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GUIDES FOR SHORT-TERM EXPOSURES OF THE PUBLIC TO AIR POLLUTANTS. 1. GUIDE FOR OXIDES OF NITROGEN

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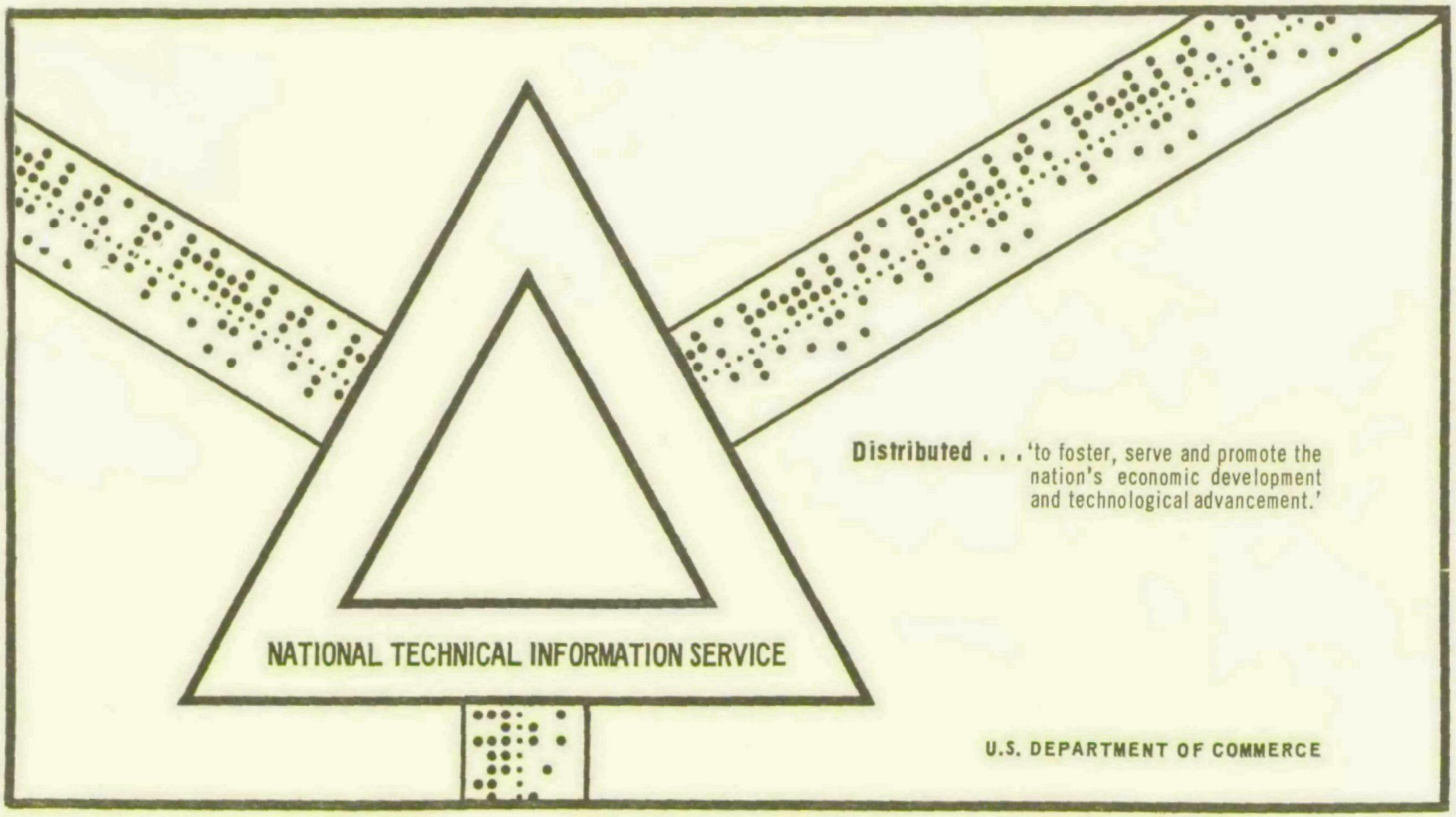

Guides for Short-Term Exposures of the Public to Air Pollutants

I. Guide for Oxides of Nitrogen

by

The Committee on Toxicology

of the

National Academy of Sciences - National Research Council

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INTRODUCTION

The Air Pollution Control Office (APCO) has focused its initial concern on long-term exposures of the public to air pollutants. It is also concerned with occasional circumstances in which the public may be exposed briefly to relatively high concentrations of air pollutants. For example, steam boilers usually have short bursts of high emissions when the tubes are blown or when the fires are started up. Similarly, batch processes in the metallurgical industry produce pulses of effluent. The testing and launching of rockets result in intermittent releases of exhaust products. Rapidly changing meteorological conditions may result in short periods of high concentration of stack effluents in localized areas. Accidental release of chemicals sometimes occur in industry or during transport, and may lead to public exposure.

Recognizing these occasional peak additions to the ambient exposure of the public, APCO has requested the assistance of the Committee on Toxicology of the National Academy of Sciences-National Research Council in providing Guides for Short-Term Exposure Limits for Air Pollutants.

In preparing these guides, the Committee utilized the principles described in the NAS-NRC document entitled "Basis for Establishing Short-Term Inhalation Exposure Limits of the Public to Atmospheric Pollutants."

In studying the literature sources for this document, primary consideration was given to material dealing with brief, intermittent exposure to the nitrogen oxides.

In this Guide the effects of oxides of nitrogen on domestic animals, fish and wildlife, vegetation, and materials are not included. Analytical and air-monitoring procedures are also excluded. These subjects are discussed thoroughly in "Air Quality Criteria for Nitrogen Oxides," to be published early in 1971 by APCO.

Nitrogen Oxides

The nitrogen oxides of possible concern for air pollution purposes are nitric oxide (NO), nitrogen dioxide (NO_2), and nitrogen pentoxide (N_2O_5). Other oxides are known to exist but are of no concern because of their relatively low toxicity or absence from ambient air.

I. Nitric Oxide

Nitric oxide is found to be of little concern as an air pollutant since it is not an irritant gas (69) and is one-fifth as acutely toxic as NO_2 (5). In the presence of oxygen, NO is converted to NO_2 at a rate described by the equation:

$$d[NO_2]/dt = k[O_2][NO]^2$$

where $[NO_2]$, $[O_2]$, and [NO] represent the concentrations of the various gases in moles/cc, t is time, and k is a rate constant for temperature having a value at 20° C of 14.8×10^{-3} m^6 $moles^{-2}$ sec^{-1} (69).

Westberg, et al.(78) have reported that the conversion of NO to NO_2 is influenced by the presence of other pollutants, such as carbon monoxide and ozone, which might also be present in the air.

II. Nitrogen Pentoxide

Conflicting reports on the toxicity of N_2O_5 are present in the literature (3). Diggle and Gage (1-2) report the toxic effects of N_2O_5 to be qualitatively similar to those of ozone (O_3) although N_2O_5 is about three times as active as a pulmonary irritant as the latter. They classify N_2O_5 as a lung irritant with a potency of the same order as that of phosgene, and claim that the increase in the toxicity of an O_3 atmosphere brought about by the presence of oxides of nitrogen can be attributed to N_2O_5 present.

On the other hand, Byers and Saltzman, as reported in Stern (5), found N_2O_5 to possess an LC_{50} for albino mice of approximately 75 ppm (~ 10X that of O_3). No time of exposure was given. Stokinger (6) in preliminary studies showed that no deaths occurred in rodents upon exposure to at least 42 ppm of N_2O_5. Stokinger expresses the opinion that the claims of Diggle and Gage are not supported by their data. Byers and Saltzman (in 5) attribute the greater apparent toxicity found by Diggle and Gage to their method of administering N_2O_5 as a solution in chloroform.

The kinetics of the decomposition as well as the synthesis of N_2O_5 have been extensively studied under various conditions of temperature, pressure, radiant energy, concentration, precursors, and co-contaminants (72-76). It becomes evident that N_2O_5 as well as NO react in air to form a variety of products, the principal one being NO_2. Because of its relative prevalence, stability, and toxicity, NO_2 is the oxide of nitrogen of primary concern as an air pollutant.

III. Nitrogen Dioxide

From the available scientific literature on the physiologic and toxicologic effects of gaseous nitrogen dioxide (NO_2), it is apparent that NO_2 as a freely diffusible gas has the potential of causing adverse effects on human health and well-being. These are summarized in Table C - Appendix II. It should be noted that the data in the literature from which Table C was derived were based on exposures of "normal" healthy human volunteers. Similarly, most of the ancillary information on animals given in the Summary, and in Tables A and B of Appendix I, is from healthy animals. The population to which this Guide is to be applied has a wide range of states of health and well-being.

Factors Affecting Human Response to NO_2

Among the most critical items to be recognized in deriving limiting exposure values for the Guides are the factors and conditions that can modify and significantly alter human response to NO_2. The five most important (temperature, predisposing disease, heredity, age, and interactions with other environmental pollutants) are discussed below.

Temperature

A commonly overlooked and disregarded condition that greatly modifies the response to NO_2 is temperature. Experimental animals exposed to the additional stress of a hot or cold environment were more susceptible to the effects of NO_2. A minimum toxic effect was observed at 15° C, with an increased effect above and below this temperature (11) and (12).

Predisposing Disease

Individuals who have asthma, chronic bronchitis, emphysema, and other forms of chronic obstructive pulmonary disease form the groups which will be most severely affected by short-term exposure to high levels of nitrogen oxides. Current evidence indicates that normal healthy individuals will not be adversely affected by short-term exposures that produce effects among these more susceptible groups (62)

Hereditary Predisposition

In addition to the well-known hypersusceptibility of the hereditary asthmatic, a recently discovered association between the hereditary defect, serum antitrypsin deficiency, and familial pulmonary emphysema indicates the presence of another group of individuals with increased susceptibility to the irritant gas NO_2 (59). Individuals hemizygous for the defect get along without respiratory difficulties until coming in contact with respiratory irritants. Excessive exposures of those persons could initiate early pulmonary emphysema. Although the frequency of hemizygotes is not known nationwide in the U. S. A., pedigrees obtained on small groups in a few states indicate a hemizygote frequency between 2. 3 and 5 percent, a not insignificant frequency (59).

Age

It is a recognized medical fact that responses to environmental influences among the very young and the very old are frequently different from those in the in-between age groups - both in degree of sensitivity and in the character of the response. Moreover, the bases for these differing responses among the very young are not the same as those among the very old. In the very young, increased susceptibility results from either as yet undeveloped metabolizing enzyme systems or from incompletely developed cellular structures. The age-susceptibility factor for the young might be estimated to be between 5 and 10, on the basis of increased neonatal deaths in mice exposed to ozone (37) (66).

Factors associated with old age, such as differences in physical activity and pre-existing cardio-respiratory disabilities, will tend to modify the susceptibility of various age groups to pollutants such as NO_2. Extremely little information exists from which to estimate these factors.

Interactions Affecting Response to Exposure

The information on NO_2 interactions is incomplete and therefore must be considered only suggestive for the purposes of Short-Term Guide development. Each instance must be evaluated individually in this respect, as to whether extrapolation of interactions to ambient pollutant levels is scientifically sound.

a) Physicochemical Interaction. It would appear from two independently derived sets of data that the acute toxic response to NO_2 may be considerably reduced when NO_2 is inhaled for short periods (20 minutes to an hour), either concomitantly with or subsequent to, solid or liquid particulates (65)(66). It proved to be immaterial whether the concomitant aerosol was a solid or liquid particulate (clays, siliceous

materials, or oils); the mice survived longer when exposed to the NO_2-particulate mixture than to NO_2 alone, indicating an interaction with reduced toxic effect. Similarly, oil mists of respirable particle size greatly reduced the toxicity of NO_2 inhaled by rats, provided exposure to the oils preceded exposure to NO_2 by a few hours (66).

On the other hand, Boren (77) has reported that inhalation of carbon particles followed by intermittent NO_2 exposure resulted in lung destruction not observed with NO_2 exposure alone. Exposure to NO_2 followed by inhalation of carbon particles resulted in a decreased macrophage response contrary to the response normally observed after exposure to carbon particles alone.

b) Physiologic Interactions. Almost complete protection from the lethal effects of inhaled NO_2 was afforded mice exposed to mixtures of NO_2 and either hydrogen sulfide or mercaptans in four-hour exposures (5). Although the level at which the different sulfur compounds negated the effects of NO_2 varied with the compound, some of them, including hydrogen sulfide, counteracted the NO_2 effects at molar ratios far below equivalency (1.5 ppm H_2S present with 82 ppm NO_2). This suggests that relatively minute concentrations of these sulfur compounds, if coexisting in the air, can negate the physiologic effects of relatively much higher concentrations of NO_2.

Microbial Interactions

In contrast to the beneficial physicochemical and physiologic interactions to be expected from certain air pollutants coexisting with NO_2, bacterial infection of the lung after NO_2 exposure would appear to have a distinctly adverse effect (23)(27)(68). A two-hour exposure to NO_2 at 3.5 ppm increased the mortality of mice infected with Klebsiella pneumoniae. Daily exposures for two months was required to produce the same increase in mortality at 0.5 ppm. In considering the relevance of these results to human responses, it is important to note that both the exposed and control mice had overwhelming bacterial exposures. Forty-seven percent of the infected controls not exposed to NO_2 died in the first instance, the 3.5 ppm level, and 68 percent of the controls in the second instance, the 0.5 ppm level. It is difficult to reconcile the preceding work of Ehrlich and Coffin with the observations of Wagner and his co-workers (21). The latter exposed rats from a colony having spontaneous pulmonary infections for 18 months at 5 ppm NO_2. They found no difference between the exposed and control groups in degree of pulmonary infection, body weight gain, or oxygen consumption.

Summary of NO_2 Toxicity

Nitrogen dioxide has been reported to produce the following physiological actions:

1) It acts as a deep-lung irritant at high concentrations (several hundred ppm for a few minutes), which may result in pulmonary edema or lead to bronchiolitis fibrosa obliterans (59).

2) At levels of 10 ppm or more, the acute effects of NO_2 are additive with the effects of O_3. At levels below 10 ppm, NO_2 mixed exposures with ozone had less than additive effects (6). The effects of NO_2 with other gaseous irritants (SO_2, aldehydes, etc.) are reported to be additive (39) (38).

3) Lipoperoxidation was observed in rats exposed to NO_2 at 1 ppm for four hours. The maximum effect was observed 24-48 hours post-exposure (22).

4) Alterations in mast-cell morphology were observed in rat lung tissue after exposure at 1 ppm for one hour or 0.5 ppm for four hours. These alterations were reversible within 24-27 hours (47).

5) NO_2 may increase the retention of particulates including microbials by its ciliostatic effect. A concentration of 100 ppm inhibited mucociliary activity within five minutes (16).

6) Chronic exposure of experimental animals to NO_2 at a concentration of 0.5 ppm followed by a pulmonary challenge with high levels of infectious organisms (K. pneumoniae) resulted in an increased mortality (24). However, no such interaction of NO_2 and bacteria was observed in "naturally" infected rat lungs, suggesting synergism only at extreme levels of bacterial challenge (21).

7) It was observed that the rate of tumor induction in mice having spontaneous pulmonary tumors might have been accelerated from daily exposures to NO_2 at 5 ppm. Final tumor size and mortality were not affected (5).

Concluding Remarks

From knowledge of the irritant action of NO_2 on the respiratory tract it is predictable that the individuals most susceptible to NO_2 action are not the healthy, but those predisposed by age, heredity, and preexisting respiratory disease. These are the persons that predictably will respond most sensitively at concentrations to which healthy individuals would be unresponsive.

The effects of NO_2 are, within limits, reversible. The extent of recovery seems to be a function of a) the degree of exposure, b) the length of the interval between exposures, and c) the health and/or age of the exposed individual.

Most experimental studies have been done with healthy animals. The effects of NO_2 exposure on animals with anemia or preexisting pulmonary disease (emphysema, chronic bronchitis, asthma, etc.) should be evaluated to provide a firmer basis for establishing short-term guides.

As a consequence of the lack of this critical information, this Guide, which has been developed for the protection of human health and well-being from short-term exposure to oxides of nitrogen, is only a "best-judgment" estimate. Hence, the following limiting values proposed should be regarded as highly tentative and subject to revision as more appropriate and pertinent information is developed.

Guide Values for Short-Term Exposure of the Public to Oxides of Nitrogen

Short-Term Public Limits (STPL's)

10 min	1 ppm
30 min	1 ppm
60 min	1 ppm
5 hr/day, 3-4 days/mo	0.5 ppm
1 hr/day/yr	1 ppm

Short-term Public Limits of 1 ppm for 10 min or less, 30 min or 60 min represent "ceiling" values not to be exceeded. Any fluctuations in concentration must not exceed a maximum allowable concentration of 1 ppm. The limit of 0.5 ppm for 5 hr/day, 3-4 days/mo represent an average value for the 5-hr period as long as the "ceiling" limit of 1 ppm is not exceeded.

These limits are suggested in order to protect asthmatics, believed to be the most susceptible segment of the population.

It has been demonstrated that persons with chronic bronchitis (a condition believed to render those so afflicted particularly susceptible to the effects of air pollutants) did not exhibit any significant pulmonary effect when exposed to NO_2 at concentrations of 1.5 ppm for 15 minutes.

Public Emergency Limits (PEL's)

10 min	5 ppm
30 min	3 ppm
60 min	2 ppm

Although under optimal conditions the short-term public limits require that there be no adverse health effects, public emergency limits envision the possibility of some temporary discomfort, provided the effect is reversible, and that no injury results from it. With respect to NO_2 exposure, it should be acceptable for an asthmatic to develop some reversible and temporary bronchial constriction provided this does not exceed the degree or duration that might occur as the result of moderate exercise, deep breathing, exposure to inert particles, or exposure to other gases or dusts normally present in the air. Such attacks do not

produce residual damage. They often are induced as a part of diagnostic procedures aimed at testing the reactivity of the tracheobronchial tree to common respiratory irritants to which the individual normally may be exposed (70). For this reason, short-term limit values of 5 ppm NO_2- 10 min or less, 3 ppm - 30 min, and 2 ppm - 60 min are recommended as Public Emergency Limits (PEL's). These levels are less than threshold limit values in industry, approximately 1/5 the Emergency Exposure Limits (EEL's) (79) for an industrial population, in keeping with the concept that an asthmatic might react with slight discomfort to 1/5 the concentration tolerated with slight discomfort by a normal person. The limitation is designed to avoid enhancing susceptibility of the lungs to K. pneumoniae rather than to completely avoid temporary, reversible bronchial constriction in asthmatics. As further evidence, one asthmatic, and a pilocarpinized normal volunteer, exposed at 5 ppm NO_2 for five min, were stated to have shown no effect (Table C of Appendix II).

Appendix I

Exposure of Experimental Animals to Nitrogen Dioxide

Mortality studies dealing with the toxic effects of inhalation of NO_2 have indicated that the primary cause of death in acute exposure is pulmonary edema (7) (8). In studies dealing with pulmonary changes in animals exposed to NO_2, Hine et al. have demonstrated that sub-lethal exposure to this gas may result in pulmonary edema, bronchiolitis, and bronchial pneumonia. Using a variety of experimental animals and exposing them at 5 to 250 ppm for 5 to 1,440 minutes, they observed responses ranging from recovery with permanent lung changes to acute asphyxia (9) (71). Methemoglobin is frequently seen in the blood of exposed animals; however, it rapidly disappears from the blood after exposure and may be absent 1-2 hours after exposure (7).

Several factors may influence the mortality due to NO_2 exposure. Hine et al. (9) and Gray et al. (11) found that exposures to relatively high concentrations of NO_2 for short periods of time had a greater lethal effect than longer exposures to lower concentrations. (Higher concentrations were more lethal than lower concentrations at an equivalent dose as expressed by multiplying the concentration by the time, CT).

Tolerance to subsequent exposures of NO_2 after previous exposure to low levels of ozone or NO_2 has been reported (13) (14). It has been found that exposure of animals at low levels of one irritant gas will produce tolerance to a subsequent higher exposure of another irritant. This is referred to as cross tolerance. Gases that are relatively insoluble in tissue fluids more readily reach the bronchioli and alveoli, which seem to be the site of action causing cross tolerance. Several gases besides NO_2 produce tolerance to themselves and cross tolerance with each other. This tolerance, however, is evidently not acquired without adverse effects. Dillman (15) reports that animals that had become tolerant to NO_2 had a 50 percent increase in the thickness of the "air-blood barrier" (all tissue elements situated between an alveolus and its capillary bed).

Physiological, Biochemical, and Morphological Changes

Depression of mucociliary activity in excised rabbit trachea was noted after exposure to NO_2, 100 ppm for 5 minutes or 60 ppm for 10 minutes (16). Changes in mucus velocity in the guinea pig respiratory tree (17) and bronchial mucus hypersecretion (18) have also been reported in acute and sub-acute exposure of experimental animals.

Murphy et al. (19) exposed guinea pigs at 5.2 to 13.0 ppm NO_2 for two or four hours and measured the respiratory function before, during,

and after exposure. In these animals the tidal volume decreased while the respiratory rate increased, the net effect being the maintenance of a nearly constant minute ventilation. In the same experiment, mice exposed at 3.7 to 7.7 ppm NO_2 for six hours exhibited a depressed running activity.

Biochemical studies by Buckley and Balchum (20) were carried out on guinea pigs at two exposure levels, a repeated acute exposure to 40 ppm NO_2 for a total of four hours, and a chronic exposure at 15 ppm continuously for 10 weeks. The animals were sacrificed at the end of the exposure periods and the lactate dehydrogenase (LDH) and aldolase activity in organ homogenates were measured. In the continuous exposure aldolase was elevated in all tissues and LDH was elevated in lung, liver, and kidney. In the short-term exposure the LDH was elevated in serum, liver, and kidney and aldolase was elevated in serum, liver, kidney, and spleen.

Wagner et al. (21) exposed dogs, rabbits, guinea pigs, rats, hamsters, and mice for 5 hours/day, 5 days/week for periods up to 18 months at 1, 5, and 25 ppm NO_2. The authors found no statistically significant differences in body weight, hematology, and biochemistry (alkaline phosphatase and Mg-activtated phosphatase) between control and experimental animals. They did find, however, a possible tumorigenic accelerating capacity for NO_2 in a strain of mice susceptible to spontaneous tumors.

Thomas et al. (22) exposed a group of rats to 1 ppm NO_2 for four hours and observed an absorption spectrum indicative of peroxidized polyenolic fatty acids in the lung lipids of these animals. These peroxidative changes were at a maximum between 24 and 48 hours post-exposure.

Other rats were exposed at the same concentration (1 ppm for four hours) but for six consecutive days. Analysis of lung lipids "suggests that the longer exposure to NO_2 produced more extensive and probably cumulative oxidative changes than the single four-hour exposure did."

In another series of experiments Thomas et al. (47) exposed rats briefly to low levels (0.5 - 1.0 ppm) of NO_2 and examined these animals for changes in the lung mast cells. In animals exposed to 0.5 ppm NO_2 for four hours or 1.0 ppm NO_2 for one hour and immediately sacrificed, there was a reduction in the number of mast cells and those remaining showed "evidence of loss of cytoplasmic granules, disorientation and rupture." Histological examination of animals sacrificed 24 or 27 hours post-exposure revealed no evidence of ruptured cells, indicating that these observed effects were reversible.

The nature of "healing" in the rat-lung post-exposure to NO_2 was examined in some detail by Freeman et al. (48). They exposed rats for 1, 4, 10, 16, or 20 weeks continuously to 15 ± 2 ppm NO_2. After exposure animals from each group were allowed to recover for 0, 8, 20, and 52 weeks. Control rats of the same age were maintained. Lung weights increased relative to those of the control animals at two different times. The first increase was shortly after exposure and was believed to be associated with hypertrophy of bronchiolar and adjacent alveolar epithelium. After several weeks the lung weights of the exposed animals tended toward normal, but a second increase in lung weight occurred in aging, exposed animals. This second increase over normal was consistent with an increase of collagen and elastic tissue in the alveolar parenchyma. Freeman et al. observed that, in the longer-exposed animals, the morphology of the lung tissue never did return to "normal."

In a series of several experiments Freeman et al. and Haydon, et al. (49-54) exposed rats continuously to NO_2 at concentrations ranging from 0.8 ppm to 100 ppm. The exposure times ranged from several days up to three years (or the "natural" lifespan of the rats).

Exposure to 100 ppm and 50 ppm continuously caused relatively rapid pulmonary damage in the rats; those exposed at 100 ppm began to die within 24 hours (symptoms and pathology were pulmonary edema, vascular congestion and focal hemorrhage), while those exposed at 50 ppm exhibited similar symptoms but not until several weeks after the exposure was initiated. Table A summarizes the exposures and findings of several of Freeman's experiments.

The emphasis of this work done by Freeman and his colleagues is on morphological changes in the lung tissue, and unfortunately almost no biochemical parameters were measured in the control and experimental animals.

Kleinerman and Cowdrey (55) exposed 48 hamsters nearly continuously (20-23 hr/day) for 10 weeks to concentrations of NO_2 ranging from 45 to 55 ppm. Over one-third (approximately 16) of the exposed animals died within three days of initiation of the exposure but only two additional deaths were observed during the final eight weeks of exposure.

After the 10-week exposure, several of the surviving animals were sacrificed immediately while the remainder were sacrificed four weeks later.

Those animals immediately sacrificed displayed "extensive epithelial hyperplasia and hypertrophy" in the region of the terminal and respiratory bronchioles and proximal alveolar ducts. Ciliated cells were rare. Inflammatory cells (neutrophils and macrophages) were found in the

respiratory bronchioles and alveolar ducts as well as in the peribronchial connective tissue. "A mild degree of pulmonary edema was observed in the alveolar structures throughout the lung."

In those animals sacrificed four weeks post-exposure, the authors observed a regression of inflammatory and hyperplastic components of the lesion as well as a lack of edema and tissue destruction. Lung volumes, significantly greater in the exposed animals immediately after exposure, tended to decrease, but had not returned to normal four weeks post-exposure. Right ventricular weight appeared significantly heavier than that of the control groups immediately after exposure, but there was no significant difference four weeks later.

An interesting statement made by the authors is that the animals were not observed to eat or drink to a significant degree during the 20-22 hours of exposure per day, yet there was no significant difference in body weight between the control and exposed groups at the end of the 10 weeks of exposure.

Kleinerman and Wright (56) exposed rats (150 ppm, 75-80 ppm, or 15-20 ppm), rabbits (200 ppm, 100 ppm, or 25 ppm), and guinea pigs (75-80 ppm or 15-20 ppm) to NO_2 for one two-hour period. They observed various responses ranging from death due to pulmonary edema to inflammation in animals exposed to a low dose. "Healing appeared to be practically complete by two weeks after the insult" in those animals surviving the initial challenge.

In a series of studies involving the "resistance of NO_2-exposed animals to Klebsiella pneumoniae, "Ehrlich (23-25) has reported an increased susceptibility to this bacterial infection in animals exposed to 3.5 ppm or higher NO_2 for two hours as well as animals exposed to 0.5 ppm NO_2 for 6 or 18 hr/day for six months.

Mice exposed to 0.5 ppm NO_2 6 hr/day for 3-12 months are reported as exhibiting indications of early bronchial inflammation with reduction of distal airway size and expansion of alveoli with signs of early focal emphysema (26). Under similar exposure conditions, a delay in bacterial clearance from the lungs was noted.

Henry et al. (57) used squirrel monkeys to demonstrate the decrease in resistance to bacterial and viral infection during chronic NO_2 exposure. Animals were exposed continuously to NO_2 at 5 ppm for two months and at 10 ppm for one month. The exposures to NO_2 were followed by challenge with K. pneumoniae (estimated dose = $4\text{-}9 \times 10^5$ organisms). Bacterial clearance was reduced in the NO_2-exposed animals and 3/11 of the exposed animals died after the bacterial challange while none of the controls (9 animals) died.

A total of 14 monkeys were challenged with influenza virus and six of these animals were then exposed to 10 ppm NO_2. Within three days all six of the animals had died while the eight controls all survived the challenge. One of three animals died five days after viral challenge and subsequent exposure to 5 ppm NO_2.

Balchum et al. (28) have observed a circulating substance or "antibody" in the serum of guinea pigs exposed to 5 ppm and 15 ppm NO_2 daily for up to 5-1/2 months. This "antibody" reacted in vitro with protein extracted from normal lung tissue. Titers of this antibody increased with increasing duration of exposure and increasing concentrations of NO_2. It was assumed that this substance was formed from the interaction of NO_2 and lung tissue in the exposed animals. No reports of human respiratory allergic responses to NO_2 exposure have been reported.

Table A

Continuous NO_2 Exposure
(From References 48-54)

0.8 ± 0.2 ppm NO_2 to 21 rats for 2-3 years	Sustained tachypnea. 20 percent over normal. Death was natural; histology unremarkable.
2 ± 1 ppm NO_2 to rats for 2-3 years	Bronchial cells enlarged, few cilia remaining. Indicative of "relative dormancy or restrained activity."
4 ppm NO_2 to rats for 16 weeks	Terminal bronchiolar epithelium was hypertrophic.
10 ± 1 ppm NO_2 (rats)	Animals began to die of respiratory failure after 16 months. Rats grew less, developed "air-containing" thoraces, and lungs were large and did not collapse under atmospheric pressure. Increased activity of goblet cells with much mucus, aggregates of macrophages with bits of proteinaceous debris. Alveolar ducts distended.
25 ppm NO_2 (rats)	All survived acute phase. Failed to gain weight normally. Deaths occurred about five months after exposure began. Rats allowed to die (not sacrificed) gained weight initially but lost up to 25 percent of their weight subsequently. Lungs were heavier and larger than those of controls. Hyperplasia and hypertrophy of epithelial cells with proliferation of connective tissue were observed. Vascular congestion and focal hemorrhage along with aggregates of macrophages were common. Respiratory rate up 2-3 fold.
50 ppm NO_2 (rats)	Two-thirds dead within two months. Remarks similar to 25 ppm.
100 ppm NO_2	Deaths (rats) began within 24 hours, pulmonary edema, vascular congestion with focal hemorrhage.

Table B

"Low" Level NO_2 Exposures

Exposure	Results Observed	Reference
0.5 ppm NO_2 6 hr/day for 3-12 mo	Early bronchial inflammation with reduction of distal airway size and expansion of alveoli with indications of early focal emphysema (mice).	(26)
0.5 ppm NO_2 for 6-18 hr /day for 6 mo	Increased susceptibility to K. pneumoniae (mice).	(23)
1 ppm NO_2 for 4 hr	Peroxidized polyenolic fatty acids in lung lipids. Max. at 24-48 hr post-exposure (rats).	(22)
1 ppm NO_2 for 4 hr/day for 6 days	Indication of cumulative changes as above (rats).	(22)
3.5 ppm NO_2 for 2 hr	Increased susceptibility to K. pneumoniae (mice).	(24)
5.2-13 ppm for 2-4 hr	Increased respiratory rate, decreased tidal volume (guinea pigs).	(19)
10 ppm NO_2 for 2 hr	Increased retention of K. pneumoniae; decreased minute volume (squirrel monkeys).	(27)
1 ppm, 5 ppm, 25 ppm NO_2 for 6 hr/day, 5 days/week for up to 18 mo	No effect different from controls with possible increase in lung tumors with 5 ppm and 25 ppm groups (rats, rabbits, dogs, guinea pigs, mice, and hamsters). No difference between control and experimental animals in spontaneous pulmonary disease.	(21)
5 ppm and 10 ppm NO_2	Increased susceptibility to K. penumoniae and influenza virus (squirrel monkeys).	(57)

Summary of Experimental Animal Exposures

It appears that there is some discrepancy relative to the chronic levels of NO_2 necessary to cause morphological as well as biochemical changes in the lungs of exposed animals. This discrepancy is probably due in part to 1) species and age variation in the experimental animals, 2) the biochemical parameters being measured as well as the relative importance placed on these parameters, 3) a certain degree of "tolerance" being exhibited by the animals. This tolerance, however, may be due to undesirable changes in the morphology of the lung, such as thickening of the alveolar walls and reduction of the rate of oxygen transfer, 4) other substances present in the atmosphere, 5) the duration of exposure as well as the time intervals between exposures.

Continuous 24-hour exposure, even to relatively low levels of NO_2, leads to greater toxicological effects than exposure at similar or even greater levels of NO_2 interrupted by inhalation of clean air. Even relatively brief interruptions of exposure seem to be beneficial in the prevention of mortality and/or morbidity.

NO_2 can increase the susceptibility of the exposed animal to other pulmonary problems, such as bacterial or viral infections and retention of inhaled particulates, either by its mucociliary effects or its deeper pulmonary effects. This synergistic effect with the viral or bacterial diseases has been seen at relatively low exposure levels and would seem to indicate the need for further investigation of NO_2 synergism with other chemical or bacterial pollutants.

Appendix II

Humans Exposed to Nitrogen Dioxide

The available experimental data on humans exposed to NO_2 are certainly not as extensive as data obtained on laboratory animals, but some work has been done with human volunteers.

Cooper and Tabershaw (10) have summarized some of the literature reports of effects of NO_2 on man, as shown in Table C. Tabershaw et al. (29) comment that, in spite of species differences, the qualitative responses of mammalian lung tissues are essentially similar and therefore many of the experimental findings with the lower animals are applicable to humans. They report the major site of action of NO_2 to be on the lower respiratory tract, the effects in the upper respiratory tract other than mild irritation being negligible.

The odor threshold to NO_2 is between 1 and 3 ppm, although nasal and eye irritation is not evident at this level. At 13 ppm, three out of eight volunteers complained of eye irritation, and seven out of eight complained of nasal irritation (10).

Reports of accidental exposures of humans to NO_2 are numerous, but the magnitude of exposure in most of these cases is not well documented and usually only estimated.

The clinical symptoms of acute inhalation of NO_2 by humans have been classified into three types (30): 1) Acute pulmonary edema developing after a latent period of up to 30 hours. 2) Acute symptoms (dyspnea, pulmonary edema, sweating) followed by a latent period sometimes lasting up to a month. These effects followed by progressive dyspnea, with severe cough and cyanosis. 3) Development of a chemical pneumonitis.

A classic example of human exposure to NO_2 is the Cleveland Clinic Disaster (31). Some of those exposed died almost immediately, possibly from the additive effects of several combustion gases (HCN, CO, NO_2, etc.). Other patients, who were practically free from any symptoms upon going into fresh air, later (6-48 hours) succumbed to acute attacks of dyspnea and cyanosis. Still others died days and even weeks later of pneumonia. These delayed responses were attributed to the heavy exposure of NO_2 arising from the combustion of cellulose nitrate x-ray film.

Norwood et al. (32) report a case of NO_2 poisoning in a welder exposed to about 90 ppm NO_2 for 40 minutes (total oxides of N was greater than 300 ppm). The welder experienced some shortness of breath and mild chest discomfort during the welding operation, which took place in

a confined space. The symptoms cleared up somewhat upon his returning to fresh air. Approximately eight hours later he experienced a gradual increase in difficulty in breathing, and 18 hours later a physical examination indicated a respiratory rate of 22-24, a vital capacity of 42 percent of predicted and moist rales. A chest x-ray revealed pulmonary congestion and edema. The patient was hospitalized for seven days and was diagnosed as normal 21 days later.

Milne (30) describes a case of NO_2 poisoning in a chemist who displayed the typical delayed response (12 hours post-exposure) after being exposed to an unknown level of NO_2. He was hospitalized with pulmonary edema and discharged from the hospital seven days later as "an apparent cure." Thirteen days later (20 days after the original exposure) the patient was rehospitalized with essentially the same symptoms, despite the fact that no further exposure of NO_2 took place. The second recovery was much slower and a transient diabetic state was observed and treated with insulin.

Kleinfeld (33) reports an exposure in which a chemist was exposed to an unknown level of NO_2 for four minutes. An 11-hour latent period was followed by the development of pulmonary edema and pneumonitis. Hospital treatment resulted in "recovery" within 15 days.

Seven men exposed to NO_2 in a mining accident were observed over a 14 month period (34). Two of these men had immediate symptoms with no latent period while the other five did not exhibit symptoms until 14 hours to four weeks later. Five patients recovered 7 to 14 months after the accident. Two of the men had previous histories of bronchitis. Their symptoms reportedly became worse after the NO_2 exposure and they are now "handicapped."

The fermentation of fresh silage can liberate NO_2 and exposure to this gas in silos produces an ailment commonly referred to as "silo-fillers disease." Lowry and Schuman (36) and Grayson (35) describe several cases, the symptoms of which are typical for acute NO_2 inhalation, i.e., initial irritation, variable latent period, and finally dyspnea, progressive weakness, etc.

Lowry estimates the following symptoms would be observed in humans exposed to varying concentrations of NO_2 for 30 minutes to an hour:

a) 500 or more ppm - acute pulmonary edema with death in less than two days.

b) 300-400 ppm - edema and bronchopneumonia fatal before 10 days.

c) 150-200 ppm - bronchiolitis obliterans with death in 3-5 weeks.

d) 50-100 ppm - bronchiolitis and focal pneumonitis with spontaneous recovery.

e) 10-40 ppm with prolonged exposure might cause pulmonary fibrosis and emphysema.

In a 24-week study involving the effects of community exposure to NO_2, Shy et al. (60-61) reported a lower three-quarter-second forced expiratory volume among second-grade children in an area defined as a "high-NO_2 area," as compared with a ventilatory performance of children in an area chosen as a "control area." However, neither the gradient of pollutant exposure nor the NO_2 concentrations on the day of ventilatory testing were related to the ventilatory performance.

As part of the same study, Shy et al. recorded an excess in respiratory-illness rate as reported by the subjects of the study in the "high-NO_2 area." The severity of illness, however, did not differ between the "high-NO_2" and the "control" areas, nor could a dose-response relationship be established for NO_2 exposure. Any effect attributed to NO_2 exposure in this study could be related only to long-term data since no correlation with short-term exposures could be demonstrated.

The acute effects of NO_2 on lung function and circulation of healthy subjects, as well as subjects with chronic bronchitis, were studied by von Nieding et al. (62). The concentrations of NO_2 ranged from 0.5 to 5.0 ppm and the length of exposure was 15 minutes. The parameters that were measured included the arterial O_2 and CO_2 partial pressures, arterial pH, end expiratory O_2 and CO_2 gas pressures, cardiac output, heart rate, stroke volume, systolic pressure in the pulmonary artery, mixed-venous O_2 and CO_2 partial pressures, and mixed venous pH. The parameters were measured before exposure, after 10 minutes of NO_2 inhalation, and 10 minutes after cessation of the 15-minute exposure.

Healthy subjects as well as those with chronic bronchitis reacted with a reduction in arterial O_2 partial pressure upon inhalation of NO_2 concentrations of 5 and 4 ppm. This was not observed when the subjects were exposed at 2 ppm or less.

Airway resistance, measured by means of a body plethysmograph, was determined in 63 subjects with chronic bronchitis who breathed air containing 0.5-5.0 ppm NO_2 for 15 minutes. A significant increase in

airway resistance was observed immediately after inhalation of NO_2 at concentrations greater than 1.5 ppm, but no significant effect was observed at exposure levels below this concentration.

The authors report that any effects which they observed to be due to the NO_2 exposure were reversed within 10 minutes after cessation of exposure in both the healthy subjects and those with chronic bronchitis.

Table C

Effects of NO_2 on Man (10)

ppm	Comment
0.05 (0.1 mg/cu m)	USSR: Maximum allowable concentrations - average during 24 hours
0.15 (0.3 mg/cu m)	USSR: Maximum allowable concentrations - single exposure
0.2	Calculated limit for space travel
0.5	Submarine maximum for 90-day dive
1 to 3	Odor threshold
2.0	Maximum allowable concentration for industry (USSR) as of 1959
5	Ceiling threshold limit value for occupational exposures (average for 8-hour day, 5 days per week)
	Exposure of one asthmatic and one pilocarpinized volunteer for 5 minutes, no effects noted
10	60-minute emergency exposure level for occupational exposure
10	Maximum permitted for one hour in submarine
10	Normal volunteer exposed for 60 minutes interpreted as not showing impairment of pulmonary function
13	8 volunteers; 3/8 had eye irritation; 7/8 nasal irritation; 4/8 pulmonary discomfort; 6/8 olfactory cognition; 2/8 CNS effects; all predominantly slight
20	Workers in HNO_3 recovery plants reputedly exposed to levels averaging up to 20 ppm for up to 18 months showed no ill effects

Appendix II (cont'd)

ppm	Comment
20	Emergency exposure limit for 30-minute exposure
25	Emergency exposure limit for 15-minute exposure
25	Human volunteers exposed for 5 minutes. Slight or moderate nasal discomfort in 5/7, pulmonary discomfort in 3/7, odor detected by 6/7. No consistent changes in expiratory reserve, vital capacity, or MBC
3-35	Workers exposed at 30-35 ppm to nitrous fumes over several years; had no ill effects
35	Emergency exposure limit for 5 minutes
50	7 human volunteers exposed for 1 minute; 3/7 had pulmonary discomfort and nasal irritation
64	Moderate irritation of larynx and increase in respiratory rate in volunteers
80	In 3 to 5 minutes volunteers got tightness of chest
100	Produced rapid, marked irritation of larynx and cough in volunteers
300-400	Few minutes' exposure will cause broncho-pneumonia and death
500	Few minutes' exposure will cause pulmonary edema

On the basis of these kinds of data, Cooper and Tabershaw recommend that "brief exposures of a general population should not exceed 3 ppm over a period of 1 hour." This is based on the possible potentiation of infections and on the odor thresholds.

Appendix III

NO_2 and Other Chemical Contaminants

Since NO_2 seldom is found as the single contaminant in the atmosphere, it is desirable to study the combined effects of several pollutants simultaneously. Bils and Romanovsky (37) exposed mice for three hours to a synthetic smog produced by illuminating a mixture of 8 ppm propylene, 2.8 ppm nitric oxide, and approximately 25 ppm carbon monoxide with ultraviolet lamps. The animals were sacrificed at intervals up to 24 hours post-exposure. The animals were ages 6 months, 8 months, 15 months, and 20 months (average life span < 2 years). It was reported that no significant change was found in the six-month-old exposed group. The eight-month-old animals sacrificed immediately after exposure exhibited a slight swelling of the epithelium and endothelium of the lungs. Delaying sacrifice for 18 hours "allowed" these changes to return to normal.

Some permanent changes seemed to take place in the 15-month-old exposed mice as well as in the 20-month-old mice. Delaying sacrifice in the older animals allowed further damage and revealed cell debris in the alveoli.

Buchberg et al. (38) produced a synthetic smog in order to study statistical relationships between various exhaust components, certain atmospheric reaction products, solar irradiation, and the eye-irritating quality of the polluted air. They conclude that:

1) Eye-irritants are produced by the photochemical oxidation of hydrocarbons - primarily the unsaturated ones.

2) Sunlight and nitrogen oxides are also necessary for the production of eye irritation.

These interactions are discussed in detail in "Air Quality Criteria for Hydrocarbons" and "Air Quality Criteria for Photochemical Oxidants," published by the National Air Pollution Control Administration as AP-64 and AP-63, respectively, in March 1970.

Abe et al. (39) studied the effects of NO_2 and a mixture of NO_2-SO_2 on the pulmonary function of five human volunteers. Each subject was exposed on separate occasions to 4-5 ppm NO_2, 5 ppm SO_2, or a mixture of 2.5 ppm NO_2 and 2.5 ppm SO_2, each for 10 minutes. In all subjects, inhalation of NO_2 caused an increase in both respiratory and expiratory flow resistance, with the maximum occurring at 30 minutes post-exposure. The author suggests that the net effect of the NO_2-SO_2 mixture is a simple additive response.

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16. Abstracts

Guides for brief, intermittent exposure to nitrogen oxides have been compiled and presented. The oxides of greatest concern are nitric oxide, nitrogen dioxide and nitrogen pentoxide. Toxicological data is presented on these. Factors and conditions that can, modify and significantly alter human response to nitrogen dioxide are discussed. The most important ones are; temperature, predisposing disease, heredity, age and, interactions to other environmental pollutants. Values for short term exposure to NO_x are tabulated. Experimental data on humans and laboratory animals exposed to NO_2 are included in the appendices.

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Air pollution
Nitrogen dioxide
Nitrogen oxide
Nitrogen pentoxide
Toxicology
Exposure
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