2 (resulting in reduced coronary venous and tissue O_2 tensions), which can lead to localized myocardial ischemia and possible tissue damage. Severe myocardial ischemia can lead to myocardial infarction (heart attack) and to abnormal

cardiac rhythms, or arrhythmias. The association of acute CO exposure to heart attacks has been described (Marius-Nunez, 1990).

(ii) Anemia and other blood disorders

Individuals with reduced blood hemoglobin concentrations, or with abnormal hemoglobin, will have reduced O_2 carrying capacity in blood. In addition, disease processes that result in increased destruction of red blood cells (hemolysis) and accelerated breakdown of hemoproteins accelerate endogenous production of CO (Berk, et al., 1974; Solanki et al., 1988), resulting in higher COHb concentrations than in normal individuals. For example, patients with hemolytic anemia have COHb concentrations 2 to 3 times those seen in normal individuals (Coburn et al., 1966).

(iii) Chronic lung diseases

Chronic lung diseases such as chronic bronchitis, emphysema and chronic obstructive pulmonary disease (COPD) are characterized by impairment of the lung's ability to transfer O_2 to the bloodstream because diseased regions of the lung are poorly ventilated and blood circulating through these regions will therefore receive less O_2 (so-called ventilation-perfusion mismatch) (West, 1987). Exertional stress often produces a perception of difficulty in breathing, or breathlessness (dyspnea) in these individuals. Although exercise increases ventilatory drive, they have a limited ventilatory capacity with which to respond (Sue et al., 1988). Reduction of blood O_2 delivery capacity due to formation of COHb could exacerbate symptoms and further reduce exercise tolerance in these individuals. Children with severe inflammatory lung diseases (e.g. frequent episodes of asthma) have been shown to have higher concentrations of CO in exhaled breath (2.17 ± .021), and thus presumably higher COHb concentrations, than healthy children (1.01 ± 0.12) (Uasuf et al., 1999). Thus, it might require less exposure to CO for them to reach a target COHb concentration of 2.5% for a given exposure time. The source of this excess CO is due to increased activity of a metabolic protein, heme oxygenase in individuals with asthma. Children with other lung inflammatory problems

(such as cystic fibrosis or possibly infections) might also have increased exhaled CO levels. Using an adaptation of the Coburn equation the average 8 hr ambient concentration required to achieve a COHb level of 2.5% for children with different baseline levels of COHb was calculated. As shown in Figure 1, as baseline COHb concentration increased, the amount of inhaled CO required to raise the blood level to 2.5% was decreased.

(iv) Pregnant women and fetuses

CO induces a strong leftward shift in the O_2Hb saturation curve (Grote et al., 1994). This may be significant for fetuses because the O_2 tension in their arterial blood is low (20 to 30 mm Hg) compared to adult values (100 mm Hg) and because fetal Hb has a higher O_2 affinity than does maternal Hb (Longo, 1976). In pregnant women, O_2 consumption is increased 15 to 25% and hemoglobin concentration may be simultaneously reduced, which can lower the O_2 carrying capacity of their blood (Pernoll et al., 1975) and reduce O_2 delivery to the developing fetus. CO exposure will further reduce O_2 delivery. Fortunately, fetal blood has higher Hb concentrations than does maternal blood (Hellman and Pritchard, 1971). There is, however, little information on the affinity of fetal hemoglobin for CO or its effect on oxygen dissociation in the fetus, and there were no relevant data on human fetuses retrieved after an extensive literature search.

(v) Children

Children have greater activity levels and smaller body masses than adults. Physiologically, children have larger metabolic demands and consequently greater oxygen uptake demands than do adults, on a per unit mass basis. Children should therefore experience higher levels of CO uptake than will adults for the same average exposure concentration. However, since intensity of health effects are likely to be a function of COHb concentration, it is important to consider whether or not the increased CO uptake in children will translate to an elevated COHb. This was addressed, using the Coburn equation (which was used by DHS to estimate the CO levels for adults to achieve 2.5% COHb for 1 hr and 8 hr exposures) to make

similar estimates for children. The estimates provided are for a child with body mass of 35 kg (as compared to a 70 kg adult). The model parameters for an adult breathing at a ventilation rate of 10 LPM were adjusted to match the condition that an 8 hr exposure to 9 ppm CO would increase blood COHb from a baseline level of 0.5% to a level of 2.5% COHb. Child-specific parameters (ventilation rate [V_A], adjusted for body mass and rate of diffusion of CO across the lung boundary) were substituted into the model. The model was then run to estimate a 1 hr exposure level that would result in a 2.5% COHb level in an adult and a child. The resulting calculations are shown in Table 1. The model predicts that a child requires lower ambient exposures to CO to achieve 2.5% COHb than an adult under comparable environmental conditions. There are little data comparing CO uptake or binding between children and adults. The model estimates use the same values for children and adults.

Table 1. Children require lower ambient exposures to CO to reach COHb concentrations of 2.5%. The estimated values use resting ventilation rates of 6 LPM for children and 10 LPM for adults which are scaled to body masses of 35 kg and 70 kg, respectively.

Exposure Duration	Child, Rest (V_A = 6 LPM)	Adult, Rest (V_A = 10 LPM)
	Ambient CO (ppm)	
1 hr Average	26	33.5
8 hr Average	8.4	9.3

A.4. HEALTH EFFECTS OF CO

A.4.1. Population-based studies

(vi) Acute exposures and their effects

Most of the population-based studies in the literature relating to the health effects of CO in humans have been concerned with exposures to combustion and pyrolysis products from sources such as tobacco, fires, motor vehicle exhaust, home appliances fueled with wood (Pierson et al., 1989), gas or kerosene, and small engines. The individuals in these studies are therefore exposed to variable, and usually unmeasured, concentrations of CO and also to high concentrations of other combustion products. Exposures to CO in occupational settings represent another substantial exposure classification, but such exposures are also often accompanied by exposures to other contaminants as well.

Acute CO intoxication most commonly results in neurologic and/or myocardial injury, with approximately 10% of patients displaying delayed neurological sequelae (Thom and Keim, 1989). Parkinsonism, which can be viewed as an outcome of some neuropathological lesions, has been associated with exposures to certain neurotoxins, including CO (Bleeker, 1988). Some of the cases involve firefighters and it is not clear that CO alone is a causal factor. Marius-Nunez (1990) reported a case of an individual who suffered an acute myocardial infarction (shown by ECG and serum enzyme findings) after an acute CO exposure. This case was of interest because the patient's medical profile was negative for coronary heart disease risk factors and because a coronary angiogram performed one week after admission failed to show coronary obstructive lesions. A similar case was reported by Ebisuno et al. (1986) and the circumstances of both cases suggest that contributing factors to the CO-induced reduction in oxygen supply to the myocardium might include induction of coronary artery spasm, inadequate myocardial perfusion, and a direct toxic effect on myocardial mitochondria. CO has a role as a neurotransmitter (Cardell et al,. 1998). Inhaled CO decreases total lung resistance and increases lung diffusing capacity for CO in a dose dependent manner (Akesson et al., 2000).

A.4.2. Chronic exposures

(vii) Cardiovascular effects

Kristensen (1989) examined the relationship between cardiovascular diseases and chronic occupation exposures, and concluded that CO exposure increases the acute risk of cardiovascular disease, at least transiently. Stern et al. (1988) performed a retrospective study of heart disease mortality in matched groups of 5,529 bridge and tunnel officers. The tunnel officers had significantly higher CO exposures than the bridge officers, and also had significantly elevated risks of coronary artery disease (61 deaths observed vs. 45 deaths expected). The risk declined after cessation of exposure, dissipating substantially after 5 years. Penney and Howley (1991) report that CO can enhance atherosclerosis in individuals with elevated serum cholesterol.

(viii) Effects on lung function

Individuals exposed to relatively high concentrations of CO in both indoor and outdoor environments may have lung function decreases. In most cases, however, causality is difficult to establish because, in addition to CO, these individuals were also exposed to high concentrations of other combustion products, many of which are respiratory system irritants.

In the study of tunnel and bridge officers, described earlier, lung functions, forced vital capacity (FVC) and forced expiration volume in 1 s ($FEV_{1.0}$), were slightly reduced in tunnel vs. bridge officers (Evans et al., 1988). Exposures of adults to typical ambient concentrations of CO, both outdoors and indoors, have not been significantly associated with lung function decrements (Lebowitz et al., 1987). Pollutants related to automotive traffic, especially CO and nitrogen oxides, were associated with the prevalence of asthma in middle-school Taiwanese students (Guo et al., 1999; Lin et al., 1999). Physician consultations in London for lower respiratory diseases were significantly correlated with NO_2 and CO levels in children, but not in adults (Hajat et al., 1999). Exposure of children with mild asthma to environmental tobacco smoke (that contains CO and other combustion products) resulted in pulmonary function

decrements, i.e. reduced $FEV_{1.0}$ (Magnusen et al., 1993).

(ix) Effects on pregnancy outcomes

A case-control study of the association between low birthweight infants and maternal CO exposures in approximately 1000 cases in Denver (Alderman et al., 1987) failed to detect a relationship between CO exposure (estimated form fixed-site outdoor monitoring data) during the last 3 months of pregnancy and lower birth weights. Mean CO levels ranged from 0.5 to 3.6 ppm at 8 monitoring locations in metropolitan Denver. The 5^{th} and 95^{th} percentile concentrations at the site with the highest (3.6 ppm) mean were 1.6 and 4.8 ppm, respectively. The odds ratio at the highest concentration site was 1.1 and the 95% confidence interval was 0.8-1.6). This study did not directly account for unmeasured sources of CO exposure, such as smoking, emissions from gas appliances and exposures to vehicular exhaust, which are limitations of the study design. A more extensive study of a cohort of 125,573 children born to women living in the Los Angeles area (1989-1993) found that exposure to ambient concentrations > 5.5 ppm (3 mo average) during the last trimester of pregnancy was associated with a significantly increased risk of low birthweight (odds ratio = 1.22; confidence interval =1.03-1.44) after adjustment for potential confounders (Ritz and Yu, 1999). Fetotoxicity has been demonstrated in laboratory animal studies. Altered brain neurochemical development and growth retardation have been demonstrated in rats exposed to CO *in utero* (Storm and Fechter, 1985; Leichter, 1993).

A.4.3. Controlled human studies

Several clinically based studies have been published which have provided a relatively coherent picture of the effects of CO on the cardiopulmonary system. Some of the key studies cited in the 1991 CO criteria document (EPA, 1991), as well as those published since then, are described below. None of these clinical studies involved children (for practical as well as ethical reasons) but are included in this report because they had a strong influence of the setting of the current CO standards.

(x) Cardiovascular Effects

Individuals with ischemic heart disease have limited ability to compensate for increased myocardial oxygen demands during exercise, hence exercise testing is often used as a means for evaluating the severity of their cardiovascular impairment. Calvert et al. (1987) determined that four useful parameters of ischemia, measurable during exercise testing, were: ST segment depression (at least 1 mV of horizontal or downsloping depression of the ST segment of an electrocardiographic tracing persisting for 70 ms in 3 successive complexes); exercise-induced angina (chest pain during exercise, which is increased with effort and then resolves with rest - some individuals may experience pain in the jaw, neck, or shoulder areas); impaired work capacity (maximum work levels expressed as a percentage of nomographically predicted, normal values (Bruce et al., 1973); and an inadequate blood pressure response to exercise (blood pressure that falls on exercise or fails to rise more than 15 mm Hg at a work level of at least 40% of the predicted norm). These non-invasive parameters, taken in combination, can identify 85 to 90% of people with coronary artery disease (Calvert et al., 1987). Since CO exposure impairs myocardial O_2 delivery, CO exposure would be expected to worsen symptoms of ischemia in individuals with coronary artery disease. Therefore exercise tests of such individuals have been an important means of providing quantitative and dose-related estimates of the potential impact of CO on health.

Sheps et al. (1987) exposed 30 subjects with ischemic heart disease, aged 38 to 75 yr., to CO (100 ppm) or air, during a 3-day, randomized, double-blind protocol, to achieve an average post-exposure COHb concentration of 3.8% on the CO exposure day (COHb on the air exposure day averaged 1.5%). After exposure to either CO or air, subjects performed an exercise stress test. Exercise was continued until anginal pain required cessation of exercise, fatigue precluded further exercise, or blood pressure plateaued or decreased, despite the increase in workload. All of the subjects were non-smokers and had documented evidence of ischemic heart disease.

The authors concluded that there were no clinically significant effects of low-level CO exposures at COHb concentrations of 3.8%.

Adams et al. (1988) subsequently extended the above study to an average post-exposure COHb concentration of 5.9%, during exercise, using an identical protocol and 30 subjects (22 men, 8 women; mean age 58 yrs). The authors concluded that exposures to CO resulting in COHb concentrations of about 6% significantly impaired exercise performance in subjects with ischemic heart disease.

Kleinman et al. (1989) exposed 24 nonsmoking male subjects with stable angina and positive exercise tests to 100 ppm CO or air to achieve an average COHb concentration of 2.9%, during exercise, on the CO exposure day. Subjects ranged in age from 51 to 66 yr., with a mean age of 59 yr. All but one of the subjects had additional confirmation of ischemic heart disease. Subjects performed an incremental exercise test on a cycle ergometer until the point at which they could detect the onset of their typical anginal pain, and then stopped exercising. The time to onset of angina was decreased after CO exposure (5.9%; p = 0.046) relative to air exposure. The duration of angina was longer after CO exposure compared to air exposure (8.3%), but this change was not statistically significant. Oxygen uptake at the angina point was slightly reduced after CO exposure compared to air exposure (2.2%; p 0.04), but the increase in oxygen uptake with increasing workload was similar on both exposure days. A subgroup of 11 subjects who, in addition to angina, exhibited arrhythmias or ST segment depressions during exercise, showed a greater reduction in time to angina after CO exposure, compared to air exposure (10.6%; p 0.016), than did the overall group. The time to significant ST segment depression was significantly reduced for the 8 subjects with this characteristic after CO exposure, compared to air exposure (19.1%; p 0.044). The number of subjects exhibiting exercise-induced ST segment depression identified in this study was small, however those subjects in whom angina preceded

detection of ST segment changes would not have been identified in the protocol used because exercise was stopped at the point of onset of angina.

The results of a multicenter CO exposure study, conducted in three different cities, have been reported by Allred et al. (1989) in which 63 men with documented coronary artery disease underwent exposure to air, 117 ppm CO or 253 ppm CO, on three separate days in a randomized, double-blind protocol, followed by an incremental treadmill exercise test. Average COHb concentrations of 2.2% and 4.3%, during exercise, were achieved on the two CO exposure days (2.0 and 3.9%, respectively, at the end of exercise). All of the subjects had objective evidence of coronary artery disease. On each of the exposure days, the subject performed a symptom-limited treadmill exercise test, was exposed to one of the three test atmospheres (clean air, 117 ppm CO or 253 ppm CO), and then performed a second exercise test at the target COHb concentration (~2% or ~4%). The time to onset of angina was significantly reduced by CO exposure, in a dose-dependent manner (4.2% at ~2% COHb, $p = 0.054$; 7.1% at ~4% COHb, $p = 0.004$). The time to onset of 1 mV ST segment depression was also reduced by CO in a dose-dependent manner (5.1% at 2% COHb, $p = 0.02$; 12.1% at 4% COHb, p 0.0001) compared to the clean air exposure. There was a decrease of approximately 3.9 ± 0.6 percent in time to ST depression for every 1% increase in COHb (p 0.0001). There was a significant correlation between the percent change in the time to onset of angina and the time to onset of ST depression of 1 mV (p 0.0001).

There is some evidence that a level of hypoxia that can result in myocardial ischemia and reversible angina, can also lead to arrhythmias (Kerin et al., 1979; Carboni, 1987; Dahms et al., 1993). Hinderliter et al. (1989) exposed 10 subjects, with ischemic heart disease and no ventricular ectopy at baseline, to air, 100 ppm CO, and 200 ppm CO; COHb concentrations averaged 4% and 6% on the two respective CO exposure days. The exposures were randomized and double-blinded. Following exposure, each subject performed a symptom-

limited supine exercise test; ambulatory electrocardiograms were obtained prior to exposure, during exposure, during exercise, and over a 5-h post-exercise period. The ECG's were analyzed for the frequency and severity of arrhythmias. Eight of the ten subjects demonstrated evidence of ischemia on one or more of the exposure days (angina, 1 mV ST-segment depression, or abnormal ejection fraction response). There were no CO-related increases in the frequency of premature ventricular beats and no multiple arrhythmias occurred. The authors concluded that low-level CO exposure (4 to 6% COHB) was not arrhythmogenic in patients with coronary artery disease and no ventricular ectopy at baseline.

However, researchers from this same team (Sheps et al., 1990), reported on a larger study population (41 subjects) with some evidence of ventricular ectopy, exposed to air, 100 ppm CO, and 200 ppm CO in a similar protocol to that described above. The frequency of single ventricular premature depolarizations (VPD's) per h increased (p 0.03) from 127 ± 28 (mean ± SD) after the air exposure to 168 ± 38 after exposure to achieve a COHb concentration of 6%. During exercise, the frequency of multiple VPD's per h increased approximately 3-fold at 6% COHb, compared to air exposure (p 0.02). No significant differences in these parameters occurred after exposures that achieved COHb concentrations of 4%, compared to air exposures. The subjects who exhibited single VPD's with increased frequency after CO exposure were significantly older than the subjects who had no increased arrhythmias. The subjects who exhibited increased frequencies of multiple VPD's were older, exercised for longer durations, and had higher peak workloads during exercise, than those who did not have complex arrhythmias. Leaf and Kleinman have also reported evidence of effects of CO exposure on cardiac rhythm after relatively low CO exposures (3% COHb) in a small group of volunteers with coronary artery disease that exhibited abnormal rhythms on one or more exercise test (Leaf and Kleinman, 1996).

In all of the above clinical studies of CO-related effects, subjects with coronary artery

disease, were maintained on individualized regimens of medications, some of which might interact with CO-induced responses, increasing the apparent variations in observed responses. Specifically, blockade of beta-adrenergic receptors (Melinyshyn et al., 1988) and alpha-adrenergic receptors (Villeneuve et al., 1986) were shown to modify hemodynamic responses to CO in animal studies. Examination of the potential influence of medications on observed responses to CO could provide additional insights on the possible mechanisms of action of CO in individuals with coronary artery disease.

A general conclusion is that the cardiological effects of CO are best understood as being due to a reduction in oxygen delivery. In Figure 2, data on reduction in time to angina from several of the recent studies are summarized as a function of % oxygen saturation of the blood. The effects increase linearly as % oxygen saturation is reduced (within the experimental limits). Also it is important to note that the studies which were conducted by different laboratories, in different areas and with different subject populations, fall along a common curve (within limits of experimental error).

(xi) Cardiopulmonary effects (lung function and exercise tolerance)

1) Normal individuals

Reduction of O_2 delivery could reduce the ability to perform work in healthy individuals. Studies of the cardiopulmonary effects of CO have demonstrated that maximal oxygen uptake during exercise ($\dot{V}_{O_2}$ max) decreases linearly with increasing COHb concentrations ranging from 2.3% to 35% COHb, in normals. The linear relationship can be expressed as percent decrease in $\dot{V}_{O_2}$ max = 0.91 [%COHb] + 2.2. The specific studies on which these findings are based have been extensively reviewed in the 1979 CO criteria document (U.S. Environmental Protection Agency, 1979), the 1984 addendum to that document (U.S. Environmental Protection Agency, 1984), Horvath (1981) and Shephard (1984). Changes in $\dot{V}_{O_2}$ max are significant because they

represent changes in an individual's maximal aerobic exercise (or work) capacity.

Horvath et al. (1988) exposed 23 subjects (11 male, 12 female) to 0, 50, 100 and 150 ppm CO, at 4 different altitudes (55, 1524, 2134 and 3048 m). Following exposure, each subject performed an incremental exercise test. COHb concentrations ranged from 0.5 ± 0.2 to 5.6 ± 0.4 percent of saturation after sea level exposures. The study showed a significant effect of increased altitude on decreased work performance and $\dot{V}_{O_2}$ max. The female subjects appeared to be more resistant to the hypoxic effects of altitude than the male subjects. The rate of CO uptake (that is formation of COHb) decreased with increasing altitude, in part due to the reduced driving pressure of CO at altitude. While this might be a mechanism by which CO could directly affect cardiac myoglobin, evidence for direct cardiotoxicity of CO is still lacking. Horvath and Bedi (Horvath, S.M. and Bedi, J.F., 1989) have demonstrated that longer term, low level (9 ppm for 8 h) exposures at 2134 m results in lower COHb concentrations than the same exposure at 55 m, again suggesting slower CO uptake during altitude exposure. McGrath (1989), however, has reported that endogenous CO production is increased in rats chronically maintained at high altitudes (1000 m to 6000m), suggesting that high altitude residents have higher initial COHb concentrations and might therefore achieve 2% or greater COHb levels (the COHb level associated with the CO NAAQS) more quickly than sea level residents. It has been reported that unacclimated workers exposed to about 25 ppm CO at an altitude of 2.3 km above sea level exhibited significantly increased symptoms of headache, vertigo, fatigue, weakness, memory impairment, insomnia and heart palpitations compared to local residents (Song, 1993). The subjects in these human clinical studies of exercise tolerance have been relatively young and all were in good health. There is not sufficient information available to determine if relationships between CO exposure, altitude and COHb concentrations would be similar for individuals with coronary artery disease, chronic lung diseases, anemia's, or in pregnant women.

Kleinman and associates have demonstrated that hypoxia due to high altitude and CO exposure may cause additive effects on exercise tolerance, hemodynamic changes and cardiologic parameters (Kleinman et al., 1998). The subjects in this study were older men with confirmed coronary artery disease.

2) Individuals with chronic obstructive pulmonary disease (COPD)

Individuals with COPD usually have limited exercise tolerance because they have low ventilatory capacity, which can result in desaturation of arterial blood and hypoxemia (a relative deficiency of O_2 in the blood) and hypoxia (a relative deficiency of O_2 in some tissue) during exercise. Exercise performance in such individuals can be improved by providing supplemental O_2 (Lane et al., 1987). Reduced O_2 carrying capacity of blood due to formation of COHb could exacerbate this limitation, hence individuals with COPD could represent a potentially sensitive group. Aronow et al. (1977) exposed 10 men, aged 53 to 67 y to 100 ppm CO for 1 h, achieving increases in COHb from baseline concentrations of 1.4% to post-exposure concentrations of 4.1%. Mean exercise time was reduced by 33%. Calverley et al. (1981) exposed 6 smokers (who stopped smoking 12 h prior to testing) and 9 nonsmokers to 200 ppm CO for 20 to 30 min (increasing COHb concentrations to between 8 and 12% COHb above baseline COHb), and measured the distance each subject walked in a 12 min period. Significant decreases in walking distance were only seen in individuals with 12.3% COHb or greater. Some individuals with severe COPD, but without clinically apparent coronary artery disease, exhibit exercise-related cardiac arrhythmias. Cheong et al. (1990) reported that these arrhythmias were associated with arrhythmias at rest but were not related to the severity of pulmonary disease, O_2Hb desaturation or ECG evidence of chronic lung disease. The Sheps et al. (1990) studies of exercise-related arrhythmias in CO-exposed subjects with coronary artery disease suggest that COPD subjects might be important to study, as well. Overall, the information available on individuals with COPD

are consistent with the hypothesis that they represent a population potentially at risk of CO-related health effects during sub-maximal exercise, as may occur during normal daily activities. The available data are however based on population group sizes that are too small and too diverse with respect to disease characteristics to draw firm conclusions.

(xii) Neurotoxicological and behavioral effects

The neurotoxic effects of relatively high level acute CO exposures have been well documented. Subtle neurotoxic effects associated with lower-level CO exposures may be underreported or not associated with CO exposure because the symptoms, which resemble those of a flu-like viral illness, may be misdiagnosed (Ilano and Raffin, 1990). Population based studies on the potential neurotoxicological and behavioral effects of chronic CO exposure at ambient concentrations have not been reported. However, clinical studies of CO-related sensory effects have evaluated several different parameters, under controlled laboratory conditions. A recent study by Hudnell and Benignus (1989) demonstrated, in a double-blind study, that visual function in healthy, young adult males, as defined by measurements of contrast threshold, luminance threshold, and time of cone/rod break, was not affected by COHb concentrations maintained at 17% for over 2 h. Von Restorff and Hebisch (1988) reported no changes in time to dark adaptation and sensitivity after adaptation, at COHb concentrations ranging from 9% to 17%. A large number of studies have investigated the effects of CO on several other behavioral parameters, however effects in general are only seen at COHb concentrations above 5%, and there are inconsistencies between the study results. Of the studies, other than those discussed above, published in 1984 and later, Bunnell and Horvath (1988) showed interactive effects of exercise and CO exposure (>7% COHb) on cognitive tasks, Insogna and Warren (1984) demonstrated a significant decrement in video game performance (targets tracked and destroyed) at 2.1 to 4.2% COHb. (Both of these were single blind studies with relatively small numbers of subjects - 15 and 9, respectively). Although many earlier studies had demonstrated significant changes in brain electrical activity, Harbin et al. (1988) showed no changes in visually

evoked response potentials in young (23 yr) and older (69 yr) subjects at 5.3% COHb. In general, neurotoxicity at COHb levels near 5% has not been convincingly demonstrated in normal healthy adults (Benignus et al., 1987).

(xiii) Fetal developmental and perinatal effects

There are both theoretical reasons and supporting experimental data which indicate that the fetus may be more susceptible to the effects of CO than the mother. Fetal Hb has greater affinities for CO and O_2 than does maternal Hb. The partial pressure of O_2 in fetal blood is about 20 to 30% of that in maternal blood, because of the greater O_2 affinity of fetal Hb. In addition, COHb shifts the O_2Hb dissociation curve to the left in maternal blood, reducing the transfer of O_2 across the placenta from maternal to fetal circulation. As in adults, the nervous and cardiovascular systems of the fetus are the most sensitive to the effects of CO. For humans, information is available for women who smoked during pregnancy or were acutely exposed to CO, however most of the available reports do not characterize the relevant CO exposure levels, and can not, in general rule out toxic effects of co-contaminants. Acute CO exposure plays a role in fetal death (Caravati et al., 1988) and environmental exposures, as well as maternal smoking, has been linked to sudden infant death syndrome (SIDS) (Hoppenbrouwers et al., 1981). Neonatal mortality and low birthweights are more prevalent in children born in high altitude regions (Lichty et al., 1957; Grahn and Kratchman, 1963), suggesting a relation to high altitude hypoxia, and further suggesting that these effects seen in children born to women who smoke are possibly a result of CO-induced hypoxia. The study of Ritz and Yu (1999) described earlier support the hypothesis that elevated CO during the last trimester of pregnancy increases the risk of low birthweight.

High level maternal CO exposures may have significant neurotoxicological consequences for the fetus, but available data come from animal studies. Significant neurotoxic effects in prenatally exposed rats included disruption of neuronal proliferation and possible disruption of markers of neurochemical transmission (Fechter, 1987). Immune system changes

have also been noted in rats exposed to CO prenatally (Giustino et al., 1993).

(xiv) CO as a risk factor in cardiovascular disease development

Evidence from population-based studies indicates that workers exposed to CO in combination with other combustion products from automobile exhaust (Stern et al., 1988) and other workers, as well (Kristensen, 1989) have increased risk of development of atherosclerotic heart disease. Also, individuals hospitalized for myocardial infarction frequently exhibit higher COHb concentrations than individuals hospitalized for other reasons (Leikin and Vogel, 1986). Central to the development of atheromatous plaques is the deposition and retention of fibrinogen and lipids within the arterial wall. It is known that cigarette smoke increases the permeability of the arterial wall to fibrinogen. Allen et al. (1989) demonstrated in a canine model that both CO and nicotine in cigarette smoke might produce an atherogenic effect, but that they act via different mechanisms. CO increases arterial wall permeability and nicotine reduces clearance of deposited fibrinogen. Activation and dysfunction of blood platelets is also thought to be important in atherogenesis (Ross, 1986) and in cardiac related sudden deaths due to the platelets role in the initiation of thrombosis. Nowak et al. (1987) reported biochemical evidence that cigarette smoking induced both platelet and vascular dysfunctions in apparently healthy individuals. Platelet dysfunction may also be a contributory cause of thrombosis during pregnancy and may increase fetal mortality and morbidity among women who smoke (Davis et al., 1987). Abnormalities in platelet aggregation after CO exposure have been seen in animal models (Kalmaz et al., 1980) and may be linked to guanylate cyclase activation (Brune and Ullrich, 1987). Davis et al. (1989) exposed 10 healthy nonsmokers passively to cigarette smoke (in hospital corridors) resulting in a small increase in COHb concentration, from 0.9% ± 0.3% to 1.3 ± 0.6%, before and after passive exposure, respectively. They showed evidence of changes in platelet aggregation and endothelial cell damage. The changes in endothelial cell counts (pre- to post-exposure) were significantly correlated to changes in COHb concentrations from before

to after exposure, but plasma nicotine levels were not. The contribution of carbon monoxide relative to other components of tobacco smoke in causing platelet dysfunction is not established.

A.5. SUMMARY AND CONCLUSIONS

The current CO ambient air standards are designed to protect susceptible individuals from exposures that would result in COHb concentrations of 2.5% and above. Occupational standards are designed to protect workers from concentrations of 5% COHb (U.S. Department of Health, Education and Welfare, 1972). Studies of individuals with coronary artery disease, and residents of New York, NY, Denver, CO, Washington, DC and Los Angeles, CA suggest that susceptible individuals frequently exceed 2% COHb in cities that frequently exceed NAAQS or California standards. Control of exposures is difficult because the sources of CO are widespread, the distribution of ambient CO is very non-uniform, and because emissions from unregulated sources, especially indoors, probably contribute substantially to individual CO doses.

The current state and federal standards were based largely on data from susceptible adult populations. This review suggests that there are specific concerns for children.

Convincing documentation for effects of CO on children and other potentially susceptible individuals at ambient exposure levels is becoming available. The most extensive body of evidence of CO effects on pregnant women, fetuses and neonates comes from the literature on smoking and from acute, high-level accidental CO exposures. In most cases actual CO exposures are poorly, if at all, documented and the contribution of co-pollutants to the observed effects cannot be assessed. Animal studies demonstrating developmental changes and associations between environmental CO and SIDS indicate that risks to pregnant women, fetuses and neonates may be important. The recent human epidemiology study by Ritz and Yu (1999), which was discussed earlier, show significant low birthweights to children born of women exposed at CO levels below the current standard (5.5 ppm and above).

Differences in body mass, activity levels and CO uptake may make children more at risk than adults. There are associations between CO exposure and asthma prevalence, but these could be confounded because in most instances CO is covariable with other products of combustion. One might also hypothesize that children with asthma or other inflammatory lung diseases could require lower exposures to CO to reach target concentrations of 2.5% COHb because their baseline COHb levels might be elevated.

It would seem from this review that both occupational and ambient standards are placed at the limits at which significant effects are seen, albeit in sensitive adults. The available information on the role of CO in the development of effects on children, including possible increased severity of asthma, low birthweight and a possible role in infant mortality suggests that children may be an import susceptible population. There are however several important gaps in our basic knowledge of the physiology and effects of disease states on baseline COHb in children and on the affinity of fetal and children's hemoglobin for CO. In addition, new, well-controlled population studies, with accurate estimates of CO exposure history are needed. Careful clinical studies with children to determine uptake and retention of CO and how these change with age would be extremely helpful.

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Figure 1. Increasing baseline COHb will reduce the time-weighted average CO concentration required to reach 2.5% COHb after a given exposure.

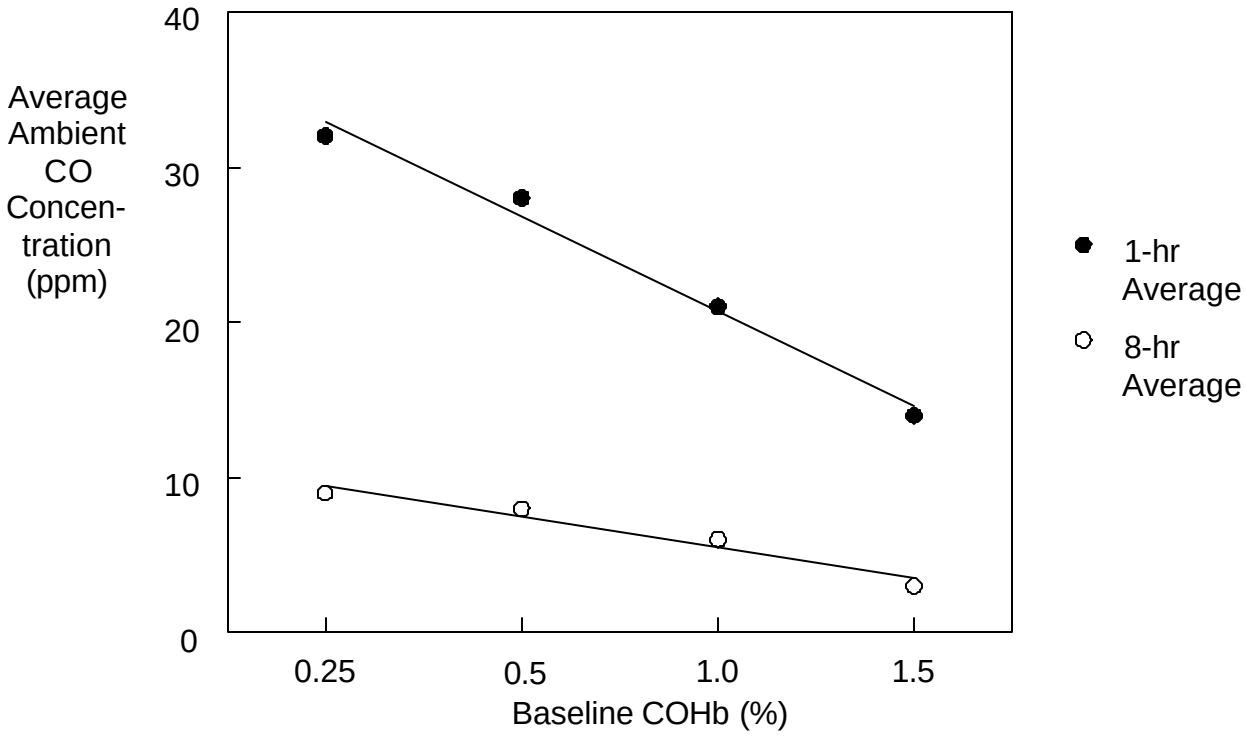
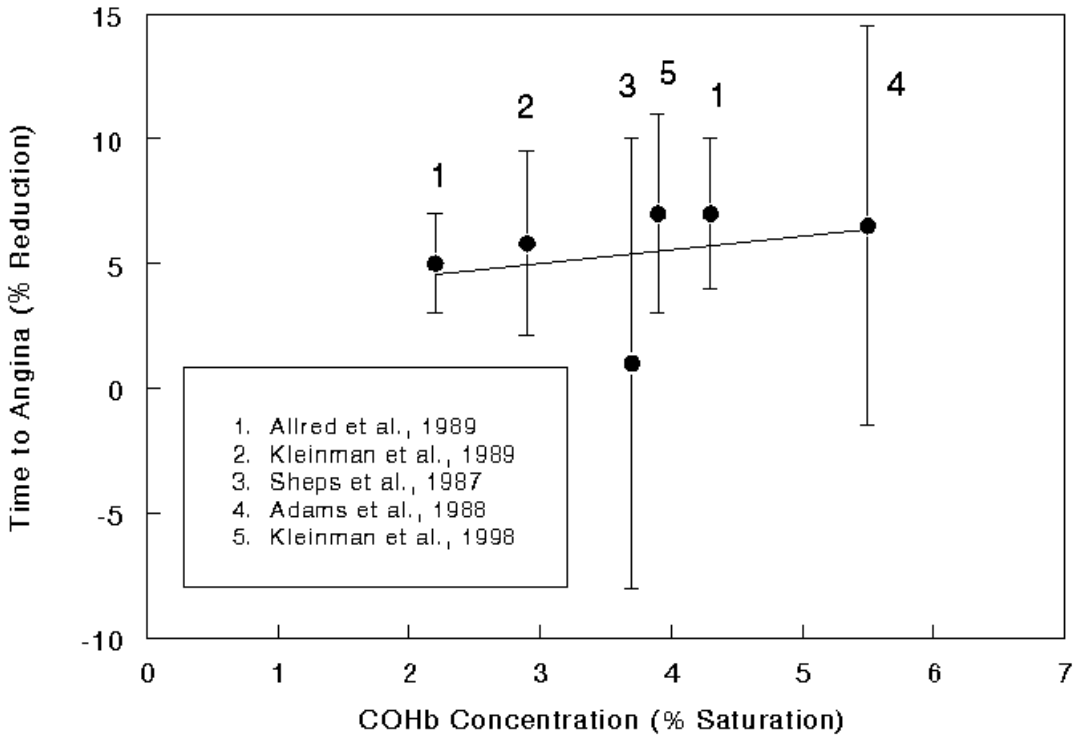


Figure 2. Reduction in Time to Angina (TTA) Following CO Exposure in Subjects with Coronary Artery Disease. Linear regression shows that TTA is reduced in a dose-dependent Manner. Values shown are mean ± SE.



CARBON MONOXIDE:
EVALUATION OF CURRENT CALIFORNIA AIR QUALITY STANDARDS WITH RESPECT TO PROTECTION OF CHILDREN

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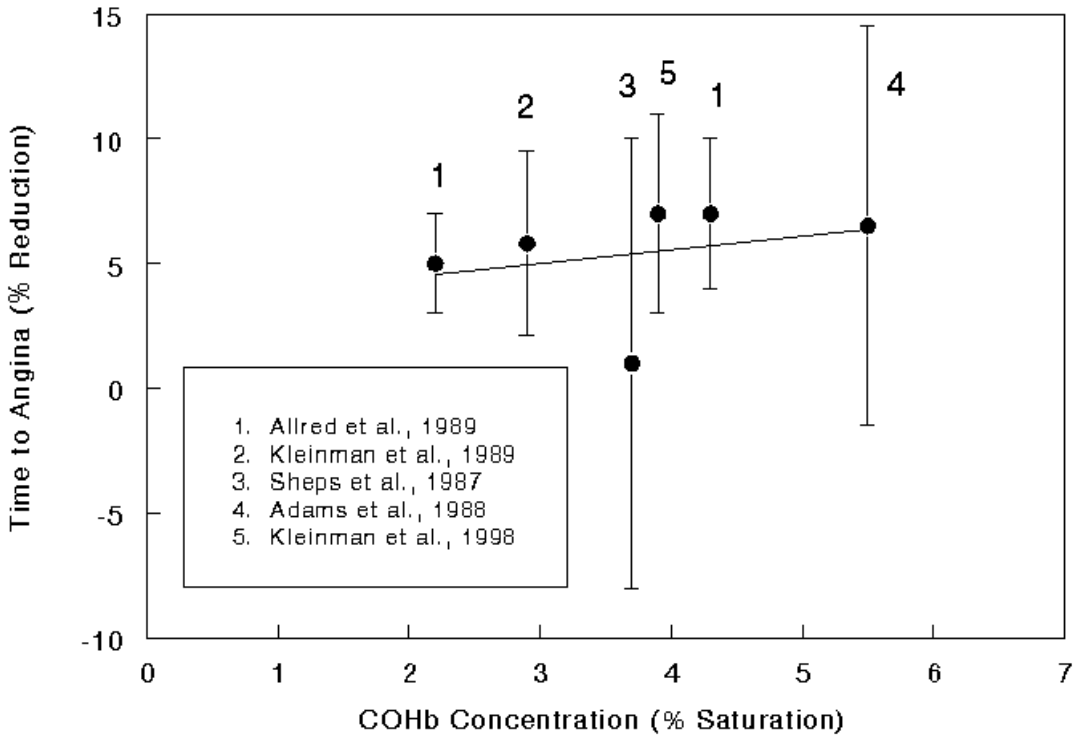
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Figure 2. Reduction in Time to Angina (TTA) Following CO Exposure in Subjects with Coronary Artery Disease. Linear regression shows that TTA is reduced in a dose-dependent Manner. Values shown are mean ± SE.



HYDROGEN SULFIDE:
EVALUATION OF CURRENT CALIFORNIA AIR QUALITY STANDARDS WITH RESPECT TO PROTECTION OF CHILDREN

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September 1, 2000

A. Extended abstract

The current California Ambient Air Quality Standard (CAAQS) for hydrogen sulfide is 0.03 ppm (30 ppb, 42 $\mu g/m^3$) for one hour. The standard was adopted in 1969 and was based on the geometric mean odor threshold measured in adults. The purpose of the standard was to decrease odor annoyance. The standard was reviewed in 1980 and 1984 (CARB, 1984), and was not changed since no new relevant information had emerged. The U.S. EPA presently does not classify hydrogen sulfide as either a criteria air pollutant or a Hazardous Air Pollutant. However, several countries have short-term (usually 30 minute) standards for hydrogen sulfide, as well as long-term (24 hour) standards.

This report focuses on key studies in humans and animals bearing on the health-protectiveness of the CAAQS for hydrogen sulfide. It also includes a discussion of whether significant adverse health effects would reasonably be expected to occur, especially among infants and children, at exposure concentrations below the CAAQS of 30 ppb, based on the findings of published studies. Additional research on odor sensitivity in infants, children, and adults would be useful in evaluating the standard. This would include: (1) testing of the odor threshold for H_2S using the most current methodology among groups of healthy persons of both sexes in different age ranges; (2) odor testing of hydrogen sulfide in adolescents or younger children to determine their odor threshold for H_2S; (3) the identification of children hypersensitive to the odor of hydrogen sulfide; and (4) physiologic testing of anosmic (either specifically anosmic to H_2S or totally anosmic) children at the CAAQS to determine if adverse physiological symptoms occur in the absence of odor detection.

B. Background

The Mulford-Carrell Air Resources Act of 1967 directed the Air Resources Board to divide California into Air Basins and to adopt ambient air quality standards for each basin (Health and Safety Code (H&SC) Section 39606). The existing California state-wide ambient air quality standard (CAAQS) for hydrogen sulfide of 0.03 ppm (30 ppb, 42 $\mu g/m^3$), averaged over a period of 1 hour and not to be equaled or exceeded, protects against nuisance odor ("rotten egg smell") for the general public. The standard was adopted in 1969 and was based on rounding of the geometric mean odor threshold of 0.029 ppm (range = 0.012 – 0.069 ppm; geometric SD = 0.005 ppm) measured in adults (California State Department of Public Health, 1969). The standard was reviewed by the Department of Health Services in 1980 and 1984, and was not changed since no new relevant information had emerged. OEHHA (1999) formally adopted 30 ppb as the acute Reference Exposure Level (REL) for use in evaluating peak off-site concentrations from industrial facilities subject to requirements in H&SC Section 44300 *et seq*. OEHHA (2000) adopted a level of 8 ppb (10 $\mu g/m^3$) as the chronic Reference Exposure Level (cREL) for use in evaluating long term emissions from Hot Spots facilities. The cREL was based on a study demonstrating nasal histological changes in mice.

At the federal level, U.S. EPA does not currently classify hydrogen sulfide as either a criteria air pollutant or a Hazardous Air Pollutant (HAP). U.S. EPA has developed a (chronic) Reference Concentration (RfC) of 0.001 mg/m^3 (1 $\mu g/m^3$) for hydrogen sulfide (USEPA, 1999). The RfC is an estimate (with uncertainty spanning perhaps an order of magnitude) of a daily inhalation exposure of the human population (including sensitive subgroups) that is likely to be without an appreciable risk of deleterious effects during a lifetime.

There are no international standards for H_2S. Many countries have "short-term" (usually 30 minute) standards, which range from 6 to 210 ppb (WHO, 1981). The World Health Organization (WHO) recommends that, in order to avoid substantial complaints about odor

annoyance among the exposed population, hydrogen sulfide concentrations should not be allowed to exceed 0.005 ppm (5 ppb; 7 $\mu g/m^3$), with a 30-minute averaging time (WHO, 1981; National Research Council, 1979; Lindvall, 1970). A very short-lived, peak concentration could also be annoying. Rule 2 of Regulation 9 of the Bay Area Air Quality Management District (BAAQMD) specifies that ambient ground level H_2S concentrations may not exceed 60 ppb averaged over 3 consecutive minutes. Regulating at averaging times less than 30 – 60 minutes may be difficult. Many countries have "long-term" (24 hour) standards (WHO, 1981).

NRC (1979), WHO (1981), Beauchamp *et al*. (1984), Reiffenstein *et al*. (1992), and ATSDR (1999) have published reviews of the health effects of hydrogen sulfide.

C. Principal sources/Exposure assessment

Hydrogen sulfide (H_2S) is used as a reagent and as an intermediate in the preparation of other reduced sulfur compounds (HSDB, 1999). It is also a by-product of desulfurization processes in the oil and gas industries and rayon production, sewage treatment, and leather tanning (Ammann, 1986). Geothermal power plants, petroleum production and refining, and sewer gas are specific sources of hydrogen sulfide in California. The annual statewide industrial emissions from facilities reporting under the Air Toxics Hot Spots Information and Assessment Act in California (H&SC Sec. 44300 *et seq*.), based on the most recent inventory, were estimated to be 5,688,172 pounds of hydrogen sulfide (CARB, 1999).

A specific concern in California has been schools located near workplaces emitting toxic substances. For example, the Hillcrest Elementary School in Rodeo (Contra Costa County; part of the BAAQMD) is adjacent to an oil refinery which, on occasion, has emitted enough malodorous sulfur compounds (including H_2S) for the school to close its doors and for the teachers and children to "shelter-in-place." Thus the school district has planned to relocate the school (West County Times, November 23, 1999). These compounds have also affected other schools in the area.

Hydrogen sulfide is produced endogenously in mammalian tissues from L-cysteine, mainly by two pyridoxal-5'-phosphate-dependent enzymes, cystathionine beta-synthetase and cystathionine gamma-lyase (Hosoki *et al*., 1997). Abe and Kimura (1996) suggested that hydrogen sulfide may be an endogenous neuromodulator in the hippocampus based on the high level of cystathionine beta-synthetase in the hippocampus and on experimental effects of activators and inhibitors of the enzyme.

D. Key studies of acute and chronic health impacts

D.1. Toxicity to Humans

D.1.1. Adults. Hydrogen sulfide is an extremely hazardous gas (ACGIH, 1991). Exposure to high concentrations of hydrogen sulfide is reported to be the most common cause of sudden death in the workplace (NIOSH, 1977). Estimates of the mortality resulting from acute hydrogen sulfide intoxication include 2.8% (Arnold *et al*., 1985) and 6% (WHO, 1981). While severe intoxication is especially of concern when exposure occurs in confined spaces, an accidental release of hydrogen sulfide into the ambient air surrounding industrial facilities can cause very serious effects. As a result of an accidental release of hydrogen sulfide due to a malfunctioning flare at an oilfield at Poza Rica, Mexico in 1950, 320 people were hospitalized and 22 died (WHO, 1981).

Most information on H_2S toxicity comes from studies that used levels of H_2S orders of magnitude above the standard of 0.03 ppm. Hazardtext (1994) reported an inhalation LC_{Lo} of 600 and 800 ppm (840 and 1,120 mg/m^3) for 30 and 5 minutes, respectively. A lethal exposure was documented for a worker exposed to approximately 600 ppm H_2S for 5 to 15 minutes (Simson and Simpson, 1971). Inhalation of 1,000 ppm (1,400 mg/m^3) is reported to cause immediate respiratory arrest (ACGIH, 1991). Concentrations greater than 200 ppm (280 mg/m^3) H_2S are reported to cause direct irritant effects on exposed surfaces and can cause pulmonary edema following longer exposures (Spiers and Finnegan, 1986). The mechanism of H_2S

toxicity, cellular hypoxia caused by inhibition of cytochrome oxidase, is similar to that for cyanide. Toxicity can be treated by induction of methemoglobin or by therapy with hyperbaric oxygen (Elovaara *et al*., 1978; Hsu *et al*., 1987).

At concentrations exceeding 50 ppm (70 mg/m³) H_2S, olfactory fatigue prevents detection of H_2S odor. Exposure to 100-150 ppm (140-210 mg/m³) for several hours causes local irritation (Haggard, 1925). Exposure to 50 ppm for 1 hour causes conjunctivitis with ocular pain, lacrimation, and photophobia; this can progress to keratoconjunctivitis and vesiculation of the corneal epithelium (ACGIH, 1991).

Bhambhani and Singh (1985) reported that exposure of 42 individuals to 2.5 to 5 ppm (3.5 to 7 mg/m³) H_2S caused coughing and throat irritation after 15 minutes. Bhambhani and Singh (1991) showed that 16 healthy adult male subjects (25.2±5.5 years old) exposed to 5 ppm (7 mg/m³) H_2S under conditions of moderate exercise exhibited impaired lactate and oxygen uptake in the blood. Subsequently Bhambani *et al*. (1994) compared the effects of inhaling 5 ppm H_2S on physiological and hematological responses during exercise. Subjects were 13 men (mean±SD for age, height, and weight = 24.7±4.6 y, 173±6.6 cm, and 73.1±8.1 kg, respectively) and 12 women (mean±SD = 22.0±2.1 y, 165±8.2 cm, and 63.4±8.6 kg, respectively). Subjects completed two 30-minute exercise tests on a cycle ergometer at 50% of their predetermined maximal aerobic power, while breathing either air or 5 ppm H_2S. There were no significant differences between the two exposures for metabolic (oxygen uptake, carbon dioxide production, respiratory exchange ratio), cardiovascular (heart rate, blood pressure, rate pressure product), arterial blood (oxygen and carbon dioxide tensions, pH), and perceptual (rating of perceived exertion) responses. No one reported adverse health effects following H_2S exposure. The authors believe that healthy adults can safely perform moderate intensity work in environments containing 5 ppm H_2S.

Bhambhani *et al*. (1996) examined the acute effects of "oral" inhalation of 10-ppm H_2S, the occupational exposure limit, on lung physiology as measured by pulmonary function in nine men and ten women. The volunteers inhaled medical air or 10 ppm H_2S through the mouth for 15 minutes each during cycle exercise at 50% of their maximal aerobic power. Routine pulmonary function tests (FVC, FEV_1, FEV_1/FVC, PEFR, maximal ventilation volume, and DL_{CO}) were administered at rest and immediately after the two exposure conditions. There were no significant changes in any of the variables derived from the flow volume loop, maximum ventilation volume, and diffusion capacity of the lung for carbon monoxide (DL_{CO}) in both genders. No subject experienced any sign or symptom as a result of H_2S. The authors concluded that inhalation of 10 ppm H_2S through the mouth at an elevated metabolic and ventilation rate does not significantly alter pulmonary function in healthy people.

Jappinen *et al*. (1990) exposed ten adult asthmatic volunteers to 2 ppm H_2S for 30 minutes and tested pulmonary function. All subjects reported detecting "very unpleasant" odor but "rapidly became accustomed to it." Three subjects reported headache following exposure. No significant changes in mean FVC or FEV_1 were reported. Although individual values for specific airway resistance (SR_{aw}) were not reported, the difference following exposure ranged from –5.95% to +137.78%. The decrease in specific airway conductance, SG_{aw}, ranged from –57.7% to +28.9%. The increase in mean SR_{aw} and the decrease in mean SG_{aw} were not statistically significant for the entire group. However, markedly (>30%) increased airway resistance and decreased airway conductance were noted in two of the ten asthmatic subjects at 2 ppm, which indicated bronchial obstruction and may be clinically important. Two ppm is 67 times the CAAQS of 0.03 ppm.

Hydrogen sulfide is noted for its strong and offensive odor. The existing CAAQS of 0.03 ppm (30 ppb, 42 $\mu g/m^3$) for 1 hour is based on rounding the geometric mean odor detection threshold of 0.029 ppm (range = 0.012 – 0.069 ppm; GSD = 0.005 ppm). The threshold was

determined for a panel of 16 presumably healthy adults (California State Department of Public Health, 1969). No information on the sex or age of the panel members has been located. Amoore (1985) reviewed 26 studies, published between 1848 and 1979, all of which reported average odor detection thresholds for H_2S. The 26 studies seem to be mainly controlled exposures and used various measurement methods. They included (1) at least two studies using only one subject, (2) a study of a panel of 35 people testing odors in natural gas in Southern California, and (3) another study of 852 untrained young adults (age range = 17.5 – 22.4 years) tested at county and state fairs in the Northwest. The average odor detection threshold in the 26 studies ranged from 0.00007 to 1.4 ppm H_2S. The geometric mean of the 26 studies was 0.008 ppm (8 ppb), approximately one-fourth the value determined by the Department of Public Health and lower than the lowest individual threshold of 12 ppb measured in the California panel. Surprisingly the Department of Public Health panel study was not one of the 26 studies used by Amoore and was not even mentioned in his 1985 report to the ARB.

Venstrom and Amoore (1968) reported that, in general, olfactory sensitivities decrease by a factor of 2 for each 22 years of age above age 20. The conclusion was based on a study of 18 odorants in 97 government laboratory workers, ages 20 through 70. Hydrogen sulfide was not tested. The geometric mean odor threshold of 8 ppb for H_2S from the 26 studies is based on an average age of 40 (possibly assumed to be the age of an average adult). Amoore (1985) estimated that an 18-year-old person would have a threshold of 4 ppb H_2S, while a 62-year-old person was predicted to have a threshold of 16 ppb. Amoore also stated that there was no noticeable trend of odor sensitivity between young adults and children down to 5 years but did not present specific data to support the statement.

Concentrations, which substantially exceed the odor threshold for, result in the annoying and discomforting physiological symptoms of headache or nausea (Amoore, 1985; Reynolds and Kauper 1984). The perceived intensity of the odor of H_2S depends on the longevity of the concentration, and the intensity increases 20% for each doubling of the concentration (Amoore,

1985). Several studies have been conducted to establish the ratio of discomforting annoyance threshold to detection threshold for unpleasant odors (Winkler, 1975; Winneke and Kastka, 1977; Hellman and Small, 1974; Adams *et al.,* 1968; and NCASI, 1971). The geometric mean for these studies is 5; therefore an unpleasant odor should result in annoying discomfort when it reaches an average concentration of 5 times its detection threshold. (Two studies that tested only H_2S had a geometric mean of 4.) Applying the 5-fold multiplier to the mean detectable level of 8 ppb results in a mean annoyance threshold of 40 ppb. Amoore (1985) estimates that at 30 ppb, the CAAQS, H_2S would be detectable by 83% of the population and would be discomforting to 40% of the population (Table 1). These "theoretical" estimates have been substantiated by odor complaints and reports of nausea and headache (Reynolds and Kauper 1984) at 30 ppb H_2S exposures from geyser emissions.

In order to avoid substantial complaints about odor annoyance among the exposed population, the World Health Organization (WHO) recommends that hydrogen sulfide concentrations should not exceed 0.005 ppm (5 ppb; 7 $\mu g/m^3$), with a 30-minute averaging time (WHO, 1981; National Research Council, 1979; Lindvall, 1970). The WHO task group believed that 5 ppb averaged over 30 minutes "should not produce odour nuisance in most situations."

Table 1. Predicted effects of exposure to ambient H_2S. (Adapted from Amoore, 1985)

H_2S (ppb)	% able to detect odor[a]	Perceived odor intensity[b] (ratio)	Median odor units[c]	% annoyed by odor[d]
200	99	2.31	25	88
100	96	1.93	12	75
50	91	1.61	6.2	56
40	88	1.52	5.0	50
35	87	1.47	4.4	47
30 (CAAQS)	83	1.41	3.7	40
25	80	1.34	3.1	37
20	74	1.27	2.5	31
15	69	1.18	1.9	22
10	56	1.06	1.2	17
8	50	1.00	1.00	11
6	42	0.93	0.75	8
4	30	0.83	0.50	5
2	14	0.70	0.25	2
1	6	0.58	0.12	1
0.5	2	0.49	0.06	0

[a]Based on mean odor detection threshold of 8.0 ppb and SD±2.0 binary steps
[b] Based on intensity exponent of 0.26 (Lindvall, 1974).
[c]H_2S concentration divided by mean odor detection threshold of 8 ppb.
[d] Based on assumption that mean annoyance threshold is 5x the mean odor detection threshold, and SD±2.0 binary steps.

Kilburn and Warshaw (1995) investigated whether people exposed to sulfide gases, including H_2S, as a result of working at or living downwind from the processing of "sour" crude oil demonstrated persistent neurobehavioral dysfunction. They studied 13 former workers and 22 neighbors of a California coastal oil refinery who complained of headaches, nausea, vomiting, depression, personality changes, nosebleeds, and breathing difficulties. Neurobehavioral functions and a profile of mood states were compared to 32 controls matched for age and educational level. The exposed subjects' mean values were statistically significantly different (abnormal) compared to controls for several tests (two-choice reaction time; balance (as speed of sway); color discrimination; digit symbol; trail-making A and B; immediate recall of a story). Their profile of mood states (POMS) scores were much higher than those of controls. Test scores for anger, confusion, depression, tension-anxiety, and fatigue were significantly

elevated and nearly identical in both exposed residents and former workers, while the scores for controls equaled normal values from other published studies. Visual recall was significantly impaired in neighbors, but not in the former workers. Limited off-site air monitoring (one week) in the neighborhood found average levels of 10 ppb H_2S (with peaks of 100 ppb), 4 ppb dimethylsulfide, and 2 ppb mercaptans. On-site levels were much higher. The authors concluded that neurophysiological abnormalities were associated with exposure to reduced sulfur gases, including H_2S from crude oil desulfurization.

D.1.2. Children. In a case report Gaitonde *et al*. (1987) described subacute encephalopathy, ataxia, and choreoathetoid (jerky, involuntary) responses in a 20-month-old child with long term (approximately one year) exposure to hydrogen sulfide from a coal mine. Levels of up to at least 0.6 ppm (600 ppb) were measured and levels were possibly higher before measurements started. The abnormalities resolved after the emission source ceased operation.

As part of the South Karelia Air Pollution Study in Finland (Jaakkola *et al*., 1990), Marttila *et al*. (1994) assessed the role of long-term exposure to ambient air malodorous sulfur compounds released from pulp mills as a determinant of eye and respiratory symptoms and headache in children. The parents of 134 children living in severely polluted (n = 42), moderately polluted (n = 62), and rural, non-polluted (n = 30) communities responded to a cross-sectional questionnaire (response rate = 83%). In the severely polluted area, the annual mean concentrations of hydrogen sulfide and methyl mercaptan (H_3CSH) were estimated to be 8 $\mu g/m^3$ (6 ppb) and 2 - 5 $\mu g/m^3$ (1.4 – 3.6 ppb), respectively. The highest daily average concentrations were 100 $\mu g/m^3$ (71 ppb) and 50 $\mu g/m^3$ (36 ppb), respectively. The adjusted odds ratios (OR) for symptoms experienced during the previous 4 weeks and 12 months in the severely versus the non-polluted community were estimated in logistic regression analysis controlling for age and gender. The risks of nasal symptoms, cough, eye symptoms, and

headache were increased in the severely polluted community, but did not reach statistical significance (Table 2). In addition, OEHHA staff noted that the highest percentages of children with symptoms were in the moderately polluted community, not in the severely polluted community. The authors concluded that exposure to malodorous sulfur compounds may affect the health of children. The odor threshold for methyl mercaptan of 1.6 ppb (Amoore and Hautala, 1983) indicates that it also likely contributed to the odor and probably the symptoms.

Table 2. Symptoms Reported in Marttila *et al*. (1994)

Symptom	*Time*	*Odds Ratio*	*95% CI*	*Time*	*Odds ratio*	*95%CI*
nasal symptoms	4 weeks	1.40	0.59-3.31	12 months	2.47	0.93-6.53
cough	4 weeks	1.83	0.75-4.45	12 months	2.28	0.95-5.47
eye symptoms	NR	NR	NR	12 months	1.15	0.43-3.05
headache	NR	1.02	0.36-2.94	12 months	1.77	0.69-4.54

NR = not reported

Studies of controlled exposures in children to study H_2S odor detection have not been located. A recent report studying children concluded that children aged 8 to 14 years have equivalent odor sensitivity to young adults (Cain *et al*., 1995), although children lack knowledge to identify specific odors by name. Koelega (1994) found that prepubescent children (58 nine-year-olds) were inferior in their detection of 4 of 5 odors compared to 15-year-olds (n = 58) and 20-year-olds (n = 112). Schmidt and Beauchamp (1988) have even tested 3-year-olds (n = 16) for sensitivity to noxious chemicals, such as butyric acid and pyridine.

In March-April 1983, 949 cases (including 727 in adolescent females) of acute non-fatal illness consisting of headache, dizziness, blurred vision, abdominal pain, myalgia, and fainting occurred at schools on the West Bank. However, physical examinations and biochemical tests were normal. There was no common exposure to food, drink, or agricultural chemicals among those affected. No toxins were consistently present in patients' blood or urine. The only environmental toxicant detected was H_2S gas in low concentrations (40 ppb) in a schoolroom at

the site of the first outbreak (from a faulty latrine in the schoolyard). The illness was deemed to be psychogenic and possibly triggered by the smell of H_2S (Landrigan and Miller , 1983; Modan *et al*., 1983).

D.1.3. Development. Xu *et al*. (1998) conducted a retrospective epidemiological study in a large petrochemical complex in Beijing, China in order to assess the possible association between petrochemical exposure and spontaneous abortion. The facility consisted of 17 major production plants divided into separate workshops, which allowed for the assessment of exposure to specific chemicals. Married women (n = 2,853), who were 20-44 years of age, had never smoked, and who reported at least one pregnancy during employment at the plant, participated in the study. According to their employment record, about 57% of these workers reported occupational exposure to petrochemicals during the first trimester of their pregnancy. There was a significantly increased risk of spontaneous abortion for women working in all of the production plants with frequent exposure to petrochemicals compared with those working in non-chemical plants. Also, when a comparison was made between exposed and non-exposed groups within each plant, exposure to petrochemicals was consistently associated with an increased risk of spontaneous abortion (overall odds ratio (OR) = 2.7 (95% confidence interval (CI) = 1.8 to 3.9) after adjusting for potential confounding factors). Using exposure information obtained from interview responses for (self-reported) exposures, the estimated OR for spontaneous abortions was 2.9 (95% CI = 2.0 to 4.0). When the analysis was repeated by excluding 452 women who provided inconsistent reports between recalled exposure and work history, a comparable risk of spontaneous abortion (OR 2.9; 95% CI = 2.0 to 4.4) was found. In analyses for exposure to specific chemicals, an increased risk of spontaneous abortion was found with exposure to most chemicals. There were 106 women (3.7% of the study population) exposed only to hydrogen sulfide; the results for H_2S (OR 2.3; 95% CI = 1.2 to 4.4) were statistically significant. Unfortunately H_2S exposure concentrations were not reported.

D.2. Effects of Animal Exposure

D.2.1. Adult/mature animals. A median lethal concentration (LC_{50}) in rats exposed to H_2S for 4 hours was estimated as 440 ppm (616 mg/m³) (Tansy *et al*., 1981). An inhalation LC_{Lo} of 444 ppm for an unspecified duration is reported in rats, and a lethal concentration of 673 ppm (942 mg/m³) for 1 hour is reported in mice (RTECS, 1994). In another study, mortality was significantly higher for male rats (30%), compared to females (20%), over a range of exposure times and concentrations (Prior *et al*., 1988). A concentration of 1,000 ppm (1,400 mg/m³) caused respiratory arrest and death in dogs after 15-20 minutes (Haggard and Henderson, 1922). Inhalation of 100 ppm (140 mg/m³) for 2 hours resulted in altered leucine incorporation into brain proteins in mice (Elovaara *et al*., 1978). Kosmider *et al*. (1967) reported abnormal electrocardiograms in rabbits exposed to 100 mg/m³ (71 ppm) H_2S for 1.5 hours.

Khan *et al*. (1990) exposed groups of 12 male Fischer 344 rats to 0, 10, 50, 200, 400, or 500-700 ppm hydrogen sulfide for 4 hours. Four rats from each group were euthanized at 1, 24, or 48 hours post-exposure. The activity of cytochrome c oxidase in lung mitochondria, a primary molecular target of H_2S, was significantly ($p<0.05$) decreased at 50 ppm (15%), 200 ppm (43%), and 400 ppm (68%) at 1-hour post-exposure compared to controls. A NOAEL of 10 ppm for inhibition of cytochrome c oxidase was identified in this study.

Fischer and Sprague-Dawley rats (15 per group) were exposed to 0, 10.1, 30.5, or 80 ppm (0, 14.1, 42.7, or 112 mg/m^3, respectively) H_2S for 6 hours/day, 5 days/week for 90 days (CIIT, 1983a,b). Measurements of neurological and hematological function revealed no abnormalities due to H_2S exposure. Histological examination of the nasal turbinates also revealed no significant exposure-related changes. A significant decrease in body weight was observed in both strains of rats exposed to 80 ppm (112 mg/m^3).

In a companion study, the CIIT conducted a 90-day inhalation study in mice (10 or 12 mice per group) exposed to 0, 10.1, 30.5, or 80 ppm (0, 14.1, 42.7, or 112 mg/m^3, respectively) H_2S for 6 hours/day, 5 days/week (CIIT, 1983c). Neurological function was measured by tests

for posture, gait, facial muscle tone, and reflexes. Ophthalmologic and hematologic examinations were also performed, and a detailed necropsy was included at the end of the experiment. The only exposure-related histological lesion was inflammation of the nasal mucosa of the anterior segment of the noses of mice exposed to 80 ppm (112 mg/m^3) H_2S. Weight loss was also observed in the mice exposed to 80 ppm. Neurological and hematological tests revealed no abnormalities. The 30.5 ppm (42.5 mg/m^3) level was considered to be a NOAEL for histological changes in the nasal mucosa. (Different adjustments were made to this NOAEL by U. S. EPA to calculate the RfC of 1 μg/m^3 and by OEHHA to calculate the chronic REL of 10 μg/m^3 (8 ppb).)

Hydrogen sulfide (0, 10, 30, or 80 ppm) was administered via inhalation (6 h/d, 7 d/wk) to 10-week-old male CD rats (n = 12/group) for 10 weeks (Brenneman *et al*., 2000). Histological evaluation revealed that rats exposed to 30 or 80 ppm had significant increases in lesions of the olfactory mucosa but not other tissues. Multifocal, rostrocaudally-distributed olfactory neuron loss and basal cell hyperplasia were seen. The dorsal medial meatus and the dorsal and medial portions of the ethmoid recess were affected. The lowest dose (10 ppm) was considered a no observed adverse effect level for olfactory lesions.

Fischer F344 rats inhaled 0, 1, 10, or 100 ppm hydrogen sulfide for 8 hours/day for 5 weeks (Hulbert *et al*, 1989). No effects were noted on baseline measurements of airway resistance, dynamic compliance, tidal volume, minute volume, or heart rate. Two findings were noted more frequently in exposed rats: (1) proliferation of ciliated cells in the tracheal and bronchiolar epithelium, and (2) lymphocyte infiltration of the bronchial submucosa. Some exposed animals responded similarly to controls to aerosol methacholine challenge, whereas a subgroup of exposed rats were hyperreactive to concentrations as low as 1 ppm H_2S.

Male rats were exposed to 0, 10, 200, or 400 ppm H_2S for 4 hours (Lopez *et al.*, 1987). Samples of bronchoalveolar and nasal lavage fluid contained increased inflammatory cells,

protein, and lactate dehydrogenase in rats treated with 400 ppm. Later Lopez and associates (1988) showed that exposure to 83 ppm (116 mg/m^3) for 4 hours resulted in mild perivascular edema.

D.2.2. Developing animals. Saillenfait *et al.* (1989) investigated the developmental toxicity of H_2S in rats. Rats were exposed 6 hours/day on days 6 through 20 of gestation to 100 ppm hydrogen sulfide. No maternal toxicity or developmental defects were observed.

Hayden *et al*. (1990) exposed gravid Sprague-Dawley rat dams continuously to 0, 20, 50, and 75 ppm H_2S from day 6 of gestation until day 21 postpartum. The animals demonstrated normal reproductive parameters until parturition, when delivery time was extended in a dose-dependent manner (with a maximum increase of 42% at 75 ppm). Pups exposed in utero and neonatally to day 21 postpartum developed with a subtle decrease in time of ear detachment and hair development, but with no other observed change in growth and development through day 21 postpartum.

Hannah and Roth (1991) analyzed the dendritic fields of developing Purkinje cells in rat cerebellum to determine the effects of chronic exposure to low concentrations of H_2S during perinatal development. Treatment of timed-pregnant female Sprague Dawley rats with 20 and 50 ppm H_2S for 7 hours per day from day 5 after mating until day 21 after birth produced severe alterations in the architecture and growth characteristics of the dendritic fields of the Purkinje cells. The architectural modifications included longer branches, an increase in the vertex path length, and variations in the number of branches in particular areas of the dendritic field. The treated cells also exhibited a nonsymmetrical growth pattern at a time when random terminal branching is normally occurring. Thus, developing neurons exposed to H_2S may be at risk of severe deficits. However, the lower level of 20 ppm for 7 hours is nearly 2 orders of magnitude above the present one-hour standard.

Dorman *et al*. (2000) examined the effect of perinatal exposure of H_2S on pregnancy outcomes, offspring development, and offspring behavior in rats. Male and female Sprague-

Dawley rats (12 rats/sex/concentration) were exposed to 0, 10, 30, or 80 ppm H_2S 6 h/day, 7 days/week for 2 weeks prior to breeding. Exposures continued during a 2-week mating period and then from Gestation Day (GD) 0 through GD 19. Exposure of rat dams and their pups (eight rats/litter after culling) resumed between postnatal day (PND) 5 and 18. Adult males were exposed for 70 consecutive days. Offspring were evaluated using motor activity (assessed on PND 13, 17, 21, and 60±2), passive avoidance (PND 22±1 and 62±3), functional observation battery (FOB) (PND 60±2), acoustic startle response (PND 21 and 62±3), and neuropathology (PND 23±2 and 61±2). No deaths occurred and no adverse physical signs were seen in F_0 males or females. There were no statistically significant effects on the reproductive performance of the F_0 rats as assessed by the number of females with live pups, litter size, average length of gestation, and the average number of implants per pregnant female. Exposure to H_2S did not affect pup growth, development, or performance on any behavioral test. The authors conclude that H_2S is neither a reproductive toxicant nor a behavioral developmental neurotoxicant in the rat at occupationally relevant exposure concentrations (i.e., at 10 ppm, the current occupational daily average exposure limits - TLV and PEL; however, the ACGIH is considering lowering the TLV to 5 ppm). The lowest level tested (10 ppm) is more than 300-fold higher than the CAAQS of 0.030 ppm.

E. Interactions between hydrogen sulfide and other pollutants

Ethanol can potentiate the effects of H_2S by shortening the mean time-to-unconsciousness in mice exposed to 800 ppm (1,120 mg/m³) H_2S (Beck *et al*., 1979).

Endogenous hydrogen sulfide may regulate smooth muscle tone in synergy with nitric oxide (Hosoki *et al*., 1997).

Hydrogen sulfide is often accompanied by other malodorous sulfur compounds, such as methyl mercaptan, dimethyl sulfide, and dimethyl disulfide. Some of these have odor thresholds

lower than that of hydrogen sulfide. The complex mixture is often referred to as TRS (total reduced sulfur).

Lindvall (1977) reported that the perceived odor strength of H_2S is increased by the simultaneous presence of 600 ppb nitric oxide (600 ppb nitric acid is imperceptible by itself).

F. Conclusions

The current standard of 0.03 ppm (30 ppb) hydrogen sulfide for one hour based on odor is well below NOAEL levels from animal experiments where exposure lasted weeks to months, including the period of intrauterine development. However, it is greater than OEHHA's chronic Reference Exposure Level (REL) of 8 ppb, which is based on histological changes in the nasal area of mice. (The chronic REL is compared to the annual average H_2S concentration.) Ideally neither of these two benchmark levels should be exceeded by the properly averaged concentration.

Additional research might help reduce uncertainties regarding the impacts of hydrogen sulfide on the health of infants and children. This would include:

a. Odor testing of hydrogen sulfide in adolescents or younger children, if ethically permissible, to determine their odor threshold. Current data on odor detection in children are not consistent. Data on H_2S odor detection in children under controlled exposure are lacking.

b. The identification of children hypersensitive to the odor of hydrogen sulfide. While the odor from very low level H_2S would not itself threaten their physical health, the odor might be alarming to hypersensitive children. Psychosomatic complaints might be more confusing to children than to adults.

c. Physiologic testing of anosmic (either specifically anosmic to H_2S or totally anosmic) children at the CAAQS would be useful in determining whether if adverse physiological symptoms occur in the absence of odor detection.

d. Testing of the odor threshold for H_2S using the most current methodology among groups of healthy persons of both sexes in different age ranges. Data from such testing would likely be an improvement over the use of either the mean of 16 people (California Department of Public Health, 1969) or the mean from 26 studies, conducted over a period of 130 years, which found thresholds spanning a 20,000 fold range, from 0.07 ppb to 1400 ppb (Amoore, 1985). (If the highest and lowest values of the range in Amoore (1985) are dropped as outliers - Amoore (1985) stated that these two studies seemed to involve only one subject - the range would be 0.43 ppb to 190 ppb, a 440-fold range).

e. Further research is needed on the topic of when odor is an adverse health effect and how much consideration should be given to psychosomatic complaints accompanying odor annoyance (Dalton *et al*., 1997; ATS, 2000). A recent American Thoracic Society position paper titled "What Constitutes an Adverse Health Effect of Air Pollution?" (ATS, 2000) indicates that air pollution exposures, which interfere with the quality of life, can be considered adverse. This suggests that, for the purpose of setting a standard, odor-related annoyance should be considered adverse, even if nausea or headache or other symptoms are not present.

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SULFUR DIOXIDE:
EVALUATION OF CURRENT CALIFORNIA AIR QUALITY STANDARDS WITH RESPECT TO PROTECTION OF CHILDREN

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A. Abstract

Sulfur dioxide is an irritant gas commonly emitted by coal fired power plants, refineries, smelters, paper and pulp mills and food processing plants. Both controlled laboratory studies and epidemiology studies have shown that people with asthma and children are particularly sensitive to and are at increased risk from the effects of SO_2 air pollution. Asthmatic subjects exposed to levels of SO_2 within regulatory standards have demonstrated increased respiratory symptoms such as shortness of breath, coughing and wheezing, and decrements in lung function. Physiological differences between children and adults such as lung volume and ventilation rate make children more sensitive to the effects of SO_2 compared to healthy adults. In general, children's exposure to SO_2 is also greater than that of adults since they spend more time outdoors and are more physically active.

Controlled exposures to SO_2 have shown statistically significant reductions in lung function at concentrations as low as 0.1 to 0.25 ppm. Epidemiologic studies have seen mortality associated with very small increases in ambient SO_2 in the range of 10 – 22 ppb. Low birth weigh is associated with SO_2 concentrations in the range of 22-40 ppb. The studies assessed in this review indicate that infants and people with asthma are particularly susceptible to the effects of SO_2, even at concentrations and durations below the current California one-our standard of 0.250 ppm.

B. Background

Sulfur dioxide (SO_2) is a water soluble, irritant gas commonly emitted into ambient air by coal fired power plants, refineries, smelters, paper and pulp mills, and food processing plants. Adverse health effects from SO_2 exposure at ambient concentrations have mainly been seen in individuals with asthma as will be summarized in this review. SO_2 exposure causes bronchoconstriction, decrements in respiratory function, airway inflammation, and mucus secretion. There is some epidemiologic evidence of a population effect from SO_2 exposure in sensitive sub-populations as listed below. However, the effects of SO_2 alone are very difficult to determine because SO_2 is often associated with PM and other pollutants. Currently, there are two standards set by California for SO_2: a one hour standard of 0.25 ppm and a 24 hr standard of 0.04 ppm..

SO_2 is also a precursor of secondary sulfates such as sulfuric acid, which is a stronger irritant than SO_2, and plays a major role in the adverse respiratory effects of air pollution. Sulfate is a major component of $PM_{2.5,}$ which has been implicated in causing adverse health effects, especially among the elderly and persons with cardiovascular and respiratory illnesses (Koenig, 1997). This review will summarize the health effects of SO_2 and some of the findings from both controlled laboratory and epidemiologic studies that are relevant to human health.

C. Principal sources and exposure assessment

C.1. Relationship between SO_2 and sulfuric acid

Since SO_2 is a water soluble and reactive gas, it does not remain long in the atmosphere as a gas. Much of the SO_2 emitted is transformed through oxidation into acid aerosols, either sulfuric acid (H_2SO_4) or partially neutralized H_2SO_4 [ammonium bisulfate or ammonium sulfate]. The ecological effects of acid aerosols (in the form of acid rain or dry deposition) have received much attention but are not the subject of this report.

C.2. Assessment of Response

Various lung measurements have been used to assess the response to inhaled SO_2 in controlled laboratory studies. Two of the most widely used tests of lung function are FEV_1 and SRaw.

FEV_1 is the volume of air exhaled in the first second of a forced expiratory maneuver. This is the most reproducible measure of acute changes in airway caliber. Stimuli that reduce airway caliber such as pollen exposure, methacholine challenges and cigarette smoke can all reduce a subject's FEV_1. Changes in FEV_1 have been widely used to assess the health effects of ambient air pollutants. SO_2, ozone, sulfuric acid, and nitrogen dioxide exposures are associated with reduced FEV_1.

Specific airway resistance (SRaw) is another sensitive measurement of airway caliber. Airway resistance is usually measured using a plethysmograph. Specific airway resistance is adjusted for a specific lung volume, often measured as thoracic gas volumes.

Provocative challenges, such as the methacholine challenge, are performed to document individual bronchial hyperresponsiveness (BHR). In the methacholine challenge test, subjects are asked to inhale increasing concentrations of methacholine (usually from 0 to 25 mg/ml) until the FEV_1 measured post inhalation drops by 20%. The results of the challenge are presented as the provocative concentration (PC) necessary to cause a 20% decrease (PC_{20}) in FEV_1.

Bronchoalveolar and nasal lavage (BAL or NL) are two techniques that provide the investigator with cells and fluids for biochemical assays. Either the airways or the nose is washed with sterile saline and the fluid collected for analysis. The elevation of cytokines, cells or inflammatory mediators are indicators of adverse effects. BAL fluid often contains alveloar macrophages, neutrophils, and eosinophils.

Respiratory symptoms such as shortness of breath, coughing, wheezing, sputum production, and medication use are also commonly used to assess the effects of air pollution exposure. Subjects are given diary forms that they complete daily for the duration of the study.

D. Description of Key Studies

D.1. Controlled Studies

Since individuals with asthma are much more sensitive to the respiratory effects of inhaled SO_2, the review of controlled laboratory studies is restricted to studies of subjects with asthma. This follows a similar decision made by the US EPA in its supplement to the second addendum to Air Quality Criteria for PM and Sulfur Oxides (EPA, 1994). As noted in the EPA document, air temperature and humidity and exercise alone can affect respiratory function in subjects with asthma. Thus, these variables need to be considered in the review as well as individual susceptibilities among those with asthma.

EPA reviewed the status of controlled exposures to SO_2 in the second addendum to Air Quality Criteria for PM and Sulfur Oxides (EPA, 1994). This report will touch on that literature briefly and concentrate on studies subsequent to 1993.

Prior to 1980 controlled exposures of human subjects to SO_2 had involved only healthy subjects. In general these studies did not find adverse respiratory effects even at concentrations of 13 ppm (Frank et al, 1962). In 1980 and 1981, Koenig et al (1980; 1981) and Sheppard et al (1980; 1981) published the results of controlled SO_2 exposures in both adolescent and adult subjects with asthma.

The studies by Koenig and Sheppard found that people with asthma were extremely sensitive to inhaled SO_2 and therefore may be at increased risk for adverse respiratory effects in communities where SO_2 concentrations are elevated even for short periods of time. A series of studies with adolescents showed gradations in SO_2 effects dependent on whether subjects had allergic vs non-allergic asthma and whether they had exercise-induced bronchoconstriction. This gradation of response in FEV_1 after SO_2 exposure is shown in Figure 1. The changes after

SO_2 exposure were statistically significant. No significant changes were seen after exposure to air. Similar studies with healthy subjects often do not find significant pulmonary function decrements after exposure to 5.0 ppm SO_2 (Koenig, 1997).

Figure 1: FEV_1 changes after SO2 exposure

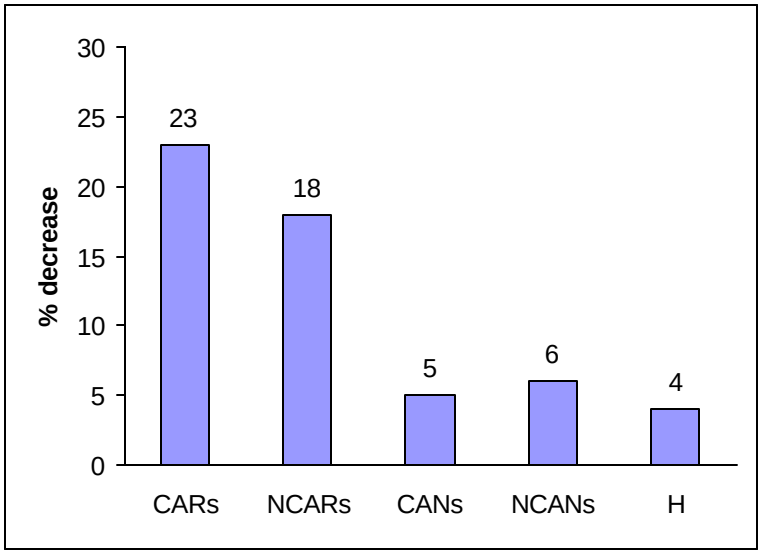


Figure 1. Average decrements in FEV_1 after exposure to 1.0 ppm SO_2 during intermittent moderate exercise. CAR- physician diagnosed, allergic asthmatic responder; NCAR- non physician diagnosed, allergic asthmatic responder; CANs- physician diagnosed, allergic non-asthmatics; NCANs- non physician diagnosed, allergic non-asthmatics; H- healthy. From Koenig et al., 1997.

Table 1. Percentage change in pulmonary function measurements after exposure to 1.0 ppm SO_2 or air in nine adolescent asthmatic subjects.

Measurement	Change from baseline	
	SO_2 exposure	Air exposure
FEV_1	23% decrease	0% change
R_T	67% increase	13% decrease
V_{max50}	44% decrease	9 % increase
V_{max75}	50% decrease	24% increase

From Koenig et al, 1981

Pulmonary function is dramatically decreased in asthmatics exposed to SO_2 as shown in Table 1 (Koenig et al., 1981) and in Figure 1 (Koenig et al., 1997). Regarding the duration of exposure necessary to elicit a SO_2 effect, Horstman and Folinsbee (1986) demonstrated that SO_2 exposure for 2.5 minutes produced a significant decrement in pulmonary function tests (PFTs). In a recent study, Trenga et al (1999) found an average 2.4% decrement in FEV_1 when adult subjects were exposed to only 0.1 ppm SO_2 via a mouthpiece. As discussed below this route of exposure may exaggerate the SO_2 response.

D.1.1. Route of exposure. SO_2 is a highly water soluble gas and is rapidly taken up in the nasal passages during normal, quiet breathing. Studies in human volunteers found that, after inhalation at rest of an average of 16 ppm SO_2, less than 1% of the gas could be detected at the oropharynx (Speizer and Frank, 1966). Penetration to the lungs is greater during mouth breathing than nose breathing. Penetration also is greater with increased ventilation such as during exercise. Since individuals with allergic rhinitis and asthma often experience nasal congestion, mouth breathing is practiced at a greater frequency in these individuals (Ung et al, 1990) perhaps making them more vulnerable to the effects of water soluble gasses such as SO_2. A number of more recent studies have shown that the degree of SO_2-induced bronchoconstriction is less after nasal inhalation than after oral inhalation (Kirkpatrick et al, 1982; Bethel et al., 1983; Linn et al, 1983; Koenig et al, 1985). Inhalation of SO_2 causes such dramatic bronchoconstriction that it appears little of the gas actually reaches the bronchial airways. Nasal inhalation on SO_2 causes significant bronchoconstriction even though it appears that little of the gas reaches the bronchial airways. Koenig and co-workers (1985) reported significant increases in the nasal work of breathing (measured by posterior rhinomanometry) in adolescent subjects with asthma. Increases in airflow rate such as resulting from exercise can increase penetration to the lung (Costa and Amdur, 1996), therefore people exercising in areas contaminated with SO_2 may suffer exacerbated effects.

D.1.2. Duration of exposure. In early studies, large changes in pulmonary function were seen after only 10 minutes of moderate exercise during SO_2 exposure. Two contrasting effects of duration with SO_2 exposure have been documented. Short durations are sufficient to produce a response and longer durations do not produce greater effects. One study showed that as little as two minutes of SO_2 inhalation (1 ppm) during exercise caused significant bronchoconstriction, as measured by airway resistance. In addition, the study showed that the increase in airway resistance after 10 minutes of exposure to 1 ppm SO_2 during exercise was not significantly increased when the exposure was extended to 30 minutes (Horstman and Folinsbee, 1986).

D.1.3. Concentration-exposure relationships. EPA in their summary of the effects of SO_2 (1986) constructed a figure representing the distribution of individual airway sensitivity to SO_2 by using the metric of doubling of SRaw. Figure 2 clearly illustrates the exposure-response relationship of SO_2.

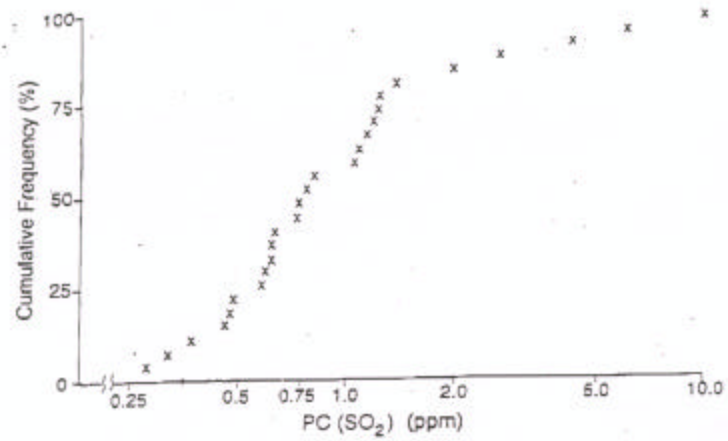


Figure 2. Distribution of individual airway sensitivity to SO_2, ($PC[SO_2]$). $PC(SO_2)$ is the estimated SO_2 concentration needed to produce doubling of SRaw in each subject. For each subject, $PC(SO_2)$ is determined by plotting change in SRaw, corrected for exercise-induced bronchoconstriction, against SO_2 concentration. The SO_2 concentration that caused a 100% increase in SRaw is determined by linear interpolation. Cumulative percentage of subjects is plotted as a function of $PC(SO_2)$, and each data point represents $PC(SO_2)$ for an individual subject. From Horstman et al (1988).

Figure 2. Distribution of individual airway sensitivity to SO_2, ($PC[SO_2]$). $PC(SO_2)$ is the estimated SO_2 concentration needed to produce doubling of SRaw in each subject. For each subject, $PC(SO_2)$ is determined by plotting change in SRaw, corrected for exercise-induced bronchoconstriction, against SO_2 concentration. The SO_2 concentration that caused a 100% increase in SRaw is determined by linear interpolation. Cumulative percentage of subjects is plotted as a function of $PC(SO_2)$, and each data point represents $PC(SO_2)$ for an individual subject. (From Horstman et al ,1988; reproduced from EPA, 1994).

Pulmonary function changes seen after SO_2 exposures are transient and usually resolve within 20 minutes (Koenig et al, 1981). However, many subjects with asthma in controlled studies of SO_2 exposure request bronchodilator therapy after exposure rather than waiting for the symptoms to diminish (Koenig et al, 1981; 1985; Trenga et al, In Press). Symptoms include shortness of breath, chest tightness and wheezing.

D.1.4. Inflammation. Dr Sandstrom in Sweden has published several papers showing that SO_2 exposure is associated with airway inflammation as well as PFT decrements. For instance, Sandstrom and co-workers (1989) reported inflammatory effects of SO_2 inhalation by evaluating bronchoalveolar lavage (BAL) fluid in healthy subjects. Both mast cells and monocytes were significantly elevated in BAL fluid 4 and 24 hours after exposure to 8 ppm SO_2 for 20 minutes compared to air exposure. The mast cells showed a biphasic response with elevated numbers at 4 and 24 hours but not at 8 hours post exposure. The monocytes showed a lesser but continuous elevation. Increased neutrophils were seen in nasal lavage fluid from subjects with asthma exposed to 1 ppm SO_2 (Bechtold et al, 1993). Also, Koenig and co-workers (1990) have shown, in a study of pulmonary function, that prior exposure to a sub-threshold concentration of ozone for 45 minutes (0.12 ppm) potentiates the response to a subsequent exposure to low concentrations of SO_2 (100 ppb). No significant reduction in pulmonary function was seen when an air exposure followed ozone. This result suggests that the ozone exposure altered bronchial hyperresponsiveness even though it did not alter pulmonary function. Whether the hyperresponsiveness was due to inflammatory changes was not assessed. It is generally agreed upon that airway inflammation is a more adverse effect than reversible PFTs.

D.1.5. Prevalence of SO_2 sensitive individuals. A recent report determined the prevalence of airway hyperresponsiveness to SO_2 in an adult population of 790 subjects, aged 20-44 years, as part of the European Community Respiratory Health Survey. The prevalence of SO_2 hyperresponsiveness (measured as a 20% decrease in FEV_1) in that population was 3.4%

(Nowak et al, 1997). Twenty-two percent of subjects with a methacholine positive response showed SO_2 sensitivity while only 2 out of 679 who were not methacholine positive had such sensitivity, although presence of asthma was not used directly as a risk factor. Another study screened adult subjects with asthma for SO_2 responsiveness defined as a 8% or greater drop in FEV_1 after a 10 minute challenge with 0.5 ppm SO_2 (Trenga et al, 1999). Of the 47 subjects screened, 53% had a drop in FEV_1 greater or equal to 8% (ranging from –8% to -44%). Among those 25 subjects, the mean drop in FEV_1 was -17.2%. Baseline pulmonary function indices (FEV_1 % of predicted and FEV_1/FVC%) did not predict sensitivity to SO_2. Although medication usage was inversely related to pulmonary function changes after SO_2 ($p < 0.05$), both SO_2 responders and non-responders were represented in each medication category. Total post exposure symptom scores were significantly correlated with changes in FEV_1 ($p<0.05$), FVC ($p<0.05$) and PEF ($p<0.01$) but not FEF_{25-75}.

D.2. Panel Studies

Higgins and co-workers (1995) studied a panel of 75 adult subjects with diagnoses of asthma or chronic obstructive pulmonary disease (COPD) for four weeks. Subjects recorded peak flow, symptoms, and bronchodilator use. Health outcomes were examined for associations with SO_2 and ozone using regression analysis. Sixty-two subjects completed the measurements. During the study period the maximum 24-hour levels of SO_2, ozone, and nitrogen dioxide were 45 ppb, 29 ppb, and 43 ppb respectively. Wheeze on the same day, 24 and 48 hours after exposure were significantly associated with SO_2. Dyspnea and cough were not. Bronchodilator use was significantly associated with SO_2 concentrations at 24 and 48 hour lags.

D.2.1. Mechanisms of response. In spite of all the research investigating the relationship between SO_2 exposure and responses in individuals with asthma, the mechanism of the SO_2 response is not known. At one time it appeared, from animal studies, that SO_2-induced bronchoconstriction was mediated by the vagus nerve (part of the parasympathetic branch of

the autonomic nervous system). Cooling or cutting the vagus nerve in cats abolished the SO_2 response (Nadel et al, 1965). Several therapeutic agents with varying sites of action inhibit the SO_2 response in human subjects as described later in the section on Interactions. Also atropine, which counteracts the effects of the parasympathetic nervous system, does not inhibit the SO_2 response in human subjects. Thus, there is not a clear understanding of why SO_2 elicits such a dramatic effect on the bronchial airways of subjects with asthma.

D.3. Epidemiology Studies

Epidemiologic studies in the field of air pollution health effects rely on various measures of effect. Some of the studies use anonymous data from visits to emergency departments, hospital admissions, and mortality. Epidemiologic studies also study panels of subjects who are asked to record daily lung function, symptoms, and medication use during a short time period. These data are then compared to daily air pollution concentrations.

Results from epidemiologic studies on SO_2 exposure have been consistent with findings from the controlled laboratory studies. Several epidemiology studies, using time series analysis have shown that exposure to ambient concentrations of SO_2 are associated with mortality and morbidity. Table 2 summarizes some of the epidemiologic studies on the associations between SO_2 and mortality and hospital admissions for respiratory diseases. These studies clearly demonstrate that children, the elderly and those with preexisting conditions are particularly susceptible to air pollution. It has been shown that hospital admissions for cardiovascular and respiratory illnesses have been associated with just a 4 ppb in SO_2 in Hong Kong (Wong et al, 1999). The mean SO2 concentration was 8 ppb. In Valencia, Spain, Ballester et al (1996) found an association between mortality in the elderly and those with cardiovascular disease with only a 4 ppb increase in SO_2. The mean SO_2 concentration was 15.3 ppb.

Table 2: Epidemiology studies involving SO_2 exposure and mortality and morbidity

study	city	SO2 conc	units	other pollutants	R	CI	CI	endpoint	comments
Zimirou (1998)	London	33.1 (Cool) 30.9 (Warm)	24 hr ave (ug/m3)	BS, NO2, O3	.02	.01	.03	cardiovasular mortality associated with 50 ug/m3 increase in SO2	1 hour max SO2, Paris, Lyon, Barcelona
	Paris	40.1(C) 20.1 (W)		BS, NO2, O3	.04	.01	.06	cardiovasular mortality	24 hr ave, London, Paris, Lyon, barcelona, Milan
	Lyon	76.8(C) 26.4 (W)		BS, NO2, O3	.01		.02	cardiovasular mortality	24 hr ave, Bratislava, Poznan, Lodz, Wroclaw, Krakow
	Barcelona	50.6 (C) 40.1 (W)		BS, NO2, O3	.02	.01	.03	respiratory mortality	1 hr max, Paris, Loyon, Barcelona
	Milan	248.6(C) 30.5(W)		TSP	.05	.03	.07	respiratory mortality	24 hr, Londaon, Paris, Loyon, Barcelon, Milan
	Krakow	134.8 (C) 59.5 (W)		BS	.01	.98	.04	respiratory mortality	24 hr, Poznan, Lodz, Wroclaw, Krakow
	Lodz	100.9 (C) 29.6 (W)		BS					
	Wroclaw	67.4 (C) 23.4 (W)		BS					
	Poznan	100.1 (C) 33.1 (W)		BS					
	Bratislava	103.5 (C) 83.0 (W)		TSP					
Anderson (1996)	London	32+11.7	24hr ave (ug/m3)	BS, NO2(ppb), O3 (ppb)	1.01	1.00	1.02	all cause mortality associated with increase of pollutant from 10th to 90th centile	all year, 1 day lag
					1.01	0.99	1.02	all cause	cool season, 1 day lag

study	city	SO2 conc	units	other pollutants	R	CI	CI	endpoint	comments
					1.02	1.00	1.03	all cause	warm season, 1 day lag
					1.00	0.99	1.02	cardiovascular	all year, 1 day lag
					1.00	0.98	1.02	cardiovascular	cool season, 1 day lag
					1.00	1.02	1.03	cardiovascular	warm season, 1 day lag
					1.02	0.99	1.05	respiratory mortality	
					1.02	0.98	1.06	respiratory mortality	
					1.02	0.97	1.06	respiratory mortality	
Rossi et al (1999)	Milan, Italy	124+127	daily means (ug/m3)	TSP, NO2	1.03	1.02	1.04	all cause mortality for 100 ug/m3 increase in SO2	
Kelsall et al (1997)	Philadelphi, 1974-1988	17.3+11.6	ppb	TSP, NO2, CO, O3	1.01	1.00	1.02	all cause mortality for increase in interquartile range of SO2 (single pollutant model)	
Ballester et al (1996)	Valencia, Spain	39.94+15.38	24 hr ave (ug/m3)	BS	1.00	0.99	1.02	total mortality in cold months (Nov-Apr) for 10 ug/m3 in SO2	
					1.02	1.00	1.04	total mortality warm months (May - Oct)	
					1.001	0.98	1.02	all cause >70 cold months	
					1.02	1	1.04	all cause >70 warm months	
					0.99	0.98	1.02	cardiovascular cold months	
					1.02	1.00	1.05	cardiovascular warm months	
					0.96	0.91	1.00	respiratory cold	
					1.00	0.95	1.05	respiratory warm	
Burnett et al, 1999	Toronto, Canada	5.35+5.89	ppb	PM2.5, PM10-2.5, PM10, CO, NO2, O3	1.01			hospital admissions for asthma attributable to increase of SO2 mean	
					1.02			respiratory infections	
					1.02			ischemic heart disease	
					1.00			obstructive lung disease	
								single pollutant model	

study	city	SO2 conc	units	other pollutants	R	CI	CI	endpoint	comments
Wong et al (1999)	Hong Kong	20.2	ug/m3	NO2, O3, PM10	1.02	1.01	1.04	respiratory admission for 10ug/m3 increase in SO2	>65 years, 0 days lag
					1.01	1.00	1.02	respiratory admission for 10ug/m3 increase in SO2	overall
					1.02	1.01	1.03	cardiovascular admission for 10ug/m3 increase in SO2	>65, 0-1 day lag
					1.02	1.01	1.03	cardiovascular admission for 10ug/m3 increase in SO2	overall, 0-1 day lag
Wong et al (cont)					1.02	1.00	1.04	asthma admissions for 10 ug/m3 increase in SO2	
					1.02	1.01	1.04	COPD	
					0.99	0.98	1.00	pneumonia and influenza	
					1.04	1.01	1.06	heart failure	
					1.01	1.00	1.03	ischaemic heart disease	
					0.99	0.98	1.00	cerebrovascular diseases	
Garcia-Aymerich et al (2000)	Barcelona	46 (W) 36.4 (S); W=Oct-Mar, S= Apr-Sep	ug/m3 24 hr ave median values	BS, NO2, O3	1.04	0.91	1.19	total mortality for 50 ug/m3 increase in SO2	cohort of COPD patients
					1.04	0.85	1.28	respiratory mortality for 50 ug/m3 increase in SO2	cohort of COPD patients
					1.04	0.81	1.33	cardiovascular mortality	cohort of COPD patients
Sunyer et al (1996)	Barcelona	46 (W) 36.4 (S); W=Oct-Mar, S= Apr-Sep	ug/m3 24 hr ave median values	BS, NO2, O3	1.13	1.07	1.19	total mortality for 100 ug/m3 increase in SO2	lag 1
					1.14	1.063	1.23	respiratory mortality	lag 1
					1.13	0.99	1.28	cardiovascular mortality	lag 0
Vigotti et al (1996)	Milan	117.7	24 h ave (ug/m3)	TSP	1.12	1.03	1.23	mortality for 100 ug/m3 increase in SO2	lag 0, SO2 levels log transformed
					1.05	1	1.1	respiratory admissions for 100 ug/m3 increase	lag 0, SO2 log transformed, ages 15-64
					1.04	1	1.09	respiratory admissions for 100	lag 0, SO2 log

study	city	SO2 conc	units	other pollutants	RR	CI	CI	endpoint	comments
								ug/m3 increase	transformed, age>64
Katsouyanni et al (1997)	Athens	50	ug/m3 (median)	BS, PM10					1 day exposure
	Barcelona	45			1.029	1.023	1.035	total mortality for 50 ug/m3 increase in SO2 (Western cities)	1 day exposure
	Bratislav	13			1.008	0.993	1.024	total mortality for 50 ug/m3 increase in SO2 (Eastern cities)	1 day exposure
	Cracow	74			1.02	1.015	1.024	total mortality for 50 ug/m3 increase in SO2 (all cities)	
	Cologne	44							
	Lodz	46							
	London	29							
	Lyons	37							
	Milan	66							
	Paris	23							
	Poznan	41							
	Wroclaw	29							

RR – Relative Risk
LCI – Lower confidence interval
UCI – Upper confidence interval

Though it is difficult to separate the effects of particulate matter and SO_2 in epidemiologic studies, SO_2 has been shown to be responsible for adverse health effects, when PM had no effect. Derriennic and colleagues (1989) found that short term exposure to SO_2 was associated with respiratory mortality in people over 65 years of age in Lyons and Marseilles, and only all cause mortality in Marseilles. Particulate matter, however, had no effect on respiratory or cardiovascular mortality in the two cites. Schwartz and Dockery (1992) estimated that total mortality in Philadelphia would increase by 5% (95% CI, 3 to 7%) with each 38 ppb increase in SO_2. However, when both total suspended particulates (TSP) and SO_2 were considered simultaneously, the SO_2 association was no longer statistically significant. This was similar to the findings of Ponka et al (1998) when they modeled SO_2 and PM_{10} simultaneously in Helsinki. Masayuki et al (1986), however, implicated SO_2 as the primary source of mortality and chronic bronchitis in Yokkaichi, Japan. Masuyuki et al (1986) and associates studied the association between mortality changes from asthma and chronic bronchitis and changes in SO_2 concentrations over a 21 year period. Mortality from bronchial asthma decreased immediately after SO_2 levels decreased because of countermeasures taken against the source of air pollution and SO_2 levels met the national ambient air quality standard (maximum 1 hr concentration of 100 ppb, maximum daily average 40 ppb. Mortality due to chronic bronchitis decreased 4-5 years after the concentration of SO_2 began to meet the air standards. Although it is very difficult to use epidemiology o identify causation, in 1971 the Japanese courts accepted epidemiologic evidence showing a relationship between SO_2 and the prevalence of respiratory disease as legal proof of causation (Namekata, 1986).

Few studies have looked at the effects of air pollution on pregnancy outcomes. Recently, Wang et al (1997) looked at the association between air pollution and low birth weight in four residential areas in Beijing, China. Low birthweight is an important predictor of neonatal mortality, postnatal mortality and morbidity (McCormick, 1985). Considering both SO_2 and TSP together, Wang and colleagues found that maternal exposures to SO_2 and TSP during the third trimester of pregnancy were associated with low birth weight. The adjusted odds ratio was 1.11 (95% CI, 1.06-

1.16) for each 38 ppb increase in SO_2 and 1.10 (95% CI, 1.05-1.14) for each 100 ug/m^3 increase in TSP. Adjusting for maternal age and other covariates, this study estimated a 7.3 g and 6.9 g reduction in birth weight for a 38 ppb increase in SO_2 and 100 ug/m3 increase in TSP. More recently, Rogers et al (2000) studied the association between low birth weight and exposure to SO_2 and TSP in Georgia, USA. This study found that exposure to TSP and SO_2 above the 95^{th} percent (22 ppb) yielded an adjusted odds ratio of 1.27 (95% CI= 1.16-7.13). Xu and colleagues (1995) found that SO_2 and TSP were also associated with preterm delivery in Beijing, China. In the study area, the average SO_2 concentration was 38 ppb, maximum 240 ppb. The estimated reduced duration of gestation was .075 week for each 38 ppb increased in SO_2. Using logistic regression, the estimated odds ratio for preterm delivery was 1.21(CI=1.01-1.46) for each ln ug/m^3 increase in SO_2 and 1.10 (95%CI=1.01-1.20) for each 100 ug/m^3 increase in TSP (ln ug/m^3 is the form used by the authors). Since children and asthmatics are particularly sensitive to the effects of air pollution several studies have focused on the respiratory effects of ambient air pollution on this susceptible population. Buchdahl et al (1996) estimated that the incidence of acute wheezing in children would increase by 12% with each standard deviation in SO_2 level in West London. The hourly average concentration of SO_2 was 8 $\pm$ 5 ppb for all seasons. Timonen and Pekkanen (1997) studied the effects of air pollution on the respiratory health of children 7 to 12 years of age in Kuopio, Finland. This study found an association between SO_2 and PEF and incidence of upper respiratory symptoms in non-asthmatic children with coughing symptoms. Infectious airway diseases (except pneumonia) and irritations of the airways were shown to be associated with SO_2 in East Germany (Kramer et al, 1999). Both SO_2 and TSP were included in the regression model simultaneously. This study showed that the decrease in SO_2 and TSP levels in East Germany since 1991 had a favorable effect on these diseases. Schwartz et al (1995) studied the acute effects of summer air pollution on respiratory symptoms in children in six U.S. cities. They found that sulfur dioxide was associated with incidences of cough and lower respiratory symptoms, using a single pollutant model. These findings, however, could be confounded by PM_{10}. Segala et al (1998) found a strong

association between short-term exposure to SO_2 and the risk of asthma attack in children in Paris. The odds ratio for an asthma attack was 2.86 for an increase of 18.9 ppb of SO_2 on the same day. In Singapore, Chew et al (1999) found that asthmatic children were sensitive to ambient levels of SO_2 and TSP that were within acceptable ranges. They reported an increase of 2.9 visits to the emergency room for every 7.6 ppb increase in atmospheric SO_2, lagged by 1 day on days when levels were above 26 ppb.

E. Children vs. Adults

Physiologic and respiratory differences between adults and children contribute to the increased sensitivity of children to air pollutants. Children have a higher alveolar surface area to body mass ratio compared to adults resulting in a larger air-tissue gas exchange area. Compared to adults the respiration rate of an infant is 40 breaths/min compared to 15 breaths/min for an adult (Snodgrass, in Similarities and Differences between Children and Adults: Implications for Risk Assessment). The higher inhalation rate in children would result in an increased uptake of an inhaled pollutant. Table 3 compares the inhalation rates of children and adults (Exposure Factors Handbook, 1997).

Table 3: Inhalation rates of children and adults

Children (<1 year)	4.5 m^3/day (average)
Children (1-12 years)	8.7 m^3/day (average)
Adult female	11.3 m^3/day (average)
Adult male	15.2 m^3/day (average)

Inhalation rates are affected by age, gender, weight, health status and level of physical activity (Exposure Factors Handbook, 1997). Linn et al (1992) conducted a study on the inhalation rates of healthy and asthmatic adults and children in the Los Angeles Area. This study reported that healthy adults (n=20) had an average ventilation rate of 0.78 m^3/hr, elementary school students (n=17) an average rate of 0.90 m^3/hr and high school students (n=19) a rate of 0.84 m^3/hr. Asthmatics were found to have higher breathing rates. Elementary and high school children with asthma (n=13) had the highest ventilation rate - 1.20 m^3/hr, whereas adult asthmatics (n=49) had

an average ventilation rate of 1.02 m^3/hr. Layton (1993) calculated breathing rates based on oxygen consumption and reported that male children between 15-18 had the highest daily ventilation rate (17 m^3/day), females 9-11 had an inhalation rate of 13 m^3/day and children 6-8 had a daily inhalation rate of 10 m^3/day. (The description of the Linn data came from Ch 5 in the Exposure Factors handbook sent to us by Dr Lipsett. The citation for the article is the Proceedings of the Second EPA/AWMA Conference on Tropospheric Ozone, 1991 pp 701-712).

The health risk associated with air pollutants is a function of air concentration, duration and frequency of exposure as well as inhalation rate. Air pollutant concentrations vary at different locations: work, school, home, outdoors. Exposure levels, therefore, depend on the amount of time spent in various locations. According to the 1997 Exposures Factors Handbook, children (ages 3-11) spend 5 hr/day (weekdays) and 7 hr/day (weekends) outdoors compared to adults who only spend 1.5 hr/day outdoors. The increased time spent outdoors predisposes children to the effects of inhaled pollutants.

The toxic effects of a pollutant depend, in part, on the frequency and duration of exposure. For outdoor pollutants, such as SO_2, the amount of time spent outdoors contributes to the dose of the toxicant. The California Children's Activity Survey (1991) was designed to estimate the time children less than 12 years of age spent in various locations and doing various activities on a typical day. The activities that were focused on were those that would likely result in significant exposure to air pollutants. Children (n=1200) from various regions of California, Southern Coast, San Francisco Bay Area, and the rest of the state completed the survey. This study reported that children spent three times as much time as adults playing sports and other vigorous activities and more than 15 times as much time in simple play activities than adults. The time children spent outdoors each day was also more than twice that of adults, 141 minutes vs. 73 minutes respectively.

F. Sensitive sub-populations

People with asthma are particularly sensitive to the effects of SO_2. Asthma is a lung disease characterized by airway obstruction, airway inflammation and increased airway responsiveness to a variety of stimuli. As of 2000, over 18 million people or 7 % of the U.S. population were estimated to have asthma. Some estimates find that 18% of children have asthma. Although death resulting from asthma is rare, hospitalization from asthma does occur regularly. Weitzman et al (1992) reported that 10% of children in the U.S. (<18 years of age) with asthma were hospitalized within the past year. It has been estimated that asthma is responsible for 27 million patient visits, 134,000 hospital admissions, 6 million lost work days and 90 million days of restricted activity. Asthma is the most common chronic illness of childhood and the primary cause of school absences. Asthma also is a multi-factorial illness with a wide range of individual susceptibilities and sensitivities. The U.S. EPA in the Second Addendum reviewed studies from 1982 to 1986 pertaining to the respiratory effects of SO_2 exposure and supported the conclusion that asthmatic subjects are more sensitive to SO_2 than are non-asthmatic individuals. Several of the studies reviewed by the U.S. EPA (1986) also showed evidence that asthmatics undergoing moderate to heavy exercise suffered from bronchoconstriction after exposure to 0.5 ppm SO_2. These studies found that bronchoconstriction can result in just 5 to 10 minutes of exposure.

Since 1986 the U.S. EPA published the supplement to the Second Addendum of the criteria document for sulfur oxides (US EPA, 1994) assessing new studies which focused on the effects of SO_2 on asthmatics. Included in this review was a study by Horstman et al (1986). The aim of this study was determine the shortest duration of SO_2 exposure necessary to induce bronchoconstriction in asthmatics. Horstman et al (1988) reported that asthmatic subjects undergoing moderate exercise (minute ventilation = 40 L/min) experienced broncoconstriction after 2 and 5 minute exposures to 1.0 ppm SO_2. Balmes et al (1987) reported bronchoconstriction in asthmatics after 1 minute of 1.0 ppm SO_2 during eucapnic hyperpnea (60 L/min). Table 4 summarizes the findings by Balmes et al. Two of the 8 subjects developed large increases in SRaw

and chest tightness after inhalation of 1.0 ppm for 1 minute and seven of the 8 asthmatic subjects developed wheezing, chest tightness or dyspnea and requested inhaled brochodilator therapy after 0.5 ppm SO_2 for 3 and 5 minutes.

Table 4: Average increases in SRaw resulting from exposure to 0.5 or 1.0 ppm SO_2 for various time periods (Adapted from Balmes et al, 1987)

SO_2 Concentration (ppm)	Duration of exposure (minute)	SRaw (L × cm H_2O/L/s)	% increase SRaw above baseline
0.5	1	25 ± 0.3	34
0.5	3	13±3.2	173
0.5	5	19.6 ± 4	234
1.0	1	7.5 ± 4.7	93
1.0	3	31.4 ± 7.4	395
1.0	5	44.1 ± 9.8	580

The above studies clearly demonstrate the increased susceptibility of asthmatics to the adverse effects of low concentrations of SO_2. In fact, asthmatics undergoing moderate to heavy exercise are even more susceptible to these adverse health effects.

Those with chronic obstructive pulmonary disease (COPD) may also be highly susceptible to the effects of SO_2. Anderson et al (1997) reported that the association between 24 hr SO_2 concentrations and hospital admissions for COPD in a meta-analysis of 6 European cities was significant in the warm season (RR=1.05, 95% CI=1.01-1.10).

G. Conclusion

In general the studies assessed in this review indicate that children and people with asthma are particularly susceptible to the effects of SO_2, even at concentrations and durations below the current California one-hour standard of 0.250 ppm. It has been clearly demonstrated that exercise exacerbates the adverse responses experienced by this sub-population. Exercising asthmatics can suffer from bronchoconstriction within minutes after exposure to SO_2 at levels of 0.25 ppm (Horstman et al, 1986; 1988). Koenig et al (1981) reported significantly greater pulmonary function decrements in a group of children with asthma exposed to 1.0 ppm during moderate exercise than in a similar group exposed at rest (Koenig et al, 1980). There is one report of decrements after 0.1

ppm SO_2 exposures (Trenga et al, In Press). Studies have also shown that children are more susceptible to outdoor air pollutants than normal, healthy adults. This may be due to the physiologic differences between adults and children as well as the increased time that children spend outdoors engaging in physical activities. Also, as shown in Table 2, epidemiologic studies have seen adverse health effects at short-term exposures to SO_2 in the range at concentrations as low as 5 ppb. Zimirou (1998) reported cardiovascular mortality at one-hour maximum values of 10 – 19 ppb. As listed in Table 2, several studies see increased mortality with a 38 ppb increase in SO_2. It appears that a one-hour standard of 0.250 ppm (such as currently in effect in California) will not protect all members of the community.

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LEAD:
EVALUATION OF CURRENT CALIFORNIA AIR QUALITY STANDARDS WITH RESPECT TO PROTECTION OF CHILDREN

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A. Introduction and Overview

In this section, we provide a general overview of the health effects of lead. In Section II, we discuss the evidence for the adverse outcome most relevant to current concentrations of blood lead in children, neurotoxicity. We also provide background on the Centers for Disease Control (CDC) guidelines concerning the blood level of concern for children. Since the health effects of lead are usually measured as a function of blood lead, rather than ambient lead, it is necessary to understand the relation between ambient lead and blood lead. Therefore, in Section III we review the quantitative evidence linking changes in air lead to subsequent changes in blood lead. In Section IV, we quantify the association between changes in air lead and the percent of exposed children whose blood levels would move above the CDC blood level of concern. This provides evidence about the protectiveness of the current ambient lead standard for California of 1.5 $\mu g/m^3$ averaged over one month. Section V provides a conclusion about whether significant health effects on children and infants are likely at concentrations below the current California ambient standard for lead.

The adverse health effects of lead were first described by Hippocrates in 370 BC. Pliny indicated that lead was a problem for both workers and residents of Rome during the first century AD (Kazantzis, 1989). In Britain in the 1880s, laws were enacted to control occupational exposure to lead. Over the last century, additional evidence of adverse effects from toxicological, clinical and epidemiological studies has continued to accumulate. These studies provide strong and consistent evidence for health effects related to current blood lead concentrations. A thorough review of health outcomes associated with lead exposure is provided by the U.S. Environmental Protection Agency (U.S. EPA, 1986, 1990a), the Agency for Toxic Substances and Disease Registry (ATSDR, 1990) and the National Research Council (NRC, 1993). At very high acute exposures to blood lead concentrations (> 125 micrograms per deciliter or µg /dl of blood), death can result. Brain and kidney damage have been reported with

blood level concentrations between 80 and 100 μg/dL. Chronic exposure to lead can cause blockage of the proximal tubule in the kidney and kidney failure. Lead-induced chronic nephropathy (kidney damage) has been observed in occupationally exposed workers at blood lead levels as low as 40 μg/dL. Other renal effects, such as decreased vitamin D metabolite levels, have been observed at 30 μg/dL. The lowest blood lead level at which these effects occur has not been determined. Chronic exposure to lead in humans can also affect the blood. Anemia in adults has been reported at blood lead levels of 40 to 60 μg/dL, and in children at 30 to 40 μg/dL. In addition, increased blood pressure in adults has been reported at blood lead concentrations as low as 10 μg/dL.

Lead is also associated with several adverse reproductive and developmental outcomes. In male industrial workers, sperm abnormalities, reduced fertility, and altered testicular function have been observed at blood lead concentrations of 40-50 μg/dL and sometimes at lower levels. Lead has also been associated with adverse effects on the fetus. Since lead in blood crosses the placenta, the fetus may be affected by maternal blood lead level elevated from current or past exposure. Several prospective studies have demonstrated an association of maternal blood lead levels of 10 to 15 μg/dL with pre-term delivery and low birthweight (NRC, 1993). Also, studies have shown lead's effects on childhood growth. For example, using the National Health and Nutrition Examination Survey (NHANES) data, small but significant reductions in early childhood growth were observed, with no apparent threshold across a range of 5-35 μg/dL (Schwartz et al., 1986). Lead levels of 10 μg/dL and below have also been associated with decreased hearing acuity (Schwartz and Otto, 1987).

Levels of lead below 25 μg/dL cause both clinical and subclinical effects on the brain and nervous system. Several long-term prospective epidemiological studies have reported an association of pre- and postnatal lead exposures with measures of intelligence, such as IQ, in

infants and young children (U.S. EPA, 1986, 1991). These effects have been noted at blood lead levels of 10 to 20 μg/dL and lower. Since children and infants are most susceptible to the neurotoxic effects of lead, these studies are discussed in greater detail in the next section. *In vitro* and *in vivo* studies reveal changes in neurotransmission and brain mitochondrial function within minutes of exposure to submicromolar concentrations of lead. The lowest levels at which these effects occur in humans have not been determined, but these neurochemical changes could plausibly form the basis for neurodevelopmental effects observed in children. These effects have great public health significance since they are likely to occur at current ambient and blood lead concentrations.

Reviewing this body of evidence, the CDC identified 10 μg/dL as a "level of concern." CDC has also recommended certain community actions dependent on the actual observed blood lead concentrations. For example, when many children in a community have blood lead levels between 10 and 14 μg/dL, community-wide childhood lead poisoning prevention activities should be initiated. All children with blood lead levels at or above 15 μg/dL should receive nutritional and educational interventions and more frequent blood lead screening. Between 15 and 19 μg/dL, environmental investigation (including a home inspection) and remediation should be undertaken if the blood lead levels persist. A child with blood lead levels between 20 and 44 μg/dL should receive environmental evaluation, remediation and a medical evaluation. Such a child may need pharmacologic treatment for lead poisoning. Above 45 μg/dL, a child would receive both medical and environmental interventions, including chelation therapy. In our analysis to determine whether effects may occur below the current ambient air standard, we will use 10 μg/dL as the level of concern for effects on intelligence, although effects may occur at lower levels. This "level of concern" is consistent with those identified by the U.S. EPA (1990a), the CDC (1991b), the National Research Council (1993) and the ATSDR (1990).

In addition to neurological effects, lead interferes with the synthesis of heme, which is essential for the functioning of cells in many organ systems, especially the brain, kidney, liver, and blood-forming tissues. Heme is a component of hemoglobin, the oxygen-carrying pigment of red blood cells. An elevated lead level can impede hemoglobin synthesis, resulting in anemia. Heme is also a constituent of cytochrome P-450 and electron transfer cytochromes. Lead can impair the function of heme-dependent liver enzymes (cytochrome P-450), which can increase vulnerability to the harmful effects of other toxic chemicals. Lead's effects on vitamin D synthesis are mediated through its effects on heme. Finally, interference with heme biosynthesis may play a role in lead's neurological effects. Decrements in an enzyme involved in heme synthesis (ALA-D) have been observed at blood lead levels as low as 10 μg/dL although the biological and medical significance of effects at this level are not well understood. Several studies using large population-based data have indicated an association of lead in blood with blood pressure in adults, particularly men, at lead levels as low as 7 μg/dL of blood (NRC, 1993).

Many of these health effects are consistent with those seen in animal and cellular studies at very low levels. Therefore, the lead levels at which these health effects are seen in humans should not be considered as threshold values, but rather as levels below which there is less certainty of the presence of adverse health effects.

Over the last 15 years, average blood lead levels have declined dramatically in both children and adults (Pirkle et al., 1994, Pirkle et al., 1998). The decline in blood lead levels is consistent with, and undoubtedly related to, continued reduction in exposure to lead from environmental sources which began in the late 1970s. From 1976 to 1990, the amount of lead used in gasoline decreased 99.8% nationally (from 205,810 tons to 520 tons). In California, dramatic decreases in average ambient air lead levels have occurred over the last two decades. The reduction and subsequent ban of lead in gasoline is most likely the greatest contributor to the observed decline in blood lead levels during this period (Pirkle et al., 1994). The major

remaining sources of environmental lead that pose a potential public health threat appear to be localized sources of lead, including but not limited to continued deterioration of lead-based painted surfaces in older buildings, and lead that has already accumulated in dust and soil, and near point sources of air emissions.

B. Neurodevelopmental Effects On Children

Lead's neurodevelopmental effects observed at low and moderate exposure levels (30 μg/dL and below) include: decreased intelligence, short-term memory loss, reading and spelling underachievement, impairment of visual motor functioning, poor perception integration, disruptive classroom behavior, and impaired reaction time (U.S. EPA, 1989d; ATSDR, 1994; Bellinger et al., 1994a; Bellinger et al., 1994b; Needleman et al., 1996).

Children are more vulnerable than adults when exposed to lead partly because they: (1) have hand-to-mouth behaviors that result in more ingestion of lead in soil and dust; (2) are more likely to exhibit pica (abnormal ingestion of non-food items); (3) absorb substantially more lead from the gut than adults, especially when they are below 2 years of age; (4) have a faster metabolic rate, resulting in a proportionately greater daily intake of lead through food; (5) have a less developed blood-brain barrier and therefore greater neurologic sensitivity (Smith, 1989); (6) have a faster resting inhalation rate; and (7) tend to breathe through their mouths when at play (less inorganic lead particulate is trapped in the nasal passages in mouth-breathers). Furthermore, children from economically disadvantaged backgrounds are especially vulnerable because they are more likely to have diets deficient in elements that suppress lead absorption, such as iron and calcium.

While teeth and bone reflect the cumulative dose of lead, blood lead levels mostly reflect recent exposures (from the past 1 to 3 months) but are also influenced by past exposures, because lead can be mobilized from bone and other storage sites. However, blood lead levels are indicative of current soft tissue exposures. In addition, blood lead levels are reproducible (to

within ± 1 μg/dL) and can be compared across studies to indicate relative levels of exposure (Smith, 1989).

Early studies of neurotoxic effects of lead were conducted by Needleman et al. (1979) using lead levels in the teeth of first and second graders. A significant association was detected between increased dentine lead level and decrements in intelligence quotient (IQ). The association was still evident when the children were tested 5 and 11 years later (Bellinger et al., 1984b; Needleman et al., 1990). Since the Needleman et al. (1979) article appeared, many studies have been published that support this finding. Most of the early studies were cross-sectional in nature, where groups with different blood lead concentrations were compared at a single point in time. Like many epidemiological studies of this type, there are concerns about exposure assessment and the ability to control for potential confounders. Despite these issues, the cross-sectional studies consistently demonstrate an association between blood lead and IQ. In an attempt to characterize the overall findings of several cross-sectional studies, Needleman and Gatsonis (1990) undertook a meta-analysis of the published IQ-blood lead studies. By pooling the results of the individual studies, the meta-analysis addressed the problem of small sample sizes with the accompanying low statistical power. The results suggested that each 1 μg/dL increase of blood lead results in a 0.24 point decrease in IQ.

Since cross-sectional studies use a single blood lead measurement as a surrogate for earlier exposures, they are more likely to suffer from exposure classification errors than prospective studies (McMichael et al., 1994). As a result, large, long-term, prospective studies were conducted in Boston, Cincinnati, and Port Pirie, Australia. In addition to minimizing recall bias, prospective studies allow investigators to measure temporal changes in outcome relative to prior levels of exposure. Because the child is followed over time, researchers can examine the effects of lead exposure at different times as well as estimate the effects of cumulative exposure.

One of the larger cohorts studied, from Boston, Massachusetts, includes several hundred middle and upper-middle class children followed from birth to 10 years of age (Bellinger et al., 1984a, 1985, 1991, 1992; Stiles and Bellinger, 1993). These studies have consistently found an association between blood lead and IQ among different age cohorts. Among the more important findings are those of older children since their IQs may be better characterized in the standardized tests. For example, at age 10 years, the children were examined again using the Wechsler Intelligence Scale for Children-Revised (WISC-R), a measure of cognitive function, as well as the Kaufman Test of Educational Achievement (KTEA) (Bellinger et al., 1992; Stiles and Bellinger, 1993). Higher levels of blood lead at 24 months were associated with significantly lower scores on FSIQ (full scale IQ) and verbal IQ. The authors observed a decrease of almost 6 points on FSIQ and 9 points on KTEA Battery Composite score for each 10 μg/dL increase in lead level at 24 months. These estimates include adjustments for maternal age, race, marital status, number of residence changes and home environment. Visual inspection of the results and analysis of an earlier data set (Schwartz, 1993) suggest a continuous response across the entire range of blood lead levels and the lack of any threshold.

In summary, in the Boston cohort, effects on intelligence were evident from both pre and postnatal blood lead. Postnatal blood lead levels at 24 months were significantly associated with FSIQ at age 10 and to some neurological function tests requiring attention for good performance. Children from lower socioeconomic status appeared to be more sensitive to effects at lower blood lead concentrations. A more recent study found that lead impacted high school classroom behavior (Needleman et al., 1996). Therefore, evidence from these studies suggests that both prenatal and postnatal exposure may be associated with adverse impacts on cognitive performance with effects from postnatal exposure persisting to at least 10 years of age. The effects of later postnatal exposure seem to be strongest.

Other large prospective studies of lead and neurodevelopment involve cohorts of inner-city children in Cincinnati, Ohio and children in Port Pirie, South Australia (NRC, 1993). Although there are differences in socioeconomics and demographics, experimental techniques, statistical models, and patterns of exposure among the three large cohort studies, their findings are consistent. Among the more relevant findings, changes in IQ at ages 6 to 10 are associated with blood lead measured either cumulatively over several years or in a single year. In addition, the magnitude of effect per μg/dL are similar among both the prospective and cross-sectional studies. Many of these studies report mean blood concentrations near 10 μg/dL.

Several researchers have reviewed or conducted qualitative or quantitative meta-analyses of the prospective studies relating low-level blood lead exposures to neurodevelopmental effects in young children. For example, researchers with the CDC (Thacker et al., 1992) reviewed 35 prenatal and early postnatal prospective cohort studies. They concluded that the weight of evidence suggested an adverse relationship between lead on the intelligence of children. Pocock et al. (1994) reviewed several types of studies to quantify the relationship between lead and IQ, including the WISC-R. The analysis concluded that for postnatal blood lead, both the cross-sectional and prospective studies indicate a significant inverse association between blood lead and IQ. In addition, Schwartz (1994) conducted meta-analyses of both longitudinal and cross-sectional neurodevelopmental studies. He used all studies published before 1993 that reported blood lead and measured full scale IQ. For the longitudinal cohorts, he selected those studies that measured exposure during the first 3 years of life when the neural network is most vulnerable to neurotoxicants. Schwartz examined the IQ loss indicated by both the cross-sectional and prospective studies and concluded that the two study designs were capturing similar effects.

To provide an estimate and range of risk, the Office of Environmental Health Hazard Assessment (OEHHA) conducted a simplified meta-analysis (Hedges and Olkin, 1985) of cohort

studies conducted in children older than 5 years (see Table 1). This age group was used because it is likely to provide the most accurate assessment of the impact of blood lead. Estimates of the mean effect were derived by weighting each of the regression coefficients by the inverse of its variance. This generated a mean decrease of 0.33 IQ points per μg/dL blood lead with a 95% confidence interval of 0.32 to 0.34. Thus, this central estimate suggests that a 1 μg/dL increase in postnatal blood lead is associated, on average, with a 0.33 point decrease in FSIQ. This level is close to the range of estimates derived from the earlier meta-analyses, cited above. OEHHA used this value in its identification of lead as a toxic air contaminant (OEHHA, 1997).

In addition to the general effect magnitude, the overall population-level impact of IQ is also important to consider. Grant and Davis (1989) have demonstrated that, if one shifts down a normal distribution of IQ scores (mean=100, standard deviation=16) by 4 points, the number of children scoring 80 or below increases by 50%. The impact of such a shift applies across the entire distribution of scores, reducing the number of children who score above the norm as well as increasing the number scoring well below the norm. Thus, while a 4-point IQ loss might not have much impact on an individual child, this decrease could have a significant public health impact in a community. Similarly, a shift of 3.3 points would increase the percent of children scoring 80 or below from 10.56% to 14.74%, a 39.5% increase.

The consistency of findings lends strong support to the conclusion that neurodevelopment effects are causally associated with blood lead, and that the CDC level of concern of 10 μg/dL is a reasonable action level.

C. The Contribution of Airborne Lead to Blood Lead Level

In order to evaluate the impact of change in air lead on health, it is necessary to determine the quantitative association between changes in air lead and subsequent concentrations of lead in the blood of exposed populations. This is necessary since most lead-

related health effects use blood lead, rather than ambient lead, as the measure of exposure. The relationship between air lead and blood lead has been extensively studied in both field studies and experimental chamber studies. Studies in experimental chambers in which air exposures are well characterized have only been conducted using adults. Since young children have higher metabolism and inhalation rates, and since they ingest more dirt and dust (Smith, 1989; Chamberlain, 1983), one would expect air lead levels to have a greater impact on blood lead in children than in adults. Thus, when assessing risks from air lead, it is important to examine the relationship between air lead and blood lead (or the blood lead/air lead "slope") in adults and children separately. In a review of the relevant studies, OEHHA examined both the magnitude of the slope estimate and the implications for lower concentrations of air and blood lead. The review included experimental chamber studies in adults, a population-based study of adults using personal monitors, and several population-based studies of children using outdoor fixed-site monitors.

Early inhalation studies assessed the effects of inhaled lead using human subjects in experimental chambers. These chamber studies allow direct calculation of the blood lead/air lead slope through the inhalation pathway. The chamber studies are useful because exposures were well characterized. The U.S. EPA estimated that when the subjects exposed to very high air lead levels were excluded, the average blood lead to air lead slope was 1.9 μg/dL per $\mu g/m^3$ (US EPA, 1986). In their critical review, OEHHA concurred with the U.S. EPA assessment of the slope from the chamber studies, noting that the exposure levels were relatively high in these studies and that the aggregate slope may be nonlinear, with steeper slopes at lower air and blood lead levels (OEHHA, 1997).

For children, there are three available models to determine the contribution of air lead concentrations to blood lead levels. These models include a disaggregate model, an aggregate model and an uptake biokinetic model. In the disaggregate model and in the biokinetic uptake

model, the total effect of air lead is estimated by separately analyzing the associated changes between blood lead and inhaled air lead as well as lead deposited onto soil, dust, food and water (U.S. EPA, 1989b). Once the impact of each separate pathway on blood lead is determined, as well as the impact of air lead on other pathways such as soil and household dust, the total effect of a change in air lead on blood lead can be determined. While this approach may yield more precise estimates of the relationship of air lead and blood lead, the contribution of each pathway must be modeled and any errors or uncertainties in these variables will reduce the precision of the estimated total exposure.

One method for developing a disaggregate model is to use a multivariate regression approach to explain blood lead with separate explanatory variables representing soil, dust and air lead in the model specification. Using a disaggregate model for children, U.S. EPA (1986) estimated a slope of 2 when only accounting for the direct influence of air lead, and a slope of 5 when incorporating both direct and indirect influences of air lead (U.S. EPA, 1989b).

A second method to estimate the effects of change in air lead on changes in blood lead is an aggregate model. This model implicitly takes into account both the direct and indirect sources of air lead. One can derive an estimate of the slope using either of two approaches. First, a regression model attempting to explain the variation in blood lead with air lead as an explanatory variable, but unadjusted for soil or household dust, can be used. Ideally, such a model would adjust for age, ethnicity and other nonenvironmental confounders. Second, a slope can be calculated using blood lead levels and air lead levels from at least two points in time or between two populations. For example, blood lead levels in a highly exposed and a control community can be related to corresponding ambient air lead levels. The slope (β) is calculated by comparing groups using the following formula:

$$\beta = \frac{\text{difference in blood lead between group II and group I } (\mu g/dL)}{\text{difference in air lead between group II and group I } (\mu g/m^3)}$$

The advantage of aggregate estimates is that they implicitly incorporate both direct and indirect pathways of air lead. Since we are estimating the total impact of air lead emissions on children's blood lead, aggregate slopes are most relevant in that they incorporate all air-related pathways. OEHHA staff reviewed the relevant studies for determining a slope (OEHHA, 1997). Their "best estimates" are developed from the studies using the lowest blood lead and air lead concentrations. Table 2 summarizes the best estimates and ranges from the available studies. Using 14 studies covering seven different study populations, OEHHA took the geometric mean of the study estimates to determine a combined slope estimate of 4.2 with a range of 3.3 to 5.2.

The third method for estimating blood lead levels in relationship to exposures from various media is the uptake biokinetic model such as U.S. EPA's Integrated Exposure Uptake Biokinetic (IEUBK) (U.S. EPA, 1989b). This model estimates specific intake, uptake and distribution of lead in the body, taking into account the route and rate of exposure, a child's age and baseline exposure. The processes of absorption, distribution, storage, mobilization and excretion are directly modeled. This personal computer-compatible model calculates probability distributions of blood lead levels for children of different ages based on a multipathway exposure analysis. Categories of exposure input variables include concentrations of lead in air, drinking water, soil, house dust, paint, diet and maternal blood lead (to account for newborn blood lead), with each having default or user-defined values. Exposures are converted into an uptake component based on amounts of lead absorbed from the lungs and gastrointestinal tract. The absorbed doses of lead are then biokinetically modeled into six different body tissues or compartments over 84 monthly time points (age 0 to 7 years) to account for age-dependent physiological parameters (e.g., increases in inhalation rates and body weights) and soil ingestion rates. Several validation efforts (Hogan et al., 1995a; U.S. EPA, 1994a; U.S. EPA, 1994b) show that the model performs well in predicting blood lead distributions. The model does not use a single blood lead/air lead slope to relate air lead concentration to blood lead concentration.

Nevertheless, with some adjustment to the IEUBK model recommended by its authors (Hogan, 1995b), aggregate slopes can be determined and are presented below for comparative purposes.

Since the model assumes a nonlinear relationship between environmental and blood lead concentrations, the slope will vary with air lead concentration. Recent studies of the model carried out by the U.S. EPA using the supplemental equations based on data from either East Helena (for which a significant monitoring program was developed) or data from 40 communities, indicate aggregate slopes of 3.7 and 5.3 μg/dL per $\mu g/m^3$, respectively, for a change in air lead level from 1.5 to 2.5 $\mu g/m^3$ (Hogan, 1995b). OEHHA also looked at the slopes generated by incremental increases between 0 and 1 $\mu g/m^3$ (OEHHA, 1997). In this range of air lead concentrations, the IEUBK model predicts approximate slopes of around 6.5 μg/dL per $\mu g/m^3$. It is important to note that the slope may be a nonlinear function of the actual air lead and blood lead levels being investigated. Many researchers report a relationship that is supralinear with steeper slopes at lower air and blood lead levels (Brunekreef, 1984; Chamberlain, 1983; Hammond, 1981; O'Flaherty, 1993). If this is true, then studies conducted at higher air and blood lead concentrations might underestimate the blood lead/air lead slope associated with relatively low air concentrations.

In summary, the population-based studies provide important information not available through chamber studies; i.e., "real world" exposure scenarios encompassing a wide range of behaviors, ages, microenvironments and climates. As expected, they indicate that "real world exposures" result in higher blood lead levels than would be directly predicted from chamber studies (slope = 2), which only measure exposure from the inhalation route. The population-based studies include deposition, accumulation and exposure from other environmental pathways as well. U.S. EPA analysis using either disaggregate (pathway specific) or aggregate models (all pathways combined) suggest a slope range of from 3 to 5 μg/dL per $\mu g/m^3$for

children (EPA, 1989a). OEHHA analysis including additional studies suggests a similar range with a best estimate of 4.2 (OEHHA, 1997). Therefore, for the subsequent analysis, we use the slope estimate of 4.2.

D. Airborne Lead and The Risks of Neurotoxicity

D.1 Background

This section examines the protectiveness of the current ambient standard for lead by providing estimates of neurodevelopment risks associated with alternative ambient air lead concentrations. Specifically, we estimate the increase in the proportion of children that will move above the CDC level of concern of 10 μg/dL as ambient lead increases from the current baseline statewide average.

To assess the impacts to children from exposure to air concentrations of inorganic lead, there are several key assumptions. These are: (1) the CDC 'level of concern' of 10 μg/dL is the appropriate blood lead concentration that should not be exceeded in order to protect the health of children; (2) 4.2 μg/dL per $\mu g/m^3$ is the most appropriate aggregate blood lead/air lead slope factor for children and is assumed to be linear over the ambient air lead concentrations of interest in California; and (3) the mean blood lead levels in one- and two-year old children in California, exposed to the baseline ambient lead average of 0.055 $\mu g/m^3$ of airborne lead, are generally comparable to one- and two-year old children in the NHANES III survey, i.e., lognormally distributed, with a geometric mean of 3.1 μg/dL, and a geometric standard deviation (GSD) of 2.1. Each of these issues will be discussed in turn below.

D.2 Identification of the Blood Lead Level of Concern

Based on current information it is not possible to identify a clear threshold blood lead level associated with adverse health effects in humans. As discussed in Section III, a level of concern where human neurodevelopmental effects are seen in children exposed either prenatally or

postnatally has been identified at 10 μg/dL. The CDC has concluded that blood lead concentrations at or near 10 μg/dL present a public-health risk to infants, children and pregnant women (CDC, 1991). This blood lead level is the CDC level of concern for communities as a whole, as well as for individuals (CDC, 1991). The level of 10 μg/dL has been designated by the U.S. Public Health Service as the maximum permissible concentration from the standpoint of protecting the health of children and other sensitive populations (NRC, 1993). In 1990, the Science Advisory Board of the U.S. EPA identified a blood lead concentration of 10 μg/dL as the maximum to be considered safe for individual young children (NRC, 1993). The National Research Council and U.S. EPA concur that neurodevelopmental effects in children are likely to occur at 10 μg/dL and possibly lower (NRC, 1993; U.S. EPA, 1990a). However, as the evidence continues to grow, it is possible that future levels of concern may drop below 10 μg/dL (NRC, 1993).

D.3 Blood Lead/Air Lead Slope

Based on the studies described in Section II, we estimate that increases in airborne lead concentrations can result in an increase in blood lead levels in children at an estimated rate of 4.2 μg/dL per $\mu g/m^3$, after all air-related exposure pathways are included and a steady state has been reached. Reasonable lower and upper bounds for the slope are 3.3 and 5.2, based on the range of geometric means. Although the studies reviewed in Section III include many different age groups, applying the results to the younger children appears reasonable. We have assumed that the slope is linear near current ambient air lead concentrations and blood lead levels so that calculations for varied exposures near these levels can be made using the aggregate slope factor.

D.4. Geometric Mean Blood Lead Level for California

There currently are no population-based blood lead data that are both specific to and representative of California as a whole. For this reason, estimates of the geometric mean blood lead level for California children are derived from the third National Health and Nutritional Examination Survey, Phase 2 (NHANES III), conducted by the National Center for Health Statistics/Centers for Disease Control and Prevention. This survey provides nationally representative estimates of blood lead levels for several population subgroups, by age, sex and race/ethnicity (Pirkle et al., 1998). Specifically, data for the years 1991 through 1994 were provided for one- and two-year old children and disaggregated for non-Hispanic whites, African-Americans (defined as “non-Hispanic blacks” in NHANES III), and Mexican-Americans. Survey sample weights were applied to the data in order to generate estimates that were representative of the U.S. population. Blood lead concentrations were measured by graphite furnace atomic absorption spectrophotometry, with a detection limit of 1 μg/dL. Analysis of each specimen was performed in duplicate, and the mean of the duplicate measurements was reported. "Blind"

sample analyses and laboratory analytical quality control and quality assurance in the blood lead data analysis.

This data set of 13,642 people provides the best blood lead concentration information available for the United States. It contains standardized estimates with a high degree of both analytical standardization and laboratory quality control and quality assurance. For these reasons, it is reasonable to extrapolate the blood lead distribution characterized by NHANES III to California. However, we are uncertain about how the levels in California compare to the national averages, since the sampling design used in the NHANES III survey does not provide representative state-level data. Consequently, we conducted sensitivity analyses to determine the impact of assuming a lower mean for California than the national average. Our sensitivity analysis indicates that the general results of our analysis are relatively insensitive to the choice of the geometric mean or geometric standard deviation (GSD).

Although several recent studies have investigated the distribution of blood lead in certain cohorts of California children, they are not necessarily representative of the state's population. For example, Haan et al. (1996) examined blood lead levels in 305 healthy children recruited from HMOs over a 5-month period in 1991-1992. In this study, the mean blood lead levels was 4.65 μg/dL, for children ages 1 through 5. However, this sample is not representative of the state as a whole. Although this clinic-based sample was representative of the HMO studied, its characteristics differ from the overall state population. Specifically, the population consists of employed families, most with two parents, with pre-paid health insurance. In addition, the sample used in this study consists of regular visitors to the well baby clinic.

As part of a cost analysis of the lead-testing program in Orange County, California, Gellert et al. (1993) analyzed a nonrandom sample of venous blood lead tests in 5115 children aged 1-5 years in the Child Health and Disability Prevention Program. The ethnicity of the sample was not representative of the state of California: 73.5% Hispanic; 12.2% Asian; 9.8%

white; 1.2% African-American; 3.3% other. Blood lead levels were found to be greater than 10 μg/dL in 7.25% of children. The geometric mean and standard deviation were not provided. The major sources of blood lead levels ≥ 20 μg/dL in children in this study were shown to be related to pica, folk remedies, use of unglazed earthenware or peeling paint. While only 7.54% of houses in the county were constructed prior to 1950, no information on the location of residence were provided for the study population. The results of this study should not be generalized to the California population because the sample was not randomly chosen, the ethnic makeup of this community differed from the state and because the age distribution of housing may not be representative of those in other urban areas.

Since it is difficult to generalize these available data to the entire state, we use the data from NHANES III, Phase 2. The NHANES III results are tabulated by age, so that data can be disaggregated for one- and two-year olds, the age group at greatest risk for lead poisoning. For this subgroup, the geometric mean blood lead was 3.1 μg/dL with 5.9% above 10 μg/dL. The NHANES III data also reveal that the geometric mean blood lead values vary by race/ethnicity within this and all other age groups. Blood lead levels for non-Hispanic white male children are the lowest (GM = 2.7 μg/dL) relative to that of Non-Hispanic blacks and Mexican-Americans (GM= 4.8 and 3.2, respectively). Regression analysis for all age groups together indicated that higher blood lead levels were found among males, those residing in large urban areas, blacks, those from families with lower education and lower income (Brody et al., 1994). Also, the data demonstrated that children between ages one and two tended to have higher blood lead levels.

Since the distribution of blood lead is log normal, the GSD provides the best summary measure of dispersion. The GSD can be used to calculate the percent of a cohort that exceeds 10 μg/dL, and *vice versa*. For the one- and two-year old age group, we use the GSD of 2.1 based upon the NHANES III data, Phase 2. We assume that this distribution is associated with average national lead exposure occurring from 1991 – 1994. During this period, the ambient

average for lead was 0.055 μg/m^3. Children exposed primarily to a local point source may be more homogeneous and have more similar exposures patterns relative to the California population as a whole. As a result, this group may be expected to have a higher mean blood lead and a lower GSD. For example, White et al. (1998) suggest a GSD values for a single city of around 1.8.

D.5. The Range of Neurodevelopmental Risks for Children Using the Aggregate Model Approach

When the U.S. EPA developed its lead standard in 1978, the aim was to protect those children most exposed to lead. U.S. EPA considered the range of blood lead concentrations, the geometric mean and the GSD reported at that time. Then they identified 30 μg/dL, the level of concern at the time, as a level not to be exceeded by 99.5% of children (U.S. EPA, 1978). From these assumptions the U.S. EPA developed the current ambient air quality standard of 1.5 μg/m^3 (arithmetic average). In a more recent analysis, U.S. EPA chose a ninety-five percent level of protection for site-specific preliminary soil remediation goals for lead at Superfund sites and soil cleanup standards for lead at RCRA (The Resource Conservation and Recovery Act) sites (Laws, 1994). The U.S. EPA calculation is designed to limit exposure such that children would have an estimated risk of no more than 5% of exceeding the 10 μg/dL level.

We have adopted a similar approach to that used in the U.S. EPA (1978) methodology, while incorporating more current information. The current level of concern is 10 μg/dL, not 30 μg/dL used by U.S. EPA in 1978. Second, at the current time approximately 5.9 percent of all one- and two-year old children already have blood lead levels exceeding 10 μg/dL blood lead (Pirkle et al., 1998) due to exposure to lead from various media, such as air, water, food, consumer products, soil, and paint. Also, decreasing the current statewide average air lead concentration of 0.055 μg/m^3, even to zero air lead, would still not protect 99.5%, or even 95% of children from exceeding 10 μg/dL, based on NHANES III data. For these reasons we focus on

quantifying the incremental change in the proportion of children with blood lead levels exceeding 10 μg/dL that would result from exposures to various concentrations of air lead. This will help determine whether the current standard is protective.

A first step in this analysis requires calculating the geometric mean blood lead levels associated with alternative air lead concentrations using a blood lead/air lead slope of 4.2. Next, assuming a constant GSD of 2.1, we calculate the proportion of the cohort expected to have a blood lead level of 10 μg/dL or greater. We assume all other sources are constant, except those that are impacted directly by increases in air emissions (i.e., soil and dust concentrations). The results are summarized in Table 3. The analysis indicates that an air lead concentration of 0.10 $\mu g/m^3$, an additional one percent of the population of one and two year old children in California would be predicted to exceed 10 μg/dL. At an air lead concentration of 0.25 $\mu g/m^3$, an additional 4.5 percent of the exposed population of one- and two-year old children would be predicted to have blood level concentrations exceeding the CDC guideline of 10 μg/dL. At an air lead concentration equivalent to the current ambient standard of 1.5 $\mu g/m^3$, more than 45% of children aged one and two would have blood lead levels above the CDC guideline of 10 μg/dL according to the aggregate model. We next examined the implication of lowering the GSD from 2.1 to 1.8. Moving from the baseline ambient concentration of 0.055 to 0.10 adds 0.6% to the number of children expected to exceed 10 μg/dL and adds 3% if the ambient concentration moves to 0.25 $\mu g/m^3$. Even with this lower GSD, 44% of the children would be expected to have blood lead levels above 10 μg/dL at an ambient concentration of 1.5 $\mu g/m^3$. Finally, if we lower the assumed GSD to 1.8 and lower the GM to 2.5, we still estimate that at the current ambient standard, almost 40% of the children would exceed the CDC level of concern. If we considered the effects on African-American children, who have a much higher baseline GM, the percent moving above 10 μg/dL in any of these scenarios would be much greater.

With an estimated total California population of 33.9 million, the estimated number of one- and two-year old children is 1.2 million (California Department of Finance 1996 projections). With a GM = 3.1 and GSD = 2.1, at the current state standard an additional 476,000 children would move above the CDC level of concern.

E. Summary

In summary, the estimates indicate that exposure to an airborne lead concentration up to the current state standard of 1.5 $\mu g/m^3$ is associated with an increase of approximately 40% of the cohort of one- and two-year old children to levels exceeding the CDC level of concern. Even an increase to only 0.50 $\mu g/m^3$, would theoretically result in an additional 10% of children having blood lead concentrations above the CDC level of concern of 10 $\mu g/dL$.

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Table 1. Regression Coefficients Indicating Change in IQ per 1.0 µg/dL Increase in Blood Lead for Crude and Adjusted Models in Prospective Studies at Later Ages

Crude Model:		
Study	Intelligence Measure	Coefficient (s.e.)
Boston[a]	WISC-R (FSIQ)	-0.71 (0.25)
Cincinnati[b]	WISC-R (FSIQ)	-0.58 (0.13)
Adjusted Model:		
Study	Intelligence Measure	Coefficient (s.e.)
Boston[c]	WISC-R (FSIQ)	-0.58 (0.21)
Cincinnati[d]	WISC-R (FSIQ)	-0.33 (0.14)
Port Pirie[e, f]	WISC-R (FSIQ)	-0.24 (0.12)
Meta-Analyses:		
Study	Intelligence Measure	Coefficient (s.e.)
Needleman and Gatsonis[g]	Varied	-0.25 (0.04)
Schwartz[h]	Varied	-0.24 (0.04)
OEHHA[I]	WISC-R (FSIQ)	-0.33

a. Blood lead at age 2, WISC-R at age 10, unadjusted analysis.
b. Mean blood lead at age 6, WISC-R at age 6.5
c Adjusted for HOME score at 10 years, maternal age, race, marital status, and number of residence changes prior to 57 months.
d. Adjusted for HOME score, maternal IQ, birth weight, birth length, child sex, and cigarette consumption during pregnancy.
e. Averaged blood lead at ages 0-4, linearized using PbB mean of 19.59, WISC-R at age 7.
f.. Adjusted for sex, parent's level of education, maternal age at delivery, parental smoking status, SES, HOME score, birth weight, birth order, feeding method, duration of breast feeding and whether or not child's parents were still living together.
g. Meta-analysis of six cross-sectional studies of blood lead and intelligence.
h. Meta-analysis using same six cross-sectional studies and one additional prospective study by Bellinger et al. (1991).
i. Meta-analysis using the three above "Adjusted Models."

Sources: Stiles and Bellinger (1993); Bellinger et al. (1992), Dietrich et al. (1993), Baghurst et al. (1992), Needleman and Gatsonis (1990), Schwartz (1993), OEHHA (1997).

Table 2. Best Estimates and Range of Slopes from Population-Based Studies in Children using Aggregate, Disaggregate and IEUBK Models..

Aggregate Study	Location	Ages (yrs)	Best Estimate[a]	Range[a]
Brunekreef et al., 1983	4 Dutch cities	4 to 6	8.50	NR
Angle et al., 1984	Omaha	1-18	1.92	NR
Roels et al., 1976; 1978; 1980 Brunekreef, 1984	Antwerp, Belgium	10-15	5.30	4.6 to 13.7
Cavalleri et al., 1981	NR	3-6, 6-11	3.65	3.3 to 4.0
Yankel et al., 1977; Walter et al., 1980; Snee, 1982.	Silver Valley, Idaho	1-10	1.70	1.0 to 2.4
Billick et al., 1979, 1980; Billick, 1983	New York	NR	2.90	NR
Hayes et al., 1994	Chicago	6 mo - 5	16.2	5.6 to 16.2
Combined estimate from Aggregate Models			4.2	3.3 to 5.2
Estimate from Disaggregate Model			5	NR
Estimate from IEUBK Models			4.5	3.7 – 5.3

a μg/dL per $\mu g/m^3$

NR= Not reported

Table 3. Association Between Ambient Air Lead and the Expected Percent of One and Two Year Old Children Equal to or Above 10 mg/dL Blood Lead.

	GM = 3.14 GSD = 2.1	**GM = 3.14** GSD = 1.8	GM = 2.5 GSD = 1.8
Average Air Lead Concentration ($\mu g/m^3$)	Percent ≥ 10 µg/dL	Percent ≥ 10 µg/dL	**Percent ³ 10 mg/dL**
0.055*	5.9	2.4	1.0
0.10	6.9	3.0	1.3
0.25	10.6	5.7	3.0
0.50	17.6	12.0	8.0
1.00	32.2	28.1	22.9
1.50	45.6	44.4	39.6

* National average air lead concentration during the period of data collection of NHANES III, Phase 2. Calculation assumes that baseline non-air sources of lead exposure including paint, household dust, soil, pottery, and tap water are constant. GM = 3.14 and GSD = 2.1 are taken from NHANES III, Phase2, and represent the blood lead distribution for children ages one and two (Pirkle et al., 1998).

Appendix E

Public Comments and ARB Responses

December 31, 2000

E.1 Introduction

Public comments were received from Jon M. Heuss (Air Improvement Resource, Inc.) and Jaroslav J. Vostal (Environmental Health Assessment Consultants, International), both in writing and verbally at the AQAC meeting. The written comments are included in Appendix E. The verbal comments made before AQAC were based on the written comments, and transcripts can be accessed at http:\\www.OEHHA.ca/gpv/air/toxic-contaminants/AQAC1.html.

E.2 Summary

The points raised by Messers Heuss and Vostal can be summarized into two categories. These points, along with ARB responses, are presented below.

Point 1. The Staff Report is an incomplete assessment and analysis of all publicly available information on the various pollutants. **ARB Response:** The purpose of the reviews presented in the staff report was to consider whether there was evidence suggesting that any of the California Ambient Air Quality Standards should be reviewed with reference to adequacy of protection of infants, children and other susceptible populations. It was not the intent of Staff to provide complete reviews on each pollutant.

Point 2. Insufficient information is presented on background concentrations of various pollutants, and on the extent to which the existing State standards are exceeded. **ARB Response:** Information on background pollutant concentrations has been added. Table 3.3.1. gives information on exceedances and maximal concentrations of the various criteria pollutants in the major air basins of the State. Also, see response to Point 1.

Comments for the California ARB Public Meeting
of the Air Quality Advisory Committee.
on the Adequacy of California Ambient Air Quality Standards:
Senate Bill 25-Children's Environmental Health Protection
Berkeley, CA, October 12-13, 2000

Jon M. Heuss
Air Improvement Resource, Inc.

Jaroslav J. Vostal
Environmental Health Assessment Consultants, International

Senate Bill 25 requires that all existing California health-based ambient air quality standards be reviewed by the Air Resources Board (ARB) by December 31, 2000. The review should determine "whether, based on public health, scientific literature, and exposure pattern data, the standards adequately protect the health of the public, including infants and children, with an adequate margin of safety." In preparation for that review, a Draft Staff Report was made available in mid-September along with a request for written comments by October 4, 2000. This is insufficient time to adequately review, evaluate, and comment on the wide range of exposure and public health issues and studies included in the Draft. Nevertheless, we want to bring several important issues to the attention of the Staff and Advisory Committee. We will be providing further discussion during the public comment period at the Advisory Committee meeting.

The September 12, 2000 Draft Staff Report is an incomplete assessment and analysis of all publicly available information on several key issues in the review. Because the Draft raises concerns about the potential health effects that may occur- in infants, children, and other potentially susceptible groups - exposed to pollutants at levels corresponding to existing California ambient air quality standards for particulate matter (PM10), ozone, and nitrogen dioxide, we focus our comments on those pollutants.

One of the factors considered in assessing the standards' health protectiveness is the "degree of exposure relative to the level of the standard." Unfortunately, Chapter 3 and Appendix B of the Draft are inadequate. They fail to mention the existence of a significant background of ozone in the troposphere that arises from sources other than California or even U. S. precursor emissions. They fail to inform the reader of the extent to which the existing state standards are exceeded throughout the state. They fail to reference a significant body of probabilistic ozone exposure analyses that include studies of children conducted by the U.S. EPA. These failures result in the omission of important facts that will have a profound influence on the health protectiveness of the existing state ozone and PM10 standards.

For example, the substantial background of ozone in the troposphere (that averages about 0.04 ppm but reaches 0.08 ppm on the order of once per year) provides a practical limit as to how low any ozone air quality standard can be set. The state ozone standard of 0.09 ppm for 1-hour is defined as an extreme value standard; it is met when the Expected Peak Daily Concentration (EPDC, that concentration expected to occur once per year) is below the level of the standard. In fact, the EPDC in the cleanest,

lowest emission density counties and air basins of California are typically between 0.075 and 0.085 ppm. This means that the amount of man-made ozone allowed by the existing state standard is on the order of 0.01 ppm. The presence of a substantial background of ozone needs to be taken into account in any decisions regarding revision of the California ozone standard.

For PM10, ARB data summaries indicate that the state 24-hour standard is exceeded throughout the state except for compliance in a few high elevation counties. The maximum EPDC in Lake County is substantially below the state 24-hour standard, but in all the other rural and remote basins, the maximum EPDC is substantially above the existing state 24-hour PM10 standard. In the Great Basin Valleys, the maximum EPDC has been on the order of 400 $\mu g/m^3$ in recent years, or 8 times the state 24-hour standard. In contrast, the state annual geometric mean standard is met in the rural and remote areas of California but not in the more urbanized air basins. However, the maximum annual geometric mean PM10 in the rural and remote basins of California (except for Lake County) varies between 20 and 30 $\mu g/m^3$. It is known that wind-blown crustal material is the major contributor to high PM10 concentrations in rural and remote areas of California. While some wind-blown dust is controllable, much is not. Therefore, the level of PM10 that is achievable with complete elimination of man-made pollution varies substantially across California. This needs to be taken into account in any decisions regarding revision of the California PM standards.

Section 3.6 on indoor and personal exposure needs to acknowledge that indoor ozone concentrations are dramatically reduced compared to outdoor concentrations (see Table B10-1) while PM exposures indoors are often elevated above outdoor concentrations. This also has important implications for the magnitude (and sources of) human personal exposure to ozone and PM10. An informed discussion of the interpretation of the existing health studies must be predicated on what is known about human exposure patterns. Therefore, the discussion of individual pollutants in Chapter 4 and Appendix C needs to include a review of the body of information on human exposure. For ozone, this includes consideration of the probabilistic analyses carried out by EPA over the past decade. For PM, this includes an expanded discussion of the body of information concerning the relation of fixed monitors to indoor and personal exposures as well as factors such as the personal cloud, indoor combustion sources, and re-suspension of coarse particles.

When EPA last reviewed the national ambient air quality standards for ozone, the probabilistic risk assessment played a key role. The U. S. EPA's Clean Air Science Advisory Committee (CASAC) concluded that because it appears that ozone may elicit a continuum of biological responses down to background concentrations, risk assessments must play a central role in identifying an appropriate level for the standard. However, when CASAC viewed the results of the probabilistic modeling, the risks for all segments of the population including outdoor children were small and the committee concluded that there was no "bright line" that distinguished any of the proposed standards as being significantly more protective of public health. The standards considered ranged from the existing 1-hour federal standard of 0.12 ppm down to levels roughly equivalent to the current California standard.

In terms of children's health, it is important to note that clinical studies show that children tolerate ozone exposures with less symptoms than do adults. Concerns that this may

result in airway injury have not been validated because they have been based on an outdated concept of ozone-induced decreases of "lung function." Studies now demonstrate that declines in the forced expiratory volume (FEV1.0) are transient and are not caused by cellular injury in the respiratory airways. Since EPA's last review, published U.S. EPA studies show that the observed "lung function" decreases are only a physiological protective mechanism that involuntarily restricts the inhaled air volume determining the outcome of the test. Declines in forced expiratory volume only represent decreases in FEV test performance and do not signal any damage to actual pulmonary function. There should be a re-interpretation, therefore, of all field studies and clinical studies using forced expiratory volumes as an index of pulmonary function changes

Many conclusions of the review are based on epidemiological studies that correlate observed health effects with monitored ambient ozone or PM10 concentrations without validating the actual personal exposures, or the delivered pollutant doses and without establishing the causal role of pollutants in these changes. The review should acknowledge that the epidemiologic studies cannot exclude other possible confounding factors and, therefore, cannot establish the causal role of ambient air pollutants in the observed effects unless plausible mechanisms are offered to explain the reported changes. These restrictions apply to all observed statistical associations of pollutants with increases in morbidity, medication consumption, or mortality. Concerns about statistical conclusions in the reported time-series studies are supported by dosimetry studies that show that the amounts of pollutants inhaled during 24 hr-exposures to current pollutant levels are too low to be responsible for complex effects such as morbidity and mortality.

As the Draft indicates, ambient PM is a mixture of many different elements and compounds, including organic, inorganic, and biologic materials. Therefore it is not surprising that EPA acknowledged in its recent PM review that there are unusually large uncertainties associated with establishing standards for PM relative to other single component pollutants. In response to the many concerns over the scientific basis for PM2.5 or PM10 standards, Congress authorized a dramatic increase in federal PM research and a National Academy of Sciences Panel was used to focus the effort on key issues. Some of that new research is now becoming available. Much more will be published over the next several years. The U. S. EPA is scheduled to release a public review draft of a new PM Criteria Document shortly. However, new studies of relevance to PM standard-setting are published monthly. As California reviews its PM standards, we urge the Staff to fully evaluate all of the available information.

In summary, we acknowledge that the California PM10 standards need to be reviewed. However, the review should be focused on identifying which, if any, of the components of ambient PM are causally related to health effects. In the case of ozone, the existing California standard is very close to peak once-per-year background levels. Since tightening the standard would not result in significant reduction in risk to children or others and any tightening of the standard would render it unachievable, we recommend against making ozone a priority for review under SB 25. The case for putting nitrogen dioxide in the first tier is weak. The controlled exposure studies cited suggest possible concern at concentrations above the existing standard. On the other hand, the existing state standard has been met everywhere in California, and ambient concentrations are expected to continue to decline for at least the next decade.

Comments for the California OEHHA/ARB Public Meeting of the Air Quality Advisory Committee on the Adequacy of California Ambient Air Quality standards: Senate Bill 25 – Children's Environmental Health Protection Berkeley, CA, October 12-13, 2000

Jon M. Heuss
Air Improvement Resource, Inc.

As noted in the comments submitted on October 4, 2000, we are focusing our comments on the first tier of pollutants recommended by OEHHA staff for review and possible revision. In particular I will focus on ozone and particulate matter (PM).

One of the five factors considered in assessing the standards' health protectiveness is the "degree of exposure relative to the level of the standard." Unfortunately, Chapter 3 and Appendix B of the Draft do not adequately discuss this factor. They fail to mention the existence of a significant background of ozone in the troposphere that arises from sources other than California or even U.S. precursor emissions. They also fail to inform the reader, except in very general terms, of the extent to which the existing state standards are exceeded throughout the state. These failures result in the omission of important facts that influence the determination of the health protectiveness of the existing state ozone and PM10 standards.

For example, there is a substantial background of ozone in the troposphere (that averages about 0.04 ppm but reaches 0.08 ppm on the order of once per year). It arises from several sources. One source is stratospheric ozone that mixes into the troposphere and is destroyed at the ground. Another source is photochemical reactions in the troposphere of natural geogenic and biogenic emissions: methane, isoprene, terpenes, and natural Nox from lightning and biological action in the soil. This background provides a practical limit as to how low any ozone air quality standard can be set. The transport of plumes of man-made ozone downwind of cities into rural areas is another phenomenon that occurs and can cause elevated ozone in rural and remote locations. However, there is also a well-documented phenomenon known as tropopause folding that inserts plumes with high concentrations of stratospheric ozone into the troposphere. These plumes are generally inserted well above ground level where they slowly mix into the general troposphere. But on rare occasions, they have been measured at ground-level with ozone concentrations up to 0.20 ppm or higher.

The state ozone standard of 0.09 ppm for 1-hour is defined as an extreme value standard; it is met when the Expected Peak daily Concentration (EPDC, that concentration expected to occur once per year) is below the level of the standard. In fact, the EPDC in the cleanest, lowest emission density counties and air basins of California are typically between).075 and).085 ppm. Similar

peak 1-hour ozone concentrations are also measured in other remote locations in the western U.S. This means that the amount of man-made ozone allowed by the existing state standard is on the order of 0.01 to 0.02 ppm. The presence of a substantial background of ozone needs to be taken into account in any decisions regarding revision of the California ozone standard. If the ARB decides to proceed with review of the state ozone standard, ARB staff should initiate detailed field studies of ozone levels and sources in remote California locations. When the current state standard was set in 1987, staff erroneously assumed that the ozone background did not exceed 0.04 ppm.

For PM10, ARB data summaries indicate that the state 24-hour standard is exceeded throughout the state except for compliance in a few high elevation counties. The maximum EPDC in Lake County is substantially below the state 24-hour standard, but in all the other rural and remote basins, the maximum EPDC is substantially above the existing state 24-hour PM10 standard. In the Great Basin Valleys, the maximum EPDC has been on the order of 400 $\mu g/m^3$ in recent years, or 8 times the state 24-hour standard. In contrast, the state annual geometric mean standard is met in the rural and remote areas of California but not in the more urbanized air basins. However, the maximum annual geometric mean PM10 in the rural and remote basins of California (except for Lake County) varies between 20 and 30 $\mu g/m^3$. It is known that wind-blown crustal material is the major contributor to high PM10 concentratio9ns in rural and remote areas of California. While some win-blown dust is controllable, much is not. Therefore, the level of PM10 that is achievable with complete elimination of man-made pollution varies substantially across California. There is also significant variation in the composition of PM10 across the state that would be expected to alter the toxicity per unit mass of PM. These variations need to be documented and taken into account in any decisions regarding revision of the California PM standards.

Section 3.6 on indoor and personal exposure needs to acknowledge that indoor ozone concentrations are dramatically reduced compared to outdoor concentrations (see Table B10-1) while PM exposures indoors are often elevated above outdoor concentrations. This also has important implications for the magnitude (and sources of) human personal exposure to ozone and PM.10. An informed discussion of the interpretation of the existing health studies must be predicated on what is known about human patterns. For ozone, this includes consideration of the probabilistic analyses carried out by EPA over the past decade. For PM, this includes consideration of the body of information concerning the relation of fixed monitors to indoor and personal exposures as well as factors such as the 0personal cloud, indoor combustion sources, and re-suspension of particles. Recent studies involving real-time measurements indicate that indoor activities such as cooking, cleaning, and even brisk walking generate high short-term exposures to ultrafine, coarse and fine PM. If outdoor PM is as dangerous as suggested by some epidemiologic studies, then these everyday human activities involve similar risks.

Another of the five factors that was considered in assessing the existing standards' health protectiveness is "the level of risk of effects anticipated at or near the level of the existing standard." When EPA last reviewed the national ambient air quality standards for ozone, the probabilistic risk assessment that will be discussed by Dr. Vostal played a key role. The U.S. EPA's Clean Air Science Advisory Committee (CASAC) concluded that because it appears that ozone may elicit a continuum of biological responses down to background concentrations, risk assessments must play a central role in identifying an appropriate level for the standard. However, when CASAC viewed the results of the probabilistic modeling, the risks for all segments of the population including outdoor children were small and the committee concluded that there was no "bright line" that distinguished any of the proposed standards as being significantly more protective of public health. The standards considered ranged from the existing 1-hour federal standard of 0.12 ppm down to levels roughly equivalent to the current California standard.

Although EPA promulgated an 8-hour ozone standard of 0.08 ppm, which is intermediate in stringency between the 1-hour federal standard and the existing California standard, EPA could not defend its choice adequately to the Court of Appeals when challenged by a group of small and large businesses as well as several states. The Court of Appeals noted that EPA regards ozone definitely and PM, likely, as non-threshold pollutants, that is ones that have some possibility of some adverse health impact (however slight) at any exposure level above zero. The court indicated that, therefore, the only concentration for ozone and PM that is utterly risk-free, in the sense of direct health impacts, is zero, and for EOA to pick any non-zero level, it must explain the degree of non-perfection permitted. However, the court found that EPA articulated no "intelligent principle" in applying the factors used to determine the public health concern associated with different levels of ozone and PM and remanded the new ozone and PM standards back to EPA. This issue is now in the U.S. Supreme Court.

No matter what the Supreme Court decides, California will have to address the same issues under SB 25 of what standards protect the public health, with an adequate margin of safety. Before any of the existing standards are revised, a much more extensive and critical review of the literature must be carried out, and some formal decision analytic framework or risk assessment procedure will be required.

For ozone, there is another factor that EPA is required to consider. The Court of Appeals ruled that the beneficial effects of ground-level ozone (in shielding the public from the harmful effects of the sun's ultraviolet rays, including cataracts and skin cancers) must be weighed in the same manner that ground-level ozone's ill effects are weighed. Although stratospheric ozone provides the main protection against UV, it is actually the total column of ozone that provides protection.

Turning to PM, as the Draft indicates, ambient PM is a mixture of many different elements and compounds, including organic, inorganic, and biologic materials. Therefore it is not surprising that EPA acknowledged in its recent PM review that there are unusually large uncertainties associated with establishing standards for PM relative to other single component pollutants. In response to the many concerns over the scientific basis for PM2.5 or PM10 standards, Congress authorized a dramatic increase in federal PM research and a National Academy of Sciences Panel was used to focus the effort on key issues. Some of that new research is now becoming available. Much more will be published over the next several years. The U.S. EPA is scheduled to release a public review draft of a new PM Criteria document shortly. However, new studies of relevance to PM standard-setting are published monthly. As California reviews its PM standards, we urge the Staff to fully evaluate all of the available information.

In summary, we acknowledge that the California PM10 standards need to be reviewed. However, the review should be focused on identifying which, if any, of the components of ambient PM are casually related to health effects. Among the hypotheses offered that may explain the PM-health associations are PM10 mass itself, fine particle mass, ultra fine PM, particle number count, particle surface area, reactive transition metals, acids, organic compounds, biogenic particles, sulfates, peroxides, elemental carbon, and gaseous co-pollutants. As noted above, there is substantial work underway to evaluate and discriminate among all these hypotheses. It is critically important to do this so that PM controls are focused on actions that improve public health.

In the case of ozone, the existing California standard is very close to peak once-per-year background levels. Since tightening the standard would not result in significant reduction in risk to children or others and any tightening of the standard would render it unachievable, we recommend against making ozone a priority for review under SB 25. The case for putting nitrogen dioxide in the first tier is weak. The controlled exposure studies cited suggest possible concern at concentrations above the existing standard. On the other hand, the existing state standard has been met everywhere in California, and ambient concentrations are expected to continue to decline for at least the next decade.

E.3 Comments to the Board

The Board received written comments from Mr. Jon Heuss prior to the December 7, 2000 Board Hearing. Copies of these comments follow, along with the ARB Staff response.

E.4 Response to Comments to the Board

As discussed in several reference books (Finlayson-Pitts and Pitts, 1999; Seinfeld and Pandis, 1998), levels of ozone worldwide before the industrial revolution appear to have been about 10-15 ppb. However, at the present time, levels of 30-40 ppb are found in even the most remote regions. This increase has been attributed to increased anthropogenic emissions of oxides of nitrogen (NO_X) and volatile organic compounds (VOCs). Much of the evidence for increased baseline levels of tropospheric ozone comes from European studies. An analysis (Volz and Kley, 1988) showed that surface ozone near Paris 100 years ago averaged about 10 ppb; current mixing ratios in the most unpolluted parts of Europe average between 20 to 45 ppb. An analysis of ozone measurements made in relatively remote European sites indicates a 1 to 2 % annual increase in average concentrations over the past 30 years.

The database of ground-level ozone observations for urban and suburban areas in California is fairly extensive. At most urban surface sites, ozone concentrations have been found to vary over a diurnal cycle with a low value recorded in the early morning hours and a maximum in the late afternoon. In addition to variation over a diurnal cycle, ozone concentrations at a given location also can vary significantly from one day to the next. It is not uncommon for the daily maximum ozone concentrations at an urban site, for instance, to vary by a factor of 2 or 3 from day to day as local meteorological conditions change. In and downwind of large urban areas, under certain meteorological conditions, emissions of NO_X and VOCs can result in ozone concentrations as high as 200 to 400 ppb. Apart from remote regions, where the *in situ* tropospheric chemical generation of ozone is driven essentially by methane, a large number of VOCs participate in ozone generation. Measurements of nonmethane organic compounds in southern California revealed over 280 hydrocarbon and oxygenated organic species, many of which contribute in some degree to ozone generation.

Background concentrations for ozone are defined as concentrations that would be observed in the absence of the ozone formed from anthropogenic precursor emissions of VOC and NO_X. Mr. Heuss's letter states that "the peak once-per-year 1-hour ozone concentrations at the most remote California monitoring sites are between 0.078 and 0.087 ppm". Due to pervasive anthropogenic influences, these do not represent a "natural background". The real challenge is to estimate what the natural background concentrations (which exclude all anthropogenic sources) are for ozone at the remote monitoring sites in California. Transported ozone, VOCs, and NO_X all affect ozone concentrations in downwind areas. It has been demonstrated that photochemically generated ozone starts accumulating during the daylight hours in urban areas, and then is transported downwind, and that precursors can continue to form ozone over distances greater than hundreds of kilometers for one or more days. Thus, the reported peak 1-hour ozone concentrations of 0.078 and 0.087 ppm at the remote California monitoring sites are likely indicative of both anthropogenic and natural impacts at those sites.

The U.S. EPA has accepted the approach of using remote monitoring sites in the world as a reasonable way to establish limits on natural ozone exposures, and believes that natural background levels of ozone range from 0.03 to 0.05 ppm. In its human health risk assessment, U.S. EPA assigned a health risk to every hourly average concentration above 0.04 ppm.

Global background ozone concentrations (typically around 40 ppb annual average) are used to estimate the anthropogenic reductions needed to attain Ambient Air Quality Standards. Due to stratospheric intrusion, this value could be higher on design value days, as Mr. Huess stated in his letter. However, stratospheric intrusion is relatively infrequent, and data are almost never available to document and quantify its influence on the design days. Also, the processes associated with stratospheric intrusion are often not associated with days with design value ozone concentrations.

Figure 1 below presents vertical profiles of temperature, relative humidity, and ozone concentration at Trinidad Head in November 2000. Data from this remote coastal site indicates a background tropospheric ozone concentration of about 40 ppb. Once the tropopause is reached (where the temperature ceases to decline adiabatically (about 12.5 km in this case), the ozone concentration in the lower stratosphere begins to increase rapidly.

The high ozone concentrations in the stratosphere can advect into the troposphere under a variety of relatively rare processes. Figure 2 illustrates some days during 1999 when ozone concentrations on Mauna Loa increased substantially (max/mean ratio >= 1.5). This ratio occurred about 5% of the time during 1999. These events are not necessarily due to stratospheric ozone intrusion, and much more research would be needed to determine the cause(s).

One potential technique for differentiating between natural and anthropogenic ozone episodes is to look at the O3/CO ratio. Theoretically, this ratio would be higher than ~0.35 (assuming background ozone about 0.035 ppm and background CO about 0.1 ppm). Unfortunately, most remote monitoring sites do not collect CO data, and often the level of detection of the instruments is too high. Figure 3 is a sample of some data collected during SCOS97 (Southern California Ozone Study, 1997) at Mt. Baldy. This is a mountain site downwind of the Southern California Air Basin, and had two observations that could possibly have some non-anthropogenic contribution.

Figure 4 provides some information on the variations in global background ozone concentrations at some "clean" sites around the world, indicating that most of these remote areas averaged between 20 and 40 ppb ozone.

A logistically sound procedure to establish an environmental quality standard must involve several steps. First, one should establish the risk to human health or welfare as a function of the dosage of a pollutant. This step involves study of the onset of adverse health effects due to a pollutant or a group of pollutants. Second, one should determine the maximum acceptable risk based on risk-benefit and other considerations. This risk level constitutes the basis for an environmental quality standard, and corresponds to a specific level of exposure. In this connection, the California air quality standards are designed to protect public health.

Thus, as the California Clean Air Act requires, we must review and consider possible revision of the health-based ambient air quality standards to assure that standards are based on the latest scientific information, and that the standards protect public health with an adequate margin of safety. The California Clean Air Act mandates that ambient air quality standards be health based. Possible impacts of stratospheric ozone or background pollutant concentrations on ambient air quality are considered in the planning process for standard implementation. Whether standards are currently achievable is also an issue for implementation of the standards, not for selection of the level of the standards.

References

Finlayson-Pitts, B.J., and J.N. Pitts, Jr. Chemistry of the Upper and Lower Atmosphere. Theory, Experiments and Applications. Academic Press, San Diego, CA. 1999.

Seinfeld, J.H., and S.N. Pandis. Atmospheric Chemistry and Physics. From Air Pollution to Climate Change. John Wiley & Sons, Inc. New York. 1998.

Volz, A., and D. Kley. Evaluation of the Montsouris series of ozone measurements made in the Nineteenth Century. Nature. 332: 240-242. 1988.

Figure 1:

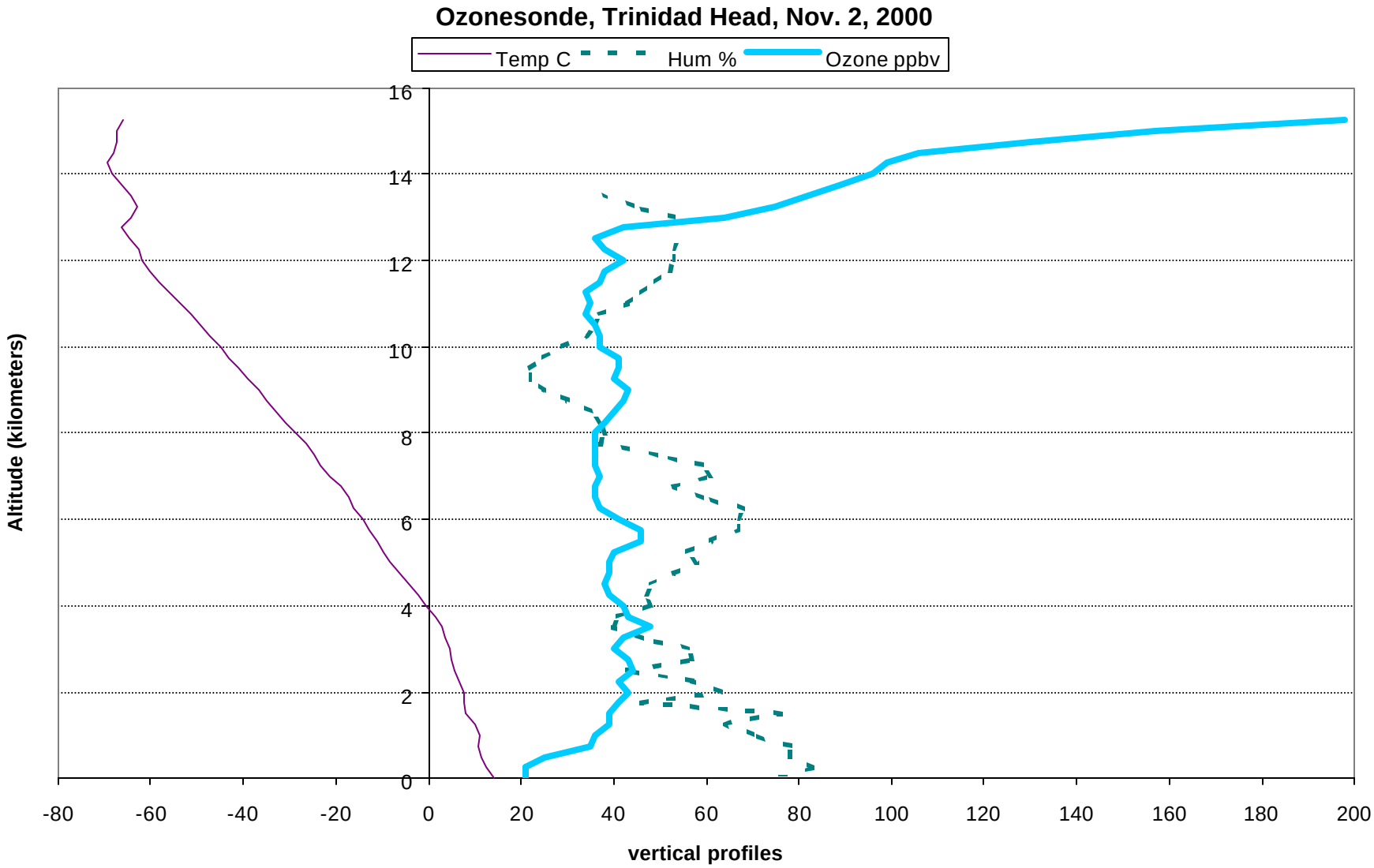

Ozonesonde, Trinidad Head, Nov. 2, 2000
Temp C
Hum %
Ozone ppbv
Altitude (kilometers)
0
2
4
6
8
10
12
14
16
-80
-60
-40
-20
0
20
40
60
80
100
120
140
160
180
200
vertical profiles

Figure 2:

Diurnal Ozone Concentrations (ppb) at Mauna Loa, HI during 1999 on days when max/mean >= 1.50

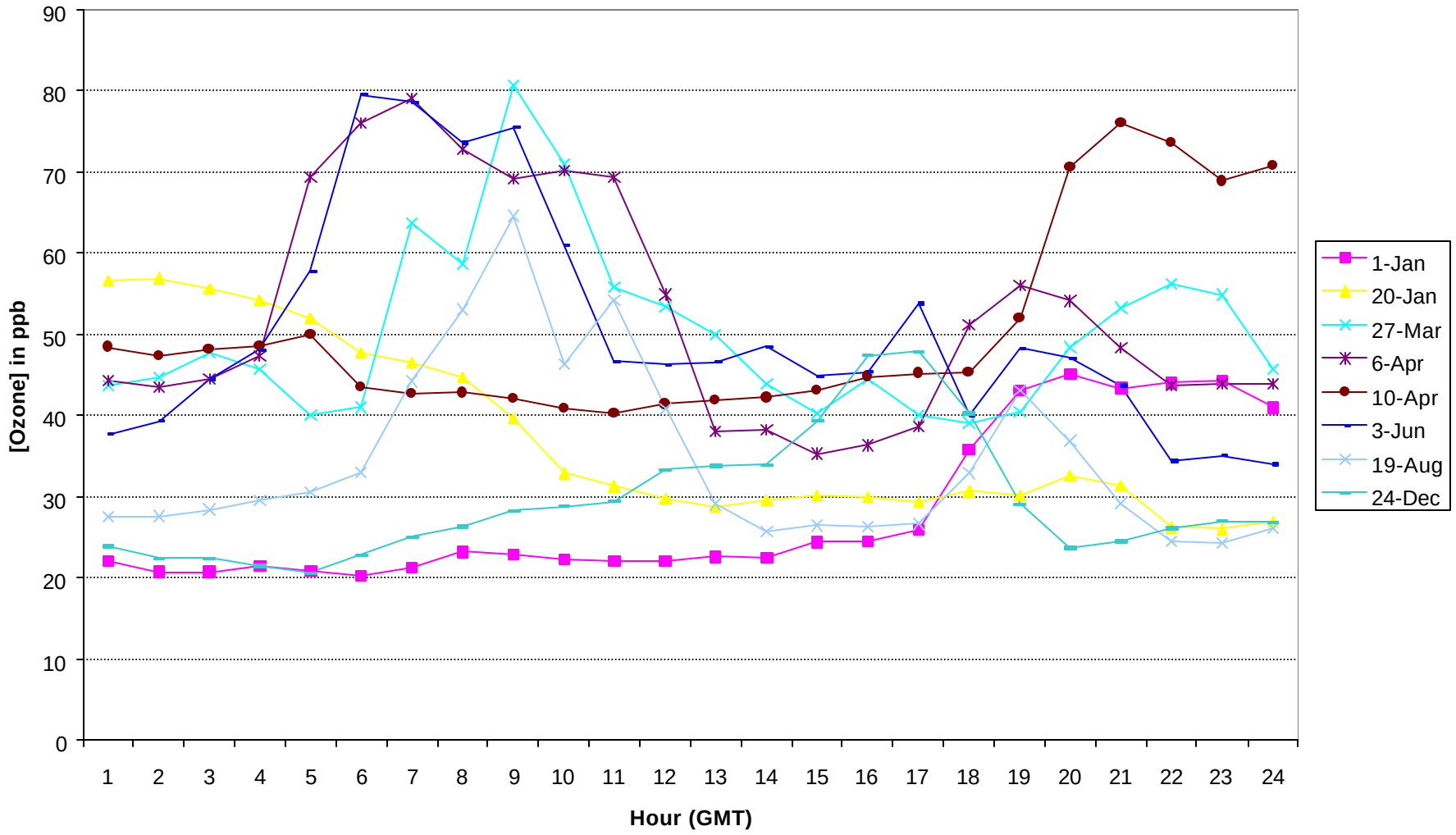


Figure 3: CO, O3 and Their Ratio on Mt. Baldy.

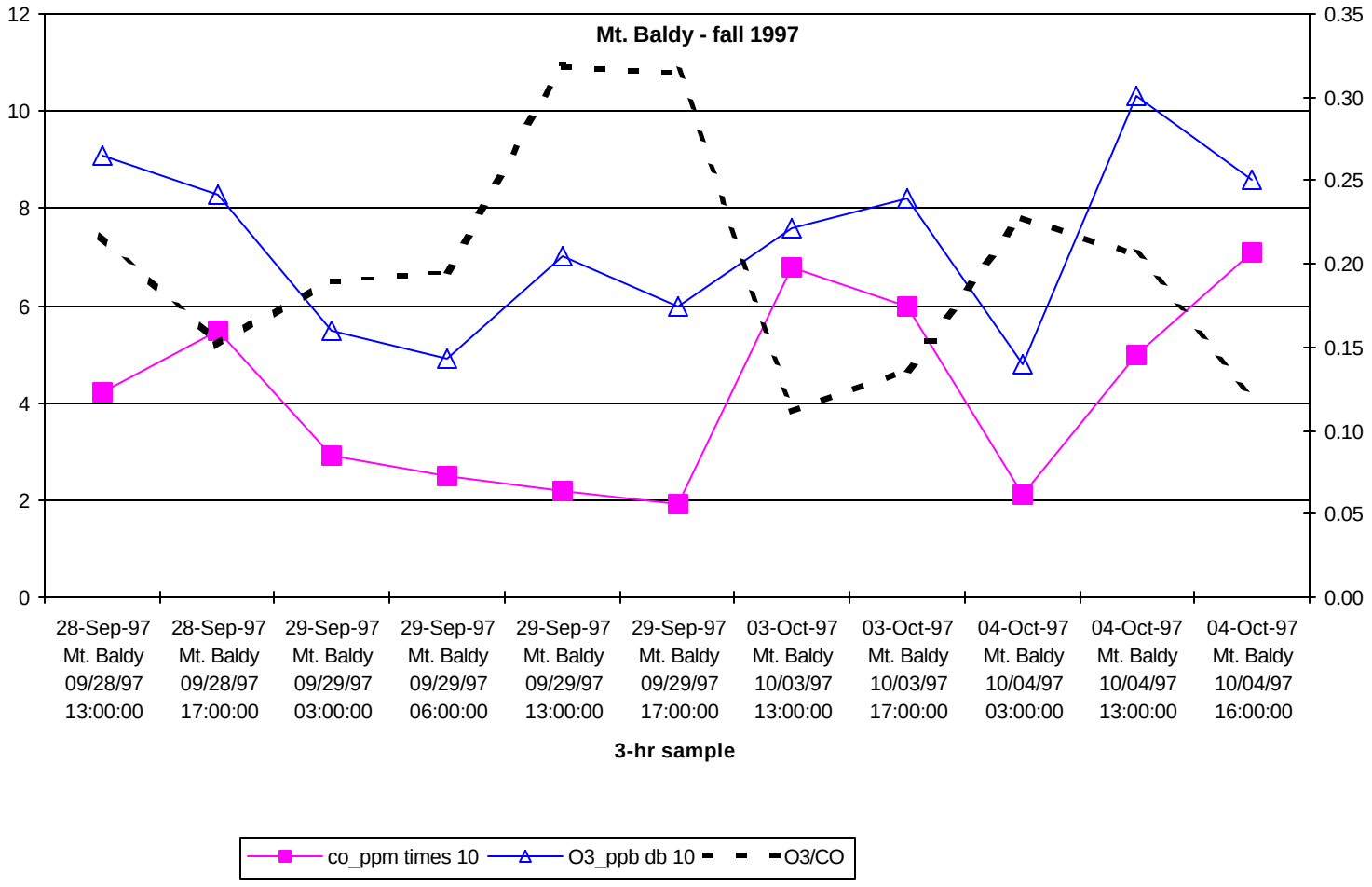
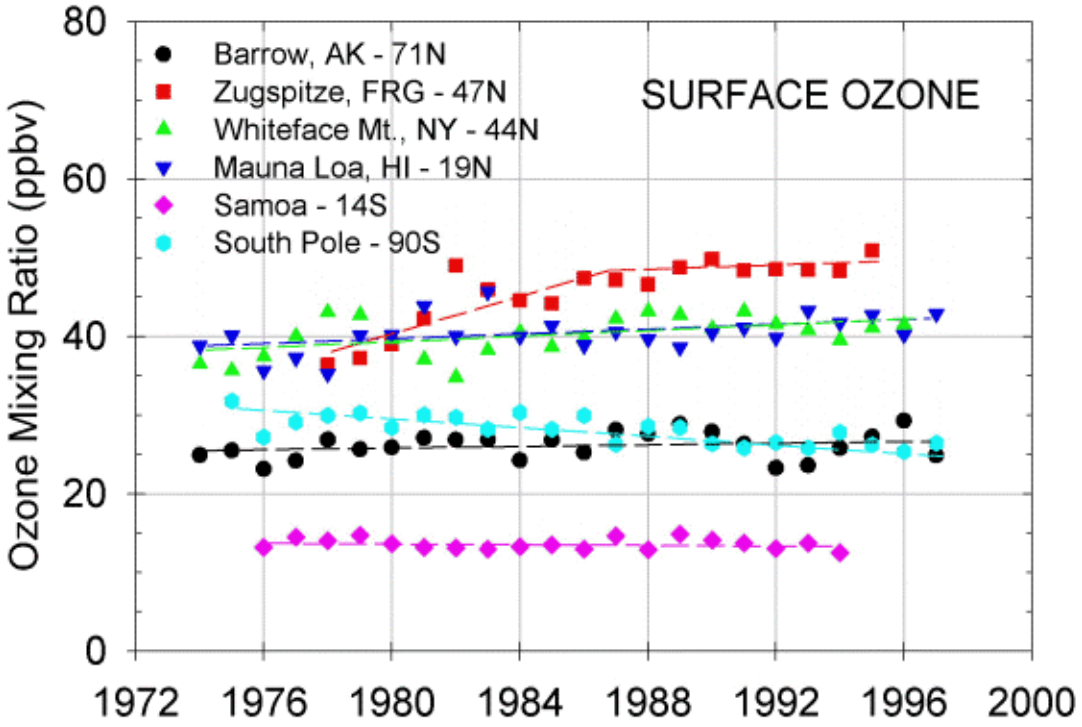


Figure 4: Surface ozone at remote sites





December 4, 2000

Clerk of the Board
Air Resources Board
P. O. Box 2815
Sacramento, CA 95812

Re: November 2, 2000 Staff Report Adequacy of California Ambient Air Quality Standards: Children's Environmental Health Protection Act

At the request of General Motors Corporation, Dr. J. J. Vostal of Environmental Health Consultants International and I provided written and oral comments on the September 12, 2000 Draft Staff Report. We were pleased that the written comments provided prior to or at the October 12-13 meeting of the Air Quality Advisory Committee were included in Attachment E of the November 2, 2000 Staff Report. However, we were disappointed in the ARB summary of and response to our comments. The summary on page E-2 lumps our comments into two general points and responds to each point in a general fashion. We believe the specific comments we made are relevant to the strength of the evidence concerning the adequacy of the current California air quality standards to protect children's health and the priority for review under SB 25.

Three points concerning the current ozone standard are particularly relevant to the recommendation that ozone should be a priority one pollutant.

First, background ozone provides a practical limit as to how low any ozone air quality standard can be set, and the current California standard is already very close to the background of ozone. The statement on page C-2 that "the background concentration of ozone is currently about ½ of the state standard, or 0.04 ppm" is misleading because it is an "apples-to-oranges" comparison. The ozone background does average about 0.04 ppm over a year, but the state standard is not an annual average concentration. The state standard is a once-per-year peak 1-hour concentration of 0.09 ppm. The peak once-per-year 1-hour ozone concentrations at the most remote California monitoring sites are between 0.078 and 0.087 ppm. The peak once-per-year 1-hour background ozone concentration has been estimated by the U. S EPA at between 0.060 and 0.075 ppm. Substantially higher concentrations of ozone due to stratospheric intrusions have been measured at ground level, albeit rarely. Although stratospheric intrusions rarely bring high ozone concentrations

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directly to the ground, they routinely insert layers of elevated ozone in the free troposphere which contribute to a substantially varying background.

A more complete analysis of the sources and levels of background ozone is attached. If the peak 1-hour background ozone at a site is 0.078 ppm, for example, that represents 87 % of the current 1-hour standard at the site and would allow only 0.012 ppm ozone from man-made emissions on the day in question.

Second, the risk assessment carried out by the U. S. EPA during its latest review of the federal ozone air quality standard documents that exposures of concern for outdoor children will be rare upon attainment of the current California standard. As noted in the Staff Report, the effects most consistently reported at low ambient concentrations in epidemiological studies are decrements in several measures of lung function. When the U. S. EPA and its Clean Air Science Advisory Committee (CASAC) evaluated the significance of small functional changes, it concluded that small functional responses in either healthy or asthmatic individuals would not be considered medically significant and would not be expected to interfere with normal activity. Even isolated events with moderate functional changes were not considered to be of public health significance. Only when moderate responses were repeated did CASAC members indicate that it was a matter of public health concern.

Third, since the 1996/1997 EPA review, new information on the mechanism of reported lung function changes has been published which substantially reduces the concern over measured changes or decrements in lung function. A 1998 U. S. EPA study has documented that the changes in performance of respiratory function tests are primarily the result of irritated nerve receptors not cellular injury in the respiratory airways. In essence, the measured declines in lung function are only declines in test performance due to the body's nervous system sensing the presence of an irritating gas and limiting maximal inspiration and not any damage or change to pulmonary function. Based on this new information, which is not discussed in the Staff Report, the public health significance of field and clinical studies using forced expiratory volume as an index of pulmonary function changes needs to be re-evaluated.

In summary, these three points taken together document the very conservative, health-protective nature of the current California ozone standard. They need to be considered by the Staff and the Air Resources Board before the decision is made to make ozone a high priority for review.

The Notice for the December 7, 2000 ARB hearing indicates that the ARB under SB 25 requires the Board to review, and if necessary revise, air quality standards "determined to be inadequate to protect infants and children with an adequate margin of safety." However, the Staff Report does not make or recommend a determination that certain standards are inadequate to protect public health. Rather it identifies pollutants "representing greater potential risks to public health at the concentrations of the current air quality standards." Further, it is indicated that "recent scientific publications suggest that health effects may occur when ambient levels of these pollutants are at or near the current State ambient air quality standards." In the response to comments (page E-2), staff indicates:

> "The purpose of the reviews presented in the staff report was to consider whether there was evidence suggesting that any of the California Ambient Air Quality

> Standards should be reviewed with reference to adequacy of protection of infants, children and other susceptible populations. It was not the intent of staff to provide complete reviews on each pollutant."

Given the stated purpose and limited nature of the Staff/OEHHA review and the many caveats in the way the results are presented, it would miss-characterize the recommendations for review as a determination that the current standards for these pollutants are inadequate. Rather the recommendations indicate that some of the current standards may or may not be adequate and thus should be reviewed, and revised if necessary, based on a full analysis of all the relevant information.

Finally, we were also disappointed that Dr. Vostal's written comments provided to OEHHA after the Advisory Committee meeting but prior to the issuance of the November 2, 2000 Staff Report were not included in Appendix E. Please include those comments in the record.

I appreciate the opportunity to provide these comments. Thank you for your consideration.

Yours truly,

Jon Heuss
Principal Scientist
Air Improvement Resource, Inc.

cc: Members of the Air Resources Board
Dr. Bart Ostro, OEHHA
Mr. Bart Croes, Chief, ARB Research Division
Mr. Sam Leonard, General Motors Corporation
Mr. Al Weverstad, General Motors Corporation
Dr. Jaroslav Vostal, Environmental Health Assessment Consultants, Int.

Att:

Attachment to 12/4/00 AIR, Inc. letter to California Air Resources Board

Summary of the scientific evidence for the sources And levels of background ozone in California

Ozone is present in the atmosphere due to both natural processes and the photochemical reactions of man-made emissions. During the Air Quality Advisory Committee meeting on October 12 Dr. Kleinman indicated:

> "ozone is one of those rare environmental pollutants that we do have a natural background of which strangely enough is right around the 30 ppb level" AQAC Transcript at page 62.

One of the main points raised by Mr. Heuss during public comments at the meeting was that there is a variable background of ozone that averages 0.04 ppm (40 ppb) but that reaches as high as 0.08 ppm (80 ppb) about once-per-year in remote locations. In response to a request from Dr. Lipsett of OEHHA to address the issue of background ozone and stratospheric intrusions into the troposphere "because we rely on you for those assessments as to what background levels are in California," ARB staff indicated:

> "We're certainly aware of the research done on tropopause folding in the eastern U. S. We have not done a comprehensive study here in California, but the data that we have looked at from our field studies and from background ozone monitors off shore indicate that the global background that we see is 0.04 ppm with no – and every excursion about the 0.04 level appears to be associated with transport from urban areas." AQAC Transcript at page 115-116.

There is particular interest in what we will call "background ozone" because it defines a lower boundary for the amount of ozone that will exist in the absence of man-made emissions. This attachment discusses the various sources of ozone in the atmosphere as well as the levels of ozone that arise from the various sources. In addition, the definition of background ozone is discussed.

Sources of ozone in the troposhere

It is well established that there is a background of ozone in that atmosphere. The U. S. EPA's 1996 Criteria Document (CD) summarizes the sources of background ozone as follows:

> "The background of O_3 can be attributed to the following sources: downward transport of stratospheric O_3 through the free troposphere to near ground level, in situ O_3 production from methane emitted from swamps and wetlands reacting with natural NOx emitted from soils and lightning strikes and from downward transport of NO from the stratosphere into the troposphere, and in situ production of O_3 from the reactions of biogenic VOCs with natural NOx. Another source to be considered is the long-range transport of O_3 from distant pollutant sources." 1996 Ozone CD at page 3-6

For the purposes of the State of California, the important question is what level of ozone would exist with total elimination of anthropogenic or man-made emissions in California. Although other definitions are possible, the practical question in California is how low ozone would be if all California man-made emissions were eliminated. There is some evidence that the background of ozone may have risen over the past hundred years, as global methane and NOx emissions have risen. There is also evidence for long range transport of man-made ozone influencing distant sites. However, the issue for California is not what natural ozone may have been in some pre-industrial past but rather what the concentrations of ozone are now due to sources outside the state and non-anthropogenic sources within the state.

The photochemical production of ozone was discovered in Los Angeles in the late 1940's when Prof. Haagen-Smit demonstrated that photochemical reactions between oxides of nitrogen and hydrocarbons in the presence of sunlight produce ozone. In the intervening years, it has been shown that natural biogenic and geogenic emissions as well as man-made emissions participate in these photochemical reactions. It has also been shown that ozone itself photolyzes in the atmosphere and reacts with various other constituents. Thus, there is both photochemical production and destruction of ozone occurring in the atmosphere.

It is also well known that ozone is formed in high concentrations in the stratosphere due to oxygen molecules absorbing short wavelength radiation from the sun (175 to 240 nm). In fact, the presence of stratospheric ozone (which absorbs the sun's radiation below 290 nm) protects humans and ecosystems by filtering out dangerous ultraviolet radiation. A major sink process for the ozone in the stratosphere is transfer into the troposphere and eventual destruction at the ground. Several mechanisms for stratospheric-tropospheric exchange have been postulated and studied. Shapiro[i] summarizes these mechanisms as follows: "The various meteorological processes by which air and its chemical constituents are exchanged between the stratosphere and troposphere may be summarized as 1) the mean meridional Hadley cell circulation; 2) the seasonal variation in the height and potential temperature of the tropical tropopause; 3) changes in the potential temperature and vertical displacement of the tropopause through radiative cooling above the jet stream and cumulonimbus cirrus clouds at the tropopause; 4) transverse mass circulations about subtropical jet stream systems; 5) vertical mass exchange during tropopause "folding" events associated with extratropical cyclonic systems; 6) cumulonimbus towers which penetrate the tropical and extratropical tropopause; 7) clear air turbulence (CAT) in the vicinity of jet streams (resulting from vertical wind shear instabilities within tropopause folds) and in the region of decreasing winds in the stratosphere above the jet core; and 8) weak eddy diffusion across the vast quiescent expanses of the tropopause."

The fifth mechanism noted above, tropopause folding events, is of particular interest because it has been amply documented that it inserts layers of high ozone concentrations into the troposphere.

Evidence concerning tropopause folding events

Published observations of stratospheric ozone in the troposphere during intrusion events began appearing in the literature in the 1960's. In 1981, Johnson and Viezee[ii] reported

on the results of 10 aircraft flights during the spring and fall of 1978 mapping the structure of stratospheric ozone intrusions over the central U. S. They concluded:

> "The intrusions typically are characterized by peak ozone concentrations at higher altitudes (6-8 km) in the range of 240-400 ppb, diminishing to 100-200 ppb at lower altitudes as mixing with surrounding air occurs. The data show that stratospheric ozone intrusions are typically 100-300 km wide in the cross-wind direction, are several hundreds of kilometers long, and can be tracked down at least as far as the top of the atmospheric boundary layer (about 2 km). Possible mechanisms for downward transport within the boundary layer include normal convective mixing, organized convection associated with cloud and precipitation processes, and organized downward motion within frontal zones."

In a follow-up paper by Viezeee, Johnson and Singh,[iii] the authors assessed the downward flux of ozone and its probable impact on ground-level ozone. They summarized and evaluated 17 aloft observations of stratospheric ozone made by aircraft or balloons and 10 published studies that in which elevated ground-level ozone measurements have been ascribed to stratospheric ozone. They estimated that direct ground-level impacts are infrequent (less than 1 percent of the time) and most likely are associated with ozone concentrations of 100 ppb or less.

One of the reasons that that direct ground-level impact seems rare is that, as documented by Johnson and Viezee, the ozone intrusion tends to become more nearly horizontal as it progresses toward lower altitudes. Viezee et al note:

> "Several investigators maintain that the stratospheric air reaches ground-level in about two days by way of surface high-pressure systems that follows travelling upper tropospheric low-pressure troughs. If this concept is correct, it will be difficult to quantify (on the basis of measurements) the stratospheric component of the near-surface ozone budget, since high-pressure areas also are favorable for air stagnation and surface transport of anthropogenic ozone."

Indeed, Wolff et al.[iv] have reported on field studies in rural locations in Kentucky and North Carolina and a remote location in South Dakota. They found that ^{7}Be, a tracer of stratospheric air, is higher on the backside of high-pressure system than on the front side. Although there are limitations to using ^{7}Be as a tracer for stratospheric air, this finding suggests that a substantial amount of stratospheric ozone does mix to the ground under conditions where anthropogenic ozone formation is also expected.

Shapiro[1] has also reported evidence for the seventh mechanism noted above - clear air turbulence (CAT) in the vicinity of jet streams (resulting from vertical wind shear instabilities within tropopause folds). He reports ozone concentrations of over 200 ppb over Southern California in March 1978.

With multiple mechanisms of stratospheric-tropospheric exchange and with multiple ways that stratospheric ozone may mix with tropospheric ozone, it is not surprising that there is a great deal of variation in free troposheric ozone concentrations. For example, Gregory et al.[v] report ozone measurements in the free troposphere at altitudes from 5 to 7.5 km measured by aircraft traversing from 44 N latitude to 46 S latitude in the fall of 1982. They reported higher ozone concentrations in the Southern Hemisphere (with a 2 degree zonal average as high as 80 ppb). During one flight, a region of elevated ozone

was determined to be of stratospheric origin with a maximum ozone concentration of 110 ppb. In contrast, similar flights in 1978 had shown higher ozone in the Northern Hemisphere. The combined data sets demonstrate that ozone levels in the free troposphere can be highly variable, so that one cannot assume that the free troposphere is a well-mixed reservoir of ozone.

Aircraft measurement over the eastern U. S. and western Atlantic during the spring of 1996 reported by Parrish et al.[vi] confirm the significant variability in tropospheric ozone concentrations. In 72 hours of measurement during nine flights, ozone concentrations varied between 30 ppb and 285 ppb. The authors used the CO-ozone relationship to discriminate between stratospheric and anthropogenic influences. The authors indicate that strong statospheric influences were observed on more than half the flights with ozone levels as high as 285 ppb. There was evidence of anthropogenic influence that resulted in net production of ozone at some times and net destruction of ozone at other times. Most data points reflected both stratospheric and anthropogenic influences

Parrish et al. also evaluated the transport of NOx species out of the boundary layer and reported that, in this springtime period, only a few percent of the emitted NOx is transported out of the boundary layer either as NOx or its oxidation products. Therefore, the authors concluded that the potential for photochemical ozone production from exported anthropogenic pollution is limited. Finally, they concluded that these measurements suggest that the direct effect of anthropogenic surface emissions on tropospheric ozone is approximately neutral in the spring.

A recent study by Beekmann, et al.[vii] used several techniques to evaluate the presence of tropopause folds. They report that:

> "on the average, folds occur twice as much in the Northern than in the Southern Hemisphere. In the Northern Hemisphere they are concentrated in the latitude band 40-70 degrees. On the average, 18.4 folds are simultaneously present in the Northern Hemisphere."

The number of simultaneous folds (estimated through analysis of a 10-year meteorological data set) is roughly four times the number estimated by Viezee, et al. in 1983. Beekmann et al. also refer to a 1996 study that shows tropopause folds are often detected in the front side of troughs, but also in their rear and in regions of zonal flow of the polar jet stream. With the meteorological analysis, Beekmann et al. found that significant tropopause folding activity was present over the ten-year period over the Northern Pacific as well as over California. (See Figure 2 of Beekmann et al.)

Emmons et al.[viii] have recently compiled data for ozone and other chemical species from a number of aircraft studies into global maps. The maps provide information on ozone averaged onto 5 degree latitude by 5 degree longitude horizontal grids with 1 km vertical resolution. The available data show elevated ozone concentrations of between 40 and 100 ppb in the grids 6-8 km over the west coast of the U. S. in the March-April-May quarter (see Plate 1 of Emmons et al.). The data for other locations, heights and time periods demonstrate significant variability in tropopheric ozone levels. This large data set clearly demonstrates that ozone levels in the troposphere are highly variable, so that one cannot assume that the free troposphere is a well-mixed reservoir of ozone.

Contributions of various sources to ground-level ozone

The evidence for tropopause folding events as a large source of stratospheric ozone that is inserted into the troposphere is overwhelming. However, the contribution of this large ozone source to ground-level ozone is still somewhat uncertain. For example, Beekmann et al. indicate:

> "Although the formation mechanisms of tropopause folds are now well-understood, detailed knowledge to which extent intruded air masses succeed in entering the lower troposphere, the planetary boundary layer, or even the ground level, is still lacking"

There is also substantial uncertainty regarding other source and sink processes that determine the tropospheric ozone budget. In 1985 Vukovich, et al.[ix] indicated:

> "Thus it is now recognized that the tropospheric ozone budget consists of four components: transport from the stratosphere; photochemical production; deposition at the ground; and photochemical destruction. Although each term contributes significantly to the tropospheric ozone budget and the estimates of each one yield a comparable order of magnitude, the quantification of each of these terms is difficult. Thus, a global estimate of any of them at the present time probably cannot be achieved to better than a factor of 2 or 3."

Even today, there is still significant uncertainty in the strengths of the various photochemical sources and sinks. For example, Parrish et al. note that many photochemical model results indicate that the net anthropogenic effect on tropospheric ozone levels is positive in all seasons, a finding which disagrees with the observations they report in the spring. There is also disagreement over how many ozone molecules are produced, on average, from each NO molecule emitted. The recent NARSTO Synthesis Report[x] indicates that more recent studies have reduced the estimated ozone production efficiency from 7 to 10 molecules ozone per molecule NOx emitted down to 1 to 3. In addition, the NARSTO report acknowledges there is substantial disagreement over key factors such as the magnitude of U. S. biogenic VOC emissions (uncertain by a factor of 2 or 3) and natural NOx emissions from soil and lightning.

Although there are various estimates in the literature for the strength of the various sources and sinks for tropospheric ozone, they all contain significant uncertainty due to the extremely complex chemistry and meteorology that is involved. Emmons et al. include several comparisons of predictions from global chemical transport models with observations. They indicate that the comparison with available observations has been able to identify incorrect emission sources, incorrect strength of convection and missing chemistry in the models. Although the problem cannot be successfully modeled yet, there is another approach that has been used to bound the problem. As discussed in the next section, actual measurements of ground-level ozone and other atmospheric constituents in upwind and remote locations have historically been used to estimate background ozone.

Background deduced from measurements

The level of background ozone became a policy issue in 1971 when EPA set the first National Ambient Air Quality Standard for Photochemical Oxidants at a concentration of

0.08 ppm for 1-hour, not to be exceeded more than once per year. In 1978, Singh et al.[xi] reported an analysis of long-term ozone data from remote sites that indicated summertime average 1-hour maxima in the 40 to 50 ppb range but maximum 1-hour concentrations that can approach or exceed 80 ppb in the spring. Singh et al. concluded that achievement of a yearly 1-hour ozone standard of 80 ppb may be impossible.

In the U. S. EPA's 1978 Criteria Document for Ozone and other Photochemical Oxidants, the Agency concluded:

> Based on the evidence of stratospheric-troposheric interchange, the annual average stratospheric contribution to ozone concentrations at ground level is estimated to be 0.022 to 0.05 ppm. The highest concentrations, at or above 0.08 ppm, from that source are expected to occur mostly during April and May."

When EPA revised the federal 1-hour ozone standard in 1979, the Agency acknowledged that:

> "Field measurements at some remote sites, where man-caused ozone is likely to be negligible, have shown low-but not insignificant- rates of exceedances of the 0.08 ppm level originally proposed for the secondary standard." 44 Fed. Reg. 8212, February 8, 1979.

In 1989, Logan[xii] reported the results of an analysis of ozone data from rural locations in the U. S. She reported that ozone concentrations above 80 ppb were common in rural areas of the eastern U. S. in spring and summer (occurring between about 2 and 8 % of the time) but were unusual at remote western sites, occurring less than 0.5 % of the time. She also pointed out that concentrations of NOx in rural areas of the east are frequently high enough to permit significant photochemical formation of ozone during favorable weather conditions, but that NOx is much lower in remote regions of the west. Importantly, Logan reported that the median ozone concentrations of 30 to 40 ppb were similar at rural sites across the country even though there is a much greater population and emission density in the eastern U. S. than in the western U. S.

Lefohn and Foley[xiii] reported in 1991 on an analysis of ozone data from 26 Class I national parks and wilderness areas. For the seven cleanest sites, the yearly maximum 1-hour average concentrations were in the range of 0.06 to 0.075 ppm.

In 1996, Altshuller and Lefohn[xiv] published an analysis of background ozone in the planetary boundary layer of the U. S. They used the following definition of background ozone:

> "The background of ozone may be considered as that portion of total surface ozone that results from photochemical reactions of biogenic or geogenic precursors and from downwind transport of stratospheric air into a specified area. The concentration of background ozone varies as a function of geographic area, elevation, season, and averaging time."

They selected 11 sites for analysis. The criteria they used included using sites receiving the cleanest air masses from the upwind flow off a continent or ocean, and sites isolated from the influence of urban plumes or regional ozone formation from anthropogenic emissions. They reported that the maximum 1-hour concentrations in the western

United States in the April through October period ranged from 50 to 98 ppb and the maximum 1-hour concentrations at coastal sites ranged from 44 to 80 ppb. Most of the exceedances of 80 ppb they reported were from Yellowstone National Park and were influenced, apparently, by forest fires.

The U. S. EPA estimated background ozone during review of the federal ozone standard in 1996/7. At that time, the agency's Staff Paper concluded:

> "…a reasonable estimate of the background O_3 concentrations near sea level in the U. S. for a 1-hour daily maximum during the summer is usually in the range of 0.03 to 0.05 ppm. At clean sites in the western U. S., the maximum annual hourly values are in the range of 0.06 to 0.075 ppm." OAQPS Staff Paper at page 20

In California, the Expected Peak Day Concentrations in the most remote California sites are also significantly above 0.04 ppm. As reported in attachment E of the September 29, 2000 ARB Staff Report on Area Designations, the yearly peak 1-hour ozone concentrations in the most remote sites are in the range of 0.07 to 0.087.

In addition to the evaluation of peak hourly concentrations in long-term monitoring at remote sites, there is also observational data and analyses in the literature that focus on specific episodes of elevated ground-level ozone that may be of stratospheric origin. As noted above, Viezee, Johnson and Singh compiled 10 episodes in which elevated ground-level ozone had been ascribed by various authors to a stratospheric source. For the purpose of this review, I will summarize four other episodes. This is not a complete list of the episodes that have been identified; rather they are meant to serve as examples.

Chung and Dann[xv] report an observation of elevated ozone that lasted for about a day in December 1980 in Regina, Saskatchewan that they ascribe to downward transport from the stratosphere. There were several peaks during the episode including one with an ozone concentration of 228 ppb. Proyou, et al.[xvi] report a three day episode of 60 ppb ozone with a peak of 85 ppb in February 1988 in Aubere France that they ascribe to stratospheric origin. Chan and Smith[xvii] report an episode of elevated ozone accompanying a frontal passage in December 1974 at a remote site in eastern Utah that averaged about 60 ppb for a day and had a peak of 80 ppb. Finally, Logan[12] in her analysis of rural ozone in the U. S. reports on a large-scale regional episode of elevated ozone in March 1978 that lasted several days and had daily maximum concentrations exceeding 120 ppb on two days. A detailed meteorological analysis by Mukammal et al.[xviii] has ascribed the high values of ozone in this episode to a stratospheric intrusion event. These examples together with the earlier examples in the literature demonstrate that ozone of stratospheric origin does reach ground-level in concentrations considerably higher than 0.04 ppm. They also demonstrate that the concentrations, duration, and meteorological conditions under which such episodes are found vary significantly. This suggests that there are several different mechanisms by which stratospheric ozone reaches ground-level at various times and places.

In many of these episodes, the elevated ozone was monitored at times when photochemical production from man-made precursors was not expected, so the data attracted attention and further analysis. However, the known patterns of tropospheric folds together with the ground-level ozone-^{7}Be analyses by Wolff et al. suggest that

stratospheric ozone also contributes significantly to ground-level ozone during times when man-made ozone is present. In these situations, routine monitoring data will not be able to distinguish the anthropogenic contribution from the stratospheric contribution.

Logan indicated that the regional intrusion episode noted above was only one of 17 multi-day episodes she found over the eastern U. S. during a two-year period. However, it is likely that stratospheric ozone contributed to some of the other 16 episodes that occurred under conditions favorable for photochemical production. Although the ARB and the U. S. EPA have "exceptional event" policies, it is clear that only a small portion of the stratospheric intrusions that affect ground-level ozone concentrations will be uniquely identified and thereby qualify for the exceptional event policy.

In summary, the scientific literature on background ozone indicates that it may average about 40 ppb, but that it is highly variable and can reach levels close to the current California 1-hour standard on the order of once per year.

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Appendix F

General Issues in the Evaluation of Children's Environmental Health

December 22, 2000

F.1 Introduction

Under the mandates of the Children's Environmental Health Protection Act (SB25, 1999), OEHHA must consider age-related differences in exposure patterns and in susceptibility to pollutant toxicity, focusing on infants and children. To this end, we have taken into account relevant published epidemiological, toxicological, and behavioral data, where available. As noted in section 4.2.1, examining age-dependent toxicity in children is a difficult task. In this Appendix, we highlight a few of the principal differences between infants and children relative to adults that may result in differential responses to ambient air pollutants and make it difficult to extrapolate effects from one age group to another.

Investigating potential air pollution-related effects in children presents challenges due to the numerous physiological factors that must be considered, including rapid growth, changes in fluid and protein content, organ function, metabolic rates and enzymatic function that characterize childhood. A child's behavior patterns, as well as his or her environment, allow for exposures that are both quantitatively and qualitatively different than adults. Premature infants, term newborns, young children, and adolescents are age groups unique in all these respects. Inter-individual variability in response due to genetic polymorphisms creates an additional dimension of complexity.

F.2 Children's Exposure Patterns

Children's exposures are influenced by their activities and where these activities take place. Compared to adults, they spend more time outdoors and in active play and sports. A study of activity patterns in California found that children under 12 years of age spent an average of 124 minutes per day engaged in active sports, hiking, or outdoor activities compared with only 21 minutes for adults (Wiley et al. 1991; see also Section 3.6 regarding indoor exposures).

Newborns and young infants spend considerable time in a single environment (e.g. a crib) compared with more mobile older children. An infant or toddler may be unable to remove him or herself from an irritating stimulant, leading to increased exposure. Infants and young children frequently play on the floor, where they may contact and assimilate (via inhalation, ingestion, or percutaneous absorption) cleaning agents, formaldehyde, and possibly pesticide residues. Vapors that are heavier than air can concentrate in the breathing zone of young children near the floor. While the breathing zone for an adult is four to six feet above the floor, for an infant it may be inches (Bearer 1995).

Infants and younger children have especially high breathing rates related to their levels of oxygen consumption. Their relatively large body surface area per unit body weight and high activity levels result in greater energy expenditure for thermogenesis than that required by adults. The average daily breathing rates of children aged 3 to 12 years are approximately twice those of adults (452 vs. 232 L/kg-d) (OEHHA 2000b). Comparison of the average breathing rates for these two groups suggests that over a one-hour period, a playing child three to twelve years of age may breath 4.5 times as much air as a sedentary adult (OEHHA 2000b). Figure 1 depicts how air intake per unit body weight declines with increasing age.

F.3 Absorption and Volume of Distribution

Characteristics of absorption of chemicals show age-related trends from birth through early childhood. The structure of the conducting airways develops completely prenatally; however, 85% of alveoli form in the postnatal period. While the full-term infant has about 50 million alveoli, some may have as few as 10 million. In contrast, the adult has approximately 300 million, though there is considerable variability (Wohl and Mead 1990). Most of the adult complement of alveoli develops in early childhood, but in some cases the number may increase to age eight or beyond (Thurlbeck 1988). As much of this growth occurs during the first three years of life, young children have a large alveolar surface per unit body weight relative to an adult for absorption of chemicals into the systemic circulation. Therefore, when viewed on the basis of dose per unit of lung surface area, the disparities between the adult and child are even greater than on a body weight basis (Plopper and Thurlbeck 1994). Alveolar multiplication coincides with postnatal increases in elastin and collagen, which contribute to the development of the mature lung's volume-pressure relationships and compliance (Wohl and Mead 1990).

Total body water as a percentage of body weight decreases from the young fetus to adulthood. At term, water constitutes 75% of body weight and fat constitutes 15%. By six months of age these percentages are 60% and 30% respectively. The proportion of extracellular fluid decreases from gestation (65%) to puberty (20%). As a consequence, water-soluble chemicals will tend to have a larger volume of distribution and slower clearance rates in younger infants and children.

F.4 Metabolism

The ontogeny of metabolic pathway development during early life may result in important changes in rates of activation to toxic intermediates, detoxification, and clearance of xenobiotic compounds. Total cytochrome P450 content of human liver microsomes is unchanged from fetal life through the first year of post-gestational life and is approximately 1/3 the total adult content (Treluyer et al., 1991*).* Although total content of these enzymes is relatively stable, P450 enzymes can be divided into at least three major groupings: fetal, early neonatal (which surges during the first day following parturition), and neonatal (whose activity increases during the weeks to months after birth). CYP1A2, a neonatal enzyme, is undetectable up to 1 month of age (Cresteil 1998).

There has been little research about the timing of development of cytochrome p450 activity in tissues other than the liver. In one study, sex- and age-related differences in CYP1A1 activity in the human brain were documented (Watzka et al. 1999). During childhood, enzyme activity increased dramatically and reached adult levels by puberty. In the lung, animal studies have shown that exposure to environmental toxicants (sidestream tobacco smoke) can alter the developmental profile of cytochrome P450 enzymes, inducing earlier activity (Gebremichael et al. 1995). Repair of injured pulmonary Clara cells by toxicants activated by cytochrome p450 enzymes is decreased in the early postnatal period in rabbits and neonatal injury alters bronchiolar organization in the adult (Smiley-Jewell et al. 1998, 2000). In general, the range of inducibility of fetal CYP forms is unknown (Hakkola et al. 1998).

Epoxide hydrolase and some glutathione S-transferases are active in fetal life while other glutathione-S-transferases and UDP-glucuronyltransferases develop in the months following birth. Metabolism of exogenous proteins and bilirubin remains extremely low in neonates less than 10 days of age (Omiencinski et al., 1994; Cresteil, 1998).

As a result of differing enzyme activity, some chemicals are metabolized by wholly different metabolic pathways at different ages. In infants, theophylline is N-methylated to caffeine. In adults this is a minor pathway, the majority being N-demethylated or C-oxidized to monomethylxanthines or methyl-uric acid. A pattern of metabolism similar to adults is achieved by seven to nine months of age (Reed 1996).

While children in general may be at increased risk for pharmacokinetic/dynamic reasons, subsets of children may be yet more sensitive due to genetic susceptibility. In an elegant set of studies, Pereira has shown significant transplacental transfer of polyaromatic hydrocarbons (PAHs) and environmental tobacco smoke constituents from mother to fetus, increased PAH DNA adduct formation in maternal and newborn white blood cells related to environmental exposure, and increased fetal sensitivity to genetic damage relative to the mother. Newborns with a specific restriction length polymorphism (CYP 1A1 Msp1), had elevated numbers of adducts compared to those without the polymorphism (Pereira 1999).

F.5 Critical Period Programming

Biologists have described sensitive time periods during which certain stimuli create irreversible effects that sometimes may not be noted until much later in life. One example is the development of functional sweat glands. While we are all born with approximately the same number of sweat glands, none respond to heat at birth. Gradually, they become functional in response to heat over the first two or three years of life. Warmer conditions during this developmental interval are associated with an increasing number of sweat glands becoming activated. By three years of age, the functional number of sweat glands is fixed irreversibly (Diamond 1991).

Early development involves rapid cell proliferation, migration, and differentiation, processes uniquely sensitive to disruption. In the brain these processes are unidirectional and occur at very specific times for different structures. Unlike many other cell types, neurons have long been considered to proliferate only during development, and each specific cell type only during a limited period. Structural maturation of neural pathways, including an increase in the diameter and myelination of axons, continues through adolescence. Chemical exposures can have profound effects on all of these neurological developmental processes (Rodier 1994, 1995; Paus et al. 1999; Golub 2000).

The development of the immune system results from a series of carefully timed and coordinated events during embryonic, fetal, and early postnatal life. Exposure of pregnant animals to immunotoxic chemicals at doses causing only transient effects in adults can produce long-lasting or permanent immune deficits in their offspring. Examples of agents for which prenatal exposure appears to produce lifelong immunosuppression include chlordane, benzo[a]pyrene, and 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD) (Holladay and Smialowicz, 2000). Development of the allergic phenotype appears to be related to aeroallergen exposure during infancy (Holt 1998). Recent data suggest that childhood exposures to several air pollutants (particulate matter, nitrogen dioxide, and acid aerosols) may result in permanent lung function deficits, with unknown clinical consequences (Gauderman et al. 2000). Other organ systems also show unique long-term consequences of early life chemical exposures that are not seen in the mature animal.

In general, however, there are few data delineating precise windows of susceptibility during gestation or post-natally.

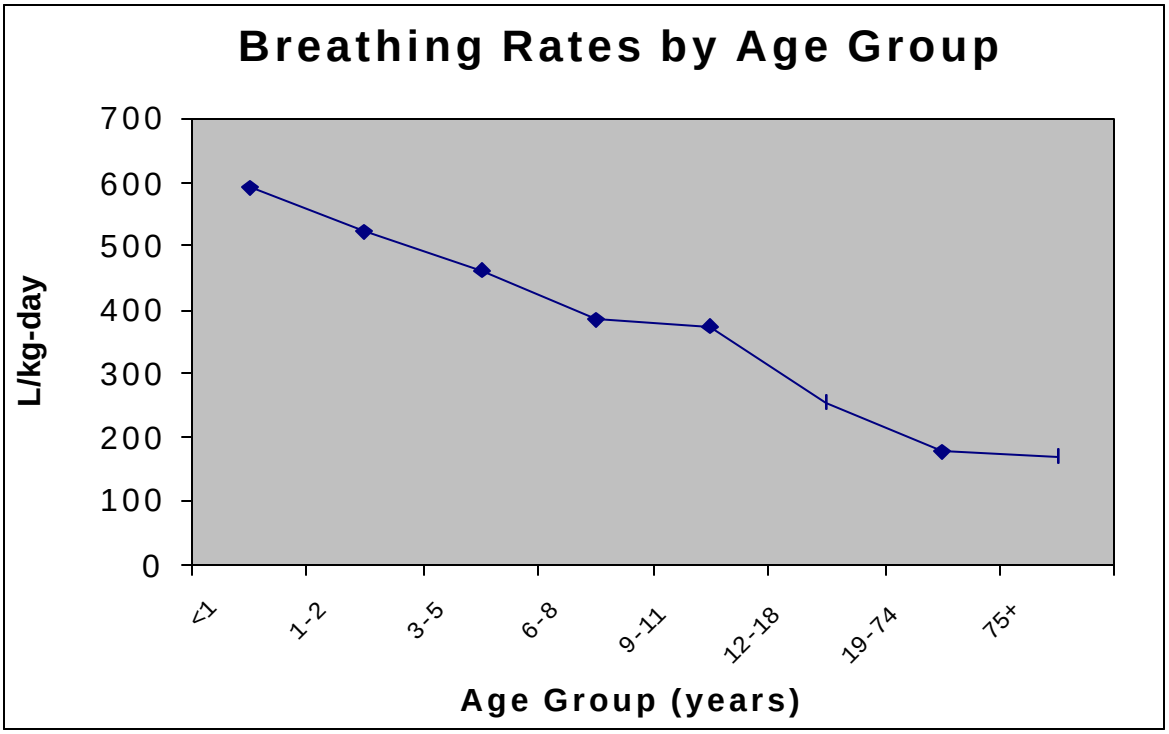


Fig.1: Breathing rates calculated by dividing daily inhalation rates (m^3/day) from Table 5 of Layton (1993) by body weights presented in Table 3 of Layton (1993) (original data from National Food Consumption Survey 1977-1978).

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