



Air Resources Board

State of California



Office Environmental Health  
Hazard Assessment

*Chairman Robert Sawyer*

Governor Arnold Schwarzenegger

*Director Joan Denton*

# **Review of the California Ambient Air Quality Standard For Nitrogen Dioxide**

*DRAFT*  
Staff Report

*April 14, 2006*

***California Environmental Protection Agency***

**Air Resources Board**

**and**

**Office of Environmental Health and Hazard Assessment**

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***California Environmental Protection Agency***

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## Acronyms and Abbreviations

AAQS	Ambient Air Quality Standard
AQAC	Air Quality Advisory Committee
ARB	California Air Resources Board
Board	California Air Resources Board
CFR	Code of Federal Regulations
CO	Carbon Monoxide
CO <sub>2</sub>	Carbon Dioxide
EPDC	Expected Peak Daily Concentration
FEV <sub>1</sub>	Forced Expiratory Volume in One Second
HDL	High Density Lipoprotein
HDM	House Dust Mite
HNO <sub>3</sub>	Nitric Acid
N	Nitrogen
NAAQS	National Ambient Air Quality Standard
Nitro-PAHs	Nitro-Polycyclic Aromatic Hydrocarbons
NO	Nitric Oxide
NO <sub>2</sub>	Nitrogen Dioxide
NO <sub>3</sub> <sup>-</sup>	Nitrate
NO <sub>x</sub>	Nitrogen Oxides
O <sub>3</sub>	Ozone
OEHHA	Office of Environmental Health Hazard Assessment
PM	Particulate Matter
PPB	Parts per Billion
PPM	Parts per Million
TrPD	Trucks per Day
UFP	Ultrafine Particle
U.S. EPA	United States Environmental Protection Agency
WHO	World Health Organization

# 1 Summary and Overview

The staff of the Air Resources Board (ARB or the Board) and Office of Environmental Health Hazard Assessment (OEHHA) have reviewed the scientific basis for the California Ambient Air Quality Standard for nitrogen dioxide (NO<sub>2</sub>) to determine its adequacy to protect public health, including the health of infants and children. Staff has reviewed the scientific literature on public exposure, atmospheric chemistry, welfare effects, and the health effects of exposure to NO<sub>2</sub>. The results of the staff review on the NO<sub>2</sub> standard are contained in the draft Technical Support Document. This draft Staff Report summarizes the results of the staff review. Based on the results of that review, OEHHA has submitted a recommendation to revise the NO<sub>2</sub> standard to adequately protect public health (Appendix A). The Staff Report also describes the formal review process by both the public and a scientific peer-review panel, before submitting the final report and staff recommendations to the Board.

NO<sub>2</sub> is a pungent, reddish-brown gas that contributes to the urban fine particle regional haze characteristic of smoggy air in California. NO<sub>2</sub> is one of the nitrogen oxides (NO<sub>x</sub>) that are emitted from high-temperature combustion processes, such as those emitted from automobiles and power plants. NO<sub>x</sub> is composed primarily of nitric oxide (NO) and NO<sub>2</sub>. Home heaters and gas stoves used for cooking can also produce substantial amounts of NO<sub>2</sub> in indoor settings. Both NO and NO<sub>2</sub> are involved in a series of chemical reactions in the ambient air to produce additional pollutants such as ozone, nitrate aerosols, nitric acid, and other nitrogen-containing compounds that are toxic.

To protect the public health and welfare from the adverse effects of NO<sub>2</sub>, the ARB established a short-term ambient air quality standard for NO<sub>2</sub> of 0.25 ppm averaged over one hour (1-hour standard). This standard was last formally reviewed in 1992.

To provide protection to the public health and welfare, the U.S. Environmental Protection Agency (U.S. EPA) established a long-term ambient air quality standard for NO<sub>2</sub> of 0.053 parts per million (ppm) averaged over one year (an annual average). The standard was last reviewed in 1995 and retained.

Based on current review and analyses of the published health-based studies, including studies of susceptible groups such as children, and adding a margin of safety, the staff of the Office of Environmental Health Hazard Assessment recommend that the level of the California ambient air quality standard for NO<sub>2</sub> be revised to 0.18 ppm, averaged over one hour. Further, the OEHHA staff recommends the addition of an annual-average standard of 0.03 ppm.

## 1.1 Setting California Ambient Air Quality Standards

An ambient air quality standard (AAQS) is the legal definition of clean air. California ambient air quality standards are defined in Health and Safety Code section 39014 and in Title 17, California Code of Regulations section 70101. Four elements are listed for this definition:

- 1) A definition of the air pollutant, 2) an averaging time, 3) a pollutant concentration, and 4) a monitoring method to determine attainment of the standard.

The AAQS establishes the maximum allowable levels of air pollutants that can be present in outdoor air for a given averaging time without causing harmful health effects to most people. Health and Safety Code section 39606(b) authorizes the ARB to adopt standards for ambient air quality that are developed “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 on the economy”. The objective of ambient air quality standards is to provide a basis for preventing or abating adverse health or ecological effects due to air pollution (Title 17, California Code of Regulations section 70101).

During the review of the State AAQS, a number of important factors are considered and evaluated by ARB, OEHHA, the Air Quality Advisory Committee (AQAC), and the public. In consultation with ARB, OEHHA provides detailed analyses of the available health information for each criteria pollutant. Health-based air quality standards are based on the recommendation of OEHHA. The AQAC, a scientific peer review committee appointed by the Office of the President of the University of California, convenes at a scheduled public meeting to independently evaluate the scientific basis of draft recommendations for revising the California AAQS. The public is involved in the review process through public meetings and workshops and may comment on the staff review and findings and recommendations in person at workshops, at the AQAC and ARB Board meetings, and using the ARB web page.

## **1.2 Children’s Environmental Health**

California Health and Safety Code section 39606 requires the Air Resources Board to adopt ambient air quality standards at levels that adequately protect the health of the public, including infants and children, with an adequate margin of safety. In December 2000, as a requirement of the Children’s Environmental Health Protection Act (Senate Bill 25, Escutia, Stats. 1999, Health and Safety Code 39606 (d)(1)), the ARB approved a report, “Adequacy of California Ambient Air Quality Standards”, (ARB and OEHHA, 2000) that contained a brief review of all of the existing health-based California ambient air quality standards. The report identified NO<sub>2</sub> as one of the highest priorities for further detailed review, after PM<sub>10</sub> and ozone, which were reviewed in 2002 and 2005, respectively.

An important underlying premise of the AAQS evaluation process is that sensitive sub-populations, such as children, be protected from adverse health effects. As a part of developing an AAQS, a margin of safety is added to account for possible deficiencies in the health data and measuring methodology.

## **1.3 Current California One-Hour NO<sub>2</sub> Standard**

The current California AAQS for NO<sub>2</sub> is 0.25 ppm averaged over one-hour, not to be exceeded. The most relevant health and welfare effects from NO<sub>2</sub> exposure are based on: “a potential to aggravate chronic respiratory disease and respiratory symptoms in sensitive groups” (Title 17, California Code of Regulations section 70200). Further, there is risk to public health implied by pulmonary and extra-pulmonary biochemical and cellular changes and pulmonary structural changes, which are observed in short-term animal tests at or above the concentration of the standard. The welfare effect cited is contribution to atmospheric discoloration by NO<sub>2</sub>.

## 1.4 Current National Long-Term Annual Average NO<sub>2</sub> Standard

The current national ambient air quality standard for NO<sub>2</sub>, initially adopted in 1971 and last reviewed in 1995, is an annual standard of 0.053 ppb (100 µg/m<sup>3</sup>) calculated as the arithmetic mean of the 1-hour NO<sub>2</sub> concentrations. The value is based, in part, on epidemiological studies conducted by Shy et al. (1970 a,b), who reported decreases in lung function (FEV<sub>1</sub>) for children (ages 7 to 8) living in areas with relatively high (greater than 0.06 ppm) annual average NO<sub>2</sub> levels. However, follow-up studies by the same investigators (Shy et al. 1973, 1978; Perlman et al. 1971) could not support these initial findings. Emphasis was placed on animal studies exposed to relatively high concentrations of NO<sub>2</sub>. Investigators reported damage to host defense mechanisms, as well as emphysematous-like lesions in the lungs. Investigators have also reported that NO<sub>2</sub> exposure caused an increase in the animal's susceptibility to infection resulting from immune system effects (U.S. EPA 1995). The U.S. EPA indicated that "based on the data available in 1985, retaining the annual NAAQS of 0.053 ppm was seen as a means of providing protection from long-term health effects and some measure of protection against possible short-term health effects (50 FR 25541, June 19, 1985). In 1995, the U.S. EPA again reviewed the NO<sub>2</sub> standard. The staff paper cited evidence for small changes in pulmonary function in asthmatics exposed to NO<sub>2</sub> between 0.2 and 0.5 ppm and increased airway responsiveness to asthmatics at rest within the range of 0.2-0.3 ppm. A meta-analysis of studies in children living in homes with gas stoves provided support for increased risk for developing respiratory disease, but it was difficult to use these studies to establish a quantitative relationship between estimated exposure and symptoms for use in determining a standard. Thus, an annual average standard of 0.053 ppm was retained during the last review.

## 1.5 World Health Organization (WHO) Guidelines

The World Health Organization (WHO) has published Air Quality Guidelines for Europe (WHO 2000, 2003, 2005) which are not ambient air quality standards, but are "the basis for protecting public health from adverse effects of air pollutants, eliminating or reducing exposure to hazardous air pollutants, and to guide national and local authorities in their risk management decisions" (WHO 2000). The WHO guidelines include both toxic air pollutants (such as benzene, for example) and criteria pollutants such as NO<sub>2</sub>.

Based on the review of the literature, the WHO indicated that the lowest observable acute effect level for NO<sub>2</sub> was near 0.2 to 0.3 ppm based on clinical studies showing increased airway responsiveness in asthmatics. However, it was difficult to determine "...a clearly defined concentration–response relationship for NO<sub>2</sub> exposure..." (WHO 2000). The WHO also indicated that it would propose a 50% margin of safety because of additional evidence of possible effects below 0.2 ppm. These include a statistically significant increase in response to a bronchoconstrictor (increased airway responsiveness) with exposure to 190 µg/m<sup>3</sup> (0.1 ppm) in one study (Orehek et al. 1976) and a pooled analysis suggesting changes in airway responsiveness in asthmatics below 365 µg/m<sup>3</sup> (0.2 ppm). On the basis of these human clinical data, the WHO (2000) proposed a 1-hour guideline of 200 µg/m<sup>3</sup> (0.106 ppm).

For long-term chronic exposure, the WHO reported that "although there is no particular study or set of studies that clearly support selection of a specific numerical value for an

annual average guideline, the database nevertheless indicates a need to protect the public from chronic NO<sub>2</sub> exposure.” Epidemiological studies of exposures to NO<sub>2</sub> from indoor sources suggested increased risk of lower respiratory illness in children, but the exposures could not be readily extrapolated to the outdoor situation. The WHO 2000 report stated, “Outdoor epidemiological studies have found qualitative evidence of ambient exposures being associated with increased respiratory symptoms and lung function decreases in children (annual average concentrations of 50–75 µg/m<sup>3</sup> (0.026–0.040 ppm or higher).” Further, the WHO indicated that these results were consistent with findings from indoor studies, although they do not provide clear exposure–response information for NO<sub>2</sub>. In these epidemiological studies, NO<sub>2</sub> has appeared to be a good indicator of the pollutant mixture. Furthermore, animal toxicological studies show that prolonged exposures can cause decreases in lung host defenses and changes in lung structure. The WHO recommended an annual value of 40 µg/m<sup>3</sup> (21 ppb) (WHO 1997, 2000), but acknowledged that there were difficulties in ascribing the observed effects solely to NO<sub>2</sub> because of other pollutants in the ambient air that were correlated with NO<sub>2</sub>. The WHO recently published an update of its guidelines (WHO 2005) and reaffirmed the WHO 2000 guideline values of 40 µg/m<sup>3</sup> (21 ppb) for annual mean and 200 µg/m<sup>3</sup> (0.106 ppm) for 1-hour mean.

## **1.6 Monitoring Methods for Current Standard**

The California ambient air quality standard for NO<sub>2</sub> (Title 17, California Code of Regulations section 70200) stipulates that gas phase chemiluminescence is the method to be used to measure NO<sub>2</sub>. The standard also allows an equivalent method to be used to determine NO<sub>2</sub> ambient concentrations (section 70200). See the draft Technical Support Document for more details.

The ARB staff recommends that the current chemiluminescence method continue to be designated as the approved method in California for determining compliance with California’s Ambient Air Quality Standard for NO<sub>2</sub>. Staff also recommends that all federally approved chemiluminescence methods be designated as “California Approved Samplers” for NO<sub>2</sub>. This will result in no change in air monitoring practices, but will align state monitoring requirements with federal requirements. To accomplish this, staff recommends modification of Title 17, California Code of Regulations section 70100.1 to read in part: “NO<sub>2</sub> Monitoring Methods. The method for determining compliance with the NO<sub>2</sub> ambient air quality standard shall be the chemiluminescence Federal Reference Method for the determination of NO<sub>2</sub> in the atmosphere (40 CFR, Part 50, Appendix F). California Approved Samplers for NO<sub>2</sub> are set forth in the Air Monitoring Quality Assurance Manual, Volume IV, Part D: Monitoring Methods for NO<sub>2</sub>.”

## **1.7 Physical and Chemical Properties of NO<sub>2</sub>**

Although NO<sub>2</sub> measured in the atmosphere can be directly emitted from combustion sources, much of the NO<sub>2</sub> is formed indirectly from emissions of NO that are subsequently converted photochemically to NO<sub>2</sub>. In sunlight, NO<sub>2</sub> is a precursor in the formation of several other air pollutants, such as ozone (O<sub>3</sub>), nitric acid (HNO<sub>3</sub>), and nitrate (NO<sub>3</sub><sup>-</sup>)-containing particles. NO<sub>2</sub> levels in air vary with direct emission levels, and with changing conditions (e.g., sunlight) that shift its relationship with other reactive airborne nitrogen oxides in a complex chemical linkage. Not only is NO<sub>2</sub> an important

precursor of anthropogenic O<sub>3</sub>, it is also the key agent in the formation of several airborne toxic substances. These include HNO<sub>3</sub>, fine particles, peroxyacetyl nitrate, nitrosamines, and nitro-polycyclic aromatic hydrocarbons (nitro-PAHs).

## **1.8 Sources and Emissions of Nitrogen Oxides**

### **1.8.1 Sources**

NO<sub>2</sub> is both directly emitted and a by-product of atmospheric photochemical reactions of other NO<sub>x</sub> species. Since emissions of other NO<sub>x</sub> species are generally higher than directly emitted levels of NO<sub>2</sub>, most emissions are primarily measured as NO<sub>x</sub>. Mobile sources (including cars, trucks, and off-road mobile equipment) made up about 81 percent of the total statewide NO<sub>x</sub> emissions in 2004. About 51 percent of the total NO<sub>x</sub> emissions were from on-road motor vehicles (cars, trucks, and buses) and 30 percent were from other mobile sources (off-road equipment, trains, ships, and farm equipment) (ARB 2005).

Stationary sources of NO<sub>x</sub> include both internal and external combustion processes in industries such as manufacturing, food processing, electric utilities, and petroleum refining. These sources were about 16 percent of the total statewide NO<sub>x</sub> emissions. Area-wide sources, which include residential fuel combustion, managed burning, and fires, contributed only a small portion of the total NO<sub>x</sub> emissions, about 3 percent.

### **1.8.2 Emissions**

Emissions of NO<sub>x</sub> vary regionally in California. For example, statewide mobile sources account for approximately 81 percent of NO<sub>x</sub> emissions even though this value ranges from 69% for San Joaquin Valley air basin to 90% for the South Coast air basin (values are expressed as percentages of the total NO<sub>x</sub> emissions for each area.)

NO<sub>x</sub> emissions for individual source categories have daily, weekly, and seasonal variations. For most NO<sub>x</sub> categories, higher emissions occur during the day rather than at night, and higher emissions occur on weekdays rather than on weekends. NO<sub>x</sub> emissions from electric utility fuel combustion are higher in summer, while emissions from fuel combustion for space heating are higher in winter. As a whole, emissions of NO<sub>x</sub> have been decreasing over the last two decades, and they are expected to have an overall decrease in the future. The NO<sub>x</sub> emission trends (tons/day, annual average) and sources of emissions are summarized in Table 1.

**Table 1. Emission Trends of NO<sub>x</sub> by Source Category.**

<b>NO<sub>x</sub> Emission Trends (tons/day, annual average)</b>										
<b>Emission Source</b>	<b>1975</b>	<b>1980</b>	<b>1985</b>	<b>1990</b>	<b>1995</b>	<b>2000</b>	<b>2005</b>	<b>2010</b>	<b>2015</b>	<b>2020</b>
<b>All Sources</b>	<b>4811</b>	<b>4982</b>	<b>4945</b>	<b>4871</b>	<b>4128</b>	<b>3629</b>	<b>3026</b>	<b>2499</b>	<b>2059</b>	<b>1811</b>
Stationary Sources	1228	1250	1009	909	696	602	506	519	538	556
Area-wide Sources	83	88	91	89	87	90	93	89	88	89
On-Road Mobile	2435	2459	2721	2675	2301	1915	1518	1127	757	532
Gasoline Vehicles	2149	1975	1936	1789	1535	1113	757	536	371	266
Diesel Vehicles	286	484	784	885	766	802	761	590	386	266
Other Mobile	1065	1185	1125	1199	1044	1022	908	764	675	634
Gasoline Fuel	43	48	52	61	60	67	74	68	62	60
Diesel Fuel	941	1052	988	1043	899	868	748	614	528	483
Other Fuel	82	85	85	95	85	87	86	83	85	90

Source: ARB, 2005a

## **1.9 Levels of NO<sub>2</sub>**

### **1.9.1 Ambient Concentrations**

NO<sub>2</sub> is monitored continuously at more than 114 sites in California. The data for each monitoring site are reported as 1-hour average concentrations. Although the 1-hour data are reported, these values can, if needed, be summarized as daily, seasonal, or annual arithmetic mean concentrations. These data are especially used in determining the number of days during which measured concentrations exceed the State NO<sub>2</sub> standard. For the purpose of evaluating long-term NO<sub>2</sub> air quality trends and population exposures, the maximum concentration usually is not the best measure, because maximum concentrations can be highly influenced by year-to-year variations in meteorology.

In contrast to the maximum values, two calculated statistics that provide more stable measures of long-term trends are the *peak indicator value* and the *moving 3-year mean*. The peak indicator represents the maximum concentration expected to occur once per year, on average. The peak indicator is based on a statistical calculation using three years of ambient monitoring data and is calculated for each monitoring site in an area. The highest peak indicator value among all sites in an area is generally used when evaluating area-wide air quality. A moving 3-year mean of the annual maximum measured concentrations also tends to be a more stable trend indicator, when compared to the measured maximum concentration. Although the moving 3-year mean is not as robust as the peak indicator, the 3-year mean does tend to moderate some of the year-to-year variation caused by meteorology. This yields data that are more suitable for trend analysis, when compared with data for individual years.

The federal NO<sub>2</sub> annual arithmetic mean standard is 0.053 ppm. The entire state has been designated as unclassified/attainment for the past decade. For example, for the year 2004, the annual arithmetic means for the air basins in California varied from

0.0065 ppm to 0.0247 ppm, for the South Central Coast and South Coast air basins, respectively, which are well below the federal annual arithmetic mean standard.

To provide a snapshot of the levels of NO<sub>2</sub> in the state during the last few years, maximum measured 1-hour NO<sub>2</sub> concentrations are presented in Table 2 for the years 2002 through 2004. During this period, the State 1-hour standard was not exceeded in any of the air basins with the exception of one exceedance in the South Coast Air Basin in 2002. This measurement, a 1-hour concentration of 0.262 parts per million (rounds to 0.26 ppm), is an exceedance of the State NO<sub>2</sub> standard. Because State designations are based on three years of data, the 0.26 ppm measurement was evaluated for designation purposes during three separate years. In all cases, the 0.26 ppm measurement was higher than the rounded peak indicator, or Expected Peak Day Concentration (EPDC or peak indicator) value, and therefore, was excluded from the State designation process as an extreme concentration event. As a result, the South Coast Air Basin maintained its attainment designation. In 2003, the maximum 1-hour value in the South Coast Air Basin had dropped significantly to 0.163 ppm.

In general, the South Coast, Salton Sea, San Diego, Sacramento Valley, and Mojave Desert air basins have higher maximum 1-hour values than the other regions. Mountain Counties did not have a sufficient amount of data for 2004 to produce any meaningful summary statistics for comparison. The maximum 1-hour values in the Mountain Counties region for 2002 and 2003 are less than half the state 1-hour standard. Currently, there are no sites collecting NO<sub>2</sub> data in the Mountain Counties region. Almost all regions have experienced noticeable variability in maximum 1-hour values over the past three years. This is expected and can be partly attributed to year-to-year meteorological variability. With the exception of the one exceedance in the South Coast, maximum 1-hour concentrations were well below the state standard of 0.25 ppm, and varied from 0.037 ppm for the North Coast air basin to 0.146 ppm for the Sacramento Valley air basin for the year 2004.

**Table 2. Maximum 1-hour NO<sub>2</sub> concentrations in each air basin for the years 2002 through 2004.**

Basin	Year	Maximum 1-Hour Concentration ppm
Lake Tahoe	2002	0.088
	2003	0.059
	2004	0.068
Mojave	2002	0.101
	2003	0.095
	2004	0.103
Mountain Counties	2002	0.043
	2003	0.019
	2004	NA
North Central Coast	2002	0.049
	2003	0.053
	2004	0.139
North Coast	2002	0.08
	2003	0.053
	2004	0.037
Sacramento Valley	2002	0.09
	2003	0.102
	2004	0.146
Salton Sea	2002	0.138
	2003	0.189
	2004	0.108
San Diego	2002	0.126
	2003	0.148
	2004	0.125
San Francisco Bay Area	2002	0.08
	2003	0.081
	2004	0.073
San Joaquin Valley	2002	0.107
	2003	0.092
	2004	0.083
South Central Coast	2002	0.064
	2003	0.103
	2004	0.071
South Coast	2002	0.262
	2003	0.163
	2004	0.157

Notes: Days exceeding State 1-hour standard are distinct areawide days, meaning the exceedance day is counted only once, even if multiple sites experienced an exceedance on the same day. The State NO<sub>2</sub> standard is exceeded when the concentration is equal to or greater than 0.25 ppm. NA = No data available.

## **1.9.2 Indoor and Microenvironmental Concentrations**

Although the ambient air quality standards are based on outdoor monitoring, indoor and microenvironmental concentrations of NO<sub>2</sub> indicate that personal exposures to NO<sub>2</sub> can be much higher than levels reflected by ambient station data.

### *1.9.2.1 Indoor Concentrations*

In California, indoor exposures to NO<sub>2</sub> are determined by the presence and use of indoor sources, particularly gas appliances, and outdoor NO<sub>2</sub> concentrations. The main factors influencing indoor NO<sub>2</sub> concentrations are gas stoves, indoor-outdoor air exchange rates, and the effects of season. Winter levels are typically higher than those in summer, and there is greater use of gas appliances in winter (Schwab et al. 1994, Spengler et al. 1994, Monn 2001).

Indoor mean NO<sub>2</sub> concentrations range from 0.008 to 0.056 ppm, measured with averaging times of days to a week, and indoor maximum levels range from about 0.1 to 0.4 ppm or greater, averaged over a similar time period. This is of concern because these indoor measurements have been made with passive monitors that utilize a long averaging time, and do not adequately reflect peak exposure levels that occur throughout the day. Continuous (or real-time) measurements indicate indoor levels can reach more than 0.4 ppm during routine cooking with a gas stove (Fortmann et al. 2001), and 0.6 ppm (mean) to 1.5 (maximum) ppm with use of unvented space heaters such as kerosene heaters (Girman et al. 1982), which are illegally used by a small percent of California homes. Therefore, Californians who spend time in a kitchen near an operating gas stove or range, or use unvented combustion space heaters, may experience very high exposures to NO<sub>2</sub>.

Indoor/outdoor NO<sub>2</sub> ratios vary greatly. They range from less than 1 for homes without an indoor source to values greater than 3 for homes with indoor sources (Lee et al. 2002, Petreas et al. 1988). In the absence of continually-emitting indoor sources, indoor NO<sub>2</sub> levels can decline quickly due to infiltration of outdoor air and reactive processes. Indoor NO<sub>2</sub> reacts on indoor surfaces to produce nitrous acid (HONO), and has a lifetime of about one hour.

Personal exposure to NO<sub>2</sub> is largely influenced by the type of fuel used for cooking in the home, and outdoor NO<sub>2</sub> concentrations. The median personal exposure level measured using a 48-hour passive badge sampler in one Los Angeles basin study was 0.035 ppm, with a 99<sup>th</sup> percentile value of 0.090 ppm (Spengler et al. 1994).

In summary, Californians can be exposed to indoor NO<sub>2</sub> levels that exceed the current ambient air quality standard. People's proximity to indoor sources such as gas stoves and unvented space heaters presents a public health concern, especially in light of recent epidemiology studies showing associations of health impacts with gas stove use.

### *1.9.2.2 Microenvironmental Concentrations*

Westerdahl et al. (2005) reported in-vehicle NO<sub>2</sub> levels on specific road segments in the Los Angeles area. In the 3-4 day study, the concentrations ranged from 0.023 (±0.016) to 0.039 (± 0.012) ppm on the road. Fitz et al. (2003) measured a number of pollutants including NO<sub>2</sub> inside and outside of diesel school buses driven on typical commute

routes in Los Angeles. The average NO<sub>2</sub> level within the conventional diesel-powered school bus was higher (about 0.076 ppm) than in the bus equipped with a particle trap (about 0.043 ppm). The concentrations of NO<sub>2</sub> measured in parallel outdoors were about 2-3 times less than NO<sub>2</sub> levels measured within the bus.

Roadside concentrations of NO<sub>2</sub> are another potential microenvironmental exposure area. A number of studies have found increased levels of NO<sub>2</sub> (and NO<sub>x</sub>) in close proximity to busy roadways with rapid decline to near background concentrations within 150-300 meters of the road (Rodes et al. 1981, Singer et al. 2005). On days when ambient ozone concentrations are low, the rate of conversion of NO to NO<sub>2</sub> may be limited by ozone concentrations (Rodes et al. 1981). Analyses of roadside concentrations of NO<sub>x</sub> and NO<sub>2</sub> have been reported by Carslaw (2000) in London during 1997-2003; the author reported a downward trend in NO<sub>x</sub>, and a steady or increasing trend for NO<sub>2</sub> levels, resulting in an increase in the NO<sub>2</sub> to NO<sub>x</sub> ratio, which the author ascribes, in part, to the increased use of diesel particulate filters fitted to buses.

## **1.10 Summary of Relevant Health Effects**

A number of investigators have reported relevant health effects from low-level exposure to NO<sub>2</sub> on sensitive human populations. Additional supportive evidence is derived from studies on animals. For more detailed information of the health effects of NO<sub>2</sub>, refer to the companion draft Technical Support Document for NO<sub>2</sub>. A summary of the scientific information regarding the relevant health effects follows.

### **1.10.1 Controlled Human Exposure Studies**

Controlled human exposure studies (also referred to as clinical studies) are conducted under defined and controlled laboratory conditions to measure and evaluate potential health effects. These types of studies are important in helping to characterize exposure-response relationships to a specific air pollutant such as NO<sub>2</sub> alone or in combination with other pollutants. Human clinical studies, however, are limited to exposures of short duration (generally from minutes to a few hours) and are designed to study mild and, at times, transient responses. Human clinical studies are limited to a relatively small number of individuals tested who are generally relatively healthy. Additionally, the acute responses reported in clinical studies cannot necessarily be used to predict health effects of chronic or repeated exposure.

Clinical studies of healthy individuals showed no evidence of effects on lung function, airway responsiveness, or airway inflammation at levels of NO<sub>2</sub> below 1 ppm.

However, individuals with asthma appear to be more sensitive to effects of NO<sub>2</sub> on airway responsiveness. For a number of studies of asthmatics, short-term exposures to NO<sub>2</sub> at 0.2-0.3 ppm resulted in an increase in airway responsiveness; however, the findings have not been consistent across other studies with similar (but not identical) protocols (see Chapter 6, Technical Support Document). The reasons may be due, in part, to differences in the subjects recruited for the various studies. Even in clinical studies where, on average, there are no differences between responses with filtered air vs. NO<sub>2</sub> exposures, the data on individual responses demonstrate that there is substantial inter-individual variability in response. Thus, the clinical studies of asthmatics suggest that some individuals experience increased airway responsiveness

after exposures to NO<sub>2</sub> in the range of 0.2-0.3 ppm. Several studies found transient decreases in lung function in asthmatics at 0.3 ppm during the initial part of the exposure, but the findings were not consistent. The effects of NO<sub>2</sub> on airway inflammation in asthmatics have not been adequately studied.

Recent clinical studies in subjects with asthma have also shown that NO<sub>2</sub> exposure increases allergen responsiveness, with effects observed at concentrations as low as 0.26 ppm. These studies found that exposures to NO<sub>2</sub> followed by inhaled allergen resulted in decrements in lung function, an increased inflammatory response, and evidence of activation of eosinophils compared with filtered air controls.

A small number of studies evaluated effects in individuals with chronic obstructive pulmonary disease (COPD); several found small decrements in lung function (FEV<sub>1</sub>) at 0.3 ppm, but the findings were inconsistent. Older smokers may also be a subgroup at increased risk of lung function decrements at NO<sub>2</sub> levels slightly above the California 1-hour standard for NO<sub>2</sub> of 0.25 ppm.

A limited number of studies explored the cardiac, vascular, and systemic effects of NO<sub>2</sub> exposure, but these data were not conclusive. Finally, limited studies explored the effects of NO<sub>2</sub> on airway responsiveness to other pollutant challenges, with inconsistent results. However, several studies found that NO<sub>2</sub> at levels only slightly above the California standard may act synergistically with SO<sub>2</sub> in enhancing responses to allergen challenge.

Overall, the clinical studies suggest NO<sub>2</sub> exposures near the current ambient air quality standard for NO<sub>2</sub> (0.25 ppm, 1-hour average) may enhance the response to inhaled allergen in people with allergic asthma. For a subset of asthmatics, exposures to NO<sub>2</sub> at levels near the current ambient air quality standard may cause increased airway reactivity.

### **1.10.2 Epidemiological Studies**

Epidemiology is the study of the distribution of a disease in a population and the factors associated with the disease. The study duration can range from a relatively short period (hours to weeks) to a long period (years). Epidemiological studies have the advantage of acquiring data from a large human study population having real-world exposures. The studies can also focus on susceptible population groups, such as children, and can evaluate chronic health effects. However, real-world exposures consist of a complex mixture of air pollutants, some of which correlate closely with NO<sub>2</sub>. Therefore, one difficulty is to separate out the NO<sub>2</sub> effects from all other air pollutant effects.

Support for the proposed long-term standard (annual average) is derived primarily from epidemiological studies. There are a number of health effects that have been associated with exposure to NO<sub>2</sub>, including mortality, hospital visits, cardiovascular effects, low birth weight, and long-term lung function decreases in children. A number of epidemiological study designs are used in these studies, including time-series analyses. Results from many of the time-series studies report an independent NO<sub>2</sub> effect (see Chapter 7, Technical Support Document). In the U.S., investigators of cardiac arrhythmias and studies of hospitalizations and emergency room visits for respiratory and cardiovascular disease found potentially independent effects of NO<sub>2</sub> in areas with

average levels between 0.023 and 0.037 ppm. With respect to children, investigators from Southern California have reported bronchitic conditions in asthmatics, and have reported decreases in lung function growth in the more polluted areas of the region (Mann et al. 2002, Peters et al. 2000, Metzger et al. 2004, Peel et al. 2005, Wellenius et al. 2005, Gauderman et al. 2004).

Health risks from NO<sub>x</sub> exposure may result from NO<sub>2</sub> itself or its reaction products, including O<sub>3</sub> and secondary particles. Alternatively, NO<sub>2</sub> may augment the effects of other pollutants. Also, since NO<sub>2</sub> concentrations are highly correlated with other traffic-related air pollutants, (e.g., fine particulate matter), NO<sub>2</sub> may be acting as a surrogate for the causal pollutant. For example, in many studies when an adjustment for particles was made, the NO<sub>2</sub> risk estimates were greatly reduced and often became non-significant. This result may indicate that the concentration response seen for NO<sub>2</sub> is largely the consequence of other pollutants. In some studies, however, especially in Europe, the strongest effect was found for NO<sub>2</sub> whereas particulate matter had a weaker effect. Specifically, stronger indications of an independent effect of NO<sub>2</sub> come from studies on hospital admissions for cardiovascular diseases and asthma, and from studies evaluating indoor effects especially among asthmatics and infants at risk of asthma. In addition, a multi-city study in Europe found that the effect of PM<sub>10</sub> was higher in cities with higher average NO<sub>2</sub> levels

#### *1.10.2.1 Summary*

A number of epidemiological studies published over the last several years have demonstrated associations between NO<sub>2</sub> exposure and several health effects. These health effects include mortality, cardiopulmonary effects, decreased lung function, respiratory symptoms, and emergency room visits for asthma. Some issues regarding these associations include: 1) determining actual exposure concentrations including indoor sources, 2) separating out confounding variables such as co-pollutants, seasonality, and weather, and 3) determining precise averaging times from these studies ranging from 1-hr maximum levels to 24-hr averages to a few weeks. Despite many of these issues, a number of studies provide data supporting the need for a long-term average standard. The finding that there are very close correlations of NO<sub>2</sub> with other pollutants such as fine particulate matter in these studies makes interpretation challenging. However, the results of the epidemiological studies are consistent with the health effects when only NO<sub>2</sub> alone is tested in the controlled chamber studies, and in the toxicological studies. These results provide additional supportive information for potential health effects and for setting NO<sub>2</sub> standards that will be protective with an adequate margin of safety.

#### **1.10.3 Toxicological Studies**

Toxicological studies with animals or cells in culture provide scientific information on the site and mechanism of action of NO<sub>2</sub>. Studies using cell labeling techniques that measure cellular injury and repair processes have shown increased proliferative activity in bronchiolar epithelium following acute NO<sub>2</sub> exposure in animals. Changes in pulmonary biochemistry observed in animal studies as a result of NO<sub>2</sub> exposure may result in altered activities of protective and repair mechanisms in the lung. For example, alteration of arachidonate metabolites related to NO<sub>2</sub>-induced damage to alveolar

macrophage (AM) cell membranes, may impede the ability of the lung to protect itself from microbial infection. Reduced superoxide release by AMs, which kills infectious organisms, may also impede lung defense.

Prolonged, repeated exposures of young ferrets and mice to NO<sub>2</sub> during lung development have shown changes in bronchiolar/alveolar structure, including proliferation of certain epithelial cells and altered cellularity, and thickness in the gas exchange area of the lung. Longer term, repeated exposures to NO<sub>2</sub> during lung development have resulted in alterations of structural protein (elastin) in lung tissue. Thus, the developing lung is a target of NO<sub>2</sub> toxicity.

Rats from a strain that is prone to obesity were exposed to NO<sub>2</sub> for 24 weeks. This exposure resulted in changes in blood levels of triglycerides, HDL, and HDL/total cholesterol ratio, suggestive of atherogenic cardiovascular effects and indicative of the possibility that animals with compromised health may be a sensitive model for NO<sub>2</sub>-induced toxicity.

Exposure of animal models to high concentrations of NO<sub>2</sub> have produced one or more indicators of allergic asthma including enhancement of delayed-type dyspneic symptoms, increased serum IgE levels, increased pulmonary eosinophilia and epithelial injury, and increased bronchial hyperresponsiveness.

*In vitro* test systems using human bronchial epithelial cells (HBEC) and human lung fibroblasts have shown an increase in excretion of proinflammatory cytokines, and cell membrane damage in response to NO<sub>2</sub> exposure. Decreased viability was observed in lung fibroblasts and HBECs exposed to NO<sub>2</sub>. A significant enhancement of release of molecules associated with allergy from HBECs of asthmatic (but not non-asthmatic) individuals has also been observed with NO<sub>2</sub> exposure. Nasal mucosal tissue in culture exposed to NO<sub>2</sub> exhibited increased histamine release, which is associated with response to allergens. Alveolar macrophages exposed to NO<sub>2</sub> released reactive oxygen species, and a number of inflammatory mediators. These *in vitro* studies provide mechanistic support for the observed enhancement of response to allergen in asthmatics.

In summary, the toxicological results are consistent with and supportive of the health effects information reported in clinical and epidemiological studies.

## **1.11 Welfare Effects**

### **1.11.1 Damage to Vegetation**

The importance of atmospheric deposition of fixed nitrogen compounds in altering the structure and functioning of plant and aquatic communities has been the subject of numerous recent reviews, as described in Chapter 9 of the Technical Support Document.

Some of the changes reported include induced nutrient deficiencies or imbalances, and interactive effects with air pollutants. With few exceptions, no visible injury to vegetation was reported at concentrations below 0.20 ppm, and these occurred when the cumulative duration of exposures extended to 100 hours or longer. Furthermore, the U.S. EPA concluded from studies with green beans as bioindicators of NO<sub>2</sub> injury, that

foliar injury symptoms were unlikely to occur on even the most susceptible plant species at concentrations of NO<sub>2</sub> prevalent even in the most polluted areas of the U.S. No reports of plant exposures to NO<sub>2</sub> published since this analysis have altered this conclusion. At concentrations at or below the current 1-hour standard, vegetation effects are not expected.

### **1.11.2 Visibility**

NO<sub>2</sub> contributes to reduction of visibility both directly, by selectively absorbing the shorter blue wavelengths of visible light, and indirectly by contributing to the formation of nitrate aerosols. Gaseous NO<sub>2</sub> turns air a reddish brown color, appearing as either a defined plume from a strong NO<sub>x</sub> source or as a component of diffuse haze. Nitrate aerosols predominantly scatter light, creating a white haze. These two pollutants are often found together, and are contributors to the hazy-brown sky conditions observed in the South Coast Air Basin, the San Joaquin Valley, and elsewhere.

During the review of the 1992 State NO<sub>2</sub> ambient air quality standard, it was determined that meeting the 0.25 ppm one hour standard would sufficiently protect against any visibility degradation, since it was calculated that the majority of the effect was due to fine particulate matter (ARB 1992).

## 2 Staff Findings

The current California ambient air quality standard for NO<sub>2</sub> is 0.25 ppm averaged over one hour. The staff review found that health effects may occur at levels near the current standard, thus indicating that the current standard alone is not sufficiently protective of human health. The following is a summary of staff's findings.

### 2.1 Short-Term Exposure Effects

1. Enhanced airway inflammatory response was reported after allergen challenge in asthmatics exposed to NO<sub>2</sub> at 0.26 ppm for 15 minutes to 30 minutes (in single or repeated doses).
2. Increased airway reactivity was found among asthmatics after exposures to NO<sub>2</sub> in the range of 0.2 to 0.3 ppm for 30 minutes to 2 hours.
3. Evidence of health effects was reported for relatively healthy asthmatics exposed in the range of the current standard for 30 minutes, demonstrating the need for a margin of safety.

### 2.2 Chronic or Long-Term Exposure Effects

1. Evidence from time-series studies showed effects of NO<sub>2</sub> on premature mortality, emergency room visits for asthma in children, and hospitalization for respiratory and cardiovascular disease. The annual average NO<sub>2</sub> level in these studies was 0.023 to 0.037 ppm.
2. Evidence from epidemiological studies showed that long-term exposures to NO<sub>2</sub> may lead to changes in lung function growth in children, symptoms in asthmatic children, and preterm birth. The annual average NO<sub>2</sub> level in these studies was 0.030 to 0.044 ppm.

### 2.3 Consideration of Infants and Children

1. Infants and children have disproportionately higher exposure to NO<sub>2</sub> than adults due to their greater ventilation rate and greater exposure duration.
2. Children may be more susceptible to the effects of NO<sub>2</sub> than the general population due to potential effects on the developing lung.

### 2.4 OEHHA Recommendations

Based on the staff's review of the scientific literature, the OEHHA has the following recommendations for the California ambient air quality standard for NO<sub>2</sub>:

1. NO<sub>2</sub> continues to be the pollutant addressed by the standard.
2. NO<sub>2</sub> **1-hour-average** ambient air quality standard – lower the 1-hour-average standard for NO<sub>2</sub> to 0.18 ppm, not to be exceeded.
3. NO<sub>2</sub> **annual average** ambient air quality standard – establish a new annual average standard for NO<sub>2</sub> at 0.030 ppm, not to be exceeded.

The basis for these recommendations is detailed in Appendix A. These recommendations will be peer-reviewed by the Air Quality Advisory Committee (AQAC) at a public meeting tentatively scheduled for June 2006.

## **2.5 Monitoring Method for NO<sub>2</sub>**

ARB staff recommends retaining the current monitoring method for NO<sub>2</sub> – gas-phase chemiluminescence – which is used for determining compliance with this State ambient air quality standard. ARB staff further recommends the incorporation by reference (Title 17, California Code of Regulations section 70101) of all federally approved chemiluminescence methods as “California Approved Samplers” for NO<sub>2</sub>. This will not result in any change in air monitoring practices, but will align state monitoring requirements with federal requirements.

## **2.6 Environmental Justice Considerations**

Environmental justice is defined as “the fair treatment of people of all races, cultures, and incomes with respect to the development, adoption, implementation, and enforcement of environmental laws, regulations, and policies” (Senate Bill 115, Solis; Stats 19999, Ch. 690; Government Code 65040.12(c)). ARB’s environmental justice policies apply to all communities in California, but environmental justice issues have been raised more in the context of low-income and minority communities. These communities may experience higher exposures to some pollutants, such as to NO<sub>2</sub>, as a result of the cumulative impacts of air pollution from roadways and stationary facilities located in their neighborhoods. The location of future homes and schools is also an important issue and is discussed in ARB’s land use guidelines summarized below. Ambient air quality standards define clean air; therefore, all of California’s communities will benefit from the proposed health-based standards.

Ambient air quality standards in the State are designed to protect the most sensitive members of the population, such as people with pre-existing lung or heart disease, and children. These air standards are also designed with a margin of safety to further protect sensitive populations.

Exposure to NO<sub>2</sub> being emitted from mobile and stationary sources may present itself as an environmental justice issue since the location of residences, schools, transportation corridors, and work, for example, may be near these sources.

To mediate these possible exposures in the future, local air pollution districts and community members need to work together in the land use evaluations to further reduce pollution exposure including exposure to NO<sub>2</sub>. The ARB has developed a guideline document on land use with respect to air quality entitled, “Air Quality Land Use Handbook: A Community Health Perspective” (ARB 2005b). Land use considerations should involve the review of the many sources that emit NO<sub>2</sub>. The ARB handbook recommends that planning agencies strongly consider proximity to these sources when considering new locations for “sensitive” land uses, such as homes, medical facilities, daycare centers, schools, and playgrounds. The handbook is available from the ARB website at <http://www.arb.ca.gov/ch/handbook.pdf>.

## **2.7 Public Outreach and Peer-Review**

The draft Staff Report and the draft Technical Support Document on NO<sub>2</sub> were released to the public on April 14, 2006. After a public review and comment period, the documents will be reviewed by the Air Quality Advisory Committee (AQAC), a scientific peer review committee appointed by the Office of the President of the University of California to independently evaluate the scientific basis of staff findings and recommendations in the draft Staff and Technical Documents. The AQAC will hold a public meeting to discuss its review of the draft Staff Report and Technical Support Document, comments submitted by the public, and staff responses to those comments.

ARB and OEHHA staff will conduct public workshops on the development of the NO<sub>2</sub> standard and invite the public to openly address questions and provide comments, including those related to environmental justice. The current documents – a draft Staff Report containing staff’s preliminary findings, and a companion detailed Technical Support Document – are available for review and comment.

Community outreach for the standard review process involves a number of methods to disseminate information, including mailings, web “list serve” announcements, public meetings, and workshop presentations. The web “list serve” notifies the public of scheduled public meetings and workshops, and the availability of the Staff Report and the Technical Support Document. Public workshops on the proposed NO<sub>2</sub> standard are planned for Sacramento and El Monte. Individuals or parties interested in receiving notifications via the list serve on NO<sub>2</sub> or related ambient air quality standard issues, may enroll at the following internet location at no cost: [www.arb.ca.gov/listserv/aaqs.htm](http://www.arb.ca.gov/listserv/aaqs.htm).

Additional information on the standards review process is also available at the NO<sub>2</sub> review schedule website at: [www.arb.ca.gov/research/aaqs/no2-rs/no2-rs.htm](http://www.arb.ca.gov/research/aaqs/no2-rs/no2-rs.htm).

## **2.8 Environmental and Economic Impacts**

Ambient air quality standards in and of themselves have no environmental or economic impacts. Standards simply define clean air. Once adopted, local air pollution control or air quality management districts are responsible for the adoption of rules and regulations to control emissions from stationary sources to assure their achievement and maintenance. The Board is responsible for adoption of emission standards for mobile sources and consumer products. A number of different implementations measures are possible, and each could have its own environmental or economic impact. These impacts must be evaluated when the control measure is proposed. Any environmental or economic impacts associated with the imposition of future measures will be evaluated when specific measures are proposed.

## **2.9 Comment Period and Board Hearing**

The recommendations in this draft Staff Report will be presented for review and comment at public workshops in Sacramento and El Monte, California. Staff findings and recommendations will be peer-reviewed by the AQAC in a public meeting to discuss their review of this draft Staff Report and Technical Support Document. Details on the workshop and AQAC meeting may be obtained from the ARB website: [www.arb.ca.gov/research/aaqs/no2-rs/no2-rs.htm](http://www.arb.ca.gov/research/aaqs/no2-rs/no2-rs.htm), or by calling 916-445-0753.

Written comments on the draft Staff Report and draft Technical Support Document and the staff recommendations for revising the standard may be addressed to Dr. Norman Kado, at the Air Resources Board, Research Division, P.O. Box 2815, Sacramento, California 95812-2815. ([nkado@arb.ca.gov](mailto:nkado@arb.ca.gov), 916-323-1500, fax 916-322-4357). **Comments received by May 31, 2006 will be forwarded to the AQAC for consideration at their meeting.**

Following the meeting of the AQAC, staff will revise the draft Staff Report and draft Technical Support Document based on comments received from AQAC members and the public. The revised Staff Report and Technical Support Document will be made available for a 45-day public comment period in advance of a public meeting of the Air Resources Board to consider the staff's final recommendations. The Board meeting is tentatively scheduled for October, 2006.

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## **Appendix A OEHHA Recommendation**

# **RECOMMENDATION FOR AN AMBIENT AIR QUALITY STANDARD FOR NITROGEN DIOXIDE**

Submitted to the California Air Resources Board

Office of Environmental Health Hazard Assessment  
Oakland and Sacramento, California

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## Office of Environmental Health Hazard Assessment



Agency Secretary

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Arnold Schwarzenegger  
Governor

### MEMORANDUM

**TO:** Catherine Witherspoon  
Executive Officer  
Air Resources Board

**FROM:** Joan E. Denton, Ph.D. *Joan E. Denton, Ph.D.*  
Director

**DATE:** April 7, 2006

**SUBJECT:** RECOMMENDATION FOR AMBIENT AIR QUALITY STANDARDS FOR NITROGEN DIOXIDE

I am transmitting to you a document describing the Office of Environmental Health Hazard Assessment (OEHHA) recommendations for Ambient Air Quality Standards, for nitrogen dioxide (NO<sub>2</sub>). Our recommendations and their underlying scientific rationale will undergo public comment and a full review by the Air Quality Advisory Committee, our independent scientific review board, later this spring. After these reviews, we will revise our recommendations accordingly and resubmit them to you. The document has been sent electronically to your staff for incorporation into the review of the NO<sub>2</sub> standard under SB 25.

California ambient air quality standards have four elements (California Health and Safety Code Section 39014, and Title 17, California Code of Regulations, Article 2, Section 70101): (1) definition of the air pollutant, (2) an averaging time, (3) a pollutant concentration, and (4) a monitoring method to determine attainment of the standard. OEHHA recommends the following revision be made to the California ambient air quality standard for NO<sub>2</sub>:

1. Retain NO<sub>2</sub> as the air pollutant indicator.
2. Lower the current 1-hour-average standard for NO<sub>2</sub> to 0.18 ppm, not to be exceeded.
3. Establish a new annual average standard for NO<sub>2</sub> at 0.03 ppm, not to be exceeded.
4. These recommendations are based on the following reasons:
  - a. Evidence of enhanced airway inflammatory response after allergen challenge in asthmatics exposed to NO<sub>2</sub> at 0.26 ppm for 15 min to 30 min (in single or repeated doses).

#### California Environmental Protection Agency

*The energy challenge facing California is real. Every Californian needs to take immediate action to reduce energy consumption.*



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Catherine Witherspoon  
April 7, 2006  
Page 2

- b. Evidence of increased airway reactivity among asthmatics after exposures to NO<sub>2</sub> in the range of 0.2-0.3 ppm for 30 min to 2 hour.
- c. The need for a margin of safety since only relatively healthy asthmatics are exposed in the chamber studies. Additionally, the chamber studies show effects on allergen responsiveness after 15-30 minutes of exposure at 0.26 ppm. Lowering the one-hour standard to 0.18 ppm would provide additional protection against brief periods of NO<sub>2</sub> at or near the current standard of 0.25 ppm.
- d. Evidence from epidemiological studies of short-term effects of NO<sub>2</sub> on premature mortality, emergency room visits for asthma in children, and hospitalization for respiratory and cardiovascular disease. The annual average NO<sub>2</sub> levels in these studies are between 0.023 and 0.037 ppm.
- e. Evidence from epidemiological studies of long-term effects (i.e., exposure over several months to several years) of NO<sub>2</sub> on lung function growth in children, symptoms in asthmatic children, and preterm birth at exposures in the 0.030 to 0.044 ppm range.
- f. Infants and children have disproportionately higher exposure to NO<sub>2</sub> than adults due to their greater ventilation rate and greater exposure duration.
- g. Children may be more susceptible to the effects of NO<sub>2</sub> than the general population due to effects on the developing lung.

We would like to thank staff in both the Research Division and Planning and Technical Support Division for working with us to provide information and technical support during the development of our recommendations.

Should you have any questions or concerns, please call me at (916) 322-6325.

cc: Val. F. Siebal  
George V. Alexeeff, Ph.D.  
Melanie A. Marty, Ph.D., Chief  
Bart D. Ostro, Ph.D., Chief

Bart Croes, ARB, Chief, Research Division  
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# DRAFT

Recommendation for an Ambient Air Quality Standard for Nitrogen Dioxide

April 6, 2006

## **OEHHA Recommendation for Standard**

### Introduction

This chapter presents the OEHHA recommendations for the nitrogen dioxide ambient air quality standard (AAQS) for California for the Board's consideration. The chapter begins with a brief history of the California and federal AAQS for nitrogen dioxide and a discussion of the Children's Environmental Protection Act and other general considerations in determining air quality standards. It then reviews the scientific evidence regarding the health effects of NO<sub>2</sub>, discusses the findings on the overall adequacy of the current standards for nitrogen dioxide with respect to protecting the health of the public, including infants and children, and concludes with recommendations for the pollution indicators, averaging times, forms, and concentrations adequate to protect public health.

### History of the Ambient Air Quality Standards (State and Federal)

In January of 1966, separate health and welfare standards for NO<sub>2</sub> were set by the Department of Public Health. A standard based on atmospheric discoloration alone was set at 0.25 ppm averaged over one hour. A separate health-based standard was set at 3.0 ppm averaged over one hour based on limited information on health effects available at that time.

The standard was reviewed and revised by the newly formed Air Resources Board in September 1969. Human Health data were still limited and the Board chose to adopt a single standard of 0.25 ppm averaged over one hour. This standard was chosen to protect both health and welfare based on the effects of NO<sub>2</sub> on laboratory animals and on atmospheric discoloration.

The CA standard was subsequently reviewed in October and December of 1985. Although the averaging time was retained at 0.25 ppm averaged over one hour, the language in Title 17 describing the most relevant effects was revised to reflect current health information. Evidence available at that time indicated the need for a standard to protect sensitive people from bronchial irritation and to prevent biochemical and cellular alterations that are indicative of adverse health effects in both normal and sensitive groups. Contribution to atmospheric discoloration also remained as a basis for the standard.

The California Air Resources Board and the Office of Environmental Health Hazard Assessment last reviewed the CA standard in December of 1992 (CARB 1992). It was recommended that the level of the California Air Quality Standard for NO<sub>2</sub> be retained at 0.25 parts per million, averaged over one hour. This level was deemed necessary because of the "potential to aggravate chronic respiratory disease and respiratory symptoms in sensitive groups." Additionally, "Risk to public health (is) implied by pulmonary and extra-pulmonary biochemical and cellular changes and pulmonary structural changes, observed in short-term animal tests at or above the concentration of the standard". Contribution to atmospheric discoloration also remained as a basis for the standard.

The Environmental Protection Agency first promulgated a National Ambient Air Quality Standard (NAAQS) for Nitrogen Dioxide of 0.053 ppm (annual average) in 1971. The NAAQS for NO<sub>2</sub> was again reviewed in 1985 and 1996 and a standard of 0.053 ppm, annual average was retained. In the 1995 EPA staff paper, an annual primary standard of 0.53 ppm was deemed adequate to protect also against the occurrence of 1-hour NO<sub>2</sub> values greater than 0.2 ppm in most areas of the country.

## Considerations in Setting an Air Quality Standard for NO<sub>2</sub>

The Children's Environmental Health Protection Act [Senate Bill 25, Escutia; Stats. 1999, Ch. 731, specifically California Health & Safety Code Section 39606(d)(2)] requires a standard that "adequately protects the health of the public, including infants and children, with an adequate margin of safety." In the development of standards, SB25 called for, to the extent that information is available, that the following information be assessed:

1. Exposure patterns among infants and children that are likely to result in disproportionately high exposures relative to the general population
2. Special susceptibility of infants and children to ambient air pollution relative to the general population
3. The effects on infants and children of exposure to ambient air pollution and other substances that have common mechanisms of toxicity
4. The interaction of multiple air pollutants on infants and children, including between criteria air pollutants and toxic air contaminants

The governing statutory language indicates that California's ambient air quality standards should also protect other vulnerable populations, in addition to infants and children, and the general public [(H&SC sections 39606(d)(2) and 39606(d)(3)]. This legislative directive is consistent with historical practice in California, where ambient air quality standards have been formulated to protect identifiable susceptible subgroups, as well as the general population. For instance, the one-hour sulfur dioxide standard was developed in order to protect the most sensitive recognized subgroup, exercising asthmatics. Nonetheless, even with standards tailored to shield vulnerable populations, there may be exquisitely sensitive individuals remaining outside the ambit of protection.

Although both the California Health & Safety Code (section 39606) and the federal Clean Air Act (section 109) refer to an adequate margin of safety, no specific legislative definition of "adequate" is provided. This judgment is left to the responsible regulatory agencies. As described in the preceding chapters, data from controlled human exposure studies demonstrate that asthmatics experienced enhanced an immune response to an inhaled allergen after NO<sub>2</sub> exposures at 0.26 ppm but has not been adequately investigated at lower concentrations. Also, some studies of asthmatics have found increased airway reactivity at 0.2-0.3 ppm, whereas others have not, suggesting that asthmatics may vary in their response to NO<sub>2</sub>.

The incorporation of a safety margin has been recognized by the California Supreme Court as integral to the process of promulgating ambient air quality standards [Western Oil and Gas Association v. Air Resources Board, 22 ERC 1178, 1184 (1984)]. To the extent that health effects associated with ambient nitrogen dioxide occur at low levels of exposure, and that there is substantial inter-individual variability in response to environmental insults, it is unlikely that any nitrogen dioxide standard will provide universal protection for every individual against all possible nitrogen dioxide-related effects. Thus, in this instance, applying the notion of an “adequate margin of safety” for nitrogen dioxide standards becomes somewhat challenging. Nevertheless, taking into account the limitations of the scientific data, we have operationalized the concept of an adequate margin of safety by recommending standards that, when attained, should protect nearly all of the California population, including infants, children, asthmatics, the elderly, and individuals with chronic diseases, such as cardiovascular disease, against nitrogen dioxide-associated effects throughout the year.

The Children’s Environmental Health Protection Act required the ARB and OEHHA to review all health-based ambient air quality standards to determine whether the standards were protective of the health of the public, including infants and children, with an adequate margin of safety. The Act also required that, depending on the outcome of these reviews, the various ambient air quality standards be prioritized for full review and possible revision. Five factors were considered in assessing the health protectiveness of each ambient air quality standard during the prioritization process:

- 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 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.

Following these reviews, the various ambient air quality standards were prioritized for full review (California Air Resources Board and Office of Environmental Health Hazard Assessment 2000). The standard for nitrogen dioxide was prioritized to undergo full review after the standards for particulate matter and sulfates and ozone. The SB25 review found that several clinical studies suggested effects of nitrogen dioxide exposure on enhancement of the immune response to aeroallergen in asthmatics at concentrations at or below that of the current State standard of 0.25 ppm, averaged over one hour. The epidemiological studies found relationships between both outdoor and indoor NO<sub>2</sub> levels and respiratory illness, decrements in lung function, and exacerbation of asthma, especially in children. Such evidence could indicate the need for a more stringent standard, an averaging time different from the current one-hour average, or both.

### **Defining an Adverse Effect**

A key issue in evaluating the public health consequences of nitrogen dioxide exposure is consideration of the definition of an “adverse health effect”. The term “adverse health effect” is incorporated in the legislative background of the Federal Clean Air Act, as well as the California Health and Safety Code, although neither provides a definition for the term. Because it is helpful to the standard review process to consider the available scientific literature in the context of guidelines as to what is meant by the term, we have used guidelines published by the Scientific Assembly for Environmental and Occupational Health of the American Thoracic Society, which developed the most commonly used guidelines in the US (American Thoracic Society 1985; American Thoracic Society 2000). Both U.S. EPA and ARB have referred to these guidelines over the intervening years in assessing the significance of pollutant-associated physiological, biological or pathological changes.

It is important to keep in mind the differences between statistical significance and medical or biological significance when considering what constitutes an adverse health effect. The 1985 ATS statement defined “adverse respiratory health effects” as medically significant physiologic or pathologic changes generally evidenced by one or more of the following: (1) interference with the normal activity of the affected person or persons, (2) episodic respiratory illness, (3) incapacitating illness, (4) permanent respiratory injury, and/or, (5) progressive respiratory dysfunction. The 2000 ATS statement expanded on the 1985 statement to include consideration of biomarkers, quality of life, physiological impact, symptoms, clinical outcomes, mortality, and population health versus individual risk when evaluating whether or not a change should be designated as an adverse health effect. The 2000 ATS review committee’s recommendations are summarized here:

1. *Biomarkers*: These should be considered, however it must be kept in mind that few biomarkers have been validated sufficiently to establish their use for defining a point at which a response becomes adverse, consequently, not all changes in biomarkers should necessarily be considered adverse.
2. *Quality of life*: In recent years, decreased health-related quality of life has become widely accepted as an adverse health effect. The review committee concluded that reduction in quality of life, whether in healthy persons or persons with chronic respiratory disease, should be considered as an adverse effect.
3. *Physiological impact*: The committee recommended that small, transient reductions in pulmonary function should not necessarily be regarded as adverse, although permanent loss of lung function should be considered adverse. The committee also recommended that reversible loss of lung function in conjunction with symptoms should be considered adverse.
4. *Symptoms*: Air pollution-related symptoms associated with reduced quality of life or with a change in clinical status (i.e., requiring medical care or a change in medications) should be considered adverse at the individual level. At the population level, the committee suggested that any detectable increase in symptom frequency should be considered adverse.
5. *Clinical outcomes*: Detectable effects of air pollution on clinical measures should be considered adverse. More specifically, the ATS committee cited as examples

increases in emergency department visits for asthma or hospitalizations for pneumonia, at the population level, or an increased need to use bronchodilator medication, at the individual level. The committee recommended that: “no level of effect of air pollution on population-level clinical indicators can be considered acceptable.”

6. *Mortality*: Increased mortality should clearly be judged as adverse.
7. *Population health versus individual risk*: The committee concluded that a shift in risk factor distribution, and hence the risk profile of an exposed population, should be considered adverse when the relationship between the risk factor and the disease is causal, even if there is no immediate occurrence of obvious illness.

Based on these recommendations, many health outcomes found to be associated with nitrogen dioxide could be considered adverse including clinical outcomes such as emergency department visits for asthma, hospitalization for respiratory and cardiovascular disease, including life-threatening cardiac arrhythmias, and mortality.

In addition, controlled human exposure studies in asthmatics have found increased in airway reactivity, inflammation, and enhancement of the allergic response to allergen at levels near the current CA standard. These endpoints may be considered adverse as they signify increases in the potential risk profile of the population of asthmatics.

In California, 8.8% of the population (nearly 3 million) had asthma symptoms at least once in the previous year, including 9.6% (nearly 900,000) of California’s children (CHIS, 2001). Asthma is a chronic inflammatory disease of the airways characterized by an influx of inflammatory cells including eosinophils, and bronchial hyper-reactivity. Given our current scientific understanding of the pathophysiology of asthma, the observed NO<sub>2</sub> effects in controlled studies of asthmatics would be considered adverse. Specifically, the clinical significance of increased airway reactivity after NO<sub>2</sub> exposures in individuals with pre-existing respiratory diseases is the potential for a flare up or exacerbation of their underlying respiratory disease. Enhancement of the inflammatory response to allergen, would contribute to cycle of chronic inflammation, airway injury, and remodeling characteristic of asthma, especially in the more severe asthmatic.

## **Summary of the Scientific Evidence**

Nitrogen Dioxide is an oxidant and strong respiratory irritant. Because of its low solubility in water, NO<sub>2</sub> penetrates deeper into the respiratory tract. The bronchoalveolar regions are the sites with the highest local concentrations. This area of the lung is especially vulnerable to NO<sub>2</sub> because the protective fluid that lines the mucosal surface of the deep airways (epithelial lining fluid) is relatively sparse in this region.

There is evidence from clinical, toxicology, and epidemiological studies that NO<sub>2</sub> can affect human health. Each investigative approach possesses advantages but also carries limitations. Controlled human exposure studies (i.e. clinical or chamber studies) provide valuable information about the acute effects of NO<sub>2</sub> exposure in humans under controlled conditions. However, the studies have, in general, been limited to healthy

subjects and mild asthmatics. Furthermore, acute responses seen in clinical studies cannot necessarily be used to predict health effects of chronic or repeated exposure.

Inhalation studies in animals allow precision in quantifying exposure duration and concentration, measurement of a wide variety of physiologic, biochemical, and histological endpoints, and examination of extremes of the exposure-response relationship. Interpretation of these studies may be constrained by difficulty in extrapolating findings from animals to humans, especially when exposure concentrations are unrealistically high. Studies done on human cells (or tissues) *in vitro* can help investigate mechanisms of toxicity but lack all (or some) of the naturally occurring defense mechanisms. Epidemiological investigations examine exposures in free-living populations and can study a wide range of subgroups. However, precise exposure characterization is difficult, and important confounders, e.g. other co-pollutant, socioeconomic status, and occupational factors, may not be fully characterized.

### **Summary of Findings from Controlled Human Exposure Studies of NO<sub>2</sub>:**

#### *Design considerations in Controlled Exposure Studies:*

Experimental exposure of human volunteers to air pollutants under controlled conditions provides useful data on pathophysiological changes that can be of direct relevance to standard setting. The carefully controlled environment allows investigators to identify responses to individual pollutants, to characterize exposure-response relationships, and to examine interactions among pollutants *per se* or with other variables such as exercise. Endpoint assessment traditionally has included symptoms, pulmonary function (e.g., FEV<sub>1</sub>, the amount of air one can exhale in one second after a deep inspiration), and airway responsiveness. More recently, studies have been extended using a variety of markers of pulmonary, systemic, and cardiovascular effects. Responses after exposure to NO<sub>2</sub> are compared with responses after exposures using filtered air as a control. The exposure protocols for some chamber studies involve single exposures to NO<sub>2</sub> of varying duration (30 min. to up to six hours) or short (15-30 min.), repeated exposures to NO<sub>2</sub>. This intermittent exposure protocol might better reflect the short-episodic high exposures to NO<sub>2</sub> seen in real-life exposure.

Human clinical studies also have limitations often due to small sample size, including limited statistical power and limited ability to adequately study the range of responses in the general population or specific subpopulations. In addition to specific subpopulations with underlying disease, such as asthmatics, there is increasing scientific evidence that genetics and other individual host factors (e.g. smoking status, prior exposure to ambient pollutant, dietary factors) may be important determinants of an individual's susceptibility to a given pollutant, and small clinical studies are unable to adequately evaluate the wide variation in susceptibility due to these host factors. Additionally, for safety and ethical reasons, among those with chronic medical conditions such as asthma or cardiovascular disease, only those with mild or moderate disease are usually studied. Infants and young children are not studied in this setting. This selection bias in recruiting volunteers reduces the ability to generalize the findings of such studies.

Finally, controlling the experimental conditions may result in failure to capture effects found in complex real-world exposures.

Additionally, studies must be limited to short durations of exposure (i.e., minutes to hours) and to pollutant concentrations that are expected to produce only mild and transient responses. The acute, transient responses seen in clinical studies are not necessarily predictive of health effects of chronic or repeated exposure.

It should be emphasized, however, that these limitations all tend to underestimate pollutant effects. Therefore, finding a response that can be related to specific exposure conditions constitutes a valuable component to the standard setting process. In contrast, given the potential limitations of human clinical studies, negative findings may in some cases reflect the constraints of study design more than biological reality.

Below, we first summarize the studies of healthy subjects exposed to NO<sub>2</sub> alone, and then consider studies of subjects with asthma, infants and children, and other potentially susceptible subgroups. Finally, we summarize the studies of NO<sub>2</sub> in combination with other pollutants.

#### *Healthy individuals*

The clinical data suggests that young healthy subjects exposed to NO<sub>2</sub> at concentrations below 4 ppm for several hours do not experience symptoms, changes in pulmonary function or increased airway resistance. However, exposures to NO<sub>2</sub> in the range of 1.5-2.0 ppm can cause small, statistically significant effects on airway responsiveness in healthy individuals (Mohsenin et al., 1987b, Frampton et al., 1991). These levels are of potential concern primarily in occupational settings (see Chapter 5 of the Technical Support Document). Additionally, exposures to NO<sub>2</sub> in the range of 1.5 to 2.0 ppm for four to six hours induced mild airways inflammation, based on several different markers. These inflammatory response were unaccompanied by symptoms or changes in lung function. Short exposures (20 min.) at similar concentrations did not show evidence of airway inflammation (Strand et al., 1990, 1991). A limited number of clinical studies in healthy individuals have reported effects of NO<sub>2</sub> on host defenses at concentrations above 1.5 ppm. Taken together, these studies suggest that in healthy adults there may be a threshold for airway inflammatory effects of single, multi-hour NO<sub>2</sub> exposures at an approximate concentration of 1 ppm. Few studies have examined responses in healthy elderly; one study suggests there may be significant decrease in lung function (FEV<sub>1</sub>) in older smokers exposed to 0.3 ppm NO<sub>2</sub> for several hours (Morrow et al., 1992).

#### *Asthmatics*

Clinical studies indicate that individuals with asthma are more susceptible to the effects of NO<sub>2</sub> compared with healthy individuals (Table 1). As discussed in Chapter 6 of the Technical Support Document, most studies of asthmatics have found no effects of NO<sub>2</sub> on symptoms or lung function at 0.1-0.5 ppm. Some studies of asthmatics found

evidence of increased airway reactivity at NO<sub>2</sub> levels in the range of 0.2-0.3 ppm (Kleinman et al. 1983 (0.2 ppm/ 2hr); Jorres et al. 1990 (0.25 ppm/30 min, Bauer et al. 1986, (0.3 ppm/30 min), Strand et al., 1996 (0.26 ppm/30 min), whereas others using similar (but not identical) exposure protocols have not found evidence of increased airway reactivity as low as 0.1-0.5 ppm. One exception was a study by Orhek et al. (1976) that found increased airway responsiveness in 13/20 subjects at 0.1 ppm/1 hr. This study was challenged because of questionable statistical analysis, and other studies have been unable to confirm effects on airway responsiveness or lung function at 0.1-0.12 ppm (see Chapter 5 of the Technical Support Document). An examination of the data on responses for individuals suggest that there is substantial inter-individual variability in airway reactivity in response to NO<sub>2</sub> at levels near the current CA 1 hr-standard of 0.25 ppm. A pooled analysis of asthmatics found evidence of increased airway responsiveness at 0.2-0.3 ppm, primarily in studies with exposures at rest (Folinsbee 1992). Thus, the lack of findings in some studies may reflect, in part, lack of statistical power due to small sample size, differences in subjects (inter-individual variability) and exposure protocols.

Few subjects have evaluated the effects of NO<sub>2</sub> on airway inflammation in asthmatics. One study found evidence of airway inflammatory mediators in BAL of asthmatics exposed at 1 ppm for 3 hr; these changes were concomitant with small decrements in lung function (Jorres et al. 1995). Healthy subjects in the same study showed a lower response as measured by these markers of inflammation and no evidence of effect on lung function.

Recent studies from the UK and Sweden suggest that, overall, subjects with asthma exposed to NO<sub>2</sub>, at rest, have an enhanced response to allergen challenge at concentrations as low as 0.26 ppm for 15 min (Barck et al., 2005) to 30 min. (Strand et al., 1997, 1998; Barck et al., 2002) and 0.4 ppm for 1 hr (Tunnicliffe et al. 1994). There was no evidence of attenuation of the enhanced response to allergen after repeated exposures to 0.26 ppm NO<sub>2</sub> (30 min. exposure each day on four consecutive days) (Strand et al. 1998)

Compared with filtered air, single and repeated NO<sub>2</sub> exposures at rest for short durations (30 min.) enhanced responses of asthmatics to allergen challenge at concentrations as low as 0.26 ppm. Enhanced responses included: a more pronounced early and/or late-phase decrement in lung function (peak expiratory flow or FEV<sub>1</sub>) and evidence of increased cellular inflammation (neutrophils) and eosinophil activity in lung lavage and/or sputum samples (Strand et al., 1997, 1998; Barck et al., 2002, 2005). Barck et al., (2005) demonstrated that brief repeated exposures on two consecutive days (15 min Day 1, 15 min x 2 Day 2) followed by allergen challenge on Day 2) increased eosinophil activity in sputum and blood. Serum levels of eosinophilic cationic protein (ECP), a product of eosinophils that contributes to airway injury in asthmatics, are increased in individuals with asthma and atopy and correlate with disease activity (Venge et al. 1999). Although the NO<sub>2</sub> exposures in these studies did not lead to a clinical asthma exacerbation in the laboratory setting, the response could be more pronounced and deleterious in those with more severe asthma. There is increasing

evidence that air pollutants with strong oxidant properties (e.g. NO<sub>2</sub>, ozone, and diesel exhaust particles) can potentiate the allergic response by similar mechanisms (Krishna et al., 1999). Animal models of allergic asthma support the observation (Gilmour et al., 1995).

The studies above clearly find that asthmatics are more susceptible to the effects of NO<sub>2</sub> compared with healthy individuals. Of note, the concentration dose-response has not been adequately studied; the one study that evaluated the allergen responses for filtered, 0.1 ppm, and 0.4 ppm for 1 hr found a significant drop in % FEV<sub>1</sub> between filtered air and 0.4 ppm but not between filtered air and 0.1 ppm (Tunnicliffe et al. 1994).

There are no studies on effects of NO<sub>2</sub> on host defenses in asthmatics; however, there is no reason to believe that the NO<sub>2</sub> effects on host defenses seen in healthy individuals (alterations in ciliary motility, oxidative stress, and enhanced susceptibility to epithelial cell injury *in vitro*) would not apply in asthmatics. Furthermore, these processes (ciliary dysmotility, epithelial cell injury, and oxidative stress) are part of the pathophysiology of asthma, and it is possible that the effects of NO<sub>2</sub> on host defenses in asthmatics might be seen at lower levels compared with normal healthy individuals. Effects of NO<sub>2</sub> on host defenses could lead to clinical consequences (e.g. exacerbations or increased severity or duration of asthma after respiratory infection), in more severe asthmatics that already have airway compromise due to their underlying disease.

**Table 1.** Summary of Human Chamber Studies on Nitrogen Dioxide: Healthy Individuals vs. Asthmatics \*

	Healthy Individuals	Asthmatics
Symptoms	No effect as high as 4 ppm for up to 5 hr	Most studies showed no effect at 0.1 ppm-0.5 ppm for 30 min-1 hr
Lung function	No effects at as high as 4ppm for up to 5 hr	Most studies showed no effect at 0.1-0.5 ppm for 30 min-1 hr
Airway responsiveness	Increased at 1.5-2 ppm for 1-3 hr	Increased at 0.2-0.3 ppm for 30 min-2 hr in some studies. Substantial between subject variability in response.
Airway Inflammation	Exposures at 1.5-2 ppm (3-6 hours), increased neutrophils and epithelial cytokines in BAL.	Only one study to date has evaluated asthmatics using BAL:

	At 1 ppm for 3 hr: BAL showed increase in one inflammatory mediator (eicosanoid) but no increase in cell counts.	At 1 ppm for 3 hr: BAL showed increase in several inflammatory mediators along with decrease FEV <sub>1</sub> but no increase in cell counts. Wider inflammatory response suggests that asthmatics more responsive at 1 ppm compared with healthy individuals in same study.
Response to NO <sub>2</sub> + allergen compared with filtered air + allergen	Not applicable	Effects of NO <sub>2</sub> plus allergen at 0.26 for 30 min (compared with filtered air) <sup>1</sup> <ul style="list-style-type: none"> <li>• larger decrement in lung function (FEV<sub>1</sub> or peak flow)</li> <li>• increased neutrophils (BAL)</li> <li>• evidence of eosinophil activation (BAL, blood, sputum).</li> </ul>

\*Lowest level at which effects observed. Unless indicated, data not available on threshold level (i.e. level where no effect seen).

<sup>1</sup>However, these responses were not consistently observed in each study. Eosinophil activation seen with repeated exposures as low as 15 min duration (Barck et al., 2005) No change in FEV<sub>1</sub> after NO<sub>2</sub> + allergen exposure at 0.1 ppm (Tunnicliffe et al. 1994).

### *Studies in Children*

Only two controlled studies of lung function after NO<sub>2</sub> exposures have examined children. Ten children with mild asthma (age 11-18 yr) exposed to NO<sub>2</sub> 0.12 ppm / 40 min did not experience changes in lung function. There was a non-significant trend of increased symptoms after NO<sub>2</sub> exposures. Asthma medications were not withheld and may have decreased the ability to detect an effect of NO<sub>2</sub> (Koenig et al., 1985). A second study of 34 asthmatics (age 8-16 yr) exposed to NO<sub>2</sub> at 0.30 ppm/ 3 hr found no effect on airway reactivity. A transient decrease in FEV<sub>1</sub> was noted for the first hour of exposure but returned to baseline during the latter part of the exposure (Avol et al. 1988). Thus, the only two studies in children with asthma did not find a clear effect of NO<sub>2</sub> on lung function or airway reactivity.

### *Other Susceptible Populations:*

Two studies of individuals with chronic obstructive pulmonary disease found small (3-5%), statistically significant, decrements in lung function (FEV<sub>1</sub>) at 0.3 ppm NO<sub>2</sub> with intermittent exercise (Morrow et al. 1992 (0.3 ppm/4 hr), Vagaggini et al. 1996 (0.3 ppm/1 hr); whereas several others did not. The lack of findings is likely due to small samples, patient selection (subject variability), and/or differences in protocol. Older smokers and non-smokers (mean age 61 years) were also studied by Morrow et al. (1992). Smokers experienced a slight, statistically significant decrease in FEV<sub>1</sub> after NO<sub>2</sub> exposures at 0.3 ppm

Several clinical studies suggest there may be systemic and cardiovascular effects of NO<sub>2</sub> exposure. These data are insufficient to be conclusive, and do not provide adequate concentration-response data. Additional studies are needed to determine whether there are cardiovascular effects of NO<sub>2</sub> exposure, and the mechanisms involved.

### **Pollutant Concentration/Dose-response functions:**

There is somewhat conflicting results among the few studies that have investigated whether the peak concentration of NO<sub>2</sub>, duration of exposure, or the total dose (concentration x duration) are more important. Studies have shown evidence of airway inflammation in healthy individuals following prolonged exposure (four to six hours) to NO<sub>2</sub> at a concentration of 2.0 ppm (Azadniv et al. 1998, Blomberg et al. 1997, Devlin et al. 1999), whereas short (20 min.) exposures to NO<sub>2</sub> at 1.5-2 ppm did not (Sandstrom et al. 1990, 1992b). These results suggest that duration, not peak concentrations are more important. In contrast, a recent study by Jenkins et al. found that in a group of mild asthmatics exposed for 3 hr to NO<sub>2</sub> (400 ppb) FEV<sub>1</sub> was decreased, whereas the same total dose but delivered at a lower concentration and over longer duration (6 hr at 200 ppb) had no effect on FEV<sub>1</sub>. The latter set of results suggests that the threshold concentration rather than the total amount of pollutant inhaled over time was more important. No studies have been conducted to investigate whether peak concentrations

or total dose are more important at lower concentrations that might be directly applicable to standard setting.

### *Pollutant Mixtures*

The database on NO<sub>2</sub> as part of air pollution mixtures remains limited, in part because of the complexity of the experimental design and the difficulty in studying the most susceptible subjects. Several studies found no effects of NO<sub>2</sub> – ozone mixtures on pulmonary function in young healthy individuals. Jorres et al. (1990) found increased airway responsiveness to SO<sub>2</sub> after exposure to 0.3 ppm NO<sub>2</sub> (Jorres et al 1990). Rusznak et al. (1996) and Devalia et al. (1994), showing increased allergen responsiveness after exposure to NO<sub>2</sub> (0.4 ppm) and SO<sub>2</sub> (0.2 ppm), but not to either gaseous pollutant alone. Drechsler-Parks (1995) found a decrease in cardiac output in elderly individuals for mixtures of NO<sub>2</sub> (0.6 ppm) and ozone (0.45 ppm) but not with individual pollutants. Overall, the data suggest that, in asthmatics, NO<sub>2</sub> at levels only slightly above the California standard may enhance airways responsiveness to other pollutant challenges, and may act synergistically with SO<sub>2</sub> in enhancing responses to allergen challenge.

### *Concentrations where adverse effects have been observed*

Studies indicate that asthmatics may have enhanced response to an inhaled allergen and increased airway responsiveness with NO<sub>2</sub> exposures at 0.2-0.3 ppm. These are two important endpoints for asthmatics. Asthma is a chronic inflammatory disease of the airways characterized by an influx of inflammatory cells including eosinophils, and bronchial hyper-reactivity. Those with allergic asthma would have a greater inflammatory response to an inhaled allergen, e.g. pollen when breathing ambient air with NO<sub>2</sub> and may experience allergic symptoms at lower pollen concentrations in the presence of NO<sub>2</sub>. In more severe asthmatics this may contribute to a worsening of asthma symptoms. The clinical significance of increased airway reactivity after NO<sub>2</sub> exposures in individuals with pre-existing respiratory diseases is the potential for a flare up or exacerbation of their underlying respiratory disease. There is little data on the effects of NO<sub>2</sub> at levels below 0.2 ppm. Studies on airway reactivity in asthmatics at 0.1-0.12 ppm have been largely negative. The one study that evaluated the allergen responses for filtered, 0.1 ppm, and 0.4 ppm for 1 hr found a significant drop in % FEV<sub>1</sub> between filtered air and 0.4 ppm but not between filtered air and 0.1 ppm (Tunnicliffe et al. 1994).

Thus, the studies to date call into question whether a standard of 0.25 ppm is adequately protective of people with asthma. Elderly smokers, and those with COPD may also have decrements in lung function at the current ambient standard of 0.25 ppm.

### **Conclusion:**

Overall, the clinical studies suggest NO<sub>2</sub> exposures near the current ambient air quality standard for NO<sub>2</sub> (0.25 ppm, 1 hour average) may enhance the response to inhaled allergen in people with allergic asthma. Responses seen included: decrements in lung function, an increased inflammatory (neutrophil) response in airways, and evidence of activation of eosinophils. However, these responses were not consistently observed in each study. For a subset of asthmatics, exposures to NO<sub>2</sub> at levels near the current ambient air quality standard may have increased airway reactivity. Limited data suggests that elderly smokers, and those with COPD may also have decrements in lung function at the current ambient standard of 0.25 ppm.

## **Summary of Findings from Toxicological Studies**

Previously reviewed studies (CARB, 1992) have observed acute effects related to allergic and inflammatory responses as well as effects associated with liver metabolism and biosynthesis of carcinogenic compounds at exposures close to the existing standard.

No measurable inflammatory effects were apparent with acute or short-term repeated NO<sub>2</sub> exposures greater than 0.25 and up to 1.0 ppm. However, epithelial cell labeling techniques have noted increased cell proliferation in bronchiolar tissue with one-day exposure to 0.8 ppm (Barth et al. 1994). This would indicate that epithelial cell labeling is a more sensitive indicator of cellular damage than conventional methods of measuring NO<sub>2</sub>-induced pulmonary inflammation.

Transient reductions in levels of particular arachidonate metabolites in BAL fluid following acute and short-term exposure to 0.5 ppm NO<sub>2</sub> and similar results in ex vivo studies suggest the potential for impeding the host's defense against microbial infection by damaging alveolar macrophages. Nonetheless, these individual effects on various components of lung host defense by NO<sub>2</sub> have not translated into an enhancement of pulmonary infection by microorganisms at NO<sub>2</sub> concentrations of 1 ppm or less (Davis et al. 1991; Nisizawa et al 1988; Rose et al. 1989).

Acute NO<sub>2</sub> exposure studies on pulmonary function (Halinen et al., 2000a; Halinen et al., 2000b; Hubbard et al., 2002) produced mixed results in different animal models. Pulmonary immune response studies with longer NO<sub>2</sub> exposures (0.5 or 1.0 ppm for 3 months) in mice produced mixed results on levels of immunoglobulins and interleukins involved in antigen-specific immune response, suggesting that the timing and level of antigen and NO<sub>2</sub> exposure are important determinants in the type of immune response.

Longer term studies have observed some morphological and biochemical changes in developing mice with NO<sub>2</sub> concentrations at 0.25 ppm. Six-week intermittent exposure to 0.25 ppm beginning at 3 weeks of age, during which lung development is still occurring, resulted in increased number and size of alveolar Type II cells (Sherwin and Richters, 1995a). While this effect was noted immediately following exposure, it was not statistically significant until 32 weeks post-exposure. Type II cell alterations long after NO<sub>2</sub> exposure has ended suggest permanent structural changes have occurred to alveolar tissue. In addition to these effects, there were alterations in measures of elastic fiber abundance in alveolar tissue up to 10 weeks post-exposure, with increased ratios

of elastin number/alveolar wall area and elastin area/alveolar wall area at 32 weeks post-exposure (Sherwin and Richters, 1995b). The increased amount and density of elastin in alveolar tissue would suggest an interstitial fibrotic consequence resulting from exposure during lung development. In other longer-term exposure studies, morphometric changes in alveolar tissue components (i.e. thickened alveolar walls, increased cellularity, altered epithelial cell volumes) occurred during lung development in young mice intermittently exposed to 0.3 ppm for 6 weeks, and in young ferrets intermittently exposed to 0.5 ppm for 15 weeks (Sherwin et al. 1985; Rasmussen and McClure; 1992). Long-term NO<sub>2</sub> exposure studies averaging 0.4 ppm or higher in adult animals have not observed morphological changes in centriacinar region tissue (Mercer et al., 1995; Tepper et al., 1993; Ichinose et al., 1991), suggesting that the developing lung is a susceptible target of NO<sub>2</sub> toxicity. Similarly, studies where exposures began at a more mature stage of animal development (7 weeks or young adult) and in a different species (rat) using higher NO<sub>2</sub> exposures did not observed morphometric changes in alveolar tissue components (Mercer et al. 1995; Tepper et al. 1993), and sensitive cell labeling methods did not detect an increase in alveolar proliferation with acute exposure (Barth et al. 1994).

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In addition to increased developmental susceptibility, use of animal models with predisposition to specific diseases provides evidence of increased susceptibility to low NO<sub>2</sub> concentrations. Obese rat strains prone to cardiovascular-type diseases exhibited increased blood levels of triglycerides and decreased HDL and HDL/total cholesterol ratio when exposed to 0.16 ppm NO<sub>2</sub> for 24 weeks (Takano et al., 2004). A related normal rat strain exposed similarly only showed decreased HDL levels. Small group numbers (n = 9 to 14) and lack of a clear dose-response effect make this finding somewhat uncertain.

In an *in vitro* study, exposure to NO<sub>2</sub> (0.2 ppm, 2 hrs) altered NO production in AMs. NO plays a role in antimicrobial defense or modification of the immune response (Hockele et al., 1998). However, comparable *in vivo* studies of NO<sub>2</sub> affects on NO production in AMs are lacking. *In vitro* data provide valuable insight into potentially sensitive indicators of acute NO<sub>2</sub>-induced cellular injury. However, there is some uncertainty in extrapolating *in vitro* data to toxic effects in intact animals. Therefore, no definitive conclusions will be drawn with regard to health effects of NO<sub>2</sub> in intact animals based on *in vitro* studies.

Pulmonary function changes with prolonged exposure include increased airway hyperresponsiveness with histamine challenge after exposure of guinea pigs to 1.0 ppm NO<sub>2</sub> for 6 weeks (Kobayashi and Miura, 1995), and a transient reduction in  $\Delta FEF_{25\%}$  with intermittent NO<sub>2</sub> exposure (0.5 ppm base with daily 2 hr peaks of 1.5 ppm) for 78 weeks (Tepper et al. 1993). Under the same exposure conditions as Tepper et al.

(1993), systemic immune changes were limited to a transient reduction of splenic natural killer cells at 3 weeks (Selgrade et al. 1991). There is also evidence that exposure of mice to 0.35 ppm NO<sub>2</sub> for 6 weeks may cause damage to the pulmonary microvasculature, thus permitting an injected murine melanoma cell line to take hold and increase metastatic lung burden (Richters and Richters, 1989).

NO<sub>2</sub> has been shown to be genotoxic and mutagenic in some bacterial and animal test systems, but no standard carcinogen animal bioassays with a sufficient number of animals/group could be located in the literature. Two published carcinogenicity and co-carcinogenicity studies were negative for lung cancer (Ichinose et al. 1991; Witschi et al. 1993). In another study that investigated NO<sub>2</sub>'s ability to modify lung tumor development, increased tumor frequency and incidence were observed in a susceptible mouse strain exposed to 10 ppm NO<sub>2</sub> for 6 months, but there was a lack of a clear dose-response effect and high variability in lung adenoma development among several control groups (Adkins et al. 1986). NO<sub>2</sub> (6 ppm) combined with a diesel exhaust particle (DEP) extract produced a synergistic increase in DNA adducts and alveolar adenomas over DEP treatment alone (Ohyama et al. 1999). NO<sub>2</sub> (0.4 ppm) and ozone (0.05 ppm average) mixtures in rats produced a small co-carcinogenic action with BHPN while mixtures of NO<sub>2</sub> and H<sub>2</sub>SO<sub>4</sub> with BHPN in rats and NO<sub>2</sub> and SO<sub>2</sub> with DEN in mice did not (Ichinose and Sagai, 1992; Heinrich et al. 1989). Thus, the overall potential for animal carcinogenicity, and by extrapolation, human carcinogenicity, at ambient air levels of NO<sub>2</sub> is uncertain.

The few relevant non-carcinogenic toxicological studies of multi-pollutant mixtures reviewed herein produce inconsistent results. For example, rats exposed to NO<sub>2</sub> (0.4 ppm) and ozone (0.4 ppm) for 2 weeks resulted in synergistic or additive increases in anti-oxidant substances and enzymes in lung and no increase in lipid peroxides (Ichinose and Sagai, 1989). Guinea pigs under the same exposure regimen produced the opposite effect; no change in pulmonary anti-oxidant levels but increased lipid peroxide formation. However, longer exposures in rats to NO<sub>2</sub> (0.4 or 0.04 ppm) and ozone (0.05 average with daily 0.1 ppm peak) did demonstrate a synergistic increase in lipid peroxides, but in general, no change in anti-oxidant substances and enzymes. Thus, pollutant interactions may be dependent on the timing and intensity of exposure as well as the species.

Some *in vitro* data on the biochemical effects of NO<sub>2</sub> on airway epithelium and AMs observed toxic effects at acute NO<sub>2</sub> concentrations of 0.5-1.0 ppm.

## Conclusions

Key non-cancer health concerns that have been associated with ambient exposure of experimental animals to NO<sub>2</sub> include: (1) morphological changes in bronchiolar-alveoli junction epithelium; (2) Immunological and biochemical changes associated with respiratory tract defense, and; (3) pulmonary function decrements. In particular, the NO<sub>2</sub>-induced effects observed by Sherwin and Richters (1995a, 1995b) suggest that potentially permanent structural changes to the lung during development may occur from prolonged exposure to relatively low levels of NO<sub>2</sub> (0.25 ppm), but may not become fully apparent until later in life. This evidence is supported by other reports of lung alterations following exposure to low concentrations of NO<sub>2</sub> in mice (0.3 ppm) and

ferrets (0.5 ppm) during lung development (Sherwin et al. 1985; Rasmussen and McClure; 1992). More studies should be conducted to confirm the findings of altered lung morphology by NO<sub>2</sub> during lung development and to determine if acute NO<sub>2</sub> exposures at more specific stages of lung development can also trigger an alteration of lung structure.

Though limited, the data for NO<sub>2</sub>-induced animal carcinogenicity has been negative or ambiguous. However, the study by Ohyama et al. (1999) showed a synergistic increase in DNA adducts and alveolar adenomas with combined NO<sub>2</sub> (6 ppm) and diesel exhaust particle (DEP) extract (compared to DEP treatment alone). This data suggests that multi-pollutant exposures including NO<sub>2</sub> may be a primary means ambient level NO<sub>2</sub> can contribute to toxic effects.

## **Summary of Findings from Epidemiologic Studies**

The experimental studies such as the chamber studies reported in this document provide valuable information about the acute effects of NO<sub>2</sub> exposure in humans under controlled conditions. Epidemiologic studies add to this evidence by evaluating both short and long-term (i.e., a year or more) effects of outdoor and indoor NO<sub>2</sub> in free-living populations. Epidemiologic studies of NO<sub>2</sub> have reported associations with such outcomes as lung function, respiratory symptoms, emergency department visits, hospitalizations and premature mortality. As such, these studies provide some additional evidence of an adverse effect of NO<sub>2</sub>, subject to certain important limitations and uncertainties.

As with all epidemiological studies on air pollution, there are both advantages and disadvantages to observational studies of NO<sub>2</sub>. Epidemiologic studies are able to examine a wide range of individuals, behaviors, subgroups, and exposure conditions. However, as indicated in Chapter 7 of the Technical Support Document, there are several disadvantages including some that are specific to the study of NO<sub>2</sub>.

First, epidemiologic studies of NO<sub>2</sub> may be subject to measurement errors. It is not possible to characterize exposure in a precise manner similar to that of a chamber study. This is particularly true for NO<sub>2</sub>, a pollutant that is more local and less regional in scope (unlike PM<sub>2.5</sub> and ozone). In addition, as a reactive gas, it does not fully penetrate into the indoor environment. In addition, there are known indoor sources of NO<sub>2</sub> such as gas stoves and fireplaces. Therefore, there will be errors in assigning exposures to individuals which will likely result in biased effect estimates.

Second, epidemiologic studies may be subject to bias from uncontrolled or poorly controlled confounders such as seasonality, weather and co-pollutants. The latter is of particular concern since NO<sub>2</sub> is often highly correlated with OC, EC, PM<sub>2.5</sub> and UF (Zhu et al 2002, Seaton 2003, Gauderman et al. 2002). Therefore, determining the independent effect of NO<sub>2</sub> can be challenging. Given the problems outlined above, the available outdoor studies were more informative when direct or indirect adjustment for measured particles concentration (PM<sub>10</sub>, PM<sub>2.5</sub>, Black Smoke) were possible, or when the studies were conducted in areas where the variability of NO<sub>2</sub> was larger than that of fine particles, or when modification of the effect of particulate matter by NO<sub>2</sub> has been

evaluated indicating consequences of exposure to traffic derived particles. However, the role of pollutants that are typically correlated and unmeasured remains unknown.

Third, the epidemiologic studies in this review used different averaging times of NO<sub>2</sub> for their exposure measurements. Many used a 24-hour average while others reported results for 1-hour maximum or 8-hour average levels. Since these metrics tend to be highly correlated, if there is a positive association between NO<sub>2</sub> and a given health effect, it is difficult to attribute the effect to a precise averaging time.

Despite these limitations, a large number of epidemiological studies published in the last several years have demonstrated associations between NO<sub>2</sub> concentrations and several health effects including overall mortality, cardiopulmonary mortality, decreased lung function, respiratory symptoms, and emergency visits for asthma. The overall findings from these studies are supported by the coherence of effects, the biological plausibility (at least at higher concentrations) obtained from animal studies, and the finding of a concentration-response relationship in many of the studies. While any given epidemiologic study may have some limitations, taken together these studies suggest the possibility of significant adverse effects on the free-living population. However, given the problems outlined above, it is difficult to use these studies to determine a likely effects level. Nevertheless, prudent public health policy suggests that these studies should contribute to important margin of safety considerations. In addition, the epidemiological studies suggest the need for an additional standard that includes an averaging time greater than one-hour. A summary of the most important findings is presented below.

#### *Outdoor time-series studies: short-term exposure*

Several studies have reported associations between daily changes in NO<sub>2</sub> and resultant changes in daily counts of mortality or morbidity, such as hospital admissions. These time-series studies typically involve several years of data for large cities in US and Europe, and examine either the entire population or subjects with pre-existing chronic diseases, such as asthma. Several studies have reported statistically significant associations between NO<sub>2</sub> and all-cause, cardiovascular and respiratory mortality. However, in some of the studies, inclusion of PM<sub>10</sub> in the regression model significantly attenuates the NO<sub>2</sub> effect. This phenomenon may be due to high correlation between the two pollutants, differential measurement error, or the lack of a true effect of NO<sub>2</sub>. For example, the analysis of the largest 90 U.S. cities first reported an association between NO<sub>2</sub> and all-cause mortality (Dominici et al. 2003). However, when PM<sub>10</sub> was added to the explanatory model, the effect estimate for NO<sub>2</sub> remained the same but became statistically insignificant.

Likewise, the meta-analysis of results from several counties by Stieb et al. (2002) found that the effect estimate for NO<sub>2</sub> and all-cause mortality became insignificant when PM<sub>10</sub> was included in the regression specification. Few, if any, of the studies reviewed for this document had low correlations between PM and NO<sub>2</sub>, making it difficult to separate the effects of these two pollutants, both of which are associated with combustion sources.

In contrast, in a study of four cities in Australia, the effect of NO<sub>2</sub> on total mortality remained about the same and was statistically significant when a fine particle measurement was added to the model (Simpson et al. 2005a). Mean NO<sub>2</sub> levels for the study period ranged from 16.3 to 23.7 ppb. A recent analysis of the effects of NO<sub>2</sub> in the APHEA-2 study (Samoli et al. 2006) included 30 European cities. In single pollutant models the percent increase in mortality for a 10 ug/m<sup>3</sup> increase in 1-hour maximum NO<sub>2</sub> was 0.30 (95% CI = 0.22-0.38) for total mortality, 0.40 (95% CI = 0.29-0.52) for cardiovascular mortality (CVD) and 0.38 (95% CI = 0.17-0.58) for respiratory mortality. In two-pollutant models, adjusting in turn for the confounding effects of black smoke, PM<sub>10</sub>, SO<sub>2</sub>, and O<sub>3</sub>, NO<sub>2</sub> associations with total and cardiovascular mortality were not confounded by any of those pollutants. Median 24-hour NO<sub>2</sub> levels in these cities ranged from 13.8 to 49.8 ppb. Furthermore time-series studies of mortality in countries such as Canada (Burnett et al. 1998), the Netherlands (Hoek et al. 2000) and Korea (Kwon et al. 2001; Hong et al. 2002) also found that the effect of NO<sub>2</sub> remained when other pollutants, including PM, were added to the models. Mean NO<sub>2</sub> levels in these studies ranged from about 17 to 32.5 ppb. Thus, there is at least some evidence suggesting the possibility of an independent effect of NO<sub>2</sub> on mortality.

In addition, NO<sub>2</sub> may modify the effect of other pollutants. The APHEA-2 study on daily mortality including 29 European cities (Katsouyanni et al., 2001) found that NO<sub>2</sub> modified the effect of PM<sub>10</sub>. The effects of PM<sub>10</sub> on daily mortality were stronger in areas with higher levels of NO<sub>2</sub> (at or above the 75th percentile of the medians of the cities, which was 37.1 ppb). The correlation coefficients between PM<sub>10</sub> and NO<sub>2</sub> ranged from 0.12 to 0.75. This positive interaction indicates that NO<sub>2</sub> may enhanced the effect of PM<sub>10</sub>, or that in areas with higher NO<sub>2</sub>, and therefore, more vehicle exhaust, PM likely contains more toxic substances than in areas with lower NO<sub>2</sub>.

Many of the time series studies on NO<sub>2</sub> and hospital admissions/emergency room visits for respiratory and cardiovascular diseases are suggestive of an effect of NO<sub>2</sub> or associated combustion-source pollutants in that the NO<sub>2</sub> effects remain after other pollutants are examined in the model. For example, studies by Wellenius (2005) , Metzger et al. (2004), and Simpson et al. (2005b) all reported effects of NO<sub>2</sub> on either hospital admissions or emergency room visits for cardiovascular disease after PM was taken into account. Mean 24 hour NO<sub>2</sub> levels in these studies ranged from 16.3 ppb to 37.2 ppb. In many other studies, control for other pollutants render the NO<sub>2</sub> effect estimates lower and sometimes statistically insignificant, and this aspect makes it difficult to draw a conclusion about the independent effects of NO<sub>2</sub>. Overall, however, the data are at least suggestive of an effect of NO<sub>2</sub> on respiratory and cardiovascular disease morbidity, but the problem of co-pollutants prevents a more definitive conclusion on adult morbidity and mortality.

Epidemiologic studies have demonstrated associations between air pollution, in general, and hospital admissions, emergency room visits, and calls to doctors for asthma in children. Most of the studies indicated an effect of particulate matter and ozone. In many studies, however, including those conducted in the United States and Europe, NO<sub>2</sub> was strongly related to hospital admissions or emergency room visits for asthma, and there are several instances where the effect remained after adjustment for other

pollutants (Peel et al., 2005; Lin et al. 2003; Barnett et al, 2005; Lee 2002). Overall, the effects on asthma outcomes in children appear to be more robust than either the time-series mortality or hospitalization studies reviewed above.

### **Panel studies on asthmatic children and adults with cardiac arrhythmias**

Overall, an effect of NO<sub>2</sub> has been noted in many panel studies evaluating aggravation of asthma. Panel studies involve the charting of health outcomes among a pre-selected cohort of individuals who are prospectively followed over a period of time, often lasting several months. In several cases, the effect was stronger for NO<sub>2</sub> than for other pollutants. In studies where multi-pollutant models were presented, the effects of NO<sub>2</sub> were fairly robust to inclusion of other pollutants such as PM<sub>10</sub>, ozone and VOCs (Delfino et al., 2002, 2003). Many studies have also been conducted in Europe where the concentrations and exposure patterns may be quite different than those observed in California. Chauhan et al (2003) followed a cohort of asthmatic children in Great Britain and found that personal exposure to NO<sub>2</sub> was associated with more severe illness and an increased risk of virus-related asthma morbidity. The results are consistent with the findings of indoor studies (see below) showing a clear effect of NO<sub>2</sub> on incidence of viral infections among asthmatics. Moshhammer et al. (2006) followed a panel of 163 elementary school children, aged 7 to 10 years, who underwent repeated lung function examinations (11 to 12 tests per child) for one school year in Linz, Austria. In a two-pollutant model with PM<sub>2.5</sub>, a 10 µg/m<sup>3</sup> change in 8-hour mean (midnight to 8:00 a.m.) NO<sub>2</sub> significantly reduced FEV<sub>1</sub> by 1.01%, MEF<sub>50</sub> by 1.99% and MEF<sub>25</sub> by 1.96%. The 24-hour mean NO<sub>2</sub> interquartile range in this study was 13.75 to 21.48 µg/m<sup>3</sup>.

Regarding cardiac arrhythmias, Peters et al. (2000) found a strong independent effect of NO<sub>2</sub> on increased risk of defibrillator discharges while Rich et al. (2005) found that the effect of NO<sub>2</sub> on ventricular arrhythmia was null when PM<sub>2.5</sub> was included in the model.

### **Outdoor Studies: chronic exposure**

The Children's Health Study (CHS) was initiated in 1993 with a cohort of 3,676 school-aged children in grades 4, 7 and 10, from 12 demographically similar southern California communities representing a wide range in air quality (Peters et al. 1999b). To date, this study has reported associations between air pollution and several outcomes, including lung function, respiratory symptoms and asthma incidence. In all these analyses PM<sub>10</sub>, PM<sub>2.5</sub> and acid vapor were highly correlated with NO<sub>2</sub> and most reported only single pollutant models, since it is difficult to determine pollutant-specific effects.

Analyses in the CHS reported significant effects of NO<sub>2</sub> on both bronchitis symptoms in asthmatics (McConnell et al. 2003) and reduced lung growth in children, regardless of history of asthma (Gauderman et al. 2004). The latter finding is particularly important since it followed lung development between the ages of 10 and 18 years of age. For girls, the lung typically stops developing at this age such significant decrements in lung function are likely to be permanent. For boys, lung development continues into the early 20s, but at a much lower rate. This study reported a strong inverse association

between long-term concentrations of NO<sub>2</sub> and lung growth, measured as the change in FEV1 over the eight-year study period. Besides NO<sub>2</sub>, the strongest associations were observed for acid vapor and elemental carbon. An association was also reported between NO<sub>2</sub> and clinically important deficits in attained lung function, measured as being below 80% of the predicted value for FEV1. These deficits are strong risk factors for cardiovascular disease and mortality in adulthood. Again, the strongest associations were reported with NO<sub>2</sub>, acid vapor and elemental carbon. For NO<sub>2</sub>, effects appear to occur after long-term exposure in the 25 to 30 ppb range.

The long-term studies described above were based on NO<sub>2</sub> measurements taken at central site monitors. Recently, studies have also examined NO<sub>2</sub> exposure at the neighborhood level. An analysis of the CHS reported associations between doctor-diagnosed asthma and both NO<sub>2</sub> measured at the children's homes and closer residential distance to a freeway (Gauderman et al. 2005). The overall average of the 2-week summer and 2-week winter measurements of NO<sub>2</sub> ranged from 12.9 ppb in Atascadero to 51.5 ppb in San Dimas. Kim et al. (2004) conducted a neighborhood study of asthma and respiratory symptoms in school children in grades 3 to 5 living in the San Francisco Bay Area, a region with good air quality. Traffic-related air pollutants including NO<sub>2</sub> measured at neighborhood schools were increased near and downwind of major roads. They found associations between respiratory symptoms and traffic-related pollutants. Among those living at their current residence for at least 1 year, the adjusted odds ratios in relationship to an interquartile difference in NO<sub>2</sub> measured at the neighborhood school were 1.04 (95% CI = 0.98 – 1.10) for asthma in the past 12 months and 1.03 (95% CI = 1.00 – 1.06) for bronchitis.

Although the findings on asthma incidence, respiratory symptoms and lung function from the studies in California are the most relevant for NO<sub>2</sub> standard setting, many other studies, most of which have been conducted in Europe, have found effects of either measured NO<sub>2</sub> or a mixture of traffic related pollutants, including NO<sub>2</sub>. However, the traffic-related pollutants are highly correlated and it is not possible to separate out the effects of NO<sub>2</sub>. Correlations between PM<sub>2.5</sub> and NO<sub>2</sub> have been as high as 0.99 (Gehring et al. 2002) in Europe.

The Harvard Six City study (Dockery et al. 1993; Krewski et al. 2000) provides some evidence from the United States of an association between long-term NO<sub>2</sub> concentrations and both all-cause and cardiopulmonary mortality. The investigators did not fit multi-pollutant models to these data, and NO<sub>2</sub> was highly correlated with PM<sub>2.5</sub>, TSP, PM<sub>1.5</sub> and SO<sub>2</sub> ( $r=0.78, 0.82, 0.77$  and  $0.84$ , respectively). Therefore, it difficult to determine whether NO<sub>2</sub> per se was associated with increased mortality in this cohort. The American Cancer Society (ACS) study (Pope, III et al, 2002) failed to find any effect of long-term exposure to NO<sub>2</sub> on cardiopulmonary mortality. Recent data from Europe (Nafstad et al. 2004), which modelled local long-term NO<sub>2</sub> concentrations, suggested an increased risk of all-cause mortality. Likewise, European studies provided some evidence of an effect of long-term exposure on lung cancer (Nyberg et al. 2000; Nafstad et al. 2004).

Finally, several studies are suggestive of an effect of NO<sub>2</sub> or traffic on birth outcomes including the likelihood of pre-term birth, intrauterine growth retardation, and low birth weight. For example, Wilhelm and Ritz (2003) found that NO<sub>2</sub> concentrations were associated with term low birth weight and preterm birth in Southern California. Median NO<sub>2</sub> levels at the nearest monitoring station were approximately 44 ppb. However, in multivariate models including NO<sub>2</sub> and quintiles of the distance weighted traffic density, the results for NO<sub>2</sub> were no longer statistically significant. A recent Canadian study (Liu et al. 2003) found that preterm birth was associated with exposure to NO<sub>2</sub> during the last month of pregnancy, while intrauterine growth retardation (IUGR) was associated with exposure to NO<sub>2</sub> during the first month of pregnancy. Elevated risks for IUGR associated with NO<sub>2</sub> persisted after adjustment for other co-pollutants. The mean NO<sub>2</sub> level for the study period (1986 to 1998) was 19.4 ppb. Ha et al. (2001) found an independent effect of first trimester NO<sub>2</sub> on low birth weight in Seoul, South Korea. This effect remained when CO, SO<sub>2</sub>, TSP and O<sub>3</sub> were all in the model. There was a reduction in birth weight of 8.41 grams for an interquartile increase of first trimester NO<sub>2</sub>. The interquartile range of average NO<sub>2</sub> concentrations during the first trimester of pregnancy was 30.8 to 35.4 ppb. For many of these studies, it is difficult to disentangle the relevance of NO<sub>2</sub> per se compared to NO<sub>2</sub> as a marker for traffic related air pollution.

### **Indoor studies**

Several epidemiological investigations have been conducted in indoor settings. These studies have the advantage of lower measurement error and less confounding by co-pollutants, relative to the outdoor studies. Burning natural gas in gas stoves or cooking produces fine and ultrafine particles in addition to NO<sub>2</sub>. Also, the effects of NO<sub>2</sub> on symptoms and lung function may be partly explained by nitrous acid, which is produced by gas appliances and is highly correlated with NO<sub>2</sub> levels. Thus, there may be toxicity from unmeasured indoor co-pollutants. Nevertheless, these studies are also suggestive of potential adverse health outcomes in response to exposure to NO<sub>2</sub>.

For example, an increased incidence of lower respiratory symptoms among children in relation to indoor NO<sub>2</sub> has been suggested from a meta-analysis of the indoor studies conducted in 1992. It concluded that long-term exposure to NO<sub>2</sub> is associated with a higher prevalence of respiratory symptoms in children younger than 12 years (Hasselblad et al, 1992). This meta-analysis, however, relied on a limited number of rather heterogeneous studies. In addition, a follow-up study of a birth cohort in Albuquerque, New Mexico (Samet et al, 1993) and a multicenter cohort study of newborn children conducted in Europe (Sunyer et al, 2004) failed to find an association between indoor NO<sub>2</sub> and respiratory illness in healthy newborns.

On the other hand, a strong association between indoor NO<sub>2</sub> measured with passive samplers and respiratory symptoms among infants with an asthmatic sibling has been recently reported in the USA (New England) (van Strien et al, 2004). Infants living in homes with an NO<sub>2</sub> concentration exceeding 17.4 ppb (highest quartile) had a higher frequency of days with wheeze and shortness of breath when compared with infants in homes that had NO<sub>2</sub> concentrations lower than 5.1 ppb (lowest quartile), controlling for

nitrous acid concentration. Investigators in the New England study also found associations between respiratory symptoms and NO<sub>2</sub> exposures dichotomized at or above 20 ppb in the older siblings with asthma (Belanger et al. (2006). Of note, the NO<sub>2</sub> measurements were made in the main living area, and interestingly, the effect was seen primarily in children living in multi-family dwellings. The authors theorized that there was less exposure measurement error for these housing units compared to those living in single-family dwellings.

Triche et al. (2005) studied the non-smoking mothers of infants in Connecticut and Virginia. When NO<sub>2</sub> exposure was dichotomized as 80 ppb or greater (top quartile for gas heater users) it was associated with chest tightness and wheeze.

Several indoor studies in Australia have found similar results. In Victoria, Australia Garrett et al. (1998) found that respiratory symptoms were more common in children exposed to a gas stove with a dose-dependent response between bedroom NO<sub>2</sub> levels and respiratory symptoms. Another Australian group (Pilotto et al. 2004) conducted an intervention study of unflued gas heaters in a group of 118 school children with asthma. The intervention reduced NO<sub>2</sub> and the likelihood of breathing difficulty, chest tightness, and asthma attacks. Mean (standard deviation) NO<sub>2</sub> levels were 15.5 (6.6) ppb and 47.0 (26.8) ppb in the intervention and control schools respectively.

The indoor air studies provide evidence that increased levels of NO<sub>2</sub> from gas stoves or other appliances are associated with respiratory symptoms. However, as discussed in Chapter 5 of the Technical Support Document (exposure chapter), operations of indoor combustion sources tend to have very high peak exposures (up to 400-1000 ppb). Therefore, it is difficult to ascertain whether the effect is due to high peak exposures or the averaged concentrations. Thus, it is difficult to extrapolate the findings in indoor air studies to ambient outdoor situations, limiting the use of these data in determining a long-term average for standard setting.

## **Conclusions**

Many epidemiological studies of NO<sub>2</sub> exposures from indoor and outdoor air are hampered by high correlations between NO<sub>2</sub> and other combustion related pollutants (PM, black carbon and PAH's). However, recent studies of adverse pregnancy outcomes, acute mortality, hospital admissions for cardiovascular and respiratory diseases, and studies evaluating the indoor effects of NO<sub>2</sub>, especially among infants at risk for asthma, suggest the possibility of an independent effect of NO<sub>2</sub>. With respect to long-term effects of NO<sub>2</sub>, analyses in the CHS reported significant effects of NO<sub>2</sub> on both bronchitis symptoms in asthmatics (McConnell et al. 2003) and reduced lung growth (Gauderman et al. 2004). The latter finding is particularly important since it followed lung development between the ages of 10 and 18 years of age. In both the short-term and long-term studies effects of NO<sub>2</sub> were observed at levels below the current state and federal standards.

## **Consideration of Infants and Children**

As noted earlier, SB25 specifically asks that OEHHA assess the proposed standard in light of four factors related to infants and children, to the extent that information is available.

1. Exposure patterns among infants and children that are likely to result in disproportionately high exposures relative to the general population

As indicated above, children who are outdoors for extended periods of time, particularly while engaged in physical activity that increases their breathing rate, should be considered as a potentially susceptible subpopulation. Under these circumstances, their effective dose of NO<sub>2</sub> would be disproportionately high relative to the general population. Infants and children inhale more air per unit body weight than adults, even at rest. Thus, young children and infants experience a greater exposure per lung surface area than adults.

2. Special susceptibility of infants and children to ambient air pollution relative to the general population

A number of animal studies have indicated that the developing lung is altered by NO<sub>2</sub> exposure. In some exposure studies, morphometric changes in alveolar tissue components (i.e. thickened alveolar walls, increased cellularity, altered epithelial cell volumes) occurred during lung development in young mice intermittently exposed to 0.3 ppm for 6 weeks, and in young ferrets intermittently exposed to 0.5 ppm for 15 weeks (Sherwin et al. 1985; Rasmussen and McClure; 1992). Alternatively, long-term NO<sub>2</sub> exposure studies averaging 0.4 ppm or higher in adult animals have not observed morphological changes in centriacinar region tissue (Mercer et al., 1995; Tepper et al., 1993; Ichinose et al., 1991), suggesting that the developing lung may be a major target of NO<sub>2</sub> toxicity.

Thus, children may be more susceptible to the effects of NO<sub>2</sub> than the general population due to effects on the developing lung. Epidemiological studies have found reduced lung growth in association with NO<sub>2</sub> and its co-pollutants. In addition, there is some evidence of associations between long-term exposure to ambient NO<sub>2</sub> or other co-pollutants and adverse birth outcomes

3. The effects on infants and children of exposure to ambient air pollution and other substances that have common mechanisms of toxicity.

In considering the epidemiological studies (including field studies), it should be noted that exposures to highly correlated traffic related pollutants in the ambient air are inherently included in the evaluation.

4. The interaction of multiple air pollutants on infants and children, including between criteria air pollutants and toxic air contaminants.

There are limited studies of the interaction of multiple pollutants, and most have not addressed effects in infants and children. NO<sub>2</sub> may modify the effect of other pollutants, including PM in some epidemiologic studies (Katsouyanni et al. 2001). Interaction between NO<sub>2</sub> and PM<sub>10</sub> was significant in a panel study of asthmatic children (Delfino et al. 2002). The human controlled exposure studies are limited but

suggest that, in asthmatics, NO<sub>2</sub> at levels only slightly above the California standard may enhance airways responsiveness to other pollutant challenges, and may act synergistically with SO<sub>2</sub> in enhancing responses to allergen challenge.

### *Other Susceptible Populations*

The clinical and epidemiological studies indicate that individuals with asthma and other chronic lung diseases are more susceptible to NO<sub>2</sub>. The epidemiological studies also indicate that elderly subjects and those with cardiovascular disease are more vulnerable to ambient NO<sub>2</sub> as highlighted by time-series studies on daily mortality and hospitalization. Other factors such as genetics, diet and other lifestyle factors may be important determinants of susceptibility to air pollutants. Gilliland et al. (2004) found that asthmatics with certain genetic polymorphisms were more responsive to diesel exhaust particles [Gilliland et al. 2004]. In addition, life-style factors such as smoking, alcohol, diet and physical activity and socio-economic status may modify the effect of air pollutants. Lower education seems to be a risk factor for higher effect estimates in outdoor NO<sub>2</sub> studies in adults [Pope, III et al. 2002;Hoek et al. 2002;Schindler et al. 1998], independent of smoking, diet and alcohol consumption. Nitrogen dioxide is a potent oxidant, and pre-treatment with vitamin C can decrease airway responsiveness to NO<sub>2</sub> (Mohsenin 1987b). Thus, life-style factors such as diet may modify the response to oxidative stress induced by NO<sub>2</sub>. In addition, diet might influence allergic airway and cardiovascular diseases.

### **Recommended Pollutant Indicator**

OEHHA recommends that NO<sub>2</sub> continue to be the appropriate indicator. However, NO<sub>2</sub> is highly correlated with all oxides of nitrogen as well as several other traffic-related pollutants. Although it is possible that other oxides of nitrogen can induce adverse health effects, most of the available controlled human studies, epidemiologic studies and toxicologic studies use NO<sub>2</sub> as the relevant exposure metric. Control of NO<sub>2</sub> and related pollutants is likely to provide significant public health protection to exposed populations. Therefore, this metric serves as a reasonable marker for standard setting.

### **Recommended Averaging Times and Forms**

The current California ambient air quality standard for NO<sub>2</sub> uses a 1-hr averaging time. Selection of this averaging period was based on the desire to protect the public against health effects associated with peak short-term exposures to NO<sub>2</sub>, based on typical NO<sub>2</sub> diurnal patterns experienced in California, particularly in the South Coast Air Basin. In addition, the State has had an NO<sub>2</sub> 1-hour average standard since 1969, and its retention has provided an historical record of trend for this pollutant. It was also recognized that a stringent 1-hr NO<sub>2</sub> standard would serve to reduce multi-hour and 24-hour average NO<sub>2</sub> concentrations, and thereby also provide protection against health effects associated with exposures longer than one hour. The studies on which the 1-hr standard was previously based (CARB 1992) indicated that exposures to NO<sub>2</sub> as low as 0.25 ppm for 30 minutes (Jorres et al. 1990) or 0.20 ppm for two hours (Kleinman et al. 1983) induced an increase in airway reactivity in asthmatics. Also, newer data suggests that short (15-30 min.) single or repeated exposures to NO<sub>2</sub> at 0.26 ppm enhance the

allergic response in mild asthmatics. As we judge these effects to be adverse, the retention of a standard with a one-hour average is warranted. OEHHA recommends that a short-term 1-hour standard be retained to protect against these possible effects.

In a real life setting, of course, individuals are exposed to not only 1-hour concentrations but also multi-hour, 24-hour and multi-day averages. As indicated above, dozens of epidemiological studies demonstrate an association between 24-hour average concentrations of NO<sub>2</sub> and a wide range of adverse health effects including premature mortality, hospitalizations, emergency rooms visits, asthma exacerbation, and respiratory symptoms. Also, studies have shown that even longer-term averages of NO<sub>2</sub>, including exposures of several months or years, may be of concern. As suggested above, exposure to NO<sub>2</sub> and its correlates is associated with permanent lung function decrements, symptoms and asthma. In addition, there is some evidence linking long-term exposure to NO<sub>2</sub> or traffic on birth outcomes including the likelihood of pre-term birth, intrauterine growth retardation, and low birth weight. Some of these studies have the potential to be confounded by season, weather and co-pollutants. Although other co-pollutants with oxidant properties, such as PM<sub>2.5</sub> and ultrafine particles, are likely to contribute to some of the observed effects in the longitudinal epidemiological studies, human exposure studies indicate that NO<sub>2</sub> is a strong oxidant that causes airway inflammation and enhanced allergic response in asthmatics. Thus, we cannot rule out that NO<sub>2</sub> plays a role in the observed adverse health outcomes. In addition, some of the effects may be likely due to multi-hour exposures to NO<sub>2</sub>, which are highly correlated with one-hour averages. Nevertheless, we cannot say with certainty that the effects observe in epidemiological studies are due to short-term effects. Thus, there is a non-zero probability that these effects are, in fact, associated with 24-hour and multi-year exposures to NO<sub>2</sub>. While the one-hour standard will protect against peaks on a given day, it may not provide enough protection from effects that may be related to longer-term averages of NO<sub>2</sub>. Therefore, prudent public health policy suggests that a standard with a longer-term average of NO<sub>2</sub> also be considered. An annual average standard would provide protection against potential effects of long-term (i.e., several months or years) exposures. In addition, by lowering the annual mean, the entire distribution of NO<sub>2</sub> would decrease as well. Thus the annual average standard would afford protection against 24-hour averages as well. Therefore, OEHHA recommends retaining a one-hour standard and adding an annual average standard for NO<sub>2</sub>.

## **Recommended Concentrations**

### **Considerations for the Margin of Safety**

Both the California Health & Safety Code (section 39606) and the federal Clean Air Act (section 109) refer to an adequate margin of safety, although neither includes a specific legislative definition of this term. The Children's Environmental Health Protection Act [Senate Bill 25, Escutia; Stats. 1999, Ch731, sec. 3; Health & Safety Code section 39404(d)(2)] requires a standard that "*adequately* protects the health of the public, including infants and children, *with an adequate margin of safety.*" Given the current state of the science, which is limited by uncertainties in the existing data sets and

methods available to analyze the impacts of low-level exposures, it is not possible to set standards for NO<sub>2</sub> that absolutely protect all individuals.

The governing statutory language indicates that California's ambient air quality standards should also protect other vulnerable populations, in addition to infants and children, and the general public [(Health & Safety Code sections 39606 (d)(2) and 39606 (d)(3)]. This legislative directive is consistent with historical practice in California, where ambient air quality standards have been formulated to protect identifiable susceptible subgroups, as well as the general population. Nonetheless, even with standards tailored to protect vulnerable populations, there may be exquisitely sensitive individuals who still have adverse responses.

In addition, NO<sub>2</sub> concentrations reported at central site monitors may be substantially lower than those found in close proximity to mobile sources such as roads and highways. Ambient concentrations of NO<sub>2</sub> vary spatially within a community due to localized emissions of NO<sub>2</sub> especially from traffic (Kim et al., 2004; Gauderman et al. 2005). In these same studies increased levels of NO<sub>2</sub> were associated with asthma symptoms in the past 12 months (Kim et al., 2004) and prevalence of asthma (Gauderman et al. 2005). A recent study (Green et al. 2004) found that 9.5% of K-12 public schools in California are located within 150 meters of a busy road (25,000 or more vehicles per day). Thus a substantial number of school children, whose lungs are still developing, experience exposures that are much higher than those indicated by central site monitors alone.

Several other factors were incorporated into the margin of safety considerations. The margin was based on the available scientific data describing population effects and variability, and on epidemiologic studies examining endpoints and subgroups that can't be studied in exposure chambers. Specifically, the following evidence was utilized:

(1) chamber studies indicating variability in human response with the existence of particularly large individual responses; (2) chamber studies indicating, at levels close to the current standard, both bronchial reactivity and enhanced airway inflammatory response to allergen challenge; (3) knowledge that individuals that may be particularly susceptible such as severe asthmatics or asthmatics with an ongoing respiratory infection, elderly people with pre-existing respiratory or cardiovascular conditions, and infants and children cannot be tested in the exposure chambers (4) animal toxicology studies supporting many of these findings and also suggesting the possibility of decreases in lung defense mechanism; and (5) epidemiologic studies reporting associations between ambient NO<sub>2</sub> and a suite of adverse outcomes including premature mortality, hospitalization, emergency room visits, respiratory symptoms and changes in lung function. The results are particularly robust for respiratory outcomes, which include premature mortality due to respiratory causes, emergency room visits for asthma, increased symptom reporting in asthma panel studies, and decreased lung function growth in long-term studies. While it is difficult to use all of the epidemiological studies quantitatively in developing a standard, the significant potential of adverse effects clearly should factor into the margin of safety considerations. Below, we provide the scientific rationale for the one-hour standards.

### **One-hour average**

We recommend that the current state standard of 0.25 ppm, not to be exceeded, be reduced to 0.18 ppm, not to be exceeded. Most of the new controlled chamber studies studying enhanced allergen response indicate group-level effects at concentrations at 0.26 ppm for short (30 minutes to one hour) durations of exposure. Additionally, some, but not all, of the controlled chamber studies have found increased airway reactivity in asthmatics after NO<sub>2</sub> exposures at 0.2-0.3 ppm for 30 min to 2 hr.

Given these findings, OEHHA recommendation is based on several factors.

First, asthmatics exposed to NO<sub>2</sub> at 0.26 ppm for 15-30 minhr (in single or repeated doses) developed an enhanced airway inflammatory response after allergen challenge in several carefully controlled human exposure studies. This enhanced response included: small decreases in lung function (Strand et al (1997, 1998), increased neutrophils and markers of eosinophil activation in airways (Barck 2002) and markers of eosinophil activation in blood and sputum (Barck et al., 2005). The eosinophil markers measured are a product of eosinophils that contributes to asthmatics; and serum levels of this marker are correlated with disease activity (Venge et al. 1999). Thus, the increased allergic response could lead to more prolonged asthma symptoms or clinical asthma attack, especially in the more severe asthmatic. The ultimate impact of the inflammatory response is unclear but repeated exposures to high NO<sub>2</sub> levels may result in restructuring of the airways, fibrosis, and possibly permanent respiratory injury. These latter outcomes are supported by animal toxicology studies, which also suggest the possibility of decreases in lung defense mechanism.

Second, several studies of NO<sub>2</sub> exposures in the range of 0.2-0.3 ppm have found that asthmatics exposed to NO<sub>2</sub> have increased airway reactivity (Kleinman et al. 1983, Jörres et al. 1998, Bauer et al. 1986), whereas other studies using similar protocols have not. The lack of findings in some studies reflects, in part, differences in NO<sub>2</sub> response among subjects (inter-individual variability). Thus, because the data suggests that some asthmatics experience increased airway reactivity to NO<sub>2</sub> at levels near the current standard, we recommend that the air quality standard should be lowered to protect these more vulnerable subpopulations. Increased airway reactivity, a hallmark of asthma, is also seen in individuals with other chronic lung diseases, such as cystic fibrosis and COPD. The clinical significance of increased airway reactivity after NO<sub>2</sub> exposures in individuals with pre-existing respiratory diseases is the potential for a flare up or exacerbation of their underlying respiratory disease. In support of this, COPD patients demonstrated small decrements in lung function after NO<sub>2</sub> exposure at 0.3 ppm for 1-4 hr (Vagaggini et al., 1996, Morrow et al. 1992). Additionally, some infants and young children develop bronchial hyper-reactivity and wheezing after viral respiratory tract infections and may or may not go on to develop asthma (Martinez et al. 1995). Thus, the observed increase in airway reactivity after NO<sub>2</sub> exposure may also affect infants and young children who wheeze with an active or recent viral respiratory tract infection but are not confirmed with asthma. In addition, the chamber studies, by design, do not include especially vulnerable populations (e.g., people with moderate to severe asthma, COPD, or heart disease, and asthmatics with concurrent respiratory infections), which may be incorporated in the epidemiologic studies. These factors were important considerations in allowing a margin of safety in OEHHA's determination of a health-protective standard.

Third, few studies have been undertaken to establish a threshold level for which no effects are observed. Tunnicliffe et al. (1994) evaluated the allergen responses for filtered, 0.1 ppm, and 0.4 ppm for 1 hr and found a significant drop in % FEV<sub>1</sub> between filtered air and 0.4 ppm but not between filtered air and 0.1 ppm for 1 hr. Jenkins et al. (1999) found that NO<sub>2</sub> at 0.4 ppm for 1 hr followed by allergen challenged resulted in a decrease in FEV<sub>1</sub> in asthmatics, whereas 0.2 ppm exposures for 3 hr did not. No studies have looked at the effects of NO<sub>2</sub>-enhanced allergen response as measured by lung inflammation or markers of eosinophil activation at levels below 0.26 ppm. Thus, the limited studies did not find an NO<sub>2</sub> effect on allergen response at 0.1-0.2 ppm. Airway reactivity in asthmatics has been documented in several studies at 0.2-0.3 ppm, but the data below 0.2 ppm is less certain.

Fourth, the studies on enhanced allergen response were seen with brief exposures (15-30 min duration) at 0.26 ppm. It is likely that the current standard of 0.25 ppm for 1 hr will not adequately protect against 15-30 min. peaks of 0.26 ppm. Lowering the one-hour standard to 0.18 ppm would provide additional protection against brief periods of NO<sub>2</sub> at or near 0.25 ppm. It is important to note that as discussed in Chapter 5 of the Technical Support Document, ambient levels of NO<sub>2</sub> vary during the day, with peaks concurrent with morning and afternoon commute times when people are more likely to be outside.

Fifth, there have been a number of short-term and long term epidemiological studies completed over the last 10 years indicating the potential for severe adverse health outcomes including premature mortality, hospitalizations, emergency room visits, preterm births, and reduced lung growth. These studies include concentrations to which the public is currently being exposed (range of study means = 0.025-0.045 ppm). One-hour peak concentrations are highly correlated with 24-hr averages and longer-term averages. Based on California air quality data, the empiric ratio of 1-hr maximum to annual average is approximately 4 to 6 for the more populated air basins (Table 1). Thus, a 1-hr standard of 0.18 ppm would provide some protection against longer-term averages of 0.03 – 0.044 ppm.

However, it is difficult to attribute these adverse outcomes to a specific NO<sub>2</sub> averaging time or concentration in observational epidemiological studies. Most of the studies used linear non-threshold models and did not explicitly test for thresholds. As indicated in the above reviews, these studies need to be viewed with some caution since it is difficult to separate out the effects of NO<sub>2</sub> from other co-varying pollutants. In addition, significant measurement error exists for NO<sub>2</sub> in relating ambient NO<sub>2</sub> to personal NO<sub>2</sub> exposure (Sarnat et al., 2001, 2005). Finally, a larger margin of safety (relative to the 1-hour 0.26 ppm from the chamber studies) may be necessary to account for the possibility of adverse impacts associated with multiple peak exposures of NO<sub>2</sub> occurring over a long period of time (i.e., one year or more). While we are proposing an annual average standard to more directly take these effects into account, a lowering of the one-hour peaks will result in a lowering of the entire NO<sub>2</sub> distribution.

### **Annual average**

We recommend an annual average standard of 0.030 ppm, not to be exceeded. Our recommendation for the annual average standard is based on the epidemiologic studies

involving longer-term (a week to several years) exposure as well as those using daily 24-hour averages. Regarding the longer-term exposures, several analyses of the Children's Health Study (CHS) in Southern California reported significant effects of NO<sub>2</sub> on symptoms in asthmatics (McConnell et al. 2003), lung function growth (Gauderman et al. 2004) and asthma (Gauderman et al. 2005). Gauderman et al. (2004) reported clinically important associations between NO<sub>2</sub> (and its highly correlated co-pollutant such as elemental carbon) and potentially permanent deficits in attained lung function, measured as being below 80% of the predicted value for FEV<sub>1</sub>. For NO<sub>2</sub>, effects appear to occur after long-term exposure in the 30 - 35 ppb range. In the asthma study the overall average of the 2-week summer and 2-week winter measurements of NO<sub>2</sub> ranged from 12.9 ppb in Atascadero to 51.5 ppb in San Dimas.

Longer-term exposures (one to several months average) to NO<sub>2</sub> have also been associated with several adverse birth outcomes including the likelihood of pre-term birth, intrauterine growth retardation, and low birth weight (Wilhelm and Ritz 2003; Liu et al. 2003; Ha et al. 2001). While two of these studies were conducted in Asia and might be less applicable to conditions here, Wilhelm and Ritz (2003) was conducted in the Los Angeles basin. The mean NO<sub>2</sub> level in this study was 44 ppb.

Regarding the short-term studies, analysis of the largest 90 U.S. cities reported an association between NO<sub>2</sub> and all-cause mortality (Dominici et al. 2003), which remained the same but became statistically insignificant in multi-pollutant models. The longer-term average of 24-hr NO<sub>2</sub> levels in those cities ranged from 11.0 to 39.4 ppb. A limited number of European studies have found independent effects of NO<sub>2</sub> (Saez et al. 2002; Hoek et al. 2000; Samoli et al. 2006). The APHEA-2 study on daily mortality including 29 cities (Katsouyanni et al., 2001) found that NO<sub>2</sub> modified the effect of PM<sub>10</sub>. The effects of PM<sub>10</sub> on daily mortality were stronger in areas with higher levels of NO<sub>2</sub> (greater than or equal to 37 ppb).

In addition, several studies outside of the United States and Western Europe found associations between NO<sub>2</sub> and mortality that appear to be independent of other pollutants (Simpson et al. 2005a; Burnett et al. 1998; Kwon et al. 2001; Hong et al. 2002). Mean NO<sub>2</sub> levels in these studies ranged from about 16.3 to 32.5 ppb.

In the U.S. a panel study of cardiac arrhythmias and studies of hospitalizations and emergency room visits for respiratory and cardiovascular disease found potentially independent effects of NO<sub>2</sub> in areas with average NO<sub>2</sub> levels between 23 and 37 ppb (Peters et al. 2000; Metzger et al. 2004; Peel et al., 2005; Wellenius et al. 2005). These findings are supported by similar findings in studies conducted outside of the U.S. (Simpson et al. 2005 b, Lin et al. 2003, Barnett et al, 2005; Lee et al. 2002).

In summary, epidemiological studies that examine both long-term and short-term exposure have found effects of NO<sub>2</sub>. In the U.S., the range of means of ambient NO<sub>2</sub> for which effects have been seen is between 23 to 44 ppb with many in the range of 30 to 35 ppb (Figure 1). While some short-term studies have suggested an independent effect of NO<sub>2</sub>, there is a real possibility that the NO<sub>2</sub> effects in both short and long-

term studies may be due to measured or unmeasured indoor or outdoor co-pollutants that are products of traffic and/or fuel combustion such as ultrafines, elemental carbon, acid vapor, fine particles or NO. For example, Seaton and Dennekamp (2003) proposed that the association of NO<sub>2</sub> levels with cardiovascular mortality and morbidity occurs because NO<sub>2</sub> is closely associated with release of ultrafine particles in ambient air. Nevertheless, prudent public health policy warrants that some level of protection from exposure to NO<sub>2</sub> be specified.

The empirical relation between the one-hour and annual average provides additional support for this proposed standard. Clearly the one-hour and annual average standards are linked. For example, attainment of the 0.18 ppm one-hour standard would succeed in lowering the entire distribution of daily exposures at all durations. Therefore, this standard will afford some increased degree of protection from longer-term exposures, and vice versa.

Our analysis of data in California indicates that that 99<sup>th</sup> percentile and the single highest value of the one-hour average NO<sub>2</sub> is roughly 4 to 6 times that of the annual average (see Table 1). Therefore, a 1-hour standard of 0.18 ppm is associated with an annual average of between 0.044 and 0.029 ppm. However, the ratio varies by district so the controlling standard will also vary by air district, as well. Taken together, the recommended annual average of 0.030 ppm is consistent with the proposed short-term standard of 0.18 ppm and should provide the additional protection needed from long-term exposures.

As such, given the seriousness of the potential effects, we recommend an annual average standard for NO<sub>2</sub> be adopted. Based on these studies we recommend that an annual average standard of 0.030 ppm be adopted. While some studies with a mean concentration below this level suggest the possibility of effects related to exposure to NO<sub>2</sub>, substantial uncertainties in the exposure metric remain. Therefore, OEHHA staff has not recommend an annual average standard that is below the means observed in all of these studies. The recommended standard is likely to afford a sufficient level of protection for both individuals.

The empirical relation between the one-hour and annual average provides additional support for this proposed standard. Clearly the one-hour and annual average standards are linked. For example, attainment of the 0.18 ppm one-hour standard would succeed in lowering the entire distribution of daily exposures at all durations. Therefore, this standard will afford some increased degree of protection from longer-term exposures, and vice versa.

### **Consideration of Infants and Children in Recommending the NO<sub>2</sub> Standard**

The recommended 1 hr standard of 0.18 ppm is based on results of the human exposure studies. These studies indicate that asthmatics are more susceptible to NO<sub>2</sub>. Also, in general, the time series studies have found that the effects of NO<sub>2</sub> on asthma outcomes appear to be more robust than either the time-series mortality or hospitalization studies, supporting that asthmatics are a susceptible population. There is no data to suggest that children with asthma are more susceptible to NO<sub>2</sub> than adults, so this was not explicitly taken into consideration when determining the recommended

standards. However, asthma is the most common chronic childhood disease; nearly 9.6% of California's children have had asthma symptoms in the last year.

Several epidemiological studies in children were considered in weighing the evidence to support a longer-term standard (annual average). These studies included: The longitudinal epidemiological studies on the association between measured NO<sub>2</sub> (indoors) and increased risk of wheezing and persistent cough in infants with a strong family history of asthma (van Strien et al. 2004, Belanger et al. 2003, 2006) are evidence that NO<sub>2</sub> has respiratory effects on young children. Additionally, using personal monitors, Chauhan et al. (2003) found that higher exposures to NO<sub>2</sub> were associated with more severe viral-related asthma exacerbations in children with asthma or at risk for asthma. Finally, the Children's Health Study conducted in Southern California between 1993 and 2001, followed children through adolescence and found that those children who resided in communities with high levels of NO<sub>2</sub> and other co-pollutants had reduced lung growth compared to those living in less polluted communities (Gauderman et al. 2004). This reduction in lung growth is especially important, as reduced lung growth as a young adult is a strong predictor for cardiovascular disease and mortality in adulthood. Although we cannot ascribe all the effects of lung growth to NO<sub>2</sub>, there is evidence that NO<sub>2</sub>, a strong respiratory oxidant, causes airway inflammation. Additionally, animal studies suggest that potentially permanent structural changes to the lung during development may occur from prolonged exposure to relatively low levels of NO<sub>2</sub> (0.25 ppm), but may not become fully apparent until later in life. Thus we cannot say with certainty that NO<sub>2</sub> at the ambient levels observed in the Children's Health Study are harmless. Further human exposure studies, toxicology studies, and epidemiological studies are needed to determine the extent of NO<sub>2</sub> toxicity in combination with other ambient co-pollutants.

**Summary of OEHHA Recommendation:**

- 1) Nitrogen dioxide continues to be the indicator for nitrogen oxide air pollutants.
- 2) Retention of a 1-hour standard and the addition of an annual average standard.
- 3) Decreases the 1-hour average standard of 0.18 ppm, not to be exceeded and add an annual average of 0.030 ppm, not to be exceeded. Such a standard would protect against both 1-hour concentrations and repeated or long-term exposures to nitrogen dioxide.

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## Appendix

**Table 1. Ratios of one-hour maximum to annual mean, by air basin, 2004**

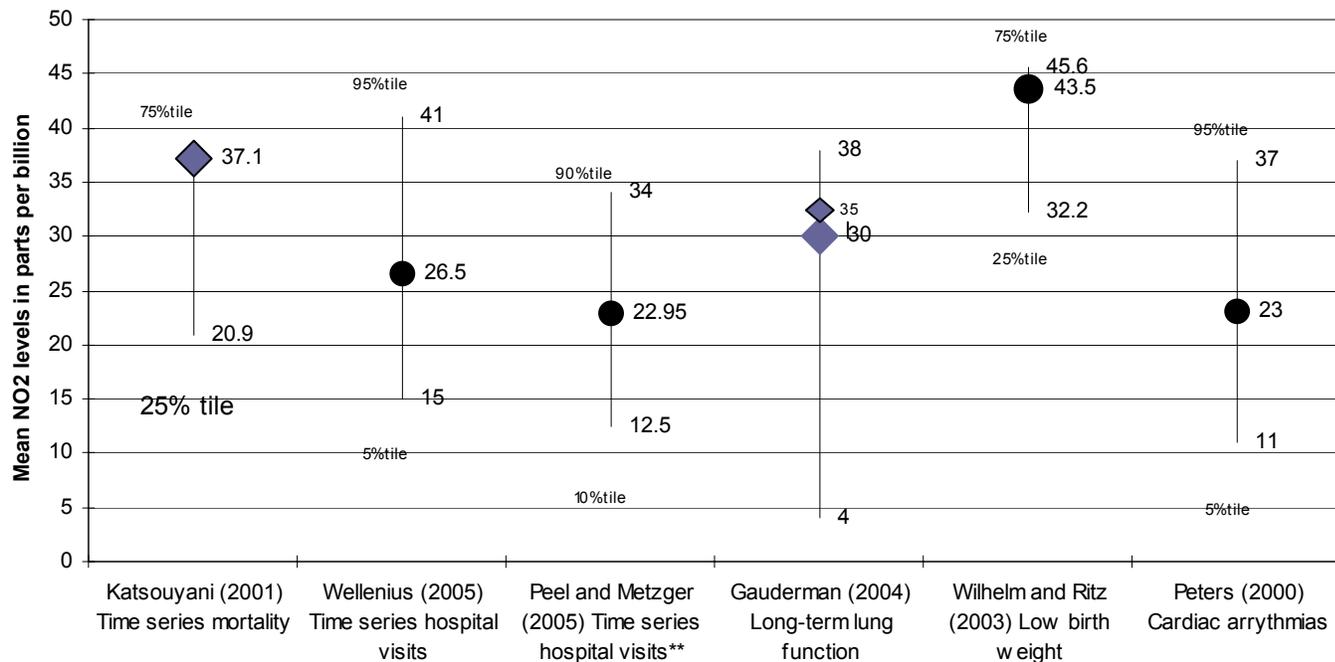
<b>Basin</b>	<b>Annual Mean (ppm)</b>	<b>Ratios of quantiles of 1-hour maximum to annual mean</b>		
		<b>95<sup>th</sup> percentile</b>	<b>99<sup>th</sup> percentile</b>	<b>Maximum</b>
Lake Tahoe	0.00462	8.22	11.47	14.71
Mexico	0.01900	3.95	5.26	10.11
Mojave Desert	0.01431	4.40	5.17	7.20
North Central Coast	0.00562	5.52	6.58	24.73
North Coast	0.00826	3.39	3.87	4.48
Sacramento Valley	0.01173	4.01	5.03	12.44
Salton Sea	0.01327	4.15	5.13	8.14
San Diego	0.01710	3.45	4.39	7.31
San Francisco Bay Area	0.01300	3.23	4.00	5.62
San Joaquin Valley	0.01393	3.59	4.52	5.96
South Central Coast	0.00685	5.11	6.42	10.36
South Coast	0.02422	2.97	3.80	6.48

Table 2. California air monitoring sites with average annual NO<sub>2</sub> levels greater than 0.0290 ppm, 2004

Air Basin_Name	Monitoring Site_Name	Annual average NO <sub>2</sub> (ppm)
South Coast	Los Angeles-North Main Street	0.0337
South Coast	Burbank-W Palm Avenue	0.0332
South Coast	Pomona	0.0312
South Coast	Pico Rivera	0.0305
South Coast	Upland	0.0305
South Coast	Hawthorne	0.0304
South Coast	Lynwood	0.0302

DRAFT- Do not cite or quote

Figure 1: Range and Mean Concentrations of Ambient Nitrogen Dioxide for U.S.



Studies\*

\*A study by Katsouyani et al. in Europe that found NO<sub>2</sub> modified the effect of PM<sub>10</sub> is also included.

Minimum and maximum or percentile of NO<sub>2</sub>

- ◆ =Effect level
- =Mean

\*\*Metzger and Peel studies measured NO<sub>2</sub> as 1-hour maximum. In California the 1-hour maximum is approximately 2 times the 24-hour measurement. Therefore Metzger and Peel NO<sub>2</sub> levels were adjusted by a factor of two to obtain an equivalent 24-hour measurement.