NITROGEN OXIDES: HEALTH AND ENVIRONMENTAL EFFECTS DOCUMENT

R. Frank and K.M. Novak

September 1981

BIOMEDICAL AND ENVIRONMENTAL
ASSESSMENT DIVISION
NATIONAL CENTER FOR ANALYSIS OF ENERGY SYSTEMS

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DEPARTMENT OF ENERGY AND ENVIRONMENT
BROOKHAVEN NATIONAL LABORATORY
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FOREWORD

This is the first Health and Environmental Effects Document (HEED) on nitrogen oxides, one of several generic HEEDs initiated by the Health and Environmental Risk Analysis Program, Office of Health and Environmental Research, Office of Energy Research, U.S. Department of Energy. It aims to provide a base for analyzing health and environmental effects of NO_x in technology-specific HEEDs such as oil shale, coal gasification, and diesel automobiles.

Knowledge of NO_x air chemistry, population exposure, and health effects is not well developed. Quantification, even of uncertainty ranges, is difficult and subject to error. Any attempt to quantify health damage due to NO_x must begin with a full understanding of available evidence. This first NO_x HEED takes this initial step and focuses exclusively on health. Continuing work will include consideration of other environmental effects and will emphasize quantification of NO_x effects.

Understanding of transport and air chemistry is essential for assessment of population exposure, environmental effects (e.g., visibility and acid rain), and interaction with other pollutants. We thank Drs. S. Schwartz and L. Newman of the Environmental Chemistry Division for helpful discussions in this area. We thank Drs. N. Barr and P. Cho at DOE, Dr. F. Lipfert of the Energy Analysis Division, our colleagues in the Biomedical and Environmental Assessment Division, Drs. H. Fischer, L. D. Hamilton, and S. Morris, and W. Medeiros and P. Moskowitz for their critical contributions. We also thank A. Link, A. Vanslyke, A. Lancsarics, and S. Walch for typing the document through several drafts.

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1. INTRODUCTION

Over 20 million metric tons of nitrogen oxides are released into the atmosphere by the U.S. every year. While this amount is small compared to natural sources, anthropogenically produced NO_x is responsible for local concentrations up to 100 times normal background levels (USEPA, 1980). Secondary transformation products of NO_x can be transported over large distances, contributing to acid deposition and photochemical smog.

Nitrogen oxides and their by-products may impose a variety of health effects on the general populace. Episodic or peaking concentrations of NO_2 may affect subgroups of the population with preexisting respiratory disease such as asthma, and individuals recovering from acute respiratory infections. Repeated exposures to NO_2, and possibly to NO as well, could also be expected to increase the incidence of acute respiratory infections in infants and children. While not clearly established, the possibility that repeated exposure is associated with chronic lung disease and increased rate of "aging" of the lung in adolescence and adulthood cannot be discounted.

The effects of other species of nitrogen oxides or of possible interactions between NO_x and other pollutants is not well understood and has not been addressed here, but synergistic and additive effects are probably detrimental.

2. CHEMICAL AND PHYSICAL PROPERTIES

2.1 Identification of Substances

Oxides of nitrogen are formed either as primary compounds during combustion[1] or secondarily in ambient air. NO_2 alone among the oxides of

nitrogen is specified in the primary National Ambient Air Quality Standards, although other members of this family of air pollutants are also potentially hazardous to health. They include nitric oxide (NO), nitrous acid (HNO_2) that dissolves in aqueous solution to form nitrite ion (NO_2), nitric acid (HNO_3), nitrogen peroxide (N_2O_2), nitrosamines [compounds formed when nitrite ion reacts with an amine to form a nitroso group (-N=O)], and nitrates (NO_4). The nitrates and nitric acid are secondary pollutants which may be transported long distances. This report deals mainly with NO_2, which has received most attention in biomedical research.

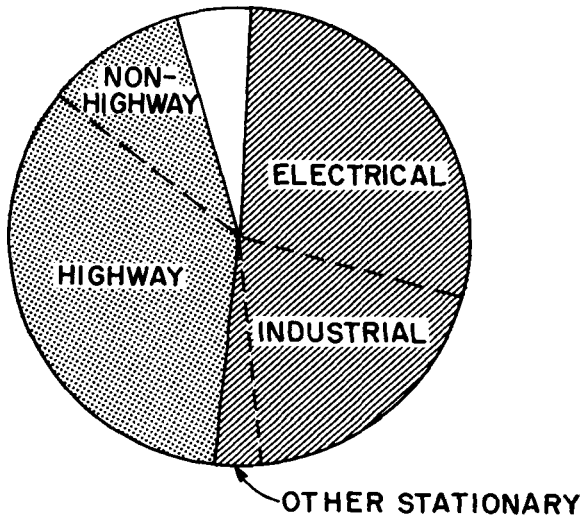
2.2 Identification Sources

While many oxides of nitrogen are produced naturally or can be traced directly to fertilizer use, those of concern to health result primarily from the high temperature combustion of coal, oil, and gasoline. Anthropogenic nitrogen oxide emission sources can be divided into two categories -- mobile and stationary. Highway vehicles, electrical utilities, and industrial emissions are the principal contributors, accounting for about 80% of NO_x emission sources in the U.S. (see Figure 1).

Since 1940, NO_x emissions have steadily accelerated (see Figure 2). This is in sharp contrast to other criteria pollutants (SO_x, O_3, Pb, TSP, CO, HC) which have shown generally decreasing trends since 1970.

European measurements in selected cities also recorded gradual increases over ten years and support the generalization that exposure to ambient NO_x levels is increasing (NAS, 1977, pp. 58-59) (see Table 1).

Measured nitrogen dioxide levels at 180 sites in the U.S. increased approximately 15% between 1975 and 1980. This increase corresponds



Source	Percent
MOBILE SOURCE COMBUSTION	44
Highway Vehicles	77
Non-highway Vehicles	23
STATIONARY SOURCE COMBUSTION	51
Electrical Utilities	56
Industrial	38
Other	6
OTHER[a]	5

[a]Includes INDUSTRIAL PROCESSES (i.e., chemical, petroleum refining, metals, mineral products, oil and gas production, and marketing; industrial organic solvent uses; and other processes); SOLID WASTE DISPOSAL; and MISCELLANEOUS (i.e.; forest wild fires and managed burning, agricultural burning, coal refuse burning, structural fires, and miscellaneous organic solvent use). (Source: USEPA, 1979).

Figure 1. National NO_x emissions in 1976.

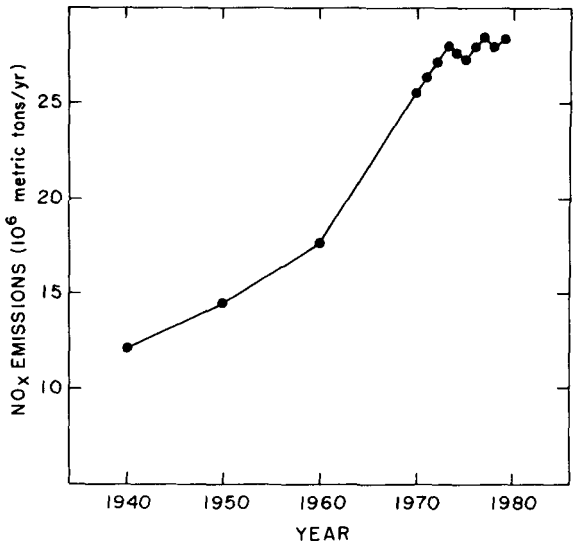


Figure 2. National trends of nitrogen oxide emission estimates (estimated as NO_2). (Source: USEPA, 1979; 1981a).

Table 1
Annual Mean Concentrations of Nitrogen Dioxide in Selected Cities[a]

	Concentration, $\mu g/m^3$						
Year	Rome[b]	Rotterdam[c]	Vlaardingen[c]	Frankfort[c]	Munich[b]	Tokyo[d]	Wash.DC[d]
1962	-	-	-	19	-	-	56
1963	-	-	-	23	-	-	56
1964	-	-	-	28	-	-	75
1965	-	-	-	30	-	-	56
1966	-	35	-	47	-	-	-
1967	-	43	-	34	56	-	75
1968	-	43	40	41	132	-	-
1969	-	43	38	63	489	77	-
1970	30	45	39	82	827	73	94
1971	36	-	-	80	-	58	75

[a]From National Atlantic Treaty Organization, Committee on the Challenges of Modern Society
[b]Method of measurement was not indicated.
[c]Concentrations measured by the Griess-Saltzman method.
[d]From WHO, 1977, p. 27.

reasonably well with the 12% increase in NO_x emissions over the same time. Electric utilities are the leading contributors among stationary sources. While emission rates from motor vehicles and generating plants have steadily decreased, primarily because of installation of air pollution controls, increased demands have more than offset the reductions. During the past decade the number of vehicle miles traveled has increased about 35%, and higher electricity use has caused utilities to burn more fuel. During this time industrial process emissions remained relatively constant while solid waste and miscellaneous emissions decreased.

2.3 Photochemical Reactions and Chemical Transformations

Figure 3 shows the principal interrelationships of NO_x. In the upper atmosphere (stratosphere) N_2O is believed to be a principal photochemical reactant affecting O_3 levels. In the lower atmosphere (troposphere), typically around urban centers, photochemical reactions involving primarily NO, NO_2, and gaseous organic molecules produce a number of reactive species, initiating in turn subsequent intermediate reactions and by-products. These secondary pollutants may be more toxic on a unit concentration basis than NO_2. The reactive species, including excited molecules and molecular fragments, may either be short-lived or found in extremely low concentrations. These intermediate reactions are complex and are affected by solar radiation, temperature, and presence or absence of reactive hydrocarbons. The interdependence between NO_2 and hydrocarbons warrants a holistic consideration of photochemical oxidant pollutants.

Smog chamber studies designed to mimic urban ambient environments and focusing specifically on the relationship between NO_x and HC and the

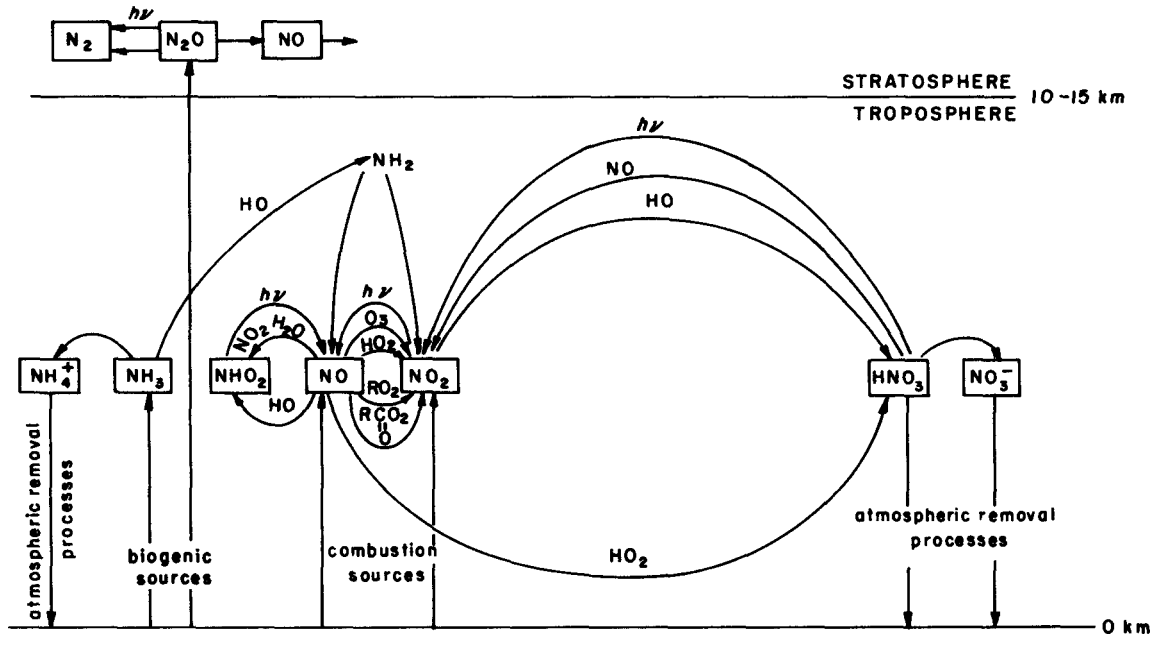


Figure 3. Interrelationships of atmospheric nitrogen oxides. (Source: Colucci and Simmons, 1978).

production of NO_2 have shown that, with other factors held constant, average and maximum NO_2 concentrations tend to be proportional to initial NO_x inputs. Generally, a 50% reduction in HC changes average NO_2 concentrations ±10% and reduces maximal NO_2 about 10 to 20%. These conclusions apply only to well-mixed urban air. NO_2 and NO are eventually converted to nitrates and nitrites.[2] Modeling of diurnal photochemistry predicts that up to half of the NO_x may be converted to nitric acid and nitrates. Theoretically, nitrates are produced when nitric acid vapor reacts with ambient ammonia forming fine ammonium nitrate particles (Figure 4). Ambient ammonia is principally thought to be produced by bacterial breakdown of organic material (Robinson and Robbins, 1972). Aerosols may also form by direct absorption of NO_x into aqueous droplets in the presence of ambient ammonia.

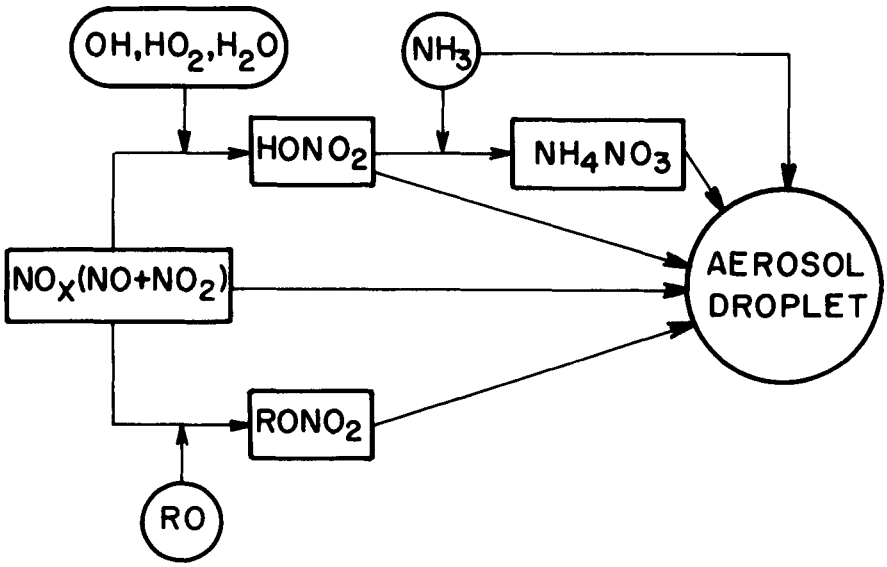


Figure 4. Paths of nitrate formation in the atmosphere. (Source: Orel and Seinfeld, 1977).

Theoretically nitrosamine may be formed by three mechanisms: (1) nonphotochemical reactions of gaseous amines with NO_x and a nitrous acid (HNO_2); (2) photochemical reactions of amines with NO_x (gas phase); and (3) heterogenous nitrosamine formation in atmospheric aerosols. The first two have been simulated in environmental chambers, and the third is purely speculative. Detailed discussion may be found in USEPA, 1979, pp. 6-1 to 6-66, and NAS, 1977, Chapter 9. Nitramines, amides, and other possible secondary products of nitrosamines formation may pose health problems and warrant further investigation.

The presence of NO_x in ambient air can also affect production of other compounds of concern to health -- produced either directly from nitrogenous reaction (i.e., ozone) or indirectly fron non-nitrogenous reactions [i.e. in the presence of high concentrations of NO_x, HC, and intense sunlight, SO_2

oxidation rates increase because of availability of OH (Colucci and Simmons, 1978; Finlayson and Pitts, 1976)].

3. AMBIENT NO_x

3.1 Transport and Deposition

The general behavior of nitroegeous species in the atmosphere can be described simply: NO emissions are partially converted to NO_2; simultaneously NO_2 is converted to nitric acid vapor while NO and NO_2 may be absorbed by aqueous particulates; this mixture of gases and particles is transported downwind of source regions; concurrently, additional NO_x gases are converted to particulate nitrates, and NO, NO_2, and gaseous nitrate may be absorbed into particle surfaces; finally rain out (absorption by droplets) and wash out (absorption in clouds) remove remaining gases and particles. Approximately 10 to 20% removal of the nitrogen may be removed by rain.

While there are similarities between long-distance transport of NO_x compounds and other air pollutants, important differences can be noted. Pollutants from tall-stack emission sources, predominantly utilities and industrial complexes, have more pronounced effects at considerable distances from the source, but ground-level emissions may also be transported long distances. On an emissions per mole basis, the secondary transformation products of NO_x may have a greater relative impact on acid deposition than those of SO_x because of the faster oxidation rates of NO_2 to nitric acid (crude estimates: SO_2 ~1%/h compared to NO_2 ~4 to 5%/h). While NO is the chief by-product of combustion, it only persists for hours in ambient air.

Ambient nitrogen dioxide persists for days and therefore can be transported some distance. Its long residence time increases its importance for population exposure. Nitric acid is removed from the atmosphere by deposition at ~1 cm/sec. Nitric acid vapor can undergo reversible transformation to solid or aqueous ammonium nitrate which may persist for a long time; however, the rate and type of transformation will depend on such variables as relative humidity and concentrations of NHO_3 and NH_3. Conversion of NO_x to nitrosamines, which may be subject to deposition, is also possible, but little is known about mechanisms and rates of conversion.[3]

3.2 Concentration Measurements

The highest concentrations of NO_x are found in heavily populated, industrialized urban areas. The mean annual concentration in urbanized areas for 1977-79 was 0.029 ppm compared to 0.01 ppm in non-metropolitan areas and 0.001 ppm in isolated areas (see Figure 5). The effect of principally fossil fuel combustion and transportation on localized NO_2 is clear. Long-term annual average concentrations are progressively lower, moving from major metropolitan centers to small cities and rural areas. Emission data provide additional evidence even though emission densities suggest a slightly more uniform pattern (USEPA, 1979, p. 5-15).

Recently identified increases in non-metropolitan country growth and outflow of industries from urban centers could disperse the existing NO_x emission pattern over areas larger than those previously observed. While annual average concentration measurements are informative in relating ambient levels to population exposures, shorter-term variations in NO_x

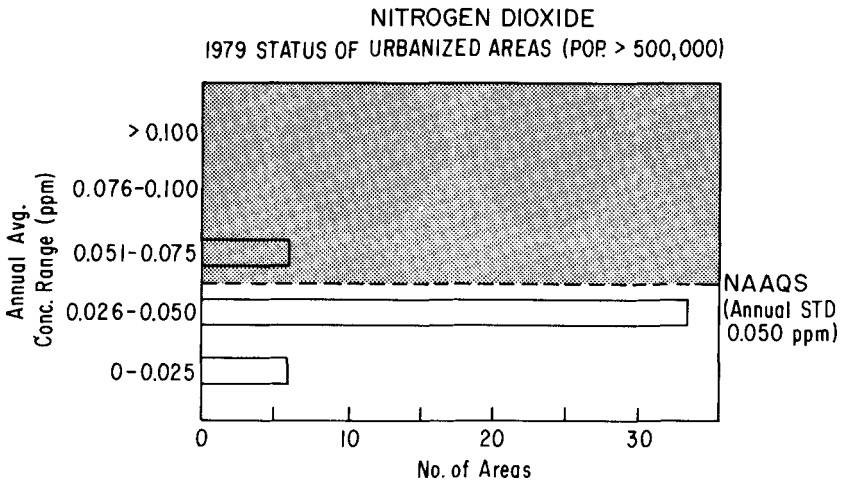


Figure 5. Comparison of 1979 nitrogen dioxide levels in urban areas with populations greater than 500,000 (Source: USEPA, 1981a).

levels also have health implications. During 1977-79, peak 1-h average concentrations of NO_2 ranged from 0.06 ppm to approximately 0.5 ppm in most areas. For all areas outside California meeting the annual primary NAAQS STANDARD (0.05 ppm or 100 $\mu g/m^3$), 1-h average concentrations exceed 0.15 ppm roughly 10 to 20 days/yr. California cities, where smog has been a continuing problem, exceeded this level more than 40 days/year even though the annual standard was met. All 186 areas for which data exist frequently exceeded 0.10 ppm for one hour. Urban NO_2 levels are characterized in Table 2. The expected number of days for which an area in compliance with the annual standard might be expected to exceed 0.15 and 0.30 ppm is given in Figure 6.

Since nitrogen oxides as a class of compounds are photoreactive, daily concentration variations in many of the species are expected. Figure 7 displays a generalized but typical hourly pattern. Seasonal variations in

Table 2
Characterization of NO_2 Levels (in ppm) in Urbanized Areas for Different Averaging Times and Forms

Distribution of Urbanized Areas	24-Hour Average		3-Hour Average	1-Hour Average Daily Maximum		
	Annual Average	1 Exceedance[a]	Daily Maximum with 1 Exceedance[a]	Met 95% of days/yr	Met 99% of days/yr	1 Expected Exceedance[a]
Minimum	0.005	0.006	0.03	0.01	0.01	0.06
50 Percentile	0.028[c]	0.075	0.14	0.06	0.09	0.15
95 Percentile	0.053	0.168	0.29	0.20	0.33	0.34
99 Percentile	0.063	0.210	0.31	0.32	0.35	0.41
Maximum	0.081	0.242	0.40	0.38	0.48	0.49
Number of urbanized areas analyzed[b]	186	186	104	104	104	104

Source of Data: 1977-1979 SAROAD data base.

Notes: (a Expected exceedance form, when the rate is $\leq$1 per year;
(b The total number of urbanized areas in the U.S. is 275; and
(c The mean annual average for isolated areas unaffected by man-made NO_2 is approximately 0.001 ppm.
(Source: USEPA, 1981b, Appendix B.)

concentration measurements were also noted (see Figure 8). Similar variations were also observed for precipitation pH, but no simple trends are apparent (USEPA, 1979, p.11-30).

3.3 Sampling Techniques

Various methods are available for sampling ambient NO_x and NO_x - derived pollutants. Nitric oxide and nitrogen dioxide may be measured separately or collectively by manual or automated techniques, including colorimetric methods and chemiluminescence. Other methods, including gaschromatography, long-path infrared spectrosopy, and electrochemistry, are also available. A detailed discussion of these methods may be found in USEPA, 1971; USEPA, 1979; WHO, 1977; and NAS, 1977.

The original reference method for determining compliance with National Ambient Air Quality Standards (NAAQS) (see USEPA, 1971) was the Jacobs-Hochheiser technique. It was discovered to have unresolvable

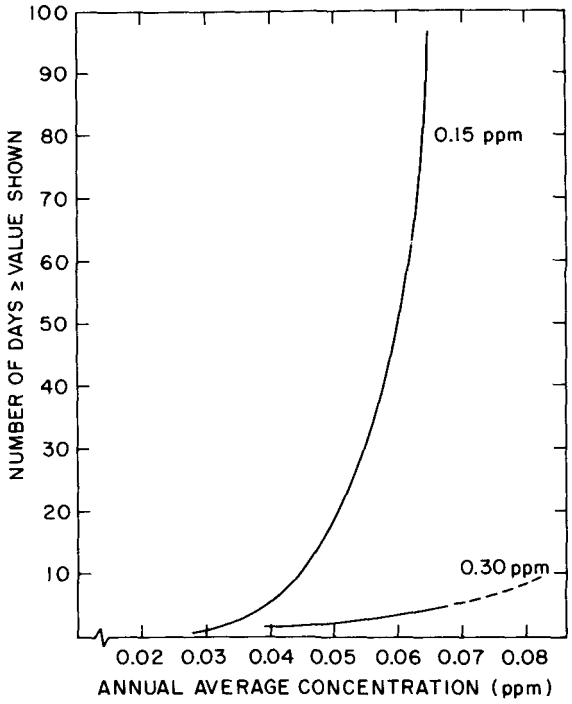


Figure 6. Expected number of days on which maximum 1-h NO_2 concentrations exceed 0.15 and 0.30 ppm associated with annual average concentrations. (Source: USEPA 1981b).

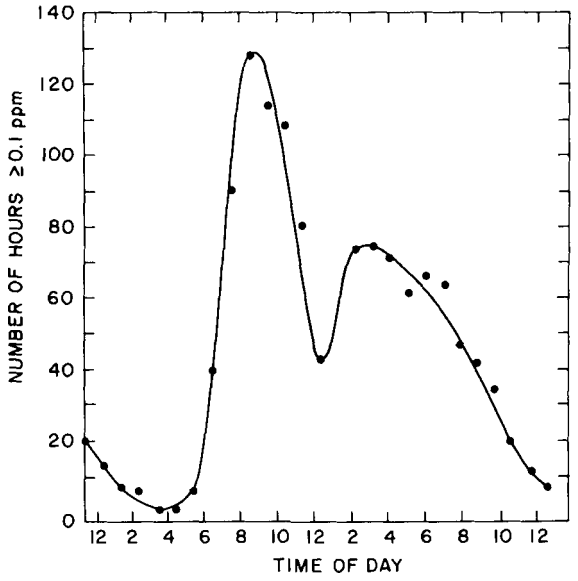
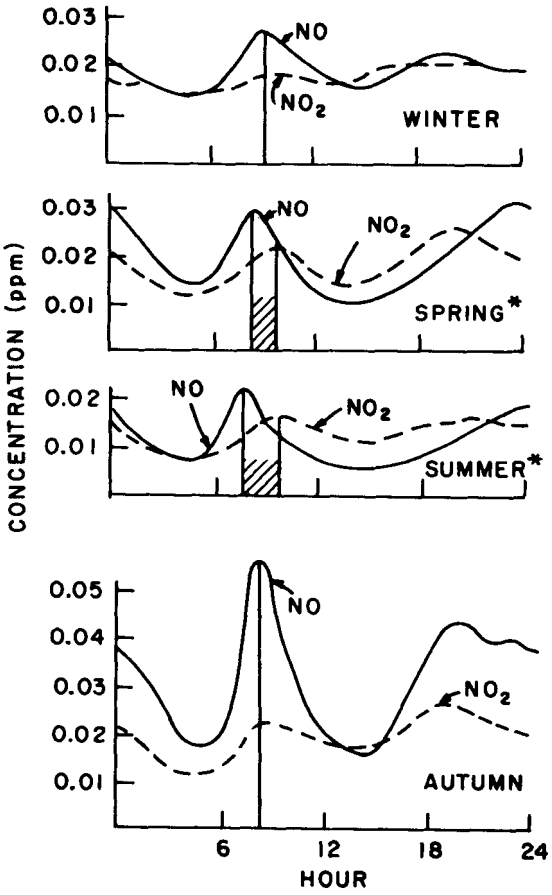


Figure 7. Idealized curve of high (>0.10) hourly NO_2 values by time-of-day (data from eight Selected cities). (Source: USEPA 1981b Appendix B).



*Shaded areas represent a time shift in peaking concentrations due to increased photochemical conversion, of NO to NO_2.

Figure 8. Diurnal trends in nitric oxide and nitrogen dioxide concentrations in Delft (Source: Guicherit, 1975 in WHO, 1977).

difficulties; it overestimated NO_2 at low concentrations, underestimated them at high concentrations, and was found to be subject to "positive interference by nitric oxide" (USEPA, 1973). On Dec. 1, 1976, the chemiluminescence measurement technique was adopted as the reference method. Unfortunately, most of the epidemiology of NO_2 relied on the Jacobs-Hochheiser method, and therefore,

> "...most of the existing data base on urban ambient nitrate concentrations must be considered to be of doubtful validity. Since positive artifact formation has been shown to be associated with conversion of ambient NO_2 and/or nitric acid (HNO_3) to nitrates and since sulfuric acid aerosol has been implicated in the removal of nitrate, data from certain background may be validated in special cases where it can be shown that concentrations of these species were sufficiently low during the period of interest." (USEPA, 1979 p. 7-7).

The manual Saltzman procedure, while not commonly used for establishing compliance with regulation, has been frequently used satisfactorly in a number of studies of the health effects of NO_2.

3.4 Uncertainty in Measurement Techniques

Consideration of differences and the errors associated with each method must be made when using measurement data to estimate potential health effect from NO_2. Errors associated with measurement of ambient NO_2 contribute to t uncertainty associated with assessing the health effects of these substances Three types of errors in measurement contribute to this problem: 1) interference is introduced by the presence of multiple airborne compounds which may produce responses indistinguishable from the pollutant under consideration (i.e., ozone); 2) systematic over or underestimation errors ar biases which are associated with a particular measurement technique; and

3) random errors refer to variations introduced by unknown factors, variability in operational parameters, and/or sensitivity of the measurement method and may statistically be expressed as a standard deviation. Only methods that measure NO_2 are addressed here; a discussion of other nitrogenous compound measurement techniques and associated errors may be found in USEPA, 1979.

Accuracy and precision of the chemiluminescent, sodium arsenate, TGS-ANSA and continuous colorimetric (Lyshkow modification) procedures for NO_2 measurements were investigated by Purdue et al., 1975. The average intramethod difference between any of the methods was never greater than 7.5 $\mu g/m^3$ NO_2, with the worst case being the continuous colorimetric where a small bias of 7.5 $\mu g/m^3$ was noted. Intermethod comparisons were highly correlated in all cases. No intercomparison difference could be attributed to interference from concentration of nitric oxide, carbon dioxide, ozone, total sulfur, or total suspended particulate matter. However significant negative interference in the continuous colorimetric method was found at NO_2 concentrations of 75 and 100 $\mu g/m^3$ in the presence of ozone at concentrations of 353 and 667 $\mu g/m^3$ but not at concentrations of 100 $\mu g/m^3$. Interference from NO concentrations up to 302 $\mu g/m^3$ in the sodium arsenite procedure was not found as had been expected. EPA also initiated a study to determine the reliability of various NO_2 analytic methods in common use obtained by collaborative testing. Results are shown in Table 3.

4. POPULATION EXPOSURE

Exposure to nitrogenous compounds occurs indoors as well as outdoors. Indoor exposure in domestic settings may result from one or multiple sources

Table 3
Summary of Reliability of NO_2 Analytical Methods in Common Use as Obtained by Collaborative Testing

Method	Range of NO_2 Concentrations Used in Test	Bias (Average for All Tests)[a]	Standard Deviation (Average for All Tests)[a]	Practical Lower Detection Limit ($\mu g/m^3$)	Comments
Chemiluminescence (Reference Method)	80-300	-8 $\mu g/m^3$ or -5%	14%	$\leq$22	One collaborator had very large biases, and another had unstable biases. For most collaborators (8 out of 10), however, the bias was small and well balanced.
Sodium Arsenite (Equivalent Method)	50-300	6.2 $\mu g/m^3$ or ~3%	11 $\mu g/m^3$	$\leq$ 9	Measurement errors were essentially uniform for all collaborators, although some dependence on NO_2 level was noted. 8 of 10 collaborators exhibited a uniform percent bias over all NO_2 levels tested.
TGS-ANSA (Equivalent Method)	50-300	9.5 $\mu g/m^3$ or ~-5%	11.6 $\mu g/m^3$ or	$\leq$15	Errors were essentially uniform for all collaborators. The biases shown were nearly independent of NO_2 level for range tested.
Griess-Saltzman (Continuous Colorimetric with dynamic calibration; both variants cited in 7.2.2.1)	90-370	16.1 $\mu g/m^3$[b]	32.7 $\mu g/m^3$	$\leq$19	Although overall results are reasonably accurate, method may produce quite inaccurate readings in an unpredictable fashion. About half of the collaborators did achieve fairly stable results. Subjectively, then, the method will produce reliable results in some hands.

[a]Depends in detail upon NO_2 concentration.
[b]Depends significantly on laboratory performing test.
(Source: USEPA, 1979.)

such as gas cooking stoves, certain types of home heating systems, kerosene area heaters, and cigarette smoking. Industries which use nitrogenous substances as well as those involving combustion processes may also expose individuals occupationally to a number of NO_x compounds. Outdoor exposures are affected by season changes, energy consumption variations, solar radiation, wind, and other atmospheric conditions. Indoor exposures may be expected to be less variable; but there are peaking exposures at various times during the day for certain individuals (i.e., children, individuals engaged in cooking, etc.). Large urban centers, particularly urban cores, have in general higher population exposure patterns than do smaller cities and rural areas. However, it should be noted that high exposures to NO_x may occur in relatively unpolluted areas when peaking ambient concentrations are

strongly correlated with human activities that produce nitrogenous compounds (e.g. individuals applying fertilizer or welding).

Few attempts to calculate exposure estimates are reported. A model was used in Los Angeles to estimate population exposure to NO_2 as a percentage of time the California Ambient Air Quality Standard was exceeded (470 $\mu g/m^3$ or 0.25 ppm for 1-h averages). The model calculated exposure estimates for "average" persons in the Los Angeles basin and attempted to address the effect of a non-static population by incorporating into the methodological framework daily migration patterns between work and residence (see Table 4).

Nationwide estimates of NO_2 exposure have also been reported. These estimates assume that the entire population of any county in the country is potentially at risk to the second highest 1-h NO_2 concentration reported for that area, "provided the monitoring station was located specifically to monitor population exposure." Results are given in Table 5.

Table 4
Regionwide Impact of Weekday-Weekend Phenomena on Population Exposure to Nitrogen Dioxide: Days and Hours Exceeding the California Ambient Air Quality Standard

Time Period	Percent of Days Exceeded[a]	Percent of Hours Exceeded[a]
All time	3.7 (3.8)	0.46 (0.50)
Weekday	4.4 (4.5)	0.57 (0.63)
Weekend	2.1 (2.1)	0.18 (0.18)
Weekday/Weekend Difference	+2.3 (+2.4)	+0.39 (+0.45)

[a]Percentages in parentheses computed based on the mobile population assumption.
(Source: USEPA 1979, p. 8-80).

These relatively crude and unsophisticated estimates should not be construed to represent actual or realistic estimates of population exposure to NO_2.

Table 5
U.S. Population at Risk to Various 1974 NO_2 Hourly Ambient Concentrations[a]

County Count	1974 Second Highest 1-h NO_2 Concentration ($\mu g/m^3$)	Total 1970 Population Potentially at Risk	% Monitored Population Potentially at Risk
68	250	41,837,864	57
24	500	21,341,617	29
6	750	10,106,698	14

[a]Computed from data in Freedman, S.J., E. Lewis-Heise, J.D. Wilson, and A.V. Hardy, Jr. Population at Risk to Various Air Pollution Exposures: Data Base "POPATRISK." EPA-600/1-78-051. U.S. Environmental Protection Agency, Research Triangle Park, North Carolina. June 1978. This data base is maintained at the Statistics and Data Management Office, Health Effects Research Laboratory, U.S. Environmental Protection Agency, Research Triangle Park, North Carolina 27711.
(Source: USEPA 1979).

5. HEALTH EFFECTS OF NO_x

5.1 Mechanisms of NO_2 Toxicity

While NO_2 alone among the oxides of nitrogen is specified in the primary National Ambient Air Quality Standard, other members of this family of air pollutants (enumerated in 2.1) are also potentially hazardous to health.[4] This report deals mainly with health effects of NO_2, which has received the most attention in biomedical research. A list of recent authoritative reviews is contained in the references.

The effects of NO_2 may be attributed to several mechanisms:

- Oxidation of unsaturated fatty acids, including lecithin, a major constituent of biological membranes, to produce stable free radicals.[5] In turn, the free radicals may:
  a. Impair biochemical and functional properties of cell frared spectromembranes.
  b. Alter structural proteins such as elastin and collagen; as a consequence, the mechanical behavior and structural integrity of the lung may be impaired. The functional and structural consequences of these reactions are generallydelayed in appearance; they may be slowly or only partially reversible.
  c. React with hemoglobin to produce methemoglobin; the latter is ineffective as a carrier of oxygen.[6]
- Formation of highly ionized acid in aqueous solutions in the respiratory tract, which probably contributes importantly to the acute irritant effects attributed to NO_2.
- NO_2 may also form nitrosamines in aqueous solution which have high carcinogenic potential.[7]

5.2 Animal and in Vitro Research

Studies of intact animals and isolated tissues have provided information on the cells, subcellular components, and biochemical systems that are vulnerable to low concentrations of NO_x (principally NO_2); on the functional and clinical consequences of such vulnerability; and on the importance of different patterns of exposure (e.g., acute, subacute, chronic, intermittent high concentrations imposed on backgrounds of low

concentrations) in determining the severity and persistence[8] of any adverse effects that may occur. The respiratory system is the principal although not exclusive target of NO_x inhalation; systemic effects may also be noted. A brief capitulation of these findings follows:

5.2.1 Structural Effects.

a. Airways: The entire length of the tracheobronchial system is subject to irritation and toxicity (implying biochemical or structural injury) from NO_2, depending on the dose.

- The cilia may undergo damage culminating in sloughing, thereby impairing mucociliary clearance.
- The "tight junctions" of contiguous columnar epithelial cells may be weakened or disrupted, with two consequences: an increased likelihood that particulate matter will penetrate epithelial and subepithelial tissues, thereby intensifying exposure; and an increase in the accessibility of subepithelial nerve endings to nonspecific irritant stimuli. The implication of the latter is considered in the section on clincial research.
- Mast cells may be disrupted, leading to a release of histamine-like substances that increase bronchomotor tone. The result is an increase in airway flow resistance[9] and work of breathing; disturbances in the distribution of ventilation and in gas-exchange between alveoli and blood may also follow.

b. Junction of Airways and Parenchyma: Perhaps the most sensitive, critical site in the respiratory system subject to damage from NO is the terminal portion of the bronchiolar tree and the adjacent

proximal alveoli.[10] The structural effects associated with both acute and chronic exposure are likely to be greatest at or near thi junction. Bronchiolar -- or small airway -- damage is considered to be a forerunner in the development of chronic obstructive lung disease.

c. Parenchyma: At least three distinct alveolar cell types appear vulnerable to the effects of relatively low concentrations of NO_2. Two of these, the epithelial Type I cell and capillary endothelial cell, are fixed tissue cells. The third, or alveolar macrophage, is motile. Injury and death of these cells is attended in rapid sequence by increased mitosis in stem (parent) cells and replacement. The Type II alveolar cell (which produces surfactant) is the stem cell for the Type I cell.

- Damage to the endothelial cell increases capillary permeability and may lead to edema, defined as an abnormal increase in extravascular fluid. In the lung, edema may involve both the interstitium and alveolar air spaces. Clinically severe lung edema has been seen following accidental occupational exposure to high concentrations (on the order of 45 ppm) of NO_2. A less severe, early stage of edema would be confined to the interstitium. The transudate of plasma protein, observed with exposure of guinea pigs to 0.4 ppm NO_2 (Sherwin and Carlson, 1973), may be viewed as an early manifestation of a process that culminates in massive edema if the insult is severe enough.

- Type I cells constitute the alveolar wall: their damage or destruction may lead to changes in alveolar dimensions (generally enlargement or "overdistension" of the alveoli) and loss of gas-diffusing surface. Alveolar enlargement was produced in rats after 2 years of continuous exposure to 2 ppm NO_2 (Freeman et al., 1968) and in mice by 3 to 12 months of exposure to 0.5 ppm NO_2 (Blair et al., 1969); the extent of the change in the latter experiment was time dependent.
- Damage to the alveolar macrophage may impede phagocytosis, slow intracellular killing of microbes, and delay the clearance of foreign material from alveoli. One significant consequence of these effects is reduction in resistance to infection. An additional likely consequence of injury to all three cell types is increase in the amount of particulate matter that penetrates the alveolar-capillary barrier.

d. Interstitium: The interstitium is a liquid matrix for cells, extracellular metabolites, and structural elements. NO_2 may cause inflammation and edema of this matrix. If exposure is severe or prolonged, there may be changes in the chemical and physical properties of elastin and collagen and, ultimately, fibrosis and distortion of adjacent structures. These effects contribute to the emphysema-like changes that may develop in animals exposed chronically to NO_2.[11]

5.2.2 Functional Effects.

a. Lung function: See Clinical Research (section 5.3).

b. Resistance to infection: The capacity of the respiratory system to ward off infection depends on integration among mucociliary clearance (essentially a mechanical function), phagocytosis (involving mechanical and biochemical functions), and immunological responses (operating both intra- and extracellularly).

- The effects of concentrations of NO_2 below 5 ppm on ciliary beat-rate, measured in vitro, or mucociliary clearance, measured in vivo, are unknown. Six weeks of exposure to 6 ppm NO_2 were observed to cause a decrease in mucociliary transport rate that is reversible within 1 week after the end of exposure (Giordano and Morrow, 1972).
- There have been a number of investigations of the effects of NO_2 on the structure and function of alveolar macrophages. Structural damage to the cells produced by continuous exposure (5 days weekly for 21 weeks or more) in vivo of mice to 0.5 ppm, interspersed with 1-h peaks of 2 ppm.
- Mortality rates after exposure to NO_2 and an infectious agent have been examined in rodents and monkeys. For a fixed dosage (7 ppm hours), high concentrations were more effective than prolonged exposure in increasing mortality rate (Gardner et al., 1977). At a specified concentration, mortality rate increased with duration of exposure: Approximately 30 days were required for 0.5 ppm NO_2 to increase mortality rate in mice exposed to Streptococcus pyogenes. Continuous exposure was more effective than discontinuous exposure (7 hours/day) in raising mortality rate

over periods of time that vary with the level of NO_2; at a concentration of 1.5 ppm NO_2, this difference persists about 3 weeks. One may conclude that fluctuating levels of NO_2, as in community air, may prove ultimately as toxic as sustained levels of the gas. Dose-response data are shown in Table 6, and Figures 9 and 10.

- The immunological response to NO_2, as with other biological systems, appears to be time and dose dependent (Holt et al., 1979). Lower concentrations and shorter intervals of exposure may stimulate immunological responses, while more severe or prolonged exposures may act as depressants. The immunological response, as measured by changes in number and chemical properties of lymphocytes, is more prominent in the lymph nodes of the lung than in distant organs such as the spleen. (Note, however, that there is a systemic component to this effect.) The clinical implications of these findings are less clear than are the mortality studies employing NO_2 and infectious aerosols.

5.2.3 Mutagenesis and Carcinogenesis

NO_2 is not mutagenic. However, it may react with other pollutants to form mutagens or to convert indirect-acting mutagens[12] to direct mutagens. An example of the former is the reaction of NO_2 with benzo(a)pyrene to produce hydroxybenzo(a)pyrene plus 1,3,-, and 6-introbenzo(a)pyrenes; an example of the latter is its reaction with pyrelene, a nonmutagen, to form 3-nitropyrelene, a potent mutagen. To date, the effect of NO_2 on the potency

Table 6
Nitrogen Dioxide Effects on the Antibacterial Defenses of the Murine Lung*

NO_2 Concentration (ppm.)	Percent Viable S. aureus Remaining at 4 Hours	
	Control	Exposed
1.9 ± 0.3	22.0 ± 4.8	23.7 ± 4.7
3.8 ± 0.5	12.7 ± 1.7	16.4 ± 1.7
7.0 ± 0.3	11.9 ± 2.2	19.0 ± 1.9*
9.2 ± 0.6	8.7 ± 0.4	22.3 ± 2.9*
14.8 ± 0.3	18.4 ± 3.6	68.5 ± 12.5*

*Adapted from Goldstein, et al. 1973.

of polycyclic aromatic hydrocarbons such as benzo(a)pyrene has not been tested in intact animals.

5.3 Clinical Research

Controlled exposures of human volunteers to NO_x have been confined to periods lasting up to several hours, administered once or on several successive days. Such studies cast little light on the role of NO_x in the pathogenesis of chronic disease. Functional and biochemical recovery tends to be rapid, and it is not known whether repeated ambient exposures of this type act cumulatively or predispose the lung to permanent damage. Instead, these studies are useful in describing short-term, reversible effects that may aggravate preexisting functional disorders (primarily cardiopulmonary) or reduce the resistance of the respiratory system to infection. Their focus has been primarily on the following:

- The effects of low concentrations of NO_2, nitrate aerosols, or nitric acid upon maximal ventilatory performance,[13] respiratory mechanics,[14] distribution of ventilation,[15] gas exchange,[16] and

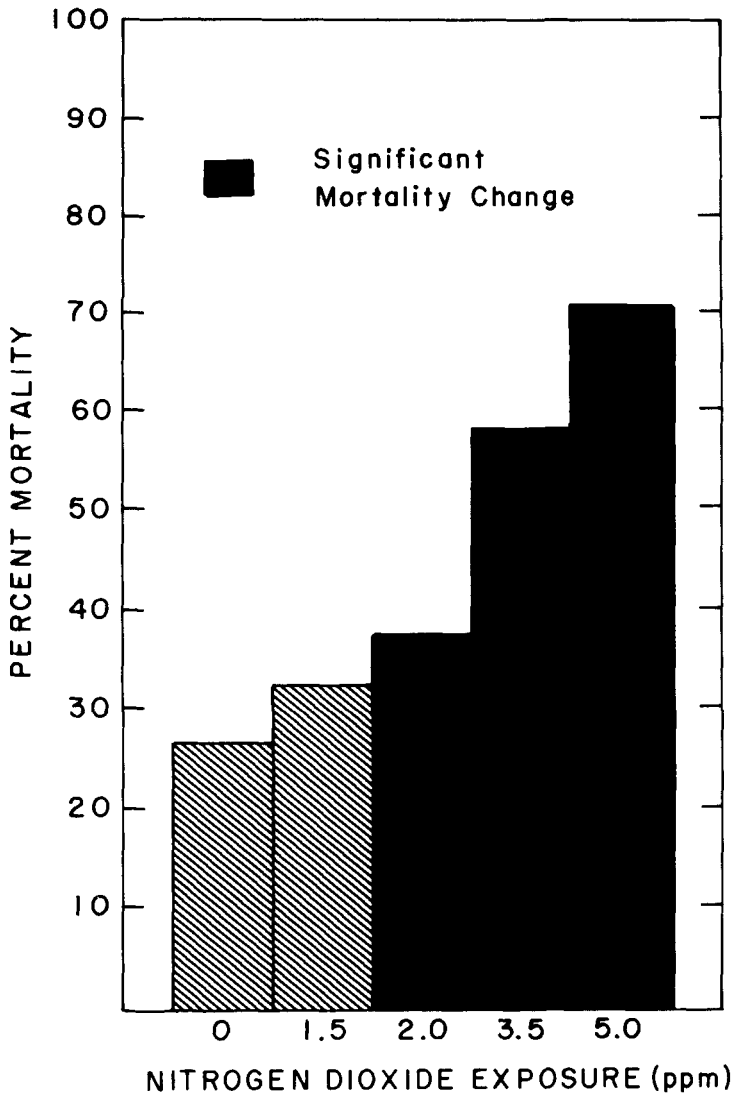


Figure 9. Mortality in mice exposed for three hours to varying concentrations of NO_2 prior to aerogenic infection with Streptococcus pyogenes. Adapted from Ehrlich et al., 1977.

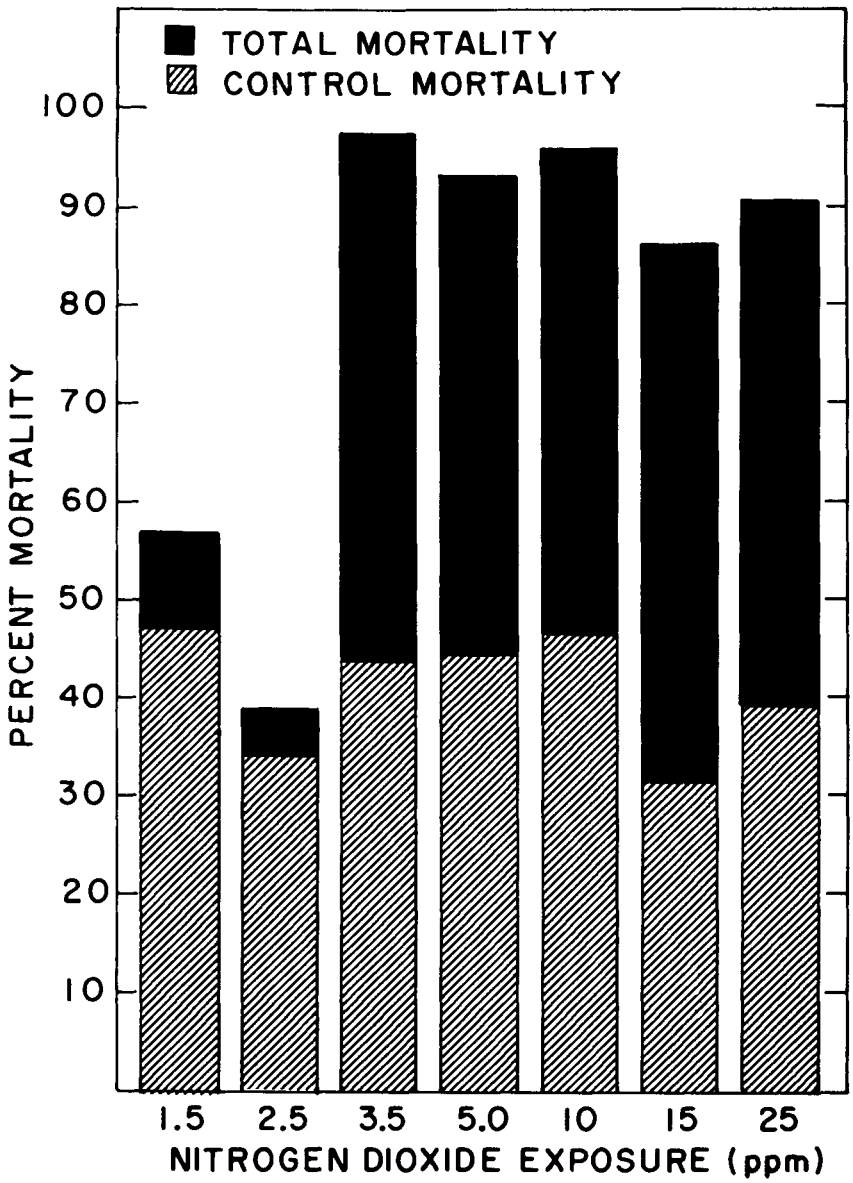


Figure 10. Mortality in mice exposed for two hours to varying concentrations of NO_2 prior to aerogenic infection with Klebsiella pneumoniae. Adapted from Ehrlich, 1966.

diffusing capacity.[17] The subjects were healthy adults and patients with asthma or bronchitis. Exposures were carried out with the subjects at rest or exercising. In general, functional impairment was not observed in healthy subjects or patients with bronchitis at or below 1.5 ppm NO_2; some asthmatics have experienced symptoms of irritation during exposure to 0.5 ppm (Kerr et al., 1979). $NaNO_3$ and NH_4NO_3 aerosols (submicrometric) in concentrations up to 3 mg/m^3 have produced no functional changes in normal or asthmatic adults. Similarly, in one study of 5 healthy adults, 1.5 ppm HNO_3 administered for 10 minutes had no functional effect (Sackner and Ford, 1981).[18]

- The effects of low concentrations of NO_2 (0.1 ppm or higher) on airway reactivity, particularly among asthmatics.

  Hyper-reactivity of the airways to non-specific environmental stress such as cold air or air pollutants is characteristic of asthma. It is thought to underly the episodic bronchospasm that defines asthma clinically. Concentrations of NO_2 as low as 0.1 ppm may aggravate this hyper-reactive state in some asthmatics as measured subsequently by a heightened response to a bronchoconstrictive aerosol, carbachol (Orehek et al., 1976; see Figure 11). One postulated mechanism for this effect is damage to the tight junctions of the epithelial layer in the airways, as noted earlier. In this same study, which remains controversial, 13 of the 20 asthmatics also exhibited bronchoconstriction (increased R_{AW}) immediately after exposure to 0.1 ppm NO_2. In

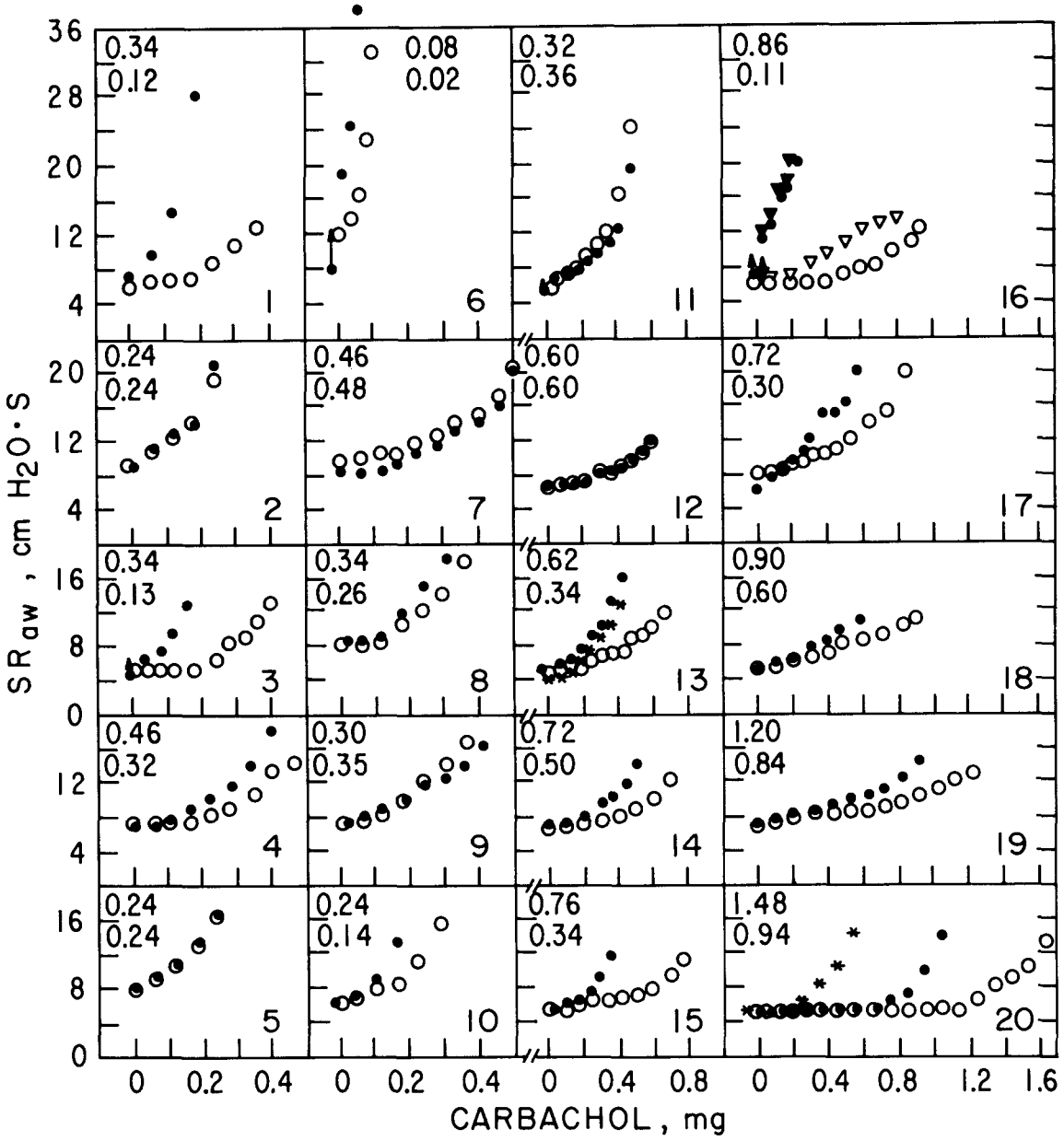


Figure 11. Effect of 1-h exposure to NO_2 on the dose-response curves established in 20 asthmatic patients obtained by using cumulative doses of inhaled carbachol aerosol (abscissa) and measuring SR_{aw} (ordinate) as an index of the response. Open symbols, control determinations; closed symbols, determinations after exposure of NO_2; circles and triangles, 0.1 ppm NO_2; stars, 0.2 ppm NO_2. Each panel shows the result for one individual. The number in the right lower corner identifies the subject. The two numbers in the left upper corner indicate the dose of carbachol, calculated from the curves and expressed in milligrams, which causes a 100% increase of initial SR_{aw} (D_{100}); the upper number refers to control D_{100}; the number below refers to D_{100} after exposure to 0.1 ppm NO_2. The arrows indicate the changes in basal SR_{aw} value observed in some subjects after exposure to NO_2. (SR_{aw} = specific airway flow resistance.) (Source: Orehek et al., 1976.)

healthy adults, airway reactivity was reported to have been unaffected by acute exposure to 2.5 and 5 ppm NO_2 in one study (Beil and Ulmer, 1976), but was increased in another study by only 0.05 ppm NO_2 (vonNieding et al., 1977). There is a clear need for confirmatory work on the possible effects of NO_2 on airway reactivity in asthmatic and healthy subjects. The possibility that NO_2-induced changes in airway reactivity may heighten the response to other irritants (for example, aldehydes or sulfuric acid) is also worthy of study.

5.4 Epidemiological Research

Children have been a principal source of information about the hazard posed by NO_2 to health.[19] The nature of the evidence has been twofold:

- Changes in incidence of acute respiratory illness, presumed to be infectious in origin (Melia et al., 1977; Speizer et al., 1980; see Table 5 and Figure 12). This evidence dovetails closely with experimental results in animals showing that NO_2 reduces resistance to infection.
- Changes in pulmonary function (Speizer et al., 1980; see Table 7 and Figure 13). It remains uncertain whether these effects constitute significant risk factors that affect the growth and development of the lung[20] or contribute to chronic lung disease in adulthood.

Most reliable information incriminating NO_2 appears to have been obtained in studies of indoor air pollution, involving homes with unvented gas-cooking stoves, rather than of community air pollution. Perhaps the most exquisitively sensitive individuals, in terms of showing an increase in acute

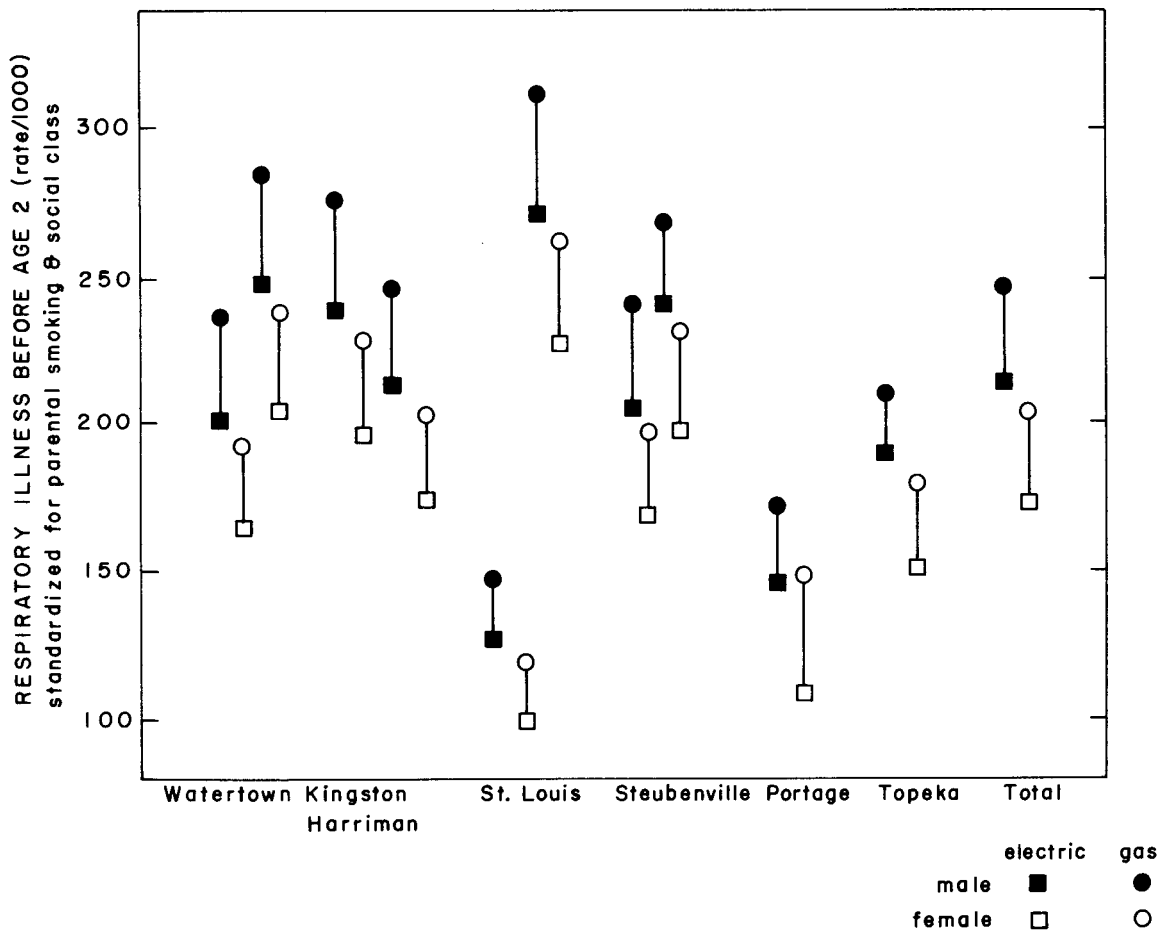


Figure 12. Respiratory illness before age 2, standardized for parental smoking and social class by cohorts in children 6 to 10 years old. Males and females separately by cohort and gas or electric stoves. (Source: Speizer et al., 1980).

Table 7
Indoor and Outdoor 24-h Levels of NO_2 in 6 U.S. Cities
(May 1977 to April 1978)

	Days (No.)	Home Cooking Units: Electric (No.)	Home Cooking Units: Gas (No.)	Geometric Mean Level of NO_2 ($\mu g/m^3$): Outdoor: Electric	Geometric Mean Level of NO_2 ($\mu g/m^3$): Outdoor: Gas	Geometric Mean Level of NO_2 ($\mu g/m^3$): Indoor: Electric	Geometric Mean Level of NO_2 ($\mu g/m^3$): Indoor: Gas	95 Percentile Measured Level of NO_2 ($\mu g/m^3$): Outdoor: Electric	95 Percentile Measured Level of NO_2 ($\mu g/m^3$): Outdoor: Gas	95 Percentile Measured Level of NO_2 ($\mu g/m^3$): Indoor: Electric	95 Percentile Measured Level of NO_2 ($\mu g/m^3$): Indoor: Gas
Portage[a]	50	8	3	7.2 (1.55)	5.9 (1.10)	3.6 (2.13)	14.7 (1.02)	31.8	25.4	17.6	39.3
Topeka	57	6	1	17.5 (1.25)	16.2 -	19.4 (1.26)	31.6 -	42.4	40.7	41.6	73.6
Kingston-Harriman	56	8	-	17.2 (1.25)	- -	10.9 (1.43)	- -	38.4	-	29.8	-
St. Louis	58	3	6	33.0 (1.17)	37.3 (1.14)	17.1 (2.01)	40.8 (1.42)	64.3	70.9	63.3	79.3
Steubenville	61	2	3	35.7 (1.00)	33.3 (1.35)	21.9 (2.59)	27.4 (2.24)	62.9	87.8	74.5	102.9
Watertown	59	2	5	49.1	49.2	41.43	54.3	101.6	106.3	95.2	116.3

[a]Based on 10-month sample. Federal 24-H standard = 100 $\mu g/m^3$. Numbers in parentheses are geometric standard deviations. (Source: Speizer et al., 1980.)

respiratory illness, are infants under two years of age; adults appear to be less vulnerable than children (Keller et al., 1979).

Early studies of Chattanooga school children (Shy et al., 1970; Pearlman et al., 1971), which suggested an association between ambient concentrations of NO_2 and altered pulmonary function and acute respiratory illness, are now considered inadequate for establishing dose-response relations owing to their reliance on faulty air monitoring (see above). In a study of Tokyo school children (Kagawa and Toyama, 1975), negative correlations were found between several pollutants--NO_2, NO, SO_2, hydrocarbons, and particulate matter--and Vmax at 50% and 25% of FVC.[21] The approximate range of hourly concentrations of NO_2 at the time the tests were performed was 40 to 360 $\mu g/m^3$ (0.02 to 0.19 ppm). To what extent NO_2 and NO among these several pollutants may have been responsible for the observed changes in pulmonary function is conjectural.

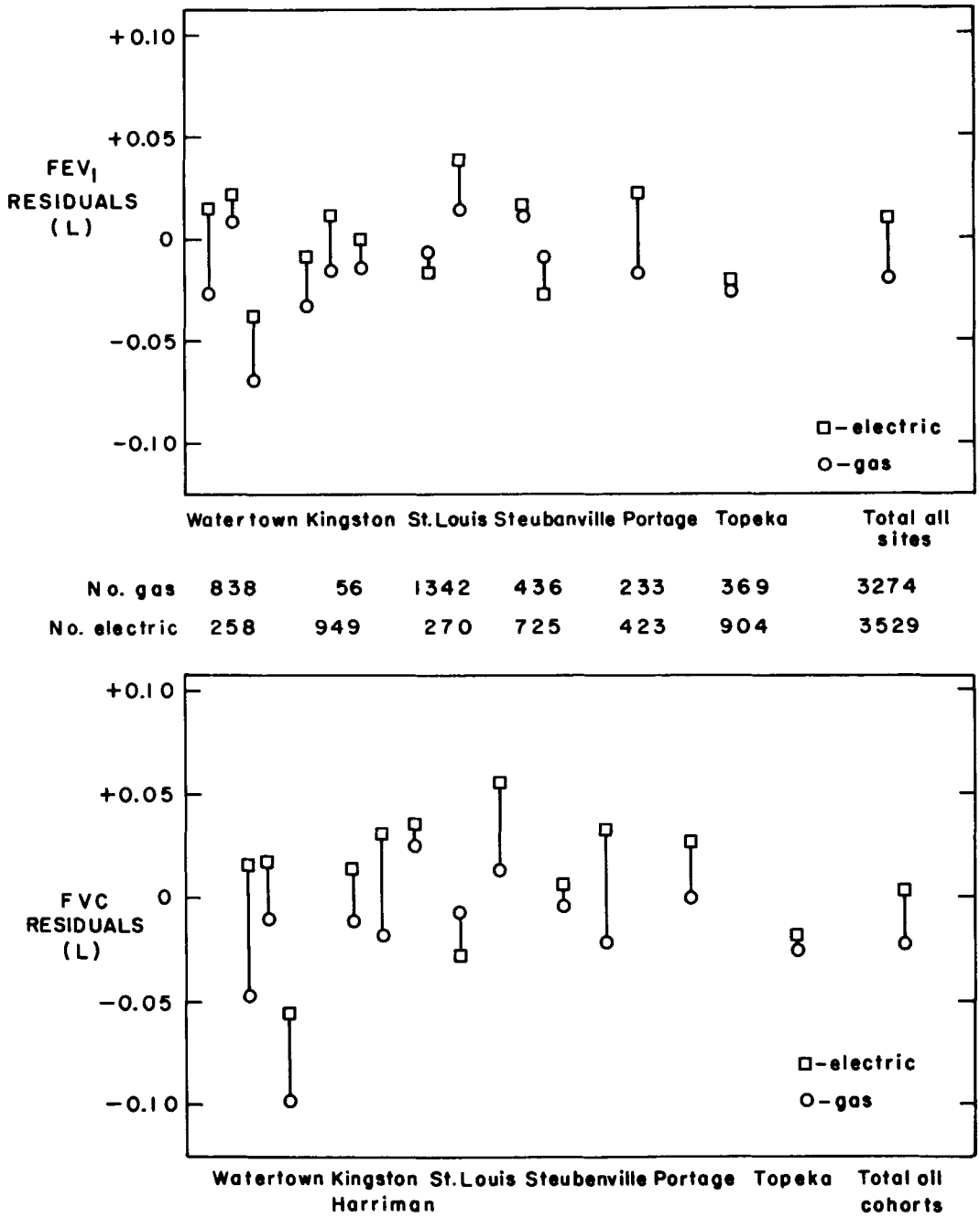


Figure 13. Forced expiratory volume in 1s and forced vital capacity residuals by cohort and gas and electric stoves in children 6 to 10 yrs old. (Numbers under the FEV values are the same for FVC values.) (Source: Speizer et al., 1980).

6. SUMMARY

Nitrogen oxides are a family of air pollutants. For health, NO_2 is the principal but not the sole pollutant of concern. NO as well as secondary by-products (HNO_3, NO_4, nitrate aerosols, nitrosamines) produced from photochemical transformations in the atmosphere have the potential for damaging health; they are also implicated in acid deposition. NO and NO_2 may pose an indirect risk to health by contributing to the formation of non-nitrogenous airborne pollutants (i.e., ozone, sulfates etc.) or through the release of toxic trace metals in drinking water, a possible consequence of acid deposition.

Principal sources of NO_x include tall-stack fossil-fuel-fired electric utilities and certain industries, as well as exhaust from transportation vehicles. The former was identified as being chiefly responsible for long-range transport of NO_x while the latter, largely though not exclusively, are responsible for ground-level concentrations in densely populated areas. Ground-level sources may also contribute to acid deposition.

Numerous methods exist today for measuring NO_x compounds, most of which are complex and expensive; others used in the past have proved to be unreliable. Consequently, while past concentration data should be viewed with reservation, there is general agreement that NO_x pollutants are increasing and that their contribution to urban pollution and acid deposition is becoming more important.

The most convincing arguments that oxides of nitrogen -- NO_2 in particular -- may pose a real risk to health are the following:

- There may be an immediate short-term effect in the form of an increase in airway reactivity (sensitivity). This heightened reactivity may render the airways more vulnerable to nonspecific, irritant stimuli, such as other pollutants and cold or dry air. The effect is likely to follow from episodic peaking concentrations of ambient NO_2. Persons with preexisting hyper-reactive airways due to asthma or to current or recent acute respiratory infections are likely to be most susceptible. Aggravation of the underlying hyper-reactive state by NO_2 could conceivably increase absenteeism and visits to medical clinics, hospitals, or physicians.
- There is more substantial epidemiological evidence for an increased incidence of acute respiratory infections, especially in infants and children, resulting from exposure to NO_2 that is possibly augmented by NO. This effect is more likely to follow repeated exposures. For this report we have not reviewed the possible associations between acute respiratory infections in childhood and the probability either that chronic lung disease will develop in adolescence and adulthood or that the growth and development of the lung will be retarded.
- There is equally strong epidemiological evidence that NO_2 (possibly augmented by NO) impairs lung function in children. The effect is also likely to follow repeated exposures. Were observed changes such as reductions in static lung volumes (FVC) or dynamic lung volumes ($FEV_{1.0}$) to persist into adulthood, they could

reasonably be regarded as indicative of foreshortened lung growth or, alternatively, accelerated aging of the lung. We intend to review evidence regarding the persistence of such functional changes beyond childhood.

- In the future we will attempt to develop exposure-effects relations for these putative effects of NO_x on populations that are at risk by reason of either increased susceptibility or environmental exposure.

FOOTNOTES

1. Designated Thermal NO_x or Fuel NO_x. The first is formed by the fixation of nitrogen in air, the second by the oxidation of nitrogen in the fuel. Thermal NO_x is strongly temperature dependent while Fuel NO_x depends on the availability of oxygen and is relatively insensitive to temperature. About 95% of the NO_x is emitted as NO and the remainder as NO_2 for most combustive equipment.

2. Gaseous species include: nitrous, nitric and peroxynitric acids; both alkyl nitrite and nitrate; peroxyacylnitrate (PAN) and peroxyalkyl nitrate, Particulate nitrites and nitrates may also be formed.

3. This material is based on discussions with Drs. S. Schwartz and L. Newman.

4. The occupational standards permit 8-hour excposures to 5 ppm NO_2 and 25 ppm NO. The assumption is that NO_2 is 5 times more toxic than NO. This is not borne out in studies of methemoglobin production (Case et al., 1979) or of immunological effects (Holt, 1979). Emphysamatous-like changes are also reported to be more severe in mice following exposure to NO (Holt et al., 1979), and equivalent for the two gases in rates (Azoulay et al., 1978).

5. Lipid peroxidation and its consequences are mitigated by anti-oxidants. Thus, vitamin E (alpha-tocopherol) reduces NO_2 toxicity experimentally (Fletcher and Tappel, 1973).

6. Methemoglobin and carboxyhemoglobin act additively to reduce the oxygen-carrying capacity of the blood. It is of interest that methemoglobin has a longer removal half-time than carboxyhemoglobin (Case et al., 1979).

7. The formation of nitrosamines is pH dependent and is likely to proceed at a faster rate in the strongly acid gastric juice than in the slightly alkaline liquid lining of the lung.

8. In one study (Gillespie and Berry, 1980), beagles were exposed to NO_2 and NO for 68 months. Functional deterioration was more pronounced in the two years following exposure than in equivalent periods during the exposure. The post-exposure functional changes included previous dose-related (NO_2) changes in residual volume (RV), total lung capacity (TLC), lung compliance measured quasi-statically (Cst), and carbon monoxide diffusing capacity (DLCO). Such changes were not observed in control animals; they are consistent with accelerated aging of the lung and possibly of progression to emphysema. The two NO_x regimes were as follows: 0.26 + 0.62 mg/m^3 NO_2 + 2.05 + 0.26 mg/m^3 NO, and 1.21 + 0.22 mg/m^3 NO_2 + 0.31 + 0.08 mg/m^3 NO.

FOOTNOTES (continued)

9. There is evidence that NO_2-induced bronchoconstriction in man is mediated humerally (vonNieding and Wagner, 1979); by contrast, SO_2-induced bronchoconstriction is mediated reflexly.

10. The distal end of the bronchiolar system in man and other primates consists of several generations of respiratory (alveolated) bronchioles. Rodents have few or no respiratory bronchioles; their terminal (nonalveolated) bronchioles lead directly into air spaces.

11. Centrilobular emphysema has been reported in rodents exposed chronically to NO_2 (Freeman et al., 1972).

12. Indirect mutagens require chemical transformation to become effective.

13. Forced vital capacity (FVC), forced expiratory volume in 1 second ($FEV_{1.0}$), and maximum flow-volume curves (Vmax/V).

14. Compliance, dynamic or static (Cdyn, Cst) flow resistance of the lung or airways (R_L, R_{AW}).

15. Nitrogen wash-out curves based on single or multiple breaths.

16. Alveolar-arterial oxygen gradients ($(A-a)PO_2$).

17. CO diffusing capacity, measured during a single breath or steady state breathing (D_{LCO}).

18. The recommended threshold limit value (TLV) for occupational settings, based on an 8-h time-weighted average sample, is 2 ppm.

19. There may be several reasons for increased vulnerability in childhood and infancy, including anatomic and biochemical immaturity, greater airway reactivity, and greater minute ventilation, corrected for body weight, compared to adults. Early life is characterized by obligatory oral breathing, which by-passes the more effective nasal scrubbing surface. Finally, children are less subject to confounding factors such as smoking and occupational exposure; tobacco smoke contains significant amounts of NO_2 and NO as do some occupational settings.

20. Evolution of respiratory bronchioles and the appearance of new alveoli may continue into early adolescence.

21. Suggestive of narrowing of small airways.

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