

California Environmental Protection Agency



Air Resources Board

Review of the
One-Hour Ambient Air Quality
Standard for Nitrogen Dioxide

Staff Report

December, 1992

State of California
Air Resources Board
Research Division

California Environmental Protection Agency
AIR RESOURCES BOARD

Staff Report

Public Meeting to Consider

**RETENTION OF REGULATIONS REGARDING THE
STATE ONE-HOUR AMBIENT AIR QUALITY STANDARD FOR NITROGEN DIOXIDE**

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I. SUMMARY

This staff report to the California Air Resources Board has been prepared in order to document and describe relevant information on the effects of nitrogen dioxide and to recommend action to the Board regarding the one-hour Ambient Air Quality Standard For NO_2 . Recommendations relevant to public health are based on the findings of the Office of Environmental Health Hazard Assessment. This staff report summarizes key information from the 1992 technical review of the California Ambient Air Quality Standard for NO_2 . A technical support document is available which contains the detailed information relied upon by staff in preparing this staff report and the recommendations.

Nitrogen dioxide is an air pollutant that is formed either directly or indirectly when any substance is burned. During combustion, nitrogen, present as a major component of air, combines with oxygen to produce a mixture of nitric oxide (NO) and nitrogen dioxide (NO_2). Nitrogen dioxide in ambient air is derived both from direct emissions and from conversion of directly emitted NO to NO_2 . Both NO and NO_2 participate in a series of chemical reactions in the ambient air to produce additional pollutants including ozone, nitrate aerosols, nitric acid, and other nitrogen compounds that are toxic and mutagenic.

To protect public health and welfare against the adverse effects of NO_2 , the U.S. Environmental Protection Agency (EPA) has established a long-term Ambient Air Quality Standard for NO_2 of 0.053 parts per million (ppm) averaged over one year.

To provide additional protection of public health and to limit visibility degradation, the California Air Resources Board has established a short-term Ambient Air Quality Standard for NO_2 of 0.25 ppm averaged over one hour. This standard was last formally reviewed in 1985.

The staff of the California Air Resources Board and the Office of Health Hazard Assessment recommend that the level of the California Ambient Air Quality Standard for Nitrogen Dioxide be retained at 0.25 parts per million averaged over one hour.

II. THE CALIFORNIA AMBIENT AIR QUALITY STANDARD STANDARD FOR NITROGEN DIOXIDE

A. AIR RESOURCES BOARD LEGAL AUTHORITY

The California Air Resources Board establishes ambient air quality standards for air pollutants "in consideration the 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" (Health and Safety Code, Section 39606b). The objective of ambient air quality standards is to provide a basis for preventing or abating the effects of air pollution (Title 17, California Administrative Code, Section 70101). The ambient standards adopted by the Board are to be achieved and maintained by means of rules and regulations adopted by regional and local air quality management districts for stationary sources, and adopted by the Board for vehicular sources (Health and Safety Code, Section 40000, 40001, and 4300).

B. CURRENT ONE-HOUR NITROGEN DIOXIDE STANDARD

1. Background of Current Standard

The history of the California Ambient Air Quality Standard for Nitrogen Dioxide is summarized in Table 1.

In January of 1966, separate health and welfare standards for NO_2 were set by the Department of Public Health. A standard based on atmospheric discoloration alone as 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 of 1969. At that time, human health data were still limited and the Board chose to adopt a single standard to protect both health and welfare based on the effects of NO_2 on laboratory animals and on atmospheric discoloration. The standard adopted was 0.25 ppm averaged over one hour.

TABLE 1

STANDARD	YEAR REVIEWED	AVERAGING TIME	CONCENTRATION	MOST RELEVANT EFFECTS	COMMENTS
Initial	1966	1 Hour	0.25 ppm	Atmospheric discoloration	Designated as* adverse level by DPH.
	1966	1 Hour	3 ppm	Bronchoconstriction	Designated as serious level by DPH.
Revised	1969	1 Hour	0.25 ppm	a. At slightly higher dosage, effects observed in animals which imply risk to public health. b. Atmospheric discoloration.	
Current	1985	1 Hour	0.25 ppm	a (1). Potential to aggravate chronic respiratory disease and respiratory symptoms in sensitive groups. a (2). 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 concentration of the standard. b. Contribution to atmospheric discoloration.	a. The standard is intended to prevent adverse health effects. b. The standard imposes an upper limit on adverse effects on welfare, including atmospheric discoloration by NO ₂ .

* Department of Public Health

Subsequently, the standard was reviewed in October and December of 1985. Although the level and averaging time were retained at 0.25 ppm averaged over one hour, the language in Title 17 describing the most relevant effects (and comments) was revised to reflect current health effects 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.

2. Monitoring Method for Current Standard

The current method used to determine compliance with California's Ambient Air Quality Standard for Nitrogen Dioxide is the Gas Phase Chemiluminescent method. This method is also the Environmental Protection Agency's (EPA) reference method for determining compliance with the National Ambient Air Quality Standard for Nitrogen Dioxide. All nitrogen dioxide analyzers currently used by the California Air Resources Board (ARB) in both the EPA as well as the State and Local Air Monitoring Stations (SLAMS) network since January 3, 1980 have been chemiluminescent analyzers. This method, along with the currently used Gas Phase Titration procedure, are specified in the Code of Federal Regulations, Part 50, Appendix F.

Nitrogen dioxide is monitored at 107 sites within California by the ARB and local air pollution control agencies. The number of sites is not static but may change due to station shutdowns or relocations. All 14 air basins in California are currently monitoring for nitrogen dioxide except the Northeast Plateau, Great Basin Valleys, Mountain Counties, North Coast and Lake County Air Basins.

III. SOURCES AND EMISSIONS OF NITROGEN OXIDES

A. SOURCES

The major sources of nitrogen oxides (NO_x) emissions in California are on-road motor vehicles, other mobile sources (e.g., locomotives, aircraft, etc.) and stationary combustion sources (e.g., oil and gas production and refining, manufacturing/industrial, and electric utilities). It is estimated that on-road mobile sources account for about 51 percent of the 1989 statewide NO_x inventory; other mobile sources and stationary sources account for 23 percent and 26 percent, respectively.

B. EMISSIONS

The 1989 statewide NO_x emission estimates are tabulated by major source category in Table 2. A review of the NO_x emissions in California shows that most of the emissions are concentrated in areas with the greatest industrial activities. A ranking of the 14 air basins in decreasing order of their 1989 NO_x emissions is shown in Table 3. The three air basins having the highest NO_x emissions are South Coast, San Francisco Bay Area, and San Joaquin Valley, which together account for approximately 65 percent of the NO_x emissions in California.

In addition to geographical variations, the NO_x emissions in the State also have daily, weekly, and seasonal variations. Nearly all major NO_x sources have higher emissions during the day than at night, and higher emissions on weekdays than on the weekends. Major sources with higher emission in the summer are on-road motor vehicles and industrial and utility fuel combustion. Emissions from residential and commercial fuel combustion for space heating are higher in the winter.

1989 STATEWIDE NO_x EMISSIONS*
(Annual Average Day)

TABLE 2

Source Category	NO _x Emissions (tons/day)
Stationary Sources	
Fuel Combustion	810
Waste Burning	7
Petroleum Process, Storage & Transfer	22
Industrial Process	72
Miscellaneous	16
Total Stationary Sources	930
Mobile Sources	
On Road Vehicles	1,800
Other Mobile	800
Total Mobile Sources	2,600
Total All Sources	3,500

* Calculated by NO₂ equivalent: Nitrogen oxide emissions are composed of several oxides of nitrogen, all of which have different molecular weights. In order to report NO emissions estimates on a equivalent basis, the weight of NO_x as emitted is adjusted to the weight after conversion to NO₂. For example, 30 tons of NO as emitted would be expressed as 46 tons of NO_x in reported emission estimates.

1989 NO_x EMISSIONS BY AIR BASIN

TABLE 3

Air Basin	NO _x Emissions (Tons/Annual Average Day)	Percent of Total
South Coast	1,168	33
San Francisco Bay Area	581	16
San Joaquin Valley	553	16
Southeast Desert	292	8
Sacramento Valley	267	8
San Diego	214	6
South Central Coast	173	5
North Central Coast	89	3
North Coast	78	2
Mountain Counties	70	2
Northeast Plateau	43	1
Great Basin Valley	12	<1
Lake County	6	<1
Lake Tahoe	3	<1
State Total	<u>3,500</u>	<u>100</u>

IV. LEVELS OF NITROGEN DIOXIDE

A. AMBIENT AIR

The federal long-term Ambient Air Quality Standard for Nitrogen Dioxide was established by the U.S. Environmental Protection Agency (EPA). The standard is attained when the annual arithmetic mean concentration, based on a minimum 75% data completeness criterion, is less than or equal to 0.053 ppm at each monitoring site. Los Angeles County was the only area in California to exceed the National Ambient Air Quality Standard (NAAQS) during the 1988-1991 period (Table 4). The only site to exceed the standard in 1990 and 1991 was Pomona.

The California Ambient Air Quality Standard (CAAQS) for NO₂ is a one-hour standard of 0.25 ppm, not to be exceeded. This standard has been exceeded only in the South Coast Air Basin in the 1988-1991 period (Table 5). During 1991, the State standard was exceeded at five sites in Los Angeles County

Table 4
 Sites Not Meeting The National Ambient Air Quality
 Standard for NO₂#
 (annual mean concentration (ppm))
 1988-1991

<u>Air Basin/County/Site</u>	<u>1988</u>	<u>1989</u>	<u>1990</u>	<u>1991</u>
<u>South Coast Air Basin</u>				
Los Angeles County				
Los Angeles-N Main	.061	.055	--*	--
Pico Rivera	.054	.055	--	--
Pomona	.056	.057	.055	.055

National Ambient Air Quality Standard is 0.053 ppm as an annual arithmetic mean and is not to be exceeded

* -- Denotes no exceedance

Table 5

SITES NOT MEETING CALIFORNIA AMBIENT AIR QUALITY STANDARD FOR NO₂[#]

Maximum 1-Hour Concentration in PPM (Number of Hours above the Standard)

<u>Air Basin/County/Site</u>	<u>1988</u>	<u>1989</u>	<u>1990</u>	<u>1991</u>
<u>South Coast Air Basin</u>				
Los Angeles County				
Azusa	-- *	.27(3)	--	--
Burbank	.26(2)	--	--	.29(2)
Hawthorne	.27(1)	--	--	--
Los Angeles-N Main	.54(12)	.28(1)	.28(3)	.38(6)
Lynwood	.31(2)	.29(3)	.26(1)	.26(2)
N. Long Beach	.28(1)	.27(1)	.27(1)	.28(2)
Pasadena-Wilson	.27(2)	.34(6)	--	.32(4)
Pico Rivera	--	.31(2)	.27(2)	--
Pomona	--	.26(1)	--	--
West Los Angeles	.26(1)	--	--	--
Whittier	--	.29(1)	--	--
Orange County				
Anaheim	.28(1)	.28(2)	--	--
Costa Mesa	.26**(1)	--	--	--
San Diego County				
San Diego - Island	.28(1)	--	--	--

California Ambient Air Quality Standard is 0.25 ppm, 1 hour average, not to be exceeded

* -- Denotes no exceedance

** Does not meet ARB's representativeness criteria

B. INDOOR AIR

Indoor concentrations of NO₂ are important in evaluating health effects because a significant portion of NO₂ exposure occurs indoors. Californians spend an average of 87 percent of their time indoors, and an average of 62 percent of their time indoors at home (Jenkins et al., 1992). Indoor residential concentrations in the Los Angeles basin are strong predictors of personal exposures to NO₂: in one study 59 percent of the variation in personal exposure over a two-day period was explained by variations in concentrations recorded in the bedroom (Ryan et al., 1992).

Several large indoor NO₂ studies have been conducted in California. However, the data from these studies do not provide a complete characterization of concentrations of indoor NO₂ because data were primarily obtained from homes in the Los Angeles basin, where outdoor NO₂ levels are particularly high. Also, measurements were taken over two-day and one-week averaging times. Such measurements are insufficient to characterize indoor NO₂ concentrations because indoor sources are used intermittently and indoor levels thus vary greatly over minutes and hours. Moreover, results from these averaging times do not permit comparisons to the California standard of 0.25 ppm (470 ug/m³), which is based on a one-hour averaging time. Nonetheless, the California studies provide very useful information regarding the relative contributions of different sources to indoor NO₂ levels.

The major sources of NO₂ in California homes are unvented or malfunctioning combustion appliances - such as gas wall and floor furnaces, and gas and kerosene space heaters - and polluted outdoor air. In one study of homes with wall or floor furnaces, peak one-week averages were .229 ppm for homes with floor furnaces and .453 ppm for homes with wall furnaces; mean one-week averages were about .040 to .047 ppm (Beals et al., 1987). In mobile homes, mean one-week average NO₂ concentrations in gas range homes have ranged from .016 to .029 ppm, while those in electric range homes ranged from .006 to .009 ppm (Petreas et al., 1988). Polluted outdoor air and gas pilot lights also can significantly affect indoor levels: the mean two-day average indoor NO₂ concentration was .049 ppm in homes with gas

ranges with pilot lights in high outdoor NO₂ areas, versus .013 ppm in homes with electric ranges in low outdoor NO₂ areas (Ryan et al., 1992). Approximately one-third of the variation in bedroom concentrations was explained by variations in outdoor concentrations (Ibid.).

Improper use of combustion appliances also can contribute to elevated indoor NO₂ concentrations. In particular, the use of gas ranges as unvented space heaters has been associated with higher indoor NO₂ concentrations. Average indoor NO₂ concentrations were found to be 1.5 to 2 times the outdoor concentration when the range was used for space heating (Beals et al., 1987).

The contributions of other types of indoor combustion sources to residential NO₂ concentrations have not been well characterized. However, cigarette smoking has been shown to contribute minimally to indoor levels. Exhaust gases from fireplaces and wood stoves that enter the home also may contribute to indoor NO₂ concentrations.

Although the results from California studies used averaging times longer than the one-hour averaging time of the California standard for NO₂, results from the studies indicate that the use of gas wall and floor furnaces and the misuse of combustion appliances, especially the misuse of gas stoves for space heating, can produce very high indoor concentrations. Some such homes investigated had indoor concentrations that approached the level of the standard, even with longer averaging times.

V. SUMMARY OF RELEVANT EFFECTS

A. HEALTH EFFECTS

Evidence is available indicating effects of low-level NO₂ exposure on sensitive human populations. Additional support is available from controlled exposure studies of animals.

1. Effects reported at or below the level of the standard

Some controlled-exposure studies of asthmatics demonstrate an increase in the tendency of the airways to narrow in response to various stimuli (bronchial reactivity). Jorres et al., 1990, report an increase in airway reactivity after exposure to 0.25 ppm for 30 minutes. Kleinman et al., 1983, report an increase in reactivity in two thirds of the subjects exposed to 0.20 ppm for two hours. Orehek et al., 1976, report increased reactivity in 13 of 20 subjects exposed to 0.1 ppm for one hour. Two studies reporting no increased reactivity include Hazucha et al., 1983 at 0.10 ppm for one hour, and Jorres et al., 1991, at 0.25 ppm for 30 minutes. Collectively, results from these studies suggest that a subgroup of asthmatics is sensitive to NO₂. Increased bronchial reactivity in asthmatics can lead to transient deterioration of their condition.

Some epidemiological studies (especially those using the presence of an un-vented gas stove as a surrogate for NO₂ exposure) suggest an increased incidence of respiratory symptoms or disease in children who experience repeated exposures to NO₂. However, the results from these epidemiological studies have been mixed suggesting a real but small effect of NO₂ exposure. Furthermore, the actual exposure assessments are limited. Thus, such studies cannot be used to indicate a specific level and averaging time for a short-term standard but remain useful in consideration of a margin of safety.

Short-term controlled-exposure studies of animals indicate several different types of effects occurring at or below the level of the standard. Hayashi and Kohno, 1985, report that NO₂ exposure at levels as low as 0.2

ppm for three hours causes an increase in the respiratory tract of cells associated with allergic and inflammatory responses. Miller (1980) reports interference with the detoxification process in the liver at exposures of 0.25 ppm NO₂ for three hours. Iqbal, 1980, reports biosynthesis of a carcinogenic compound associated with NO₂ exposures of 0.20 ppm for four hours.

Longer-term studies at 0.25 ppm suggest that repeated low-level NO₂ exposures may adversely affect the immune system. In mice, exposure for 12 weeks to six months appears to decrease one of the essential cell-types of the immune system (T-cells) (Richters and Damji, 1988; 1990)

In general, these animal studies suggest cause for concern but, because of limitations in extrapolation between species, cannot be used to establish a clearly harmful effect in humans at concentrations of NO₂ below 0.25 ppm. However, these studies are of use in determining an appropriate margin of safety.

2. Effects Reported at Concentrations Between 0.25 and 0.50 ppm

Several controlled-exposure studies of asthmatics indicate increased bronchial reactivity in response to higher concentrations of NO₂. Bauer et al., 1986, report increased reactivity with exposure to 0.30 ppm for 30 minutes. Bylin et al., 1985 report an increase at 0.48 ppm for 20 minutes. Mohsenin, 1987, reports an increase at 0.50 ppm for one hour. Other studies at similar levels report no effect (Rubinstein et al., 1990; Avol et al., 1988; 1989; Roger et al., 1990). As with studies at lower levels, these studies suggest that a subpopulation of asthmatics is sensitive to the effects of NO₂.

The few controlled-exposure studies available of patients with chronic obstructive pulmonary disease (COPD) give mixed results. Morrow et al., 1992, report a progressive impact in patients exposed to 0.30 ppm for four hours. Although two other studies, using Los Angeles patients, report no effect, it is possible that subject selection from an area with high levels of air pollution may have obscured the effect (Hackney et al., 1992; Linn

et al., 1985). Another study, limited by the size of the study group, reports no effect (Kerr et al., 1979).

Short-term animal studies provide further cause for concern about exposures to NO₂. Thomas et al., 1967, report alterations in cells involved in allergic and asthmatic responses after exposure to 0.50 ppm NO₂ for four hours. Damage to the lung-blood barrier occurs at 0.40 ppm after one week (Sherwin and Carlson, 1973) and at 0.47 after ten days (Sherwin and Layfield, 1976). At 0.30 ppm after two weeks, decreased function occurs in cells responsible for immune defense of the respiratory system (Schlesinger et al., 1987). Somewhat longer-term (six-week) studies indicate: changes in the population of cells in the lung involved in respiration after exposure to 0.34 ppm (Sherwin and Richters, 1982); and 0.5 ppm (Chang et al., 1986, 1989). Collectively, these animal studies lend support to controlled-exposure and epidemiological studies of humans indicating a role for NO₂ in increased bronchial reactivity in asthmatics, increased incidence of respiratory illness, and potential exacerbation of chronic obstructive lung disease.

3. Conclusions

Because of the limited evidence of adverse effects resulting from exposure to NO₂ at concentrations below the standard, there does not appear to be a clear need to make the standard more stringent at this time. However, the evidence of the effects occurring at or below the standard together with the effects occurring somewhat above the standard cause sufficient concern to require a recommendation that the level of the standard not be relaxed. Epidemiological studies and controlled exposure studies of humans and animals provide evidence for adverse effects of NO₂ exposure but do not suggest a new or different standard.

The Technical Support Document produced by staff discusses in more detail studies producing both positive and negative results.

B. VISIBILITY EFFECTS

1. Discoloration Effects

The visibility impacts of NO_2 are a result of its very effective absorption of light in the ultra-violet, blue and green bands. Since it is virtually transparent to longer wavelengths, NO_2 at atmospheric concentrations does not actually obscure scenes, but only colors them.

Plumes of NO_x from large combustion sources (e.g., power plants) under conditions of moderate to poor dispersion and clean background air can form linear clouds of NO_2 which appear as darkened, brownish streaks in the sky. In an enclosed basin or under calm winds, the same source can create an elevated layer of NO_2 which appears as a dark lens or band in the sky. Attainment of ambient NO_2 standards is not necessarily affected by these effects, which occur well above the ground, isolated from conventional monitoring stations. However, such elevated plumes can sometimes become mixed into the surface layer of the atmosphere. Urban NO_2 pollution is usually associated with concomitant high levels of other gaseous and particulate pollutants, but the NO_2 contributes significant discoloration and is primarily responsible for the brown appearance of urban haze.

2. Modeling Analysis

NO_2 -caused visibility degradation was modeled by staff to calculate the ambient concentrations which cause specific optical effects, and to characterize the effects of concentrations corresponding to the one-hour standard.

The threshold for the average human observer to distinguish two elements of a scene (e.g., an object against its background) is a contrast difference of 2%; the detection of red discoloration of a white object by the average observer requires a 10% reduction in the relative radiance of blue versus red light. Using these threshold values, the following effects levels were calculated.

A white target (e.g., clouds or a snow-covered slope) viewed at one mile in particle-free air would have a detectable red coloration at 0.036 ppm NO₂. This example is within the range of possible effects of a large NO_x source in a "clean" rural site.

The optical effect of NO₂ is somewhat masked by the presence of large amounts of fine particulate matter, or aerosols, as occurs in urban areas. Threshold concentrations for visual detection of NO₂ were calculated for a hypothetical Los Angeles atmosphere containing just enough aerosol to limit visual range for a black object to 10 miles. Under these conditions, the threshold NO₂ concentration causing detectable reddening of the horizon sky is roughly 0.032 ppm. (The assumptions about the characteristics of the aerosol and its illumination affect the calculation; therefore this is only an approximate value). At the modeled concentration (about 80 ug/m³), the aerosol itself appears white on the horizon, but causes reddening of a white target. Therefore, NO₂ will add to detectable reddening at any level.

At the one-hour standard concentration, 0.25 ppm NO₂, the optical effects are pronounced. In particle-free air the calculated visual range (in green light) is 17 miles (compared to about 120 miles without NO₂), the horizon is darkened and reddened, and a white target has detectable coloration at a range of 0.19 mile. For the case with aerosols, and the standard level of NO₂, the horizon is darkened and reddened, and a white target has detectable coloration at 0.44 mile.

For comparison with the 10-mile State standard for visibility-reducing particles, the concentration of NO₂ which reduces green based visual range to 10 miles is 0.463 ppm in particle-free air. At this concentration the atmosphere is nearly opaque to blue light, the horizon is quite dark and strongly reddened, and a white target has perceptible reddening at 0.11 mile.

3. Conclusions

Optical effects occur at much lower levels than do known health effects. The current short-term standard concentration, 0.25 ppm, results

in intense discoloration at short distances, and contributes strongly to urban brown haze. In addition, an ambient ground-level standard has no direct control over the occurrence of elevated NO₂ plumes or layers. However, a 0.25 ppm standard serves generally to limit the intensity of atmospheric discoloration by NO₂. Significant reduction in the occurrence and intensity of discoloration effects would require a standard five to ten times more stringent than the current level. Based on current health information, such a reduction in the standard would not be accompanied by commensurate additional health benefits.

VI. RECOMMENDATIONS

A. OFFICE OF ENVIRONMENTAL HEALTH HAZARD ASSESSMENT

The Office of Environmental Health Hazard Assessment recommends that the California Ambient Air Quality Standard for Nitrogen Dioxide be maintained at 0.25 parts per million, averaged over one hour.

B. AIR RESOURCES BOARD STAFF

The Air Resources Board Staff recommend that the level of the California Ambient Air Quality Standard for Nitrogen Dioxide be retained at a concentration of 0.25 ppm, averaged over one hour.

The Staff finds that this level of the standard remains appropriate and that the wording in Title 17 included in the "Most Relevant Effects" and "Comments" sections for NO₂ remains correct.

As currently indicated in Title 17 (Table 1), a NO₂ standard at this level is "intended to prevent adverse health effects". A NO₂ standard at this level is necessary because of the "potential to aggravate chronic respiratory disease and respiratory symptoms in sensitive groups." Futhermore, "Risk to public health (is) 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". Futhermore, because of the contribution (of NO₂) to atmospheric discoloration, "the standard imposes an upper limit on adverse effect on welfare, including atmospheric discoloration by NO₂"

VII. ALTERNATIVES TO THE RECOMMENDED ACTION

Because the recommended action is retention of the current standard, there will be no adverse environmental impact, and alternatives which would reduce this impact need not be discussed. This action will neither affect the geographical extent of noncompliance with the standard nor entail any significant change in public health risk. The alternatives considered in reviewing the standard were: no change; a more stringent standard; and a less stringent standard. A more stringent standard could be generally more protective. It would somewhat reduce welfare effects, but it is not expected to provide any substantially increased protection of health, based upon an analysis of existing health effects data. A less stringent standard would aggravate welfare effects, and, depending on the level chosen, is likely to have significant adverse public health impacts. The staff believes that the current standard is sufficiently protective of the public health, based upon the evidence available from a review of the research literature and the analysis presented in the Technical Support Document and the recommendation of the Office of Environmental Health Hazard Assessment.

VIII. IMPACTS

A. ENVIRONMENTAL IMPACTS

The proposed retention of the one-hour Ambient Air Quality Standard for Nitrogen Dioxide, alone, will have no negative environmental impacts. Ambient air quality standards establish the maximum allowable levels of air pollutants. The objective of ambient air quality standards is to provide a basis for preventing or abating the effects of air pollution. However, standards should not be interpreted as permitting, encouraging, or condoning the degradation of present air quality which is superior to that stipulated in the standards. Once a standard is adopted by the ARB, local air pollution control districts are responsible for the adoption of rules and regulations to control emissions from stationary sources to attain and maintain the standard. The ARB is responsible for adoption of emission standards for mobile sources. Once standards are attained and maintained, the air quality will be improved with corresponding benefits to the environment and public health and welfare.

B. SMALL BUSINESS IMPACTS

The Government Code requires the ARB to discuss how complying with a proposed regulation could adversely affect small businesses. (Small businesses are defined by Government Code Section 11342 et. seq.) The proposed retention of the one-hour Ambient Air Quality Standard for Nitrogen Dioxide will not have an adverse economic impact on small business. In fact, this action will not have a direct effect on any business. If the attainment designation triggers air quality planning by a local air pollution control or air quality management district, subsequently implemented by the adoption of rules affecting businesses or individuals in the area, the district must consider the economic impacts of the plan or control measures implemented under the plan. (Health and Safety Code section 40703; Western Oil and Gas Ass'n v. Air Resources Board (1984) 37 Cal. 3d 502, 517.)

C. LOCAL AGENCY OR SCHOOL DISTRICT IMPACTS

This action will not result in a mandate to any local agency or school district, the costs of which are reimburseable pursuant to Part 7 (commencing with section 17500), Division 4, Title 2 of the Government Code.

IX. AVAILABILITY OF THE TECHNICAL SUPPORT DOCUMENT

A technical support document has been prepared in order to document and describe information relevant to the review of the California Ambient Air Quality Standard for Nitrogen Dioxide. This document provides technical information on the atmospheric chemistry of nitrogen dioxide, measurement methods and monitoring, sources and control, and both ambient and indoor occurrences. In addition, this document provides technical information on the effects of nitrogen dioxide. Chapters on controlled human exposure studies, epidemiological studies, and animal toxicological studies provide information on health effects. Chapters on vegetation and materials damage and on visibility impairment provided information on welfare effects. The Technical Support Document is incorporated by reference in the staff report and is available to the public upon request or for inspection at Air Resources Board's Public Information Office 2020 "L" Street, Sacramento, CA 95814.

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APPENDIX A

NOV 13 1992

California Environmental Protection Agency

State of California

Pete Wilson, Governor

OFFICE OF ENVIRONMENTAL HEALTH HAZARD ASSESSMENT



M E M O R A N D U M

TO: James Boyd
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FROM: Steven A. Book, Ph.D. 
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DATE: November 3, 1992

SUBJECT: Recommendation for an Ambient Air Quality Standard for Nitrogen Dioxide

Enclosed is a recommendation for an ambient air quality standard for nitrogen dioxide (NO₂) developed by staff members of the Office of Environmental Health Hazard Assessment (OEHHA). Based on a thorough review of the published health effects literature, OEHHA is recommending retention of the existing standard, i.e., 0.25 ppm NO₂ averaged over one hour. This recommendation was peer-reviewed by this department's Air Quality Advisory Committee (AQAC) on July 20, 1992. Committee members' suggestions were incorporated into a second draft, which was re-circulated for review. Several Committee members submitted additional comments, most of which have been incorporated in the final recommendation.

While a majority of the Committee concurs with the recommendation, several members felt that the existing standard may not confer a substantial enough margin of public health protection. This concern is based on the potential for increased susceptibility to infection and injury at levels near the standard. The theoretical implications of some recent research findings are that repeated NO₂ exposure may adversely affect both respiratory and systemic immunity in susceptible individuals.

OEHHA staff share this concern, but believe that there is insufficient quantitative information to support the recommendation of an alternative standard. The Board may, however, feel that an additional margin of safety should be incorporated to the current standard to address this uncertainty. At a minimum, our staff strongly recommends that the Board sponsor additional research designed to quantitatively delineate the range of low-level NO₂ effects in humans. The OEHHA recommendation contains several examples of the types of studies that could be useful the next time the NO₂ standard is

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James Boyd
November 3, 1992
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reviewed. OEHHA staff would be willing to work with the ARB's Research Division to define the data gaps of highest priority.

If you have questions about this letter or the recommendation, please contact Michael Lipsett, M.D., Air Pollution Epidemiology Unit, at (510) 540-3324 or ATSS 8/571-3324.

RECOMMENDATION FOR AN AMBIENT AIR QUALITY STANDARD FOR NITROGEN DIOXIDE

Submitted to the California Air Resources Board

Air Pollution and Epidemiology Unit
Hazard Identification and Risk Assessment Branch
2151 Berkeley Way, Annex 11
Berkeley, CA 94704

November 1992

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Reviewers

A draft version of this document was reviewed in public session by members of OEHHA's independent Air Quality Advisory Committee on July 20, 1992. Additional useful written and oral comments were received on the subsequent draft from the following Committee members:

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Helpful comments on the penultimate draft were also received from Mark Frampton, M.D., Pulmonary Unit, University of Rochester Medical Center, New York.

1. Recommendation

The Office of Environmental Health Hazard Assessment (OEHHA) recommends that the California ambient air quality standard for nitrogen dioxide (NO₂) be maintained at 0.25 parts per million (ppm), averaged over one hour.

2. Rationale for Recommendation

The original state standard for NO₂ was based on concerns about atmospheric discoloration and effects of low-level NO₂ exposure on experimental animals. Among the health effects of concern were increased susceptibility to infection and emphysematous changes in the lungs of mice as well as biochemical changes in the lungs of other rodents (Technical Advisory Committee 1969). At that time there was no published literature linking low-level NO₂ exposure to effects in humans, although high-level occupational exposures had caused serious respiratory injuries and fatalities (Lipsett 1992).

During the most recent (1985) review of the evidence by the Department of Health Services (DHS), retention of the 0.25 ppm 1-hour standard was recommended, based primarily on evidence of effects in experimental animals associated primarily with subchronic and chronic NO₂ exposure in the range of 0.2 ppm to 0.5 ppm. Among the outcomes cited by DHS were: (1) effects on hormone (prostaglandin) metabolism (0.2 ppm); (2) impairment of barbiturate detoxification (0.25 ppm); (3) subtle changes in mouse lung development (0.3 ppm); (4) facilitation of lung colonization by injected tumor cells (0.3 ppm); (5) decreased antibody production (0.4 ppm); (6) adverse effects on lung biochemistry and metabolism (0.4 ppm); (7) decreased resistance to streptococcal infection (0.5 ppm); and (8) pathological changes in lung similar to emphysema (at concentrations as low as 0.6 ppm, but generally 1 ppm or higher) (California Department of Health Services 1985). Because of a dearth of information on kinetics and sites of NO₂ uptake, metabolic fate, and so forth, in humans as well as animals, no attempt was made to extrapolate these effects quantitatively across species. DHS concluded that the weight of

the scientific evidence at that time warranted retention of the 0.25 ppm standard. As indicated below, OEHHA staff still concur with this assessment.

The conclusions of the 1985 DHS review were based principally on the results of animal studies. Since then, a number of studies involving human exposure to low levels of NO₂ have been published. Ambient air quality standards are intended to protect susceptible or sensitive subpopulations as well as healthy members of the general population. Several recent studies suggest effects of low-level NO₂ exposure on sensitive subgroups of humans and on human defenses against respiratory infection. Specifically, brief (20 minutes to 4 hours) controlled NO₂ exposures demonstrate: (1) an increase in the bronchial reactivity or airway responsiveness (i.e., tendency of the airways to narrow in response to various stimuli) of some asthmatics; and (2) decreased lung function in some patients with chronic obstructive lung disease. Increased airway responsiveness in asthmatics may lead to transient clinical deterioration of their condition. Although increased responsiveness has been demonstrated repeatedly, there is substantial variability among asthmatics' reaction to NO₂. Some laboratories have not been able to detect such an increase, suggesting that subtle differences in experimental design or as-yet-unidentified host factors are important determinants of this outcome. The range of NO₂ concentrations at which this effect has been observed (albeit inconsistently) is 0.1 to 0.5 ppm, but no clear dose-response pattern is evident. The reported effect of NO₂ on lung function in chronic bronchitics (0.3 ppm) is a recent finding that has not been noted in other studies using different exposure protocols or study populations (Morrow et al. 1992). Epidemiologic studies (especially those using the presence of a gas stove in the home as a surrogate for NO₂ exposure) suggest that NO₂ may influence the occurrence of respiratory illness in humans. However, the concentration(s) and duration(s) of exposure capable of producing such effects cannot currently be determined.

Several research reports indicate that repeated low-level NO₂ exposures may adversely affect the integrity of the immune system. In particular, several publications suggest that subchronic (i.e., 6 weeks or more) exposure of mice to 0.25 or 0.35 ppm NO₂ for 7 or 8 hours/day resulted in small, but detectable effects on percentages of different immune cell subpopulations in

the animals' spleens and blood. While it is striking to see any systemic effect of NO₂ at these concentrations, the potential clinical implications of these changes are unclear, especially since the experiments examined relative percentages, not absolute numbers, of different immune cell populations. Nevertheless, given that NO₂ does appear to affect respiratory defenses against infection and cancer metastases, these studies indicate that more research in this area is clearly needed. For the purpose of standard-setting it would be especially important to ascertain whether acute exposures to low-level NO₂ would have similar impacts and whether the absolute numbers of immune cells were affected.

Thus, recent studies indicate the potential for acute effects of NO₂ exposure on susceptible individuals, which may be of clinical significance. Besides asthmatics and chronic bronchitics, potentially susceptible subgroups would include those with other pre-existing respiratory diseases, with compromised immune function, or both. Examples of such groups would include infants and young children, people with cystic fibrosis, cancer patients (especially those undergoing radiation or chemotherapy), people with immune deficiencies, either congenital or acquired (such as AIDS), and the elderly. There are likely to be other conditions and illnesses that could render individuals more sensitive to NO₂-related effects. Thus, potentially susceptible subgroups comprise a significant fraction of the general population.

The large number of studies recently performed using potentially susceptible individuals allows us to consider human studies in evaluating the health-protectiveness of the current NO₂ standard. However, the diversity of exposure protocols and, more importantly, the inconsistent results and the ostensible absence of clear dose-response relationships in the clinical studies do not present a compelling case for calculating another standard, either in terms of a specific exposure concentration or an averaging time. Both epidemiologic and animal investigations provide supporting evidence for adverse effects of low-level NO₂ exposure, but likewise do not indicate a need for a new or different standard. Therefore, OEHHA staff recommend retention of the existing ambient air quality standard for NO₂. At the same time, however, OEHHA staff strongly recommend that the Air Resources Board sponsor

additional research focusing on exposures of humans and appropriate animal species using NO₂ concentrations bracketing the current standard and a variety of averaging times. Although there is a substantial body of literature on this substance, there is a paucity of data useful for delineating a lower bound of NO₂-related adverse health effects. Of particular importance would be controlled dose-response studies of humans examining the effects of multi-hour and multi-day NO₂ exposures on the integrity and functioning of various components of the immune system. Such studies should include careful dosimetric assessment. In addition, epidemiologic and field studies of susceptible populations involving carefully defined measures of exposure and response would be useful.

3. Absorption and Metabolism

NO₂ is poorly soluble in water, and hence penetrates to the deep lung, its principal site of toxicity. When measured in inhaled and expired air, NO₂ appears to be efficiently absorbed and deposited in the human lung, with a range of absorption between approximately 70% and 90% (Bauer et al. 1986; Wagner 1970). The absorption of NO₂ appears to be governed by its rate(s) of reaction with lung tissue (Postlethwaite et al. 1990). Studies with radiolabeled NO₂ demonstrate extensive binding of this pollutant (or its reaction products) in the lung (Goldstein et al. 1980). NO₂ has an unpaired electron and is therefore capable of initiating free radical reactions, such as peroxidation of fatty acids in cell membranes (Pryor 1981). Although NO₂ combines with water to form nitric (HNO₃) and nitrous (HNO₂) acids, its specific tissue reactions have not been extensively characterized. An in vitro experiment using rat lung found that most absorbed NO₂ was converted to nitrite ion (NO₂⁻), possibly via formation of HNO₂ as an intermediate (Postlethwaite et al. 1989).

4. Selected Aspects of NO₂ Toxicology

The toxicity of NO₂ is thought to be due to its capacity to initiate free radical reactions and to oxidize cellular proteins and other biomolecules (Sagai et al. 1987). Such reactions can disrupt the structural and functional integrity of cell membranes, enzymes, DNA and various organelles. Acute and

chronic lung injury caused by NO₂ is greatest at the junction of the airways and the alveoli. At very high doses, NO₂ can cause fatal pulmonary edema in both animals and humans. Sublethal exposures in animals produce inflammation and various degrees of tissue injury characteristic of oxidant damage (Evans 1984). The changes produced by low-level acute or subchronic exposure appear to be reversible when animals are allowed to recover in clean air. Chronic NO₂ exposure causes focal emphysema-like structural alterations in the lungs of experimental animals (Freeman et al. 1972).

Adverse outcomes of particular concern in relation to low-level NO₂ exposure include: (1) effects of acute exposure on some asthmatics and possibly on some persons with chronic bronchitis; (2) effects on respiratory tract defenses against infection; (3) effects on the immune system generally; (4) initiation or facilitation of the development of chronic lung disease; and (5) interaction with other pollutants. Section 5 considers effects of acute exposure on potentially sensitive subgroups with chronic lung conditions. The other effects have been investigated primarily in animal studies and are summarized below.

a. Effects on Respiratory Tract Defenses

Infectious respiratory diseases are major causes of morbidity and mortality, particularly among the very young and elderly members of the population. Effects of pollutants such as NO₂ on defenses against infections can be studied by: (1) investigating whether experimental infections of animals or humans are increased in frequency or virulence by exposure to NO₂, or (2) examining the effect(s) of NO₂ on individual components of respiratory tract defenses. Numerous epidemiologic investigations suggest that indoor NO₂ exposure is associated with increased risk of respiratory illness, though the exposure patterns or concentrations required to produce such effects are unknown (See Section 6).

Infectivity models present an integrated perspective of the functioning of respiratory tract defenses. Experimental animals are typically subjected to the pollutant(s) of interest in varying patterns and intensity of exposure, accompanied or followed by challenge with an infectious aerosol. Frequency or

severity of infection or mortality in the exposed group is then compared with that observed in a control group exposed to clean air instead of the pollutant. In such experiments, acute and subchronic exposures to NO₂ have resulted in increased susceptibility to infection by viruses, bacteria and mycoplasma (Rose et al. 1988; Parker et al. 1989; Ehrlich et al. 1977). Subchronic exposures to NO₂ concentrations in the range of 0.5 to 1.0 ppm were reported to produce such effects (Ehrlich et al. 1979; Ehrlich and Henry 1968). Superimposition of short (1-hour) NO₂ spikes on a lower continuous background exposure enhances the effects on infectivity in mice (Graham et al. 1987).

Goings et al. (1989) exposed 7 groups of human volunteers to clean air or 1.0, 2.0 or 3.0 ppm NO₂ for 2 hours on 3 consecutive days, with intranasal administration of live (but attenuated) influenza virus on the second day of exposure. Outcomes examined included several objective measures of new infection by this viral strain. Infection rates were higher in the NO₂-exposed than in the control groups, but the differences were not statistically significant. Reasons proffered by the investigators for the inconclusive results included insufficient statistical power, probable inability of this virus to infect the lower respiratory tract, and a simultaneous influenza epidemic caused by a related viral strain that may have affected the results. Thus, whether NO₂ affects the concerted operation of human respiratory defenses, as measured using an infectivity model, is still an open question.

NO₂ adversely affects several major components of the lung's defense system, usually at exposure concentrations above 1 ppm. Structural and functional aspects of ciliary clearance are impaired by NO₂ exposure, including decreased numbers of cilia, changes in ciliary morphology, depressed ciliary motility and beat frequency (Rombout et al. 1986, Heller et al. 1986, Nakajima et al. 1980). Below the ciliated portion of the lung, migratory alveolar macrophage (AM) cells are responsible for (among other things) engulfing and killing inhaled micro-organisms, removing other foreign particles, and participating in various immune functions. Numerous studies on AMs from experimental animals exposed to NO₂ at concentrations ranging from 0.3 ppm to more than 10 ppm indicate changes in AM morphology and functional capabilities (Aranyi et al. 1976; Amoruso et al. 1981, Suzuki et al. 1986).

At least two studies have investigated the effect of NO₂ on human AMs. Frampton et al. (1989a) reported that AMs retrieved by bronchoalveolar lavage (BAL) from four of nine subjects exposed for three hours to 0.6 ppm NO₂ showed decreased ability to inactivate influenza virus in vitro. BAL involves inserting a flexible tube down the throat into an airway and flushing a segment of the lung with a small volume of saline solution, which is then withdrawn and examined chemically and microscopically. This finding was of marginal statistical significance in the group as a whole (p<.07), which is not surprising given the small sample size. No such effects were observed when the exposure protocol involved three 15-minute spikes of 2.0 ppm NO₂ superimposed on a continuous exposure of 0.05 ppm. Such research suggests that this important constituent of the human lung's defense system may be impaired by exposure to low concentrations of NO₂. In contrast to this finding, however, Pinkston et al. (1988) found no effect on human AM viability and several immunoregulatory functions when exposed in vitro to 5, 10, and 15 ppm NO₂ for 3 hours. Unlike the Frampton study, the AMs were exposed to NO₂ after extraction from BAL fluid from 15 healthy adults. Although Pinkston et al. examined effects other than viral inactivation, the results of these two studies suggest that human AMs may be more strongly affected by in vivo than in vitro exposure. This observation is supported by investigations in mice indicating that in vivo NO₂ exposure (to 5 ppm) significantly diminished the ability of the animals' AMs to inactivate a pathogenic virus (Rose et al. 1988). In addition, in vitro exposures may introduce experimental artifacts not present when in vivo exposures are utilized.

Low-level NO₂ exposure has been shown to facilitate colonization of the lung by injected tumor cells, a model for cancer metastasis (noted in the 1985 review of the standard). More recently, Richters et al. (1989) reported that six-week exposure to 0.35 ppm NO₂ injured lung capillaries and resulted in formation of small blood clots (microthrombi), which were correlated with increased tumor cell colonization in a small number of mice. This work suggests that NO₂-related damage may impair host mechanisms of clearance of neoplastic cells as well as infectious micro-organisms.

b. Other Effects on the Immune System

Immunoregulation is complex and incompletely understood. It is recognized, however, that appropriately targeted antibodies and immune cells other than AMs (e.g., various subcategories of lymphocytes) are important not only for defense against infection, but also for surveillance against malignancy. Most studies of the effects of NO₂ on the immune system have used exposure concentrations equal to or greater than 1.0 ppm. A few studies report effects at lower exposure concentrations. For example, Fujimaki et al. (1982) found that antibody production was decreased in a dose-related manner in mice exposed for four weeks continuously to 0.4 and 1.6 ppm NO₂.

Several experiments conducted at the University of Southern California suggest effects on the mouse immune system from chronic exposure to as little as 0.25 or 0.35 ppm NO₂ (Richters and Damji, 1988, 1990; Kuraitis and Richters 1989). These experiments involved exposure of mice for 7 or 8 hr/day, 5 day/week, for between 6 and 12 weeks to 0.25 or 0.35 ppm NO₂, followed by a microscopic examination of subpopulations of white blood cells (particularly lymphocytes) in the animals' spleens and blood. Generally, modest decreases of lymphocyte subpopulations were observed, though only a few of the apparent decreases were statistically significant. The potential clinical implications of these investigations are unclear, however. The changes noted were small measured percentages, not absolute numbers, of different cell types. Even the decreased percentages were not out of the range of normal variability. Human immune systems can function with fewer than normal numbers of lymphocytes; nevertheless, given the widespread prevalence of primary and acquired immune deficiency diseases, there may be some people who may be at the critical margin. In addition, if acute exposures to NO₂ concentrations near the current standard were to cause transient decrements in human lymphocyte populations, this could theoretically result in a significant public health impact because NO₂ exposure (indoors and outdoors) is so common.

Recently, Sandström et al. (1992) reported that exposures of human volunteers to 1.5 ppm NO₂ for 20 minutes every other day (6 exposures total) resulted in decreased numbers of certain immune cells (suppressor T-lymphocytes and natural killer cells) in BAL fluid. In contrast, Rubinstein

et al. (1991) found that 2-hour exposures of human volunteers to 0.60 ppm NO₂ on four days during a one-week period did not affect the number or distribution of immune cells in BAL fluid or in the blood, except for a slight increase in natural killer cells in BAL fluid. The experiments of Rubinstein et al. involved subacute (not chronic) exposures, did not test the functional capabilities of the immune cells, and were limited to only five healthy adults.

These findings raise doubts about the adequacy of the existing ambient NO₂ standard. However, the database relating exposure, absorption and distribution of NO₂ in animals in relation to humans is extremely limited, rendering cross-species dosimetric extrapolation very uncertain. While it would be helpful to have additional investigations of comparative NO₂ dosimetry in various animal species and humans, it may be more fruitful (for purposes of standard-setting) for the ARB and other organizations to sponsor more research to clarify whether and to what extent acute low-level NO₂ exposure may affect immune function in humans. Examples of such investigations include well-controlled dose-response studies of single NO₂ (and later, multi-day) controlled exposure studies, involving examination of immune cell numbers and functional status, as well as epidemiological studies of immunocompromised individuals with and without significant NO₂ exposure.

c. Effects on Development of Chronic Lung Disease

Chronic inflammation of the airways and alveoli associated with an imbalance of proteolytic enzymes (proteinases, particularly elastase) and antiproteinase compounds (e.g., α_1 -proteinase inhibitor [α_1 PI]) are thought to be important in the etiology of chronic obstructive pulmonary disease (COPD) (Idell and Cohen 1987). Chronic obstructive pulmonary disease (COPD) is typically due to long-term cigarette smoking and is generally considered to subsume emphysema and chronic bronchitis. However, genetic deficiency of α_1 -PI also results in early-onset emphysema. Long-term NO₂ exposure has been associated with emphysema-like lesions in a variety of animal species, usually at concentrations in excess of 5 ppm (Hayden et al. 1967; Freeman et al. 1972). Lafuma et al. (1987) found that subchronic exposure (8 hr/day, 5 days/week for 8 weeks) of hamsters to 2 ppm NO₂ exacerbated experimentally

induced emphysema. The lowest concentration reported to cause such lesions in animals is 0.6 ppm (1.2 mg/m³), to which beagles were exposed 16 hr/day for 68 months (Hyde et al. 1978). In contrast to short-term NO₂ exposure studies, the lesions in these dogs were clearly irreversible, since the pathological examination took place 32 to 36 months after the exposure ended. (It should be noted that these exposure regimens also included 0.25 ppm (0.31 mg/m³) nitric oxide (NO). However, in a parallel experiment with high NO (≈1.6 ppm) and low NO₂ (≈0.14 ppm), such lesions were not observed. In other species, subchronic and chronic exposure to concentrations ≥ 0.34 ppm NO₂ have resulted in constellations of findings representing various degrees of tissue damage, inflammation and repair (Sherwin and Richters 1982; Rombout et al. 1986; Kubota et al. 1987; Blair et al. 1969; Hayashi et al. 1987). That such findings have been made in multiple species suggests that there may be at least qualitative relevance for humans.

Whether long-term NO₂ exposure affects the development or progression of chronic lung disease in humans is difficult to study. Epidemiologic investigations of such phenomena are complex and are always bedeviled by uncertainties regarding of exposure assessment. There is a suggestion in the occupational literature that NO₂ exposure among coal miners may be related to chronic lung disease (Kennedy 1972). However, NO₂ clearly is not the only respiratory toxicant to which workers are exposed. A similar difficulty affects epidemiologic studies of populations exposed to ambient NO₂.

Euler et al. (1988) studied the chronic effects of air pollution in a large population of Seventh Day Adventists in various locations in California (Los Angeles, San Francisco, San Diego, and several rural locations). The outcome measured was self-reported symptoms of COPD. In order to estimate long-term exposures, the investigators limited the analysis to subjects who had had a stable residence for 10 or more years. The exposures of those individuals were matched to the closest air pollution monitors. Pollutant measurements included hours per month that concentrations of oxidants, total suspended particulate matter (TSP), SO₂ and NO₂ exceeded certain levels. A multiple logistic model was used to analyze the relationships between these pollutants and the prevalence of self-reported COPD symptoms. Statistically significant associations were found for TSP and oxidants, but not NO₂. It

should be noted, however, that the mean NO₂ levels measured were quite low in this study, and that peak NO₂ concentrations were not used in the analysis. Also, because NO₂ concentrations are often strongly correlated with both TSP and oxidants, the effects of the latter pollutants may have overshadowed any effect of NO₂.

The UCLA Chronic Obstructive Respiratory Disease (CORD) study investigated long-term effects on lung function of residents in several different communities in the greater metropolitan Los Angeles area. Numerous publications have resulted from the CORD study, which involved cross-city comparisons of respiratory symptoms or lung function and analysis of the differences in relation to mean ambient air pollution levels (Detels et al. 1987, 1991). The CORD researchers compared baseline and 5-year follow-up lung function measurements in Lancaster and Glendora, and found both lower baseline values and more rapid deterioration of lung function in Glendora, in which the mean levels of all pollutants measured (oxidants, SO₂, NO, NO₂, SO₄ and TSP) were greater (Detels et al. 1987). More recently, these investigators undertook a similar comparison of Lancaster and Long Beach residents. Mean levels of oxidants were higher in Lancaster during the periods of interest, while Long Beach had higher levels of NO₂, TSP and sulfur oxides. In this investigation, Long Beach residents exhibited greater deterioration of lung function than residents of Lancaster, and there were marked differences between children of the two areas (Detels et al. 1991). However, the design of this study precludes assigning an etiologic role in the deterioration of lung function to any single pollutant. Nevertheless, the potential role for NO₂ cannot be excluded.

To avoid difficulties concerning exposure assessment inherent in epidemiology, short-term chamber investigations of NO₂ effects on physiological and biochemical factors thought to be associated with chronic lung disease have been undertaken. These are reviewed in Section 5 (See Table 3). Of particular note are: (1) brief (20 min) exposures to 4.0 ppm resulted in an influx of certain kinds of inflammatory cells into the airways and/or alveoli, which was not observed to occur in exposure protocols involving lower NO₂ concentrations (Sandström et al. 1991; Frampton et al 1989b); (2) though α_1 PI (α_1 -proteinase inhibitor; see above) was reduced in healthy nonsmokers by

a 3-hr exposure to 3 or 4 ppm NO₂, this finding could not be replicated at lower concentrations (1.5 continuously for 3 hour or 0.05 ppm with three 15-minute spikes of 2 ppm) (Mohsenin et al. 1987; Johnson et al. 1990). The implications of these findings are that the inflammation and proteinase-antiproteinase imbalance thought to be prerequisite to the development of COPD may not occur in humans at low (\leq 0.60 ppm) NO₂ concentrations. On the other hand, even at 0.60 ppm Frampton et al. (1989b) did note an increase in pulmonary α_2 -macroglobulin, which may also modulate the local proteinase-antiproteinase balance. Though the lack of a dramatic inflammatory response at concentrations more than twice the ambient standard is reassuring, it would be premature to conclude that there is little likelihood of chronic effects in humans.

d. Interactions with Other Pollutants

Exposures to multi-pollutant mixtures demonstrate that NO₂ may show additive or synergistic effects with other pollutants (notably ozone), but may also show no effect over and above that attributable to the other pollutant(s). The degree of interaction depends on the outcome(s) of interest, the exposure sequence and intensity, the sensitivity of the experimental species, and other factors. Generally, interaction has been demonstrated in animal toxicology studies, while controlled exposure studies of lung function in humans have typically shown at most an additive effect of low-level NO₂ exposure in relation to other pollutants. There are many investigations of the phenomenon of interaction: those cited below are intended to be illustrative, not exhaustive. Most have used exposure concentrations substantially in excess of the NO₂ ambient standard.

Exposures of mice to various combinations of NO₂ and O₃, followed by an aerosolized bacterial challenge resulted in either additive or synergistic effects on mortality in the mice, at least where the concentration of either gas above would also have been sufficient to evoke a response (Graham et al. 1987). Three-day exposures of rats to O₃ (0.3 ppm) and NO₂ (1.2 ppm) showed more than additive effects on several lung enzyme activities (Lee et al. 1990). Collagen synthesis in the lung was increased synergistically by a combined exposure of NO₂ (2 or 5 ppm) and sulfuric acid (H₂SO₄ at 1 mg/m³) for

up to 7 days (Last 1989). Schlesinger found both additive and synergistic effects of NO₂ (0.3 and 1 ppm) and H₂SO₄ (500 µg/m³) on various aspects of rabbit AM function, while such patterns of interaction were not observed on the clearance of particles from rabbit lungs (Schlesinger 1987; Schlesinger and Gearhart 1987). Kleinman et al. (1989) found that mixtures including NO₂ (2.5 ppm) and O₃ (0.6 ppm) approximately tripled the area of damaged rat lung in comparison with the effect of O₃ alone, while the addition of aerosolized metals and sulfates to the mixture did not significantly augment the joint NO₂/O₃ effect. (It should be noted, however, that such mixtures also contained nitric acid vapor (0.8 ppm), and possibly other unmeasured reactive nitrogen species, which may have contributed to the effects observed.

In contrast to the above, controlled exposure studies of human volunteers using NO₂ and other pollutants, concurrently or in sequence, have usually failed to show an effect of NO₂. However, since almost all of these studies have been conducted in healthy adults using NO₂ concentrations which would not be expected to affect the outcomes measured (usually standard pulmonary function tests), this result is not surprising. For example, joint exposure to 0.6 ppm NO₂ and 0.3 ppm ozone produced effects that were not statistically different from those caused by ozone alone, while NO₂ exposures without concomitant O₃ had no significant effect on lung function or respiratory symptoms (Adams et al. 1987). Another study involving 2-hour exposure to 0.45 ppm O₃, alone and in various combinations with 0.60 ppm NO₂ and 0.13 ppm peroxyacetyl nitrate also found that the addition of NO₂ did not enhance effects attributable to O₃ (Drechsler-Parks et al. 1989). Folinsbee et al. (1981) found similar results in young men exposed to a mixture of ozone (0.50 ppm) and NO₂ (0.50 ppm) using various combinations of relative humidity and temperature. Koenig et al. (1988) found that 1-hour joint exposures to (0.12 ppm) O₃ and NO₂ (0.30) ppm caused no effects on lung function in healthy and well-controlled asthmatic adolescents. Two recent studies produced contradictory results with respect to effects on airway reactivity in asthmatic volunteers exposed briefly to NO₂ (0.25 or 0.30 ppm), followed by challenge with the bronchoconstrictor sulfur dioxide (Jörres et al. 1990, Rubinstein et al. 1990) (See section 5, below). In a controlled exposure study of a complex mixture (0.5 ppm NO₂, 0.5 ppm SO₂ and aerosols of zinc sulfate, ammonium sulfate and sodium chloride), there were no statistically

significant differences in lung function or symptoms in healthy adult volunteers (Kleinman et al. 1985).

Thus, the animal toxicology studies cited indicate the potential for NO₂ (generally at concentrations substantially in excess of the California ambient standard) to add to or multiply the adverse effects of other pollutants. Nevertheless, it should be noted that such toxicologic interaction effects are not always observed. Human exposure studies examining traditional outcomes (lung function and respiratory symptoms) generally do not suggest interaction of NO₂ with other pollutants; however, there are virtually no data on outcomes similar to those used in the animal studies. Evidence of interactive effects tend to affect the margin of safety or uncertainty in an ambient air quality standard. With respect to the NO₂ standard, it would be helpful to have additional human studies of potential interactions involving nontraditional endpoints. An example would include investigations of effects of controlled multi-hour and multi-day exposures using various pollutant mixtures on immune cell number and function.

5. Controlled Exposure Studies

Experimental exposure of human volunteers to various pollutants under controlled laboratory conditions can provide useful pathophysiological information of direct relevance to standard-setting. The principal advantages of this methodology over epidemiological studies is that exposure to the pollutant(s) of interest can be precisely measured, and thus exposure-response relationships determined. While exposure conditions can also be controlled in animal experiments, the obvious strength of human chamber studies is that no cross-species extrapolation is required. On the other hand, microscopic or biochemical examination of pollutant-induced tissue damage is more limited in humans by both ethical and practical considerations. Other limitations of controlled human exposures need to be acknowledged: (1) only short-term responses to relatively brief exposures (i.e., minutes to hours) can be evaluated; (2) there is often limited statistical power to detect effects, due to the typically small number of subjects; (3) controlling the experimental conditions may result in failure to capture effects found in complex real-world exposures; (4) multiple selection biases in recruiting volunteers reduce

the generalizability of such studies (e.g., systematic exclusion of people with a history of recent respiratory infection; relatively few studies of children, adolescents or other potentially susceptible subgroups). 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 in the standard-setting process. In contrast, given the potential shortcomings of this genre of investigation, negative findings may in some cases reflect the constraints of study design more than biological reality.

a. Design Considerations in Controlled Exposure Studies

The basic study designs of controlled exposure studies are similar. Volunteers are generally healthy young adults who are exposed to one or more carefully measured pollutants through a mouthpiece (oral breathing only) or in a chamber (oronasal breathing). Because potentially sensitive subpopulations are also of interest for purposes of setting ambient standards, controlled exposures of NO₂ (and other pollutants) have also included people with pre-existing lung conditions (asthma and COPD), as well as children and older adults. The subjects may be at rest or may exercise intermittently, which can increase the quantity of pollutants reaching the deep lung, particularly for relatively insoluble compounds such as NO₂. Data collected usually include graded respiratory symptoms and a variety of indices of pulmonary function, such as the amount of air one can exhale in one second after a deep inspiration (FEV₁) or the lung's resistance to airflow (Raw or SRaw). A number of studies involving low-level NO₂ exposures have also examined bronchial reactivity in asthmatics (described below). Healthy volunteers have not been shown to react symptomatically or functionally to exposure concentrations of NO₂ substantially higher than the current ambient standard (Hackney et al. 1978, Kerr et al. 1979, Linn et al. 1985). Thus, this section focuses primarily on effects observed in people with pre-existing respiratory disease.

Chronic airway inflammation and episodic, reversible bronchoconstriction are hallmarks of asthma. Inflammation is associated with bronchial hyperreactivity or hyperresponsiveness, which refers to an exaggerated

tendency of the airways to constrict when exposed to respiratory irritants or other substances. This phenomenon is also observed in many persons with COPD and in otherwise healthy individuals during and after respiratory tract infections and after exposure to respiratory irritants such as ozone. In general, however, such reactivity is markedly greater in asthmatics compared with nonasthmatics. Airway responsiveness to numerous stimuli can be measured in clinical studies. Methods used to induce and measure nonspecific bronchial reactivity in asthmatics include exercise, hyperventilation with cold or dry air, or inhalation of pharmacologic agents (histamine, methacholine, or carbachol), sulfur dioxide or dilute (hypotonic) or concentrated (hypertonic) saline solutions. Although the above-listed pharmacologic agents also cause bronchoconstriction in healthy individuals, asthmatic airways constrict at much lower exposure concentrations. Most of the studies of the effects of NO₂ in asthmatics include an evaluation of its effect on airway hyperresponsiveness. There is no generally accepted criterion regarding what magnitude of increased responsiveness should be considered significant from a regulatory perspective. However, the clinical significance of increased airway reactivity is the potential for a flare or exacerbation of asthma, with heightened bronchial responses to other nonspecific airborne irritants.

As previously noted, NO₂ is relatively insoluble and therefore can penetrate to the deep lung, where pathologic damage tends to be concentrated. Tissue damage evokes an inflammatory response demonstrated repeatedly in animals. The potential of NO₂ to produce respiratory tract inflammation in humans has been examined in several clinical studies using BAL. Techniques such as BAL may ultimately provide better information about the low-level toxicity of poorly soluble, reactive compounds such as NO₂ than standard tests of lung function (Utell 1989).

b. Studies of Asthmatics

There have been numerous clinical investigations of the effects of low-level NO₂ exposure on individuals with asthma. Most of these studies have involved measurement of airway reactivity, lung function and respiratory symptoms (See Table 1). At exposure concentrations relevant to the current ambient standard (i.e., 0.25 ppm, 1-hour average) there appears to be little,

if any, effect on respiratory symptoms. Most studies also indicate no grouped effect on a variety of measures of lung function, though where individual data are presented it is clear that there is substantial inter-individual variability in response. However, the most commonly measured indices of pulmonary function relate to the caliber of the large central airways and larynx, which are less likely to be affected by NO₂ than the small peripheral airways of the deep lung. Nevertheless, in two studies measuring different indices of effect on the peripheral airways, no effect of NO₂ was found (Mohsenin 1987; Rubinstein et al. 1990).

Exercise is often incorporated in the exposure protocol to simulate the breathing rates (and hence the increased deep lung dose of pollutants) accompanying outdoor activities. However, exercise itself may modify the outcomes of interest in studies of asthmatics. Exercise-induced bronchospasm (EIB) occurred when subjects were exposed to filtered air as well as NO₂, suggesting that, within these experimental contexts, exercise had a greater effect on the lung function parameters tested than NO₂. This observation may be due in part to an interesting epiphenomenon of EIB: repeated exercise results in a decreasing tendency to EIB (Edmunds et al. 1978). This refractoriness persists over several hours, and may affect responses to some environmental insults as well. Similarly, exercise appears to transiently decrease asthmatics' airway reactivity to methacholine (Inman et al. 1990). Thus, incorporating exercise into the exposure protocol may obscure potential effects of NO₂ on lung function and airway reactivity. In the absence of a mechanistic understanding, though, this is speculation, especially since exercise enhances the pulmonary effects of ozone, another poorly soluble oxidant pollutant (Folinsbee et al. 1988; Horstman et al. 1990).

Increased airway reactivity associated with NO₂ exposure was found in some studies of asthmatics, but not in others using similar (but not identical) exposure protocols. That this outcome occurred in at least six separate studies (See Table 1) indicates that it is not a spurious or chance event (Orehek et al. 1976; Kleinman et al. 1983; Jörres et al. 1990; Bauer et al. 1986; Bylin et al. 1985; Mohsenin 1987a). Still, failure to detect this effect in a similar number of investigations is puzzling. In a report of two sets of experiments, the investigators found increased airway reactivity after

exposure to 0.30 ppm NO₂, but were subsequently unable to demonstrate this effect in a subsequent dose-response study using 0.15, 0.30 or 0.60 ppm NO₂ (Roger et al. 1990). (Six subjects who participated in both studies showed a greater increase in airway reactivity in the single-concentration study (0.30 ppm) than in the stepped exposures.) Differences in experimental protocols (mouthpiece versus chamber exposure; exercising versus sedentary subjects; different agents for testing reactivity; medication withheld or not; time of year when exposures took place) and patient populations (baseline airway obstruction and need for medication; use of vitamin C or other anti-oxidants; residence in a polluted environment) may provide partial explanations for the inconsistent results among studies. Reconciliation of these findings will require additional research, as will exploration of the clinical ramifications.

At higher concentrations (1.5 - 2.0 ppm) NO₂ also induces increased airway reactivity in healthy subjects (Frampton et al. 1991; Mohsenin 1988). The mechanism for increased reactivity attributable to NO₂ exposure is unknown, but can be blocked in healthy volunteers by oral pre-treatment with the anti-oxidant vitamin C (Mohsenin 1987b). Often increased airway reactivity is associated with inflammation, yet low-level NO₂ exposure does not appear to cause an obvious inflammatory response (See Table 2 and accompanying text). Exposure of rats to 0.5 ppm NO₂ for four hours (or 1.0 ppm for one hour) causes mast cells in the lungs to release granules containing chemical mediators associated with inflammation and acute asthmatic reactions (Thomas et al. 1967). Continuous exposure to 0.2, 0.4 and 0.6 ppm NO₂ for several days also increases the number of mast cells in rat airways (Hayashi et al. 1987). The implications of these findings for humans are unclear, however, though Sandström et al. (1990, 1991) have also shown increased numbers of mast cells in BAL fluid of healthy humans exposed briefly to higher (>2 ppm) concentration of NO₂. What is clear, however, is that there is considerable variability of response to NO₂ among asthmatics, which for now, cannot be predicted a priori.

c. Studies of Subjects with Chronic Obstructive Pulmonary Disease

Persons with COPD by definition have compromised lung function and less of a respiratory reserve capacity than healthy individuals, and therefore may be less able to compensate for environmental insults. There have been few controlled investigations using low-level exposure of patients with COPD. Such patients' impaired cardiopulmonary function places certain constraints on the experimental design - i.e., exercise intensity can only be mild and of short duration, and long-acting medications, which could affect the experimental results, may not be withheld.

The four studies with exposure concentrations relevant to the current standard are summarized in Table 3. Of these, the only clear and potentially significant effect is the progressive impact on expiratory air flow in the study by Morrow et al. (1992). The pattern of changes in lung function suggests that the main physiological effect was on the subjects' ability to take a deep breath. The exposure duration in this study was longer than in two of the earlier investigations cited in this section: the time- (and apparently dose-) related effect on lung function is similar to that observed in low-level ozone studies (Folinsbee et al. 1988; Horstmann et al. 1990), suggesting the need for additional research involving longer exposures. The recent study by Hackney et al. (1992) was intended to replicate the exposure protocol of Morrow et al., using a study population residing in the Los Angeles metropolitan area.

The longer exposure duration of the study by Morrow et al. may be one reason why this study's results diverge from those of Kerr et al. (1979) and Linn et al. (1988), though the overall dose of NO₂ reaching the participants' lungs were likely to have been greater in the latter investigations (because of the higher concentrations employed). The number of chronic bronchitics in the Kerr study was too small to have detected anything other than a major effect. However, it is more difficult to explain the discrepant results between the Morrow and the investigations in Los Angeles (Linn et al. 1985; Hackney et al. 1992). One possibility is that the subjects in the latter studies may have "adapted" to the high-oxidant environment of the Los Angeles basin, which may have conferred relatively greater protection against the

easily measurable short-term effects of NO₂ on lung function. Differences in baseline lung function were unlikely to have played a role here, since the Linn study group had more severe obstruction, while the subjects in the Morrow and Hackney groups had comparable degrees of airflow limitation. The effects of the subjects' oral medications cannot be assessed. Thus, as with the studies of airway reactivity in asthmatics, there is no fully satisfactory explanation for the ostensibly inconsistent results.

d. Studies Involving Nonstandardized Outcomes

As noted earlier, adverse effects associated with NO₂ exposure include acute and chronic inflammatory changes in the respiratory tract and damage to many components of pulmonary defenses against infection. Epidemiological studies are inconclusive on the question of whether such exposures lead to the chronic effects seen in animal research (Euler et al. 1988; Detels et al. 1988, 1991). Community-based epidemiologic studies investigating effects of NO₂ exposure (via the surrogate of gas stove usage) suggest that such exposure may result in increased infectious respiratory illness (Hasselblad et al. 1992). The outcomes of bronchial inflammation and potential for reducing human defenses against infection as a function of NO₂ exposure have also recently been studied in controlled exposure studies.

At least 5 studies have investigated the effects of NO₂ on various aspects of inflammation, as measured by BAL subsequent to exposure (summarized in Table 2). Inflammation is a fundamental, stereotyped biological response to injury which includes in part a localized increase of vascular permeability and release of numerous chemical mediators, followed by an influx of inflammatory cells. With short (20 minute) exposures characteristic of industrial environments (2.25 - 5.5 ppm), analysis of BAL fluid suggests an increase of some types of inflammatory cells in a pattern quite different from that usually seen in NO₂-induced inflammation in animals (Sandström et al. 1990, 1991). In contrast, two reports from investigators at the University of Rochester, using a variety of exposure protocols corresponding more closely to nonindustrial settings, showed no effect on inflammatory cell numbers, viability or distribution (Frampton et al. 1989a, 1989b). These investigators noted, however, that continuous exposure to 0.60 ppm NO₂ for 3 hours was

associated with a decreased capability of the predominant immune cell in the lung (alveolar macrophages) to inactivate influenza virus in vitro in a subgroup of the volunteers. This same exposure regimen resulted in an increase in α_2 -macroglobulin (α_2M), a protein probably involved with local proteinase-proteinase balance and modulation of the lung's immune response (Frampton et al. 1989b). The biological significance of this finding, however, is unclear because: (1) no such increase was found when the NO_2 exposure concentration was 1.5 ppm, and (2) other cellular and noncellular components of the BAL were not affected, indicating that epithelial permeability was not enhanced by these exposure regimens.

A characteristic feature of emphysema is the destruction of alveolar walls, which is thought to be due to elastases released by inflammatory cells. Two chamber studies using BAL have examined whether NO_2 can inactivate endogenous α_1 -PI (α_1 -proteinase inhibitor; see section 4.c., above), the principal recognized inhibitor of elastase activity. Mohsenin and Gee (1987) exposed 10 healthy adult subjects to either 3 or 4 ppm NO_2 for 3 hours, after which α_1 -PI quantities and activities were assayed in BAL fluid retrieved from the subjects' lungs. Seven different control subjects also underwent BAL. These investigators found that, although the exposed and control subjects had similar quantities of α_1 -PI in their BAL fluid, the functional activity of this protein was 45% lower in the NO_2 -exposed group. (It should be noted, however, that individuals with a hereditary deficiency of α_1 -PI of about 50% do not develop early-onset emphysema, unlike those whose α_1 -PI activity is 20% or less of normal.) Using a more "environmentally relevant" exposure protocol, Johnson et al. (1990) found no difference in α_1 -PI activity between NO_2 and air exposures in healthy nonsmoking volunteers. In addition to the lower NO_2 concentrations used in this experiment (1.5 ppm X 3 hr or 0.05 ppm X 3 hr with three 15-minute 2 ppm peaks), there were several differences in the study design and analysis that may account for the discrepancy between their results and those of Mohsenin and Gee (1987).

6. Epidemiologic Studies

a. Introduction

Epidemiologic studies can be of value to the standard-setting process since they attempt to evaluate actual human exposures on the population at large. Individuals who typically might be excluded from a chamber study, such as severe asthmatics or individuals with recent respiratory illness, can be observed within an epidemiologic study design. Therefore, it is possible to determine the effects of a pollutant on the general population, under a variety of exposure scenarios. Examinations of the effects of NO₂ have included both community-based studies using outdoor fixed-site monitors and indoor studies that characterize NO₂ exposure by the presence or absence of sources inside the home, particularly gas stoves. Unfortunately, the evidence provided by epidemiologic studies to date is only of limited use in determining an NO₂ standard. This is primarily a result of problems in measuring exposure, and by the lack of any consistent findings (which may be related, in part, to the measurement problems).

Typically, classification of exposure tends to be the most formidable task in an epidemiologic study of air pollution. The measurement of exposure to nitrogen dioxide presents particular problems because of the relevant period of exposure, the sources of exposure, and spatial characteristics of ambient NO₂. First, for acute health effects, toxicologic studies indicate that short-term peaks of exposure to nitrogen dioxide are of greater concern than longer-term exposures such as 24-hour or weekly averages. This adds considerable difficulty to any study and may necessitate constant monitoring of both exposure and response, in order to link the two. Such surveillance is extremely resource-intensive, since it would also require many days of study in order to be representative and have sufficient statistical power to detect an effect. As a result, many studies use longer-term averages, thereby incorporating large measurement errors and reducing the likelihood of detecting an effect. This may be a particular problem for the community-based epidemiologic studies that use outdoor fixed-site monitors to measure NO₂ exposure. In addition, only a moderate association exists between outdoor concentrations of NO₂ and personal exposures. Using data from Wisconsin,

Quackenboss et al. (1986) showed that during the summer, the correlation between outdoor NO₂ and personal NO₂ exposure was approximately 0.5, while during the winter the correlation dropped to 0.25. Indoor-outdoor NO₂ exposure correlations may well be different in California, however.

A second factor that presents problems for exposure measurement and that limits the use of epidemiologic studies for standard-setting for NO₂ is related to the sources of NO₂ exposure. The highest exposures to NO₂ typically occur indoors, during the first few minutes of use of a gas stove (Goldstein et al. 1988). Evidence suggest that the use of a gas stove in the home may add 25 ppb (30 µg/m³) to the average concentrations of NO₂, as measured over a two-week period (Quackenboss et al. 1986; Samet et al. 1987). This has led many researchers to examine the effects that the presence of a gas stove in the home on respiratory symptoms. However, short-term peaks of NO₂ may be 10 to 20 times higher than the typical measurement of two-week averages (Spengler and Sexton 1983). In addition, the correlation between the peak and the weekly average concentration of NO₂ is low (Brunekreef et al. 1990). Therefore, although some of these studies do find an association between gas stoves in the home and respiratory symptoms, the relevant dose of NO₂ is unclear. Health effects related to presence of a gas stoves may be due solely to the very high peaks associated with their use.

A third factor limiting the use of epidemiologic studies is the high covariation of NO₂ with other outdoor pollutants. Most studies have failed to find an effect associated with outdoor NO₂. When an effect of NO₂ is found, the pollutant is usually part of a complex mixture of pollutants, typically including particulate matter and ozone. Furthermore, NO₂ is a precursor of nitric acid vapor and of nitrate particles, which constitute a relatively large fraction of fine particulate matter. Thus, it has been difficult to attribute an effect to NO₂ alone. In addition, NO₂ concentrations can vary considerable within a given airshed, thereby limiting the appropriateness of using a fixed-site monitor.

Because of the limitations of the epidemiologic studies of NO₂, therefore, only the general findings of these studies are summarized below.

Most of these studies have focused on the relationships between exposure to NO₂ and respiratory symptoms and illnesses and on pulmonary function.

b. Outdoor Community-based studies

Early epidemiologic studies of NO₂ found associations between higher concentrations and both lung function in school children and respiratory disease among families (Shy 1970a,b). However, these studies relied on a pollution measurement technique that is not accurate enough for quantitative purposes. Subsequent epidemiologic studies using more appropriate monitoring equipment generally have been unable to detect any consistent association between NO₂ and various indicators of morbidity. In general, effects from outdoor NO₂ on either children or adults are rarely observed. For example, studies that report an effect of other pollutants but not NO₂ include examinations of peak flow and symptoms (Vedal et al. 1987), emergency room visits (Bates et al. 1990; Samet et al. 1981), absenteeism and respiratory disease (Ponka 1990), respiratory symptoms (Krupnick et al. 1990) and hospital admissions (Bates and Sizto 1987). The lack of an association may be due to the large error related to measuring outdoor NO₂ or to the occurrence of effects only at much higher levels of NO₂. Among the more recent exceptions, however, are studies by Schwartz and Zeger (1990) and Schwartz et al. (1991).

Schwartz and Zeger (1990) examined the effects of air pollution among a population of student nurses in Los Angeles in the early 1970s. Study participants recorded a variety of symptoms on a daily basis, including cough, phlegm, and chest discomfort. Pollutants under investigation included oxidants, sulfur dioxide, nitrogen dioxide and carbon monoxide. In models corrected for autocorrelation, a significant association was found between NO₂ and phlegm. Hourly concentrations of NO₂ averaged approximately 0.13 ppm. Although high correlations between NO₂ and ozone typically are observed in the L.A. basin, correlation coefficients were not provided. Subsequent data published for September 1978 to March 1979 for L.A. indicated a correlation between NO₂ and ozone of 0.62, and between NO₂ and coefficient of haze (COH, a measure of airborne particles) of 0.84 (Krupnick et al. 1990). Likewise, data for Southern Ontario indicate a high correlation between summer NO₂ and both

ozone (0.64) and COH (0.70) (Bates and Sizto, 1987). Correlations of this magnitude make it difficult to attribute an effect to NO₂ alone.

In a longitudinal study of five German cities, Schwartz et al. (1991) examined the association of total suspended particulate matter (TSP) and NO₂ with clinic-based reporting of several respiratory symptoms and illnesses among a sample of children. Both these pollutants were observed at low levels - roughly half of the current U.S. average ambient air quality standards. Nevertheless, an association was found between daily reported cases of croup and both TSP and NO₂. However, a stronger effect was found for TSP, and a high correlation between these pollutants was reported. Again, from these data, it is difficult to identify NO₂ as the pollutant of concern.

c. Indoor Studies

Most of the gas stove investigations involve cross-sectional surveys of schoolchildren. In these studies, researchers typically assess current symptoms and lung function, and past illness. NO₂ concentrations are not measured but inferred based on simple questions concerning the presence of stoves or unvented heaters using gas as a fuel source. For example, among the earliest studies using the presence of gas stoves to characterize NO₂ exposure, Melia et al. (1977) compared respiratory symptom and illness rates among schoolchildren living in homes using gas versus electric cookers. This study surveyed 5,700 children randomly selected from throughout England and Scotland. Parents completed questionnaires about their children's symptoms and illnesses in the previous year including morning cough, colds going to the chest, wheezing, and bronchitis. Although the authors reported a statistically significant effect of gas stoves only for girls living in urban areas, subsequent reanalysis of the data using a multiple logistic model found a statistically significant effect for both boys and girls (Hasselblad et al. 1992).

Many studies have now been completed over a wide range of countries, climates and levels of home ventilation. In general, the findings have been mixed (Samet and Utell 1990; Samet et al. 1987). A few well designed studies have found a positive and statistically significant association between the

presence of a gas stove in the home and the likelihood of more frequent respiratory illness or decreased pulmonary function in children living in those homes (Melia et al. 1980; Neas et al. 1991). However, in many other studies, the association has been either positive or negative, and not statistically significant using conventional hypothesis tests (Melia et al. 1982; Ware et al. 1984; Dijkstra et al. 1990). A recent review of studies providing quantitative information of risks is provided by Hasselblad et al. (1992).

In certain cases, the lack of statistical significance in the indoor studies may be due to inherent problems in accurately characterizing NO₂ exposure, as suggested earlier. Such random measurement error will reduce the likelihood of finding an effect and increases sample size requirements. For example, Whittemore and Keller (1988) examined the data of Melia et al. (1980) as described by Florey et al. (1979) and found that a 20% misclassification rate of the exposure category results in an underestimate of the logistic regression coefficient by as much as 50%. In addition, many of these cross-sectional studies fail to control for differences in outdoor air pollution, including NO₂. Billick (1990) reported that a substantial proportion of the variation in bedroom concentrations of NO₂ was explained by outdoor levels of NO₂ alone ($R^2 = 0.369$).

In cases where it may be difficult to accurately estimate risk from any single study, simultaneous evaluation of many studies may be achieved using the method of meta-analysis. Such an analysis of the gas stove studies was recently conducted and provides evidence for an association between NO₂ and respiratory symptoms (Hasselblad et al. 1992). A total of 11 studies that examined respiratory symptoms in children were included in the meta-analysis. Though there are indications that increased concentrations of NO₂ are associated with more respiratory illnesses, the ambient concentration level at which these effects occur cannot be identified from these studies. In addition, some of the health effects ascribed to NO₂ may be due to nitrous acid (HONO), another gas stove combustion product which has received little attention. Thus, the indoor community studies can only play a supporting role in the standard-setting process.

TABLE 1: Controlled Exposure Studies of Asthmatics

<u>Reference</u>	<u>Exposure *</u>		<u>Subjects (n)</u>	<u>Results</u>		<u>Comments</u>
	<u>Concentration</u>	<u>/Duration</u>		<u>Airway Reactivity</u>	<u>Lung Function</u>	
	<u>(ppm)</u>					
Orehek et al. (1976)	0.1/1 hr (R)	Chamber	20	Increased (carbachol) in 13/20	Increased airway resistance	Questionable statistical analysis. Reanalysis by Dawson and Schenker (1979) gave similar results, however.
Hazucha et al. (1983)	0.1/1 hr (R)	Chamber	15	No effect (Methacholine)	Slight increased airway resistance (NS)	Inconsistent with results of Orehek (1976) and Ahmed (1982). Mild asthmatics. No effects on symptoms.
Koenig et al. (1985)	0.12/60 min (R)	Mouthpiece	10	Not tested	No effect	Subject age range 11-18. Medications not withheld. NS trend of increased symptoms after NO ₂ exposure.
Koenig et al. (1987)	0.12/40 min (3OR/10E) 0.18/40 min (3OR/10E)	Mouthpiece	10	Not tested	No effect	Subject age range 11-19. Medications withheld only for 4 hr preceding testing. "No significant reports of subjective symptoms."
Kleinman et al. (1983)	0.2/2 hr (IE)	Chamber	31	Increased in @ 2/3 of subjects (methacholine)	No effect	Parametric and nonparametric statistical tests were not uniformly consistent.
Jorres et al. (1990)	0.25/30 min (R)	Mouthpiece	14	Increased (SO ₂ challenge)	No effect	No effect on symptoms.
Jorres et al. (1991)	0.25/30 min (20 (R)/10 (E))	Mouthpiece	11	No effect (histamine)	No effect	Mild stable asthmatics.

TABLE 1: (Continued) Controlled Exposure Studies of Asthmatics

<u>Reference</u>	<u>Exposure *</u>		<u>Subjects (n)</u>	<u>Results</u>		
	<u>Concentration/Duration</u> (ppm)	<u>Exposure</u>		<u>Airway Reactivity</u>	<u>Lung Function</u>	<u>Comments</u>
Bauer et al. (1986)	0.3/30 min (E) Mouthpiece		15	Increased to hyperventilation with cold air	Transient decrease in FEV ₁	
Rubinstein et al. (1990)	0.30/30 min (20E/10R) Chamber		9	No effect (sulfur dioxide)	No effect on various lung function indices	No effect on symptoms. Also included test of small airways (single breath nitrogen).
Koenig et al. (1988)	0.30/60 min (IE) Mouthpiece		12	Not tested	Slight transient decrease in FVC	No change seen when combined with 0.12 ppm ozone.
Avol et al. (1989)	0.30/3 hr (IE) Chamber		34	No effect (cold dry air)	Decreased after 1st hour, but improved by 3rd hour of exposure	Subject age range 8-16. Lower respiratory symptoms increased during week following NO ₂ exposure.
Avol et al. (1988)	0.086 (in ambient air) 0.3/2 hr (IE) 0.6 Chamber		36 59	No effect (cold air)	No effect	No effect on symptoms. Analysis of results from subset of 20 more severe asthmatics showed similar lack of effect on symptoms and lung function. Incomplete data on airway reactivity in this subset.
Roger et al. (1990)	(a) 0.3/110 min (IE) Chamber (b) 0.15/80 min (IE) 0.30/80 min (IE) 0.60/80 min (IE) Chamber		13 21 21 21	Not tested No effect	Decreased FEV ₁ , FVC Increased SRaw No grouped effects	Also showed slight increase in upper respiratory symptoms. Baseline asthma severity slightly less than in single-dose experiment. No significant changes in symptoms.

TABLE 1: (Continued) Controlled Exposure Studies of Asthmatics

<u>Reference</u>	<u>Exposure #</u> <u>Concentration/Duration</u> <u>(ppm)</u>	<u>Results</u>			
		<u>Subjects (n)</u>	<u>Airway Reactivity</u>	<u>Lung Function</u>	
Bylin et al. (1985)	0.12/20 min (R)	8	Increased at 0.48 ppm. (Histamine)	No effect on SRaw	Reactivity tested only at 0 and 0.48 ppm NO ₂ . NS trend for increased SRaw at lower NO ₂ and decreased SRaw at 0.48 ppm.
	0.24/20 min (R)				
	0.48/20 min (R) Chamber				
Mohsenin (1987a)	0.5/1 hr (R) Chamber	10	Increased	No effect on various lung function indices	No effects on symptoms. Unlike most other studies, included tests of airflow at low lung volume.
	0.5/1 hr (E), 1 hr (R)	13	Not tested	No effect	Increased symptoms in 7/13.

* During exposures the subjects were at rest (R), doing mild to moderate exercise (E), or both (IE = intermittent exercise). All results are statistically significant unless noted otherwise.

TABLE 2: Controlled Studies of Healthy Humans Exposed to NO₂ Followed by Bronchoalveolar Lavage

<u>Reference</u>	<u>Exposure *</u> <u>Concentration/Duration</u> <u>(ppm)</u>	<u>Subjects(n)</u>	<u>Results</u>		<u>Comments</u>
			<u>Cellular</u> <u>Components</u>	<u>Noncellular</u> <u>Components</u>	
Frampton et al. (1989a)	0.60/3 hr (IE) 0.05/2 hr 15 min (IE) plus 3 15-min peaks at 2 ppm	9 15	Not increased Not increased	See comments Not reported	AMs from 4/9 showed decreased ability to inactivate influenza virus. AM culture supernatant in these four also showed increased IL-1 (an inflammatory mediator).
Frampton et al. (1989b)	0.60/3 hr (IE) (early BAL)	8	Not increased	Increased only alpha-2M	Biological significance of increased alpha-2M is unclear (see text).
	0.60/3 hr (IE) (late BAL)	8	Not increased	Not increased	
	0.05/2 hr 15 min (IE) with 3 15-min peaks at 2 ppm	8	Not increased	Not increased	
	1.5/3 hr (IE) (early BAL)	15	Not increased	Not increased	
Rubinstein et al. (1991)	0.60/2 hr X 4 days (IE)	5	Slight increase in natural killer cells	Not reported	Functional activity of immune cells not measured.
Johnson et al. (1990)	.05 with/3 hr (IE) 3 15-min peaks at 2 ppm 1.5/3 hr (IE)	9 15	Not increased	No change in alpha-1-PI activity	Unlike Mohsenin et al. (1987) subjects served as own controls.
Sandstrom et al. (1992)	1.5 x 20 min (15 min E) every second day (6 exposures)	8	Decreased suppressor T-cells; decreased natural killer cells	No change in albumin or total protein	Decreased lymphocytes in blood also found. No change in AM, mast cells, or T-helper cells in BAL.

TABLE 2: (Continued) Controlled Studies of Healthy Humans Exposed to NO₂ Followed by Bronchoalveolar Lavage

<u>Reference</u>	<u>Exposure *</u> <u>Concentration/Duration</u> <u>(ppm)</u>	<u>Subjects(n)</u>	<u>Results</u>		<u>Comments</u>
			<u>Cellular</u> <u>Components</u>	<u>Noncellular</u> <u>Components</u>	
Sandstrom et al. (1991)	2.25/20 min (15E) 4.00/20 min (15E) 5.5/20 min (15E)	8 8 8	Increased mast cells Increased mast cells and lymphocytes Increased mast cells and lymphocytes	Unaffected Unaffected Unaffected	Pattern of inflammatory response different from animal studies. Did not use filtered air controls.
Mohsenin et al. (1987)	3 or 4/3 hr (IE)	10 (exposed) 7 (control)	See comments	@ 45% decrease in alpha-1-PI	Did not use same groups for NO ₂ and air exposures. Therefore, interindividual differences may have overshadowed effects of NO ₂ exposure.
Sandstrom et al.	4/20 min (IE)	32	Increased mast cells and lymphocytes at 4, 8 and 24 hr, but not at 72 hr.	Not reported	See above comments for Sandstrom (1991).

E = exercise, IE = intermittent exercise, AM = alveolar macrophage, BAL = bronchoalveolar lavage, alpha-2M = alpha-2-macroglobulin, alpha-1-PI = alpha-1-proteinase inhibitor

TABLE 3: Controlled Exposure Studies of Patients with COPD using NO₂ Concentrations Relevant to Ambient Standard

<u>Reference</u>	<u>Exposure *</u>		<u>Results</u>		
	<u>Concentration/Duration</u> <u>(ppm)</u>	<u>Subjects</u>	<u>Lung Function</u>	<u>Symptoms</u>	<u>Comments</u>
Morrow et al. (1992)	0.3/4 hr (IE) Chamber	20	Progressive (but small) decrease in FEV ₁ and FVC.	No effect	Oral bronchodilator medication not withheld in a majority of participants. Lung function decrements reversed by bronchodilator administration. Greater effect on lung function among subjects with milder disease.
Hackney et al. (1992)	0.3/4 hr (IE) Chamber	26	Slight (8-3%) decrease in peak flow in first two hr of exposure. Otherwise no effect.	No effect	Study also involved personal NO ₂ monitoring for 2 weeks combined with home lung function measurements. No relationship was found between personal NO ₂ exposure and lung function or symptoms.
Linn et al. (1985)	0.5/1 hr (IE) 1.0 2.0 Chamber	22	No effect	Minimal to mild increase in respiratory symptoms, regardless of NO ₂ concentration.	Oral bronchodilator medication not withheld in a majority of participants. No NO ₂ effect on arterial oxygen saturation.
Kerr et al. (1979)	0.5/2 hr (IE, IR) Chamber	7	No effect	No effect	Very small study group.

* During exposures the subjects were at rest (R), doing mild to moderate exercise (E), or both (IE = intermittent exercise).

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APPENDIX B

PROPOSED

State of California AIR RESOURCES BOARD

Resolution -

January 14, 1992

Agenda Item No.:

WHEREAS, Health and Safety Code Section 39606(b) requires the Air Resources Board ("ARB" or "Board") to adopt ambient air quality standards in consideration of the public health, safety and welfare, including but not limited to health, illness, irritation to the senses, aesthetic value, interference with visibility, and effects on the economy;

WHEREAS, Health and Safety Code Section 39606(b) further provides that standards relating to health effects shall be based upon the recommendation of the Office of Environmental Health Hazard Assessment;

WHEREAS, the Board periodically reviews existing State ambient air quality standards to ensure that they reflect current scientific knowledge. (California Code of Regulation, Title 17, Section 70101);

WHEREAS, the existing ambient air quality standard for nitrogen dioxide (NO₂) of 0.25 parts per million (ppm) averaged over one hour is based upon: (1) evidence of the potential to aggravate chronic respiratory disease and respiratory symptoms in sensitive groups and that the risk to public health is implied by pulmonary and extra-pulmonary biochemical and cellular and pulmonary structural changes, which are observed in short-term animal tests at or above the concentration of the standard; and (2) the need to impose an upper limit on adverse effects on welfare, including atmospheric discoloration by NO₂;

WHEREAS, recently published scientific research findings support the existing basis for the current state nitrogen dioxide ambient air quality standard;

WHEREAS, ARB staff and Office Environmental Health Hazard Assessment (OEHHA) staff have reviewed the recent health effects studies and concur in their recommendation to the Board that the current statewide ambient air quality standard for nitrogen dioxide adequately protects public health and welfare, and regulatory action to revise the standards is not necessary at this time;

WHEREAS, the Board has held a duly noticed public meeting at which it has received and considered evidence, both written and oral, presented to it by staff, other scientists, and members of the public relating to the standards;

WHEREAS, the California Environmental Quality Act and Board regulations require that action not be taken as proposed if feasible mitigation measures or alternatives exist that would substantially reduce any significant adverse environmental effects of the proposed action;

WHEREAS, the Board has determined, pursuant to the requirements of the California Environmental Quality Act and Board regulations, that this regulatory action will have no significant adverse impact on the environment;

WHEREAS, the Board finds that the current State nitrogen dioxide ambient air quality standard of 0.25 parts per million averaged over one hour is necessary because of the potential to aggravate chronic respiratory disease and respiratory symptoms in sensitive groups and that the risk to public health is implied by pulmonary and extra-pulmonary biochemical and cellular and pulmonary structural changes, which are observed in short-term animal tests at or above the concentration of the standard; and

WHEREAS, the Board also finds that the current State nitrogen dioxide ambient air quality standard of 0.25 parts per million averaged over one hour is necessary because of the need to impose an upper limit on adverse effects on welfare, including atmospheric discoloration by NO₂.

NOW, THEREFORE, BE IT RESOLVED that the Board hereby affirms that the existing State ambient air quality standard for nitrogen dioxide is adequate to protect the public health and welfare and regulatory action is not necessary to revise the standard at this time.

BE IT FURTHER RESOLVED that the Board directs the Executive Officer to continue to monitor research efforts and regulatory issues relevant to this standard and to inform the Board of any significant new developments.

BE IT FURTHER RESOLVED that the Board also directs the Executive Officer to review these standards again in five years, or sooner if new information indicates that the existing standards may no longer be appropriate.