

Health effects of nitrogen dioxide and oxidants

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LINDVALL T. Health effects of nitrogen dioxide and oxidants. *Scand J Work Environ Health* 11 (1985): suppl 3, 10–28. The document is an evaluation of the health effects of nitrogen dioxide (NO₂) and ozone (O₃) intended to serve as a basis for establishing Swedish air quality standards. The specific effects of nitrogen dioxide and ozone are reviewed on the basis of published studies on animals, tissues and cells, controlled studies on humans, and epidemiologic studies. The focus is on the importance of the gases in relation to sensitive groups, outdoor-indoor exposure relationships, the question of short- or long-term limit values, and their combined effects with other pollutants. The minimum adverse effect level for human short-term exposure is assessed to be 900 µg/m³ for nitrogen dioxide and 200 µg/m³ for ozone; for sensitive persons these values should possibly be even lower. Large safety factors should be added to these values before they are used for air pollution control purposes.

Key terms: acute health effects, air quality standards, combined effects, health criteria document, limit values, outdoor-indoor exposure relationships, public health, pulmonary function effects, sensitive groups, sensory effects.

Introduction

In the field of air pollution the term “oxidants” refers to a number of compounds with oxidizing properties; these compounds often appear as a result of complex chemical reactions in the atmosphere under the influence of radiation from the sun. Typical examples of atmospheric oxidants are nitrogen dioxide (NO₂), ozone (O₃), and peroxyacynitrates (PAN).

This review concerns the acute health effects of nitrogen dioxide and ozone or, in some instances, the effects of complex air pollution when the concentrations of nitrogen dioxide or ozone are thought to have played a major role. Thus the discussion does not include the health effects of related compounds such as nitrates, nitrites, nitrogen acids, ammonia, nitroso compounds, or the peroxyacynitrates. Chronic effects such as cancer are not discussed.

Occurrence of nitrogen dioxide

Oxides of nitrogen (NO_x) are formed chiefly during the combustion of fuels, for example, in the engines of motor vehicles and power stations. They are also emitted by plants manufacturing nitric acid and explosives, and they are formed in thundery weather. Indoor air may be contaminated by nitrogen oxides through tobacco smoking and the use of gas heating and cooking appliances. Practically all nitrogen oxides deriving from combustion processes are discharged as nitrogen monoxide (NO) and gradually converted to nitrogen dioxide in the atmosphere. At high con-

centrations of the oxides the proportion of nitrogen monoxide is also high, whereas at low concentrations it is the dioxide that is the main component. How rapidly the conversion to nitrogen dioxide takes place and what influence the external conditions exert are unclear. Together with atmospheric oxygen and ultraviolet radiation, nitrogen dioxide participates in a series of reactions that ultimately lead to the formation of photochemical smog. By these reactions nitrogen oxides may contribute to the formation of nitric acid and nitrates (eg, peroxyacynitrates).

Among the nitrogen oxides, the dioxide form is the main, but maybe not the only, compound of health importance in ambient air pollution. Nitrogen dioxide is a reddish-brown gas with a pungent odor. In contrast to other nitrogen oxides it is a strong oxidizing agent, and it is biologically highly reactive. In this report a nitrogen dioxide level of 1 ppb has been set equal to 1.88 µg/m³.

In European countries environmental levels of nitrogen dioxide have been increasing in recent years (32). Nitrogen oxides have been claimed to be responsible for part of the continual increase in the acidity of rainfall. Locally, nitrogen dioxide may be of direct health importance.

The background concentration of nitrogen dioxide in rural areas usually ranges from 0.5 to 10 µg/m³. In urban areas the levels vary widely, depending on the location and the time. Annual means are about 20–90 µg/m³; for example, the mean annual concentration for 186 urbanized areas in the United States (US) during 1977–1979 was 55 µg/m³. The peak 1-h average ranged from 110 to 940 µg/m³ (155). In temperate climate the urban ambient levels are higher during the winter because of periods of meteorological stagnation in combination with heavy traffic and heating by fossil fuels.

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The indoor concentrations are generally somewhat lower than the outdoor values, but gas heating and cooking appliances can increase the indoor level, which may occasionally rise in places to several thousand micrograms per cubic meter (70, 95, 136, 161). However, compared to the contents of outdoor air on a long-term basis, only 5–10 $\mu\text{g}/\text{m}^3$ higher levels were caused in room air by domestic heating and cooking systems in homes of the eastern part of the United States (136).

Large amounts of nitrogen oxides are inhaled through tobacco smoking, the intake having been calculated to be 160–500 $\mu\text{g}/\text{cigarette}$ (72). Fresh mainstream smoke does not contain much nitrogen dioxide; instead there is mainly the monoxide form. Although the monoxide is oxidized to the dioxide form during the ageing of the smoke, the smoking of 5 to 10 cigarettes in an unventilated box (30 m^3) results initially in a nitrogen dioxide level of only about 40–80 $\mu\text{g}/\text{m}^3$ (165).

There is an important difference in the results of the chemical analysis of nitrogen dioxide by different methods. According to a personal communication from Dr R Letz, Harvard School of Public Health, Boston, the modern chemoluminescence technique will give 30–50 % higher values than the old wet-chemical analysis techniques using bubblers.

Occurrence of ozone and related oxidants

Ozone and many other oxidants are formed as a result of reactions between oxides of nitrogen and photochemically reactive hydrocarbons. These substances are discharged from, for example, motor vehicles, power stations, and chemical plants. The ozone concentration is commonly employed as an index of the oxidizing atmospheric pollutants formed by photochemical processes (compounds formed by the agency of atmospheric oxygen and the sun's ultraviolet radiation). In this report an ozone level of 1 ppb has been set equal to 2 $\mu\text{g}/\text{m}^3$.

The composition of oxidants varies with the discharge of hydrocarbons that occurs in different towns and different countries. For example, an increase in the olefine content of gasoline may raise the level of unsaturated aldehydes in the oxidant mixture during pollution episodes. Such a mixture will presumably possess more strongly irritant properties than one obtained from a gasoline with aliphatic hydrocarbons (12).

The difference between the natural levels of oxidants and the concentrations that are harmful to man is often only small. In areas remote from towns and industrial plants 1-h means of more than 200 $\mu\text{g}/\text{m}^3$ have been recorded. Close to large towns the ozone concentration often exceeds 200 $\mu\text{g}/\text{m}^3$ when the temperature is high and the sunlight strong. The most familiar example of this situation is the smog experienced in the Los Angeles area of the United States. The high-

est concentrations of oxidants occur not in the city centers but in the suburbs, downwind from the central area. In 1976 a value of 200 $\mu\text{g}/\text{m}^3$ was exceeded on one occasion in central Göteborg, Sweden, and on 17 occasions at a place 40 km from the center of the city (12). Ozone is also formed naturally by the action of solar radiation in the stratosphere at altitudes between 15 and 35 km. The intrusion of ozone from the stratosphere has been calculated to cause hourly concentration values of 30–80 $\mu\text{g}/\text{m}^3$ (153).

It has also been found that the formation of photochemical oxidants has a macroregional background; thus under certain meteorological conditions discharges throughout northwest Europe may react and result in comparatively high atmospheric concentrations of oxidants over southern Scandinavia. For example, episodes of elevated levels of ozone in the ambient air of the west coast of Sweden have been found to have originated elsewhere in Europe. During the summers of 1972–1979 the maximum measured 1-h means of ozone ranged from 200 to 400 $\mu\text{g}/\text{m}^3$.

Indoor sources of ozone include the welding process, ultraviolet lamps, and photocopying machines. The ozone levels are usually lower indoors than outdoors because of the oxidation of surface material.

Common features of nitrogen dioxide and oxidants

Nitrogen dioxide is partly dissolved in the mucus of the upper airways. Available data suggest, though, that, when inhaled, it is fairly evenly distributed throughout the respiratory tract and is further spread in the body by the circulatory system. Absorption probably occurs in the lung in the form of nitric acids or nitrous acids or their salts, as indicated by the appearance of nitrites and nitrates in the urine following exposure to nitrogen dioxide (144).

Approximately 90 % of inhaled ozone (at concentrations well below 2 000 $\mu\text{g}/\text{m}^3$) is estimated to be taken up during quiet respiration (171). As ozone is only slightly dissolved in the respiratory mucus, the uptake is largest in the lower airways (159).

Usually nitrogen dioxide and other oxidants affect humans only locally, but the sites are multiple, and the effects are caused by a number of mechanisms. Oxidant air pollutants exert much of their action via reactions mediated by free radicals (13). Nitrogen monoxide and nitrogen dioxide are themselves free radicals and may initiate radical lipid peroxidation reactions in the cell (147). Ozone is not a free radical, but by interaction with polyunsaturated fatty acids radicals are produced (121).

From animal studies it seems that short-term exposure to high concentrations of nitrogen dioxide and ozone are more effective in creating health effects than long-term exposures to lower concentrations, the doses being equivalent (52). Both nitrogen dioxide and ozone also seem to interact with other environmental factors

that sometimes cause additive or synergistic effects, eg, with sulfur dioxide or bacterial infections. Animals and humans seem to develop some tolerance against the effect of oxidants, and the repair of slight tissue injuries from prolonged exposures can take place.

In the construction of dose-effect relationships for pulmonary function, data suggest that the effective dose for pulmonary irritants is best expressed as exposure rate per minute (Dmin) or as total exposure dose (19). Both dose expressions are equally well correlated with the pulmonary function effects of exposure to ozone, but for nitrogen dioxide increases in airway resistance are possibly better correlated with the former.

Nitrogen dioxide and many oxidants are sensory as well as pulmonary irritants. Like other sensory irritants they stimulate the free nerve endings in the throat or the eyes and produce a burning and itching sensation and sometimes tear flow. The odor threshold levels of nitrogen dioxide and ozone are not very low, and they are easily raised by adaptation. Thus the sensory warning properties of these compounds are insufficient. The dominant irritation effects of the substances are localized to the deeper airways. By various mechanisms the smooth muscles of the deeper airways are contracted (bronchoconstriction) and result in increased airway resistance.

Specific effects of nitrogen dioxide

Studies on animals, tissues, and cells

Nitrogen dioxide causes a number of systemic biochemical changes at continuous and high exposures, as demonstrated by animal or in vitro studies. Similar to the effects of other oxidants, tissue and subcellular damage is mainly attributed to the oxidizing properties of the compound. Pulmonary phospholipid synthesis is possibly disturbed by lipid peroxidation after excessive exposure to nitrogen dioxide (147, 149). Tissue damage and the acute response of the organism to stress is reflected by an increased oxygen consumption in the tissues (9), protein leakage from the cells (129), and increased corticosterone levels in the plasma (150). Probably the biochemical effect of nitrogen dioxide is counteracted by cellular defense mechanisms as is the case with certain antioxidants, peroxide decomposers (eg, heme proteins), and enzymes, such as glutathione peroxidase. (For an overview see, eg, reference 108).

Many of the cellular and subcellular changes occur primarily in the lung tissues, but other systems of the body are involved as well. By using the inhalation of radiolabeled nitrogen dioxide, Goldstein et al (59) demonstrated that the gas is fairly uniformly distributed in the lung and retained for a prolonged period of time in monkeys. The dissemination of nitrogen dioxide to extra pulmonary sites was shown to take place via the blood stream.

The wide involvement of the body during exposure to airborne nitrogen dioxide is shown by the increased oxygen consumption in the spleen and kidney, the increased cytochrome activity in the liver, kidney, spleen and serum, and, in some cases, by polycythemia (49). These general mechanisms are only partly understood. For instance, theoretical calculations and findings from in vitro studies imply that methemoglobinemia could be produced by nitrogen dioxide exposure, although to a minor extent compared to that caused by nitrate ingestion by food and water. However, animal studies have failed to show methemoglobinemia at low to moderate exposure levels in spite of the finding by Svorcova & Kaut (144) that nitrogen dioxide is rapidly converted to nitrite and nitrate ions in the lung and excreted in the urine.

Morphologically the damage caused in animal pulmonary tissues by prolonged exposure to nitrogen dioxide at fairly high concentrations (around 600—2 000 $\mu\text{g}/\text{m}^3$ or above) is inflammatory. Signs of peribronchitis and bronchitis are typical findings (80). The collagen fibers may be damaged and the alveoli expanded (6). By increasing concentration long-term exposure produces, eg, hypertrophy of the bronchial epithelium and loss of bronchial cilia (21, 44, 45, 139). The mast cells of the lung have been shown to rupture (148), possibly in association with histamine release.

The most evident effect of exposure to nitrogen dioxide is changes in pulmonary function. In rats, increased respiratory rates have been observed at 1 500 $\mu\text{g}/\text{m}^3$ after long-term exposure (45). The same effect has been found in other animals at higher levels (non-human primates, guinea pigs, cats) although the sensitivity between species seemingly varies (68, 107, 174). At still higher concentrations some species show increased airway resistance during prolonged exposure (22). Short-term exposure to nitrogen dioxide at about 10 000 $\mu\text{g}/\text{m}^3$ with guinea pigs (107) and about 20—30 000 $\mu\text{g}/\text{m}^3$ with squirrel monkeys (67) resulted in decreased tidal volumes.

Increased susceptibility to airway infections after exposure to nitrogen dioxide has been demonstrated in a number of animal experiments. Following exposure to airborne bacteria (*Klebsiella pneumoniae*) combined with a 2-h exposure to nitrogen dioxide at a concentration of 6 600 $\mu\text{g}/\text{m}^3$ or above, the mortality among mice, hamsters, and squirrel monkeys has been found to be higher than among control animals (26, 67). An increase in mortality has been recorded for mice exposed for a long period to nitrogen dioxide at 940 $\mu\text{g}/\text{m}^3$ and then infected with airborne bacteria (29, 67), but in a recent study another research team was not able to confirm these results (92). Increased sensitivity to other bacteria or viruses after exposure to nitrogen dioxide has been observed (16, 51, 52, 74, 158).

The increased susceptibility to airway infections caused by exposure to nitrogen dioxide might be due to an effect of the gas on the lung macrophages, the

mucociliary clearance mechanism, or the immune system. In *in vitro* studies alveolar macrophages have been found to be affected after short-term exposure at a concentration of $200 \mu\text{g}/\text{m}^3$ (160). A number of earlier studies have shown similar results *in vivo* but at higher concentrations (eg, 50, 158).

Depression of the mucociliary transport has been reported after long-term exposure to nitrogen dioxide at $11\,000 \mu\text{g}/\text{m}^3$ (55). Reduced pulmonary clearance of inhaled microbes was reported by Blair et al (6) and Ehrlich & Henry (29).

Nonspecific immunologic changes have been shown in a number of studies (28, 30, 37). Long-term exposure to concentrations at about $4\,000$ – $9\,000 \mu\text{g}/\text{m}^3$ depressed the formation of serum neutralization antibodies in squirrel monkeys and mice. At moderate levels of long-term exposure (around $2\,000 \mu\text{g}/\text{m}^3$) the antibody titers of squirrel monkeys increased (28). However, Antweiler et al (2) did not demonstrate any influence of nitrogen dioxide on the production of precipitating antibodies in guinea pigs after long-term exposure at much higher concentrations ($10\,000 \mu\text{g}/\text{m}^3$).

Effects of nitrogen dioxide on the nervous system have been found in rats in the form of delayed conditioned reflexes at $600 \mu\text{g}/\text{m}^3$ after long-term exposure (75). Salamberidze (127) could not find any effects on the central nervous system at $100 \mu\text{g}/\text{m}^3$ after long-term exposure. Behavioral changes of a performance type have been observed in rodents at considerably higher levels, $9\,400$ – $14\,000 \mu\text{g}/\text{m}^3$, after short- or long-term exposures (107, 151). From the present data it cannot be judged whether the effects of nitrogen dioxide on the nervous system are primary or secondary.

Controlled studies on humans

Pulmonary function. The experimental studies on man's exposure to nitrogen dioxide have chiefly concerned the effects on pulmonary function for periods ranging from about 10 min to 2 h. The mechanism underlying most of the changes in lung function ascribed to such exposure is still unclear but would appear to be the irritation of smooth muscles or specific receptors. A possible relationship with prostaglandins has also been proposed (97).

Healthy subjects exposed to nitrogen dioxide at a concentration of $9\,400 \mu\text{g}/\text{m}^3$ have been found to display increased airway resistance and evidence of impaired oxygen exchange in the lungs (112, 113). von Nieding and his co-workers also observed a decrease in the lung's diffusion capacity for carbon monoxide resulting from only a 15-min inhalation of nitrogen dioxide at $9\,400 \mu\text{g}/\text{m}^3$. The works by von Nieding and his colleagues (1973–1979) first met some criticism from American physiologists because their measurement technique differed from the one used in the United States. However it is now generally agreed that the methods used by von Nieding provide valid qualitative information.

Although the results by Suzuki & Ishikawa (142) are difficult to interpret, it seems from their report that airflow resistance in healthy subjects may increase after 10-min exposure to nitrogen dioxide at concentrations from $1\,300$ to $3\,800 \mu\text{g}/\text{m}^3$. According to Beil & Ulmer (4) short-term exposure of healthy subjects at $1\,800 \mu\text{g}/\text{m}^3$ has no effect on airway resistance, but an effect is obtained at $\geq 4\,700 \mu\text{g}/\text{m}^3$.

Folinsbee et al (43) did not find any changes in pulmonary, cardiovascular, or metabolic functions in nonsmoking young males after short-term exposure to $1\,150 \mu\text{g}/\text{m}^3$. Similar results were reported by Hackney et al (62) and Kerr et al (79). However, during 2 h of exposure at about $1\,800 \mu\text{g}/\text{m}^3$, 5 of the 16 healthy subjects in the Hackney study reported "chest restriction." In the Kerr study, 5 of 13 asthmatic subjects reported "chest tightness" after 2 h of exposure to about $900 \mu\text{g}/\text{m}^3$. Sackner et al (126) were unable to show any immediate or delayed effects at all on pulmonary function in normal adults. They used 4 h of controlled exposure to 190, 570, 950, and $1\,900 \mu\text{g}/\text{m}^3$.

A few studies have been directed towards possible interactions between subthreshold concentrations of pollutants in mixture. von Nieding et al (113) found no effect on the pulmonary function of healthy subjects during 2-h exposures to a combination of nitrogen dioxide ($100 \mu\text{g}/\text{m}^3$), ozone ($50 \mu\text{g}/\text{m}^3$), and sulfur dioxide ($300 \mu\text{g}/\text{m}^3$). Hackney & Linn (61), in exposing normal as well as presumed sensitive adults to mixtures of ozone, nitrogen dioxide, and carbon monoxide (simulating exposure to Los Angeles air pollution during 2–4 h), found little or no effects of nitrogen dioxide on pulmonary function at $560 \mu\text{g}/\text{m}^3$.

The data on the effect of nitrogen dioxide on lung clearance are far from complete. In a study on three subjects the alveolar clearance of soot particles measuring 0.07 – $1.0 \mu\text{m}$ was slower when inhaled together with nitrogen dioxide at $9\,000 \mu\text{g}/\text{m}^3$ than when breathed alone or together with carbon monoxide at $55\,000 \mu\text{g}/\text{m}^3$ or sulfur dioxide at $13\,000 \mu\text{g}/\text{m}^3$ (130). In a study of eight healthy subjects with a radioactively labeled test aerosol the mucociliary clearance in the larger bronchi was not significantly affected by exposure to nitrogen dioxide at levels of 500 or $2\,000 \mu\text{g}/\text{m}^3$ for 1 h (122).

Patients with chronic lung disease seem to be sensitive to nitrogen dioxide since a progressive increase in airway resistance has been found between acute exposures of $3\,000$ and $9\,400 \mu\text{g}/\text{m}^3$. Exposures below $2\,800 \mu\text{g}/\text{m}^3$ did not have any effect (112, 113). Sackner et al (125) were unable to show any effects on pulmonary function in asthmatic adults during 4 h of controlled exposures to 190 – $1\,900 \mu\text{g}/\text{m}^3$.

In two recent studies the effect of nitrogen dioxide on airway resistance has been examined by whole-body plethysmography. Among eight nonasthmatic subjects airway resistance increased slightly but statistically significantly after 20-min exposure to $460 \mu\text{g}/\text{m}^3$ and

decreased slightly after 20-min exposure to 910 $\mu\text{g}/\text{m}^3$. Among eight asthmatic subjects the trend was the same but not statistically significant (11). In another study (122) a group of eight nonasthmatic subjects showed a slight but statistically significant increase in airway resistance after 1 h of exposure to 500 $\mu\text{g}/\text{m}^3$ but not after similar exposure to 2 000 $\mu\text{g}/\text{m}^3$. Neither of these studies yielded conclusive results.

Bylin et al (11) have suggested that the data in the literature (4, 11, 62, 65, 116, 122) give some support to the hypothesis that there is a nonmonotonous dose-effect relationship for airway resistance induced by nitrogen dioxide in the low-to-moderate concentration range. It would be explained by consecutive and competing effects that are induced in the airways by nitrogen dioxide and caused by different mechanisms of action. At low concentrations sensory and other receptor-mediated reactions may result in bronchoconstriction.

It is interesting to note that Menzel (98) has shown inhibited metabolism of bronchodilating prostaglandin in rat lung after short-term exposure to nitrogen dioxide at 400 $\mu\text{g}/\text{m}^3$. Orehek et al (115) have demonstrated that deep inspirations in some asthmatic subjects may decrease an induced bronchoconstriction.

Studies have been performed on bronchial reactivity induced by nitrogen dioxide in which the lung function was tested for sensitivity to agents that contract the airways. Orehek et al (116) have reported increased bronchial reactivity in asthmatics at fairly low concentrations (190 $\mu\text{g}/\text{m}^3$) during 1-h exposures. The results of this study are supported by those by von Nieding et al (113), who suggested that acute effects on pulmonary acetylcholine sensitivity to nitrogen dioxide may take place at very low levels (100 $\mu\text{g}/\text{m}^3$) in combination with sulfur dioxide (300 $\mu\text{g}/\text{m}^3$) and ozone (50 $\mu\text{g}/\text{m}^3$). These results are inconclusive — in the Orehek study mainly because the grouping of the subjects was made after the pulmonary tests with no independent criterion for pulmonary sensitivity and in the von Nieding study because the results were inconsistent.

In a recent study conducted to check the Orehek result, no significant effect of 1-h exposure to nitrogen dioxide at 190 $\mu\text{g}/\text{m}^3$ was found on bronchial reactivity either in asthmatics or in normal subjects (65). The bronchial reactivity of asthmatic subjects, though, was found to increase significantly after 20-min exposure at 910 $\mu\text{g}/\text{m}^3$, but no tests at lower levels were made (11).

Effects on the nervous system. Sensory information on nitrogen dioxide includes only odor detection thresholds. For young male humans the odor threshold has been reported to lie between 200 and 440 $\mu\text{g}/\text{m}^3$ for acute exposure of the unadapted sense (36, 69). In an unpublished study by T Rehn, Karolinska Hospital, Stockholm (personal communication), the absolute odor threshold (50 % effective dose) to

nitrogen dioxide was much lower (median value 50 $\mu\text{g}/\text{m}^3$) for 52 persons aged 17 to 53 (median 32) years.

Perception of the nitrogen dioxide odor is probably enhanced by high air humidity, and it is strongly attenuated by the duration of exposure. Henschler et al (69) claimed that, by slowly increasing the nitrogen dioxide concentration over a period of about 1 h, the odor is not perceived even at about 50 000 $\mu\text{g}/\text{m}^3$. Kerr et al (79) reported that most test subjects became unaware of the odor after 15 min of exposure to 1 000 $\mu\text{g}/\text{m}^3$.

Epidemiologic studies

Occupational exposure to oxides of nitrogen can occur in, for example, recently filled silos and in the course of rock blasting. A task group (169) of the World Health Organization (WHO) judged from such experiences that short-term exposure to nitrogen dioxide at levels of about 560 000–940 000 $\mu\text{g}/\text{m}^3$ can lead to fatal pulmonary edema and that levels of 47 000–140 000 $\mu\text{g}/\text{m}^3$ can cause bronchitis and pneumonia. Unfortunately, there are no available dose-response data for occupational exposure to low concentrations of oxides of nitrogen.

In a report by the US Environmental Protection Agency (154) two Russian reports and one Czechoslovakian report on disease incidences in or around chemical plants emitting, among other things, nitrogen oxides are discussed (54, 119, 120). Their results are unclear however, because the reports lack important methodological information.

In areas differing in nitrogen dioxide exposure, children have been investigated with regard to pulmonary function and the incidence of acute respiratory illness (131, 132). Little or no effect was seen at annual average levels of 150–280 $\mu\text{g}/\text{m}^3$. Pearlman et al (118) conducted a retrospective study in the same area, partly reanalyzing the data, and reported a slight increase in bronchitis morbidity at the same levels. No effects were found with regard to other respiratory illnesses. However, the investigations mentioned are not fully reliable because the nitrogen dioxide measurements were conducted with an unreliable method of analysis (Jacobs-Hochheiser).

Kagawa & Toyama (77) studied the weekly variations in the pulmonary function of 20 schoolchildren in relation to ambient temperature and air pollutants. Correlations were found between the results of lung function tests on the one hand and temperature and the concentrations of ozone, nitrogen dioxide, nitrogen monoxide, sulfur dioxide, and particulates on the other. However, the relationships are difficult to interpret. At typical 1-h mean nitrogen dioxide levels ranging from 40 to 360 $\mu\text{g}/\text{m}^3$ temperature was found to be the factor having the strongest correlation with lung function. In a US study positive correlations have been reported between exacerbations of asthma in children and the monthly average concentrations of

nitrogen monoxide ($420 \mu\text{g}/\text{m}^3$), hydrocarbons (61 ppm), and airborne allergens (123). There were negative correlations with ozone ($140 \mu\text{g}/\text{m}^3$) and sulfur dioxide, temperature, and relative humidity. The monthly average concentration of nitrogen dioxide was $260 \mu\text{g}/\text{m}^3$.

In a study by Mostardi et al (103, 104) on schoolchildren living at different distances from an industrialized area, an association was reported between acute respiratory illness and the ambient air levels of sulfur dioxide and nitrogen dioxide (annual means $21\text{--}78 \mu\text{g}/\text{m}^3$ and $37\text{--}55 \mu\text{g}/\text{m}^3$, respectively). At the polluted school results of daily diaries and repeated pulmonary tests indicated a higher incidence of symptoms among the children, as well as slight impairments of pulmonary function (reduced airway flow values). The data must be regarded as inconclusive until confirmed by other study results. It is too early to tell whether air pollutants at levels below or close to present US air quality standards can aggravate acute respiratory illness in schoolchildren. Furthermore the specific role of nitrogen dioxide remains unclear until supporting evidence is available from other studies on situations with different pollutant combinations.

The few epidemiologic studies performed on adults have not disclosed whether nitrogen dioxide in the ambient air produces harmful effects. At annual mean values of up to $100 \mu\text{g}/\text{m}^3$ no effects on the respiratory tract were observed (17, 134, 135). In a Japanese investigation of nitrogen dioxide quoted in a WHO report (169), a dose-response correlation was found between the annual mean level of $23\text{--}76 \mu\text{g}/\text{m}^3$ in combination with sulfur dioxide, nitrogen monoxide, carbon monoxide, and particulates and the occurrence of cough. The Japanese results are difficult to interpret, however, owing to shortcomings in the analyses of the measurements and in the statistical analysis and to the fact that only part of the report has been translated into English.

People living in temperate climatic zones spend most of their time indoors; children probably spend 60–80 % of the day indoors during schooldays (5). Among the familiar factors that are important predictors of respiratory disease may well be the large amount of time spent breathing a common atmosphere (64). A number of studies have indicated a relationship between parental smoking and respiratory disease or other pulmonary effects on children (18, 64, 136, 145). Some of these effects might be related to nitrogen oxides emitted by smoking. Although tobacco smoking is a source of oxides of nitrogen indoors, controlled studies have shown that smoking does not produce high indoor levels of nitrogen dioxide (165).

In addition to passive smoking, the use of gas in homes may have health implications. Gas cooking appliances can produce considerable indoor levels of nitrogen dioxide. Melia et al (94) and Hasselblad et al (64) reported more respiratory symptoms or reductions in forced expiratory volume (FEV) among girls

from homes using gas for cooking in comparison with children in homes with electric stoves. However, since the Melia result was not confirmed in subsequent studies (41), the researchers of the group are inclined to believe it was a chance finding (personal communication from Dr C du V Florey, Ninewells Hospital and Medical School, Dundee, United Kingdom). In another study by Melia et al (95) a higher incidence of respiratory symptoms was found in children from homes with gas stoves, but only for residences in urban areas, not in rural areas. Speizer et al (136) in the first of a series of studies, reported children (6–10 years of age) from homes with gas stoves to have lower lung function test values [FEV in 1s ($\text{FEV}_{1.0}$), forced vital capacity (FVC)] and a greater history of respiratory illness before two years of age. In later follow-up studies these findings were not confirmed (137, 163). Keller et al (78) found no differences among school-age children from homes with gas or electric stoves with regard to reported incidence of respiratory illnesses, frequency of symptoms, or frequency of respiratory findings in a physical examination. However, the latter sample of children was considerably smaller than the samples in earlier cited reports. In addition du V Florey et al (41) found no relationship between nitrogen dioxide concentrations in either bedrooms or kitchens and the results of lung function tests on school-age children. However, the prevalence of respiratory illness was found to increase with the nitrogen dioxide levels in the bedrooms of children in homes with gas stoves.

In an epidemiologic study of male adults, gas cooking was found to be significantly associated with chronic cough, wheeze, breathlessness, and impairment of lung function among never smokers (101). Differences due to gas cooking among current smokers were minimal. In a population of adult, rural, non-smoking women Fischer et al (40) recently found statistically significant associations between pulmonary function and home exposure to nitrogen dioxide, as well as to tobacco smoke. The results refer to cross-sectional analyses. Longitudinal analyses yielded inconsistent results.

The inconsistent data in the literature are illustrated by the fact that, when Speizer et al reanalyzed the same data that they had previously reported on (136) with additional cohorts from the same population and a more-detailed assessment of socioeconomic status, the results were less significant (137, 163). The latter study also demonstrated that, in children annually tested with respect to the rate of change of lung function, no effect of gas-stove exposure was revealed.

The divergencies in the results between different investigators can partly be explained by differences in the design of the investigations, measurement methods, sample size, and sample composition. As pointed out by Speizer et al (137), the adjustments made for socioeconomic status may represent overadjustment. Part of a possible gas-stove effect may be masked in the adjustments since the presence of gas stoves and

socioeconomic status are correlated. There is also the possibility of a significant misclassification of exposure among children since there are large difficulties in estimating exposure from the history of the presence of having a gas stove in one's home (85). Finally, there is the possibility that nitrogen dioxide at these concentration levels and temperatures does not affect human airways. Further studies are required to get conclusive evidence of the importance of nitrogen dioxide concentrations indoors in respect to health.

Evaluation of reported effects of nitrogen dioxide

Evaluations made by others

The health effects of nitrogen oxides have been reviewed and evaluated in a number of reports during the last several years (23, 38, 39, 102, 152, 154, 155, 156, 169). Nitrogen dioxide is almost exclusively discussed, presumably because it is the only or the dominant adverse compound of the nitrogen oxides.

Relatively few epidemiologic studies have been done on the general population concerning the health effects of nitrogen dioxide. However, the epidemiologic information available does not contradict conclusively the results of controlled studies on animals and humans. It has been necessary to establish at least crude guidelines for exposure limits for nitrogen dioxide to protect public health. Unfortunately, the nitrogen dioxide concentrations in many urban areas approach or surpass the suggested limits. Thus, there is a strong demand for more precise and reliable guidelines than can be achieved on the basis of the present scientific facts.

Morrow (102) and Ferris (38, 39) concluded that a limit value of $100 \mu\text{g}/\text{m}^3$ is reasonable for nitrogen dioxide as an annual average of 24-h values. This value has been adopted as a primary air quality standard in the United States on a yearly basis. However, a task group of WHO (169) did not find the available information sufficient to establish long-term exposure limits.

A hearing of experts on nitrogen dioxide was arranged by the Environmental Protection Agency of the Federal Republic of Germany (124, 152). There were divided opinions among the experts, but an average annual limit value of as low as $50 \mu\text{g}/\text{m}^3$ was suggested by some. By this value it was believed that a safety factor of 10–20 to the lowest concentrations eliciting adverse effects in animals would be accomplished. In the Federal Republic of Germany the long-term air quality standard for nitrogen dioxide was lowered in 1978 from 100 to $80 \mu\text{g}/\text{m}^3$ [TA Luft 1978: arithmetic mean of all half hourly averages per year (166)]. A long-term limit value of $50 \mu\text{g}/\text{m}^3$ has been adopted by Switzerland, evidently on the basis of the German evaluation. A long-term guide value for

nitrogen dioxide has been adopted by the Council of the European Communities (32) at $50 \mu\text{g}/\text{m}^3$ at the 50 percentile. Member states are obliged to take action when this value is exceeded.

Concerning the short-term limit value, the WHO Task Group (169) selected the concentration of $940 \mu\text{g}/\text{m}^3$ as an estimate of the lowest concentration of observed effect for nitrogen dioxide. The basis for this decision is the judgement that animal and human laboratory studies from this concentration and up more or less consistently indicate serious adverse effects after both short- and long-term exposures. At the minimum level of $940 \mu\text{g}/\text{m}^3$, the mortality rate of mice due to laboratory-induced respiratory infection increased after long-term exposure. From a level of $3\,000 \mu\text{g}/\text{m}^3$ on (short-term value), a progression in airway resistance was found in patients with chronic lung disease. Tissue damage in the respiratory tract has been found at around $2\,000 \mu\text{g}/\text{m}^3$ after prolonged exposure.

Today the potential hazards with short-term exposures to nitrogen dioxide from about $1\,000 \mu\text{g}/\text{m}^3$ up seem to be recognized by many scientists. The crucial point is how important the studies are that indicate effects on humans well below that level.

The WHO Task Group chose a classical, pragmatic approach and agreed on a safety factor of 3–5, which resulted in suggested limit values between 190 and $320 \mu\text{g}/\text{m}^3$ for 1-h exposures. Although this procedure was judged unsophisticated by Dawson & Schenker (23), they admit that the job would be difficult to do convincingly better. Ideally it should be up to standard setting bodies to decide what degree of risk society will accept, based on available data and modern probabilistic techniques of risk estimation. In a manner similar to that of the WHO Task Group, German experts to the environmental authorities in Germany (152) used a safety-factor to arrive at a reasonably safe short-term limit value for nitrogen dioxide. With the use of a safety factor of 4–15 for concentrations convincingly shown to elicit pulmonary changes in healthy adults during acute exposures ($1\,260$ – $5\,000 \mu\text{g}/\text{m}^3$), a short-term limit value of $300 \mu\text{g}/\text{m}^3$ was suggested.

The recommendation of the WHO Task Group (169) contrasts with the earlier suggestion by the Committee on Toxicology of the US National Academy of Sciences (20). They recommended that the short-term exposure limit for the general public should be established at $1\,800 \mu\text{g}/\text{m}^3$.

Ferris (38) found the study by Orehek et al (116) valid but recognized the need for replication of the study over a wider range of exposure levels. He suggested that an appropriate exposure limit might be $480 \mu\text{g}/\text{m}^3$ for 1 h, not to be exceeded more than two to three times per year. Ferris recently recommended to the Canadian Government (39) that the maximum acceptable nitrogen dioxide concentration should be $750 \mu\text{g}/\text{m}^3$ for 1 h (based on a review of human volunteer studies on pulmonary function), $470 \mu\text{g}/\text{m}^3$ for 24 h (based on extrapolation of the results of volunteer

studies and epidemiologic data on resistance to respiratory infection), and $100 \mu\text{g}/\text{m}^3$ for one year (based on the results of epidemiologic studies).

As a result of a thorough review and revision of the health and welfare criteria for nitrogen dioxide, the US Environmental Protection Agency (155) proposed to retain the existing annual average for the ambient-air quality standard for nitrogen dioxide ($100 \mu\text{g}/\text{m}^3$). This organization is continuing to evaluate the evidence bearing on whether a separate short-term standard is sufficient to protect public health. The lowest level at which single short-term peak exposures have been observed to produce effects of definite health concern in humans is believed to be approximately $2\,000 \mu\text{g}/\text{m}^3$. Below that level subtle effects have been reported, but they are regarded as of uncertain health significance and are considered solely as a factor in judging which standard will provide an adequate margin of safety.

Community epidemiology and community studies of gas stove use provide some qualitative evidence of a relationship between human exposure to near ambient levels of nitrogen dioxide and adverse health effects. However, in the opinion of the US Environmental Protection Agency, various limitations in these studies preclude derivation of quantitative dose-response relationships. Given the uncertainty associated with the extrapolation from animal to man, the seriousness of the observed effects and the inability to determine an effect level for humans, the Agency believes it would be prudent public health policy to maintain the current US annual standard of $100 \mu\text{g}/\text{m}^3$. This standard is believed also to provide adequate protection against repeated short-term exposures.

In the Federal Republic of Germany the short-term air quality standard for nitrogen dioxide was unchanged at $300 \mu\text{g}/\text{m}^3$ from 1974 to 1980 (95 percentile of all half hourly averages per year). From 1981 on, however, this value has referred to the 98 percentile. The Council of the European Communities (32) has adopted a limit value for the ambient air concentration of nitrogen dioxide of $200 \mu\text{g}/\text{m}^3$ on a 98 percentile calculated from the hourly mean values recorded throughout the year on a continual basis. This limit is also expected to account for the effects of nitrogen dioxide on the atmospheric phenomena of photochemical air pollution and acid deposition. As a short-term guide the Council has adopted $135 \mu\text{g}/\text{m}^3$ at the 98 percentile. The guide value is intended as a warning that should oblige member states to take action when exceeded.

Importance to sensitive groups

Many researchers agree that limit values should consider also the sensitive part of the population. The WHO Task Group has declared that the uncertainty concerning the lowest adverse effect level and the high

biological activity of nitrogen dioxide require the use of a considerable safety factor.

It is highly probable that many persons with pre-existing respiratory disease will be sensitive at concentrations to which healthy adults do not respond at all. It has also been shown that viral upper respiratory tract infections in otherwise healthy human subjects cause transient airway hyperreactivity (31).

Sensory effects in humans have been reported at levels well below $1\,000 \mu\text{g}/\text{m}^3$; the limit of odor detection is found around $200 \mu\text{g}/\text{m}^3$ or maybe even lower. Thus, sensory reflex reactions are possible theoretically.

The relevance of the study by Orehek et al (116) is still being debated. Increased bronchial reactivity was reported after short-term exposure of asthmatic persons to a nitrogen dioxide concentration of about $200 \mu\text{g}/\text{m}^3$. The effect was determined as increased airway resistance, caused by nitrogen dioxide in combination with a bronchoconstricting agent. However, a very similar study by Hazucha et al (65) was not able to confirm the results reported by Orehek et al. An effect of a combined challenge to healthy persons may have been observed by von Nieding et al (113), who reported acute effects on pulmonary acetylcholine-sensitivity at a nitrogen dioxide level of $100 \mu\text{g}/\text{m}^3$ in combination with low levels of sulfur dioxide and ozone. Both the Orehek and the von Nieding data seem to be inconclusive and in contrast to the study by Beil & Ulmer (4). In healthy subjects the latter found no increase in sensitivity to acetylcholine at nitrogen dioxide levels of $4\,700$ and $9\,400 \mu\text{g}/\text{m}^3$ during 2 h. However, the basic mechanism of increased adverse effects of two combined challenges to the respiratory system is supported also by the Beil & Ulmer data. Furthermore, Bylin et al (11) recently demonstrated increased bronchial reactivity in asthmatic subjects after short-term exposure to $910 \mu\text{g}/\text{m}^3$.

In a study of the distribution of airway responsiveness in a population sample of adults and children, Weiss et al (167) found a wide variability in responsiveness to a respiratory challenge (cold air). Airway responsiveness ($\text{FEV}_{1,0}$) was normally distributed in adults, but in children it was skewed toward greater responsiveness. Also median airway responsiveness was greater in children than in adults. These data support the suspicion that children as a group are sensitive to respiratory irritants like nitrogen dioxide.

For ethical reasons no controlled studies of the effects of nitrogen dioxide on children have been conducted. However, some of the epidemiologic studies conducted in homes using gas or electricity for cooking indicate that girls (64, 94) may have more respiratory symptoms in homes using gas for cooking. The importance of age in the effects of nitrogen dioxide is further illustrated by the findings of Speizer et al (136) that children from homes with gas stoves had a worse history of respiratory illness before two years of age. Indeed there are contrasting negative reports (41, 78,

137, 163). But in view of the great variability in responsiveness to respiratory challenges in the population and the differences in type and size of the samples used in the epidemiologic studies, it is probable that some children do show adverse effects to nitrogen dioxide concentrations sometimes present in daily life.

Another group sensitive to nitrogen dioxide exposure may be nonsmoking adults. In an epidemiologic study by Meyer et al (101), a significant association was found among male never smokers between gas cooking and impairment of forced expiration. Female never smokers showed similar but nonsignificant trends. The rates of impairment among male current smokers were the highest observed (increasing with number of cigarettes smoked), but they were not higher in homes using gas than in those using electric stoves. A recent study in The Netherlands (40) indicates that the pulmonary function of nonsmoking adult women may be affected by nitrogen dioxide pollution, as well as by passive smoking in their homes. Both studies must be judged as indicative but nonconclusive because of the great number of intervening variables that may affect the results.

In discussions of the sensitivity of persons to nitrogen dioxide exposure, it seems appropriate also to consider the sensitivity of the methods applied to reveal small effects of nitrogen dioxide. Although the compound is a pulmonary irritant that may well affect the alveoli of the lung and gas exchange, very few investigations have studied these effects specifically. The pulmonary tests in the epidemiologic studies have all been mechanical tests which mainly reflect the condition in the bronchial tree. In the epidemiologic study by Mostardi et al (104) it was found that, in spite of very minute (but statistically significant) differences in pulmonary function tests between population groups (FVC, FEV_{1.0}), questionnaire reports of severity and duration of acute respiratory illness demonstrated clear differences associated with air pollutant levels. Furthermore, it should be pointed out that, in the study by Hackney et al (62), 5 of 16 healthy subjects reported "chest restriction" during short-term exposures to 1 800 $\mu\text{g}/\text{m}^3$, but the pulmonary function tests were negative. Similarly, in the study by Kerr et al (79), 2 h of exposure to 900 $\mu\text{g}/\text{m}^3$ caused 5 of 13 asthmatic subjects to report "chest tightness" in spite of negative pulmonary function tests.

Outdoor-indoor exposure relationships

Not until recently has the question of the general public's exposure to indoor air pollution acquired adequate interest. The problem area has been thoroughly discussed by the US National Research Council (157). Unvented gas-combustion appliances have been shown to give indoor peaks of nitrogen dioxide of up to about 1 300 $\mu\text{g}/\text{m}^3$. The Council estimates that hourly indoor concentrations of nitrogen dioxide in homes may vary between 100 and 1 000 $\mu\text{g}/\text{m}^3$, with typical week-

ly values between 40–200 $\mu\text{g}/\text{m}^3$. The upper values in these ranges are associated with the use of unvented gas appliances. As discussed earlier, some epidemiologic studies in Great Britain and the United States suggest an association between gas cooking and adverse respiratory effects.

In Sweden the use of gas for cooking or heating is limited to a moderate number of homes (approximately 250 000), and this number is currently decreasing. However, the use of gas in Sweden in the future is an open question. Furthermore, Nordic homes are probably well insulated against natural air infiltration as a consequence of advanced building technology and sometimes exaggerated energy saving measures. Nitrogen oxides concentration may also rise indoors as a result of tobacco smoking and attached garages in combination with a deficient ventilation system. On the other hand airtight buildings, in combination with controlled ventilation and adequate locations of air intake, may protect against street pollution, including nitrogen dioxide. However, according to a personal communication from CE Boström, Swedish National Environment Protection Board, Stockholm, studies in the metropolitan area of Stockholm have shown that the decline in the concentration of nitrogen dioxide is only 20–25 % from the street level to the roof level (air intake) of buildings. The vertical concentration gradient of nitrogen monoxide is probably larger, which is important because inflated levels of nitrogen monoxide may be a source of indoor nitrogen dioxide.

One important aspect of indoor air pollution is the time that is spent at home indoors by the average person. In the report by the US National Research Council (157) a number of examples are given, all indicating that the population spends 65–73 % or more of its time inside homes, but the figures differ for different subgroups such as workers, children, the elderly, etc. As most epidemiologic data on air pollution and related health effects in the general population are based on air pollution monitoring outdoors, such data must be used with great caution. The critical exposure levels obtained through epidemiologic studies may underestimate the effects of nitrogen dioxide on health, if the concentration levels of nitrogen dioxide inside residential buildings are lower than outdoors (eg, in electrically heated, airtight buildings with controlled ventilation). Or these studies may overestimate the risk if nitrogen dioxide levels indoors are much higher than outdoors (eg, by gas cooking and gas heating in buildings with uncontrolled ventilation). It is obvious that detailed knowledge is required of the outdoor-indoor relationships before (i) critical levels of nitrogen dioxide are established on the basis of pollutant monitoring outdoors and (ii) ambient air quality standards based on epidemiologic studies and outdoor pollutant monitoring are used also as air quality standards for the indoor environment.

In recent years, some attempts have been made to estimate the frequency distribution of human air-

pollution exposures. One approach would be to use personal monitors (167); another would be to model human exposures by relating the activities of persons as a function of time and air pollutant concentrations. For example, Ott & Mage (117) developed a technique for simulating the true exposure of pedestrians to carbon monoxide by collecting integrated pollutant samples over the routes that they walk. Other examples of models are presented by Fugas and her co-workers (47, 48) and reviewed by the US National Research Council (157).

Short- or long-term limit values?

The effects of nitrogen dioxide on the human organism is mainly local in that the compound acts as a sensory as well as a pulmonary irritant. The typical effect is increased airway resistance mediated by the stimulation of local receptors or other reflex mechanisms that do not need to be specific to nitrogen dioxide. A number of experiments have shown that challenge with nitrogen dioxide to the pulmonary system increases the bronchial sensitivity of the system. These facts lead to the general impression that the organism might be more sensitive to short-term exposures of high concentrations of nitrogen dioxide than to long-term exposures to low concentrations. This view is supported by the findings of an animal study by Gardner et al (52) on the influence of exposure mode on the toxicity of nitrogen dioxide in combination with bacteria. They found that when a constant concentration $\times$ time level was employed, a short-term exposure to a high concentration produced a greater effect than exposure to a lower concentration administered over a longer period.

It is obvious that at low nitrogen dioxide levels most people have a significant reserve capacity with regard to measurable changes in airway resistance (4, 11). It is likely that for the individual there is a threshold concentration below which adverse respiratory effects do not occur.

The determination of individual or population thresholds to nitrogen dioxide is complicated by the fact that (i) there is a large variation in sensitivity to nitrogen dioxide between individuals, (ii) most controlled studies have not included the most sensitive parts of the population (children, patients with respiratory disease, and persons with a proved lowered tolerance to sensory irritants), (iii) synergistic effects seem to occur between other bronchoconstricting environmental chemicals, particulates and infectious microbes, and (iv) knowledge on the typical exposure patterns among different parts of the population is incomplete.

No investigation has convincingly found an association between the long-term mean of exposure to ambient nitrogen dioxide and chronic respiratory disease in adults. With regard to the acute respiratory disease effects, the early epidemiologic studies by, eg,

Shy et al (131, 132) and Pearlman et al (118) are inconclusive because the dosage measurements of the ambient air are not considered reliable. At annual averages of 43–100 $\mu\text{g}/\text{m}^3$, later studies showed no or questionable effects on respiratory symptoms (17, 134, 135). In a recent study by Mostardi et al (104), however, slight but statistically significant differences in pulmonary function tests (FVC, FEV_{1.0}) have been found in favor of clean areas in comparison to areas with annual concentrations of about 55 $\mu\text{g}/\text{m}^3$ for nitrogen dioxide and 78 $\mu\text{g}/\text{m}^3$ for sulfur dioxide. But the specific role of nitrogen dioxide is unclear.

Some of the epidemiologic studies focusing on the indoor environment have indicated an association between acute respiratory symptoms and illness rate and indoor combustion, by which nitrogen dioxide is presumably formed as a dominant pollutant (64, 94, 136). Speizer et al (136) speculated that repeated exposures to high peak levels of nitrogen dioxide may be very important to the suggested increased incidence of respiratory illness. The reason would be the finding by Spengler et al (138) that in the United States there is no important difference in long-term annual average levels of nitrogen dioxide between homes with gas stoves and homes with electric stoves. In addition in homes with electric stoves, there were no intermittent marked peak concentrations of nitrogen dioxide as was the case in houses with gas stoves. In American homes using gas for cooking, a number of studies have shown daily peak 1- to 2-h average values for nitrogen dioxide of between about 80 and 1 000 $\mu\text{g}/\text{m}^3$ (single peak values approaching 2 000 $\mu\text{g}/\text{m}^3$), 24-h average levels in the range of about 40–130 $\mu\text{g}/\text{m}^3$, and annual average levels ranging from 40 to 115 $\mu\text{g}/\text{m}^3$ [as reviewed by the US Environmental Protection Agency (154)]. For comparison it can be noted that the ambient concentrations of nitrogen dioxide in the United States in 1975–1976 (154) equaled or exceeded 760 $\mu\text{g}/\text{m}^3$ (1-h peaks) only rarely in a few locations. Annual average levels of nitrogen dioxide in 1976 exceeded 100 $\mu\text{g}/\text{m}^3$ in some heavily populated areas.

The view that short-term exposures to nitrogen dioxide may be of major importance gets some support from controlled studies conducted on humans. Ten-minute exposure to nitrogen dioxide at 1 300–3 800 $\mu\text{g}/\text{m}^3$ may have caused increased airflow resistance in healthy subjects (142). Three-minute exposure to $\geq 3 000 \mu\text{g}/\text{m}^3$ caused increased airway resistance for chronic bronchitics (111), and 15-min exposure to $\geq 3 800 \mu\text{g}/\text{m}^3$ caused decrements in blood gas parameters for both healthy adults and bronchitics (112). Seven of 13 asthmatics reported mild symptomatic effects after 2 h of exposure to about 1 000 $\mu\text{g}/\text{m}^3$ (79). Beil & Ulmer (4) reported no increased sensitivity to acetylcholine following exposure to 9 400 $\mu\text{g}/\text{m}^3$ during 2 h, but effects followed exposure to the same level during 14 h. Bylin et al (11) found increased bronchial reactivity among asthmatics after 20 min of exposure to 910 $\mu\text{g}/\text{m}^3$.

Studies on the toxicity of nitrogen dioxide in mice in combination with bacteria indicate that the frequency and amplitude of short-term peaks are of significance even though the exposure is interrupted with periods of a zero concentration of nitrogen dioxide (52). In the study on mice by Ehrlich (26) resistance to respiratory infection was reduced after 30 d of intermittent exposure to about $900 \mu\text{g}/\text{m}^3$ during 6 h a day, 5 d a week, but not after 30 d of continuous exposure to the same concentration. It should be noted that in most other controlled studies the exposure levels have been continuous and constant with no peaks similar to real-life exposures.

Combined effects

Boushey (8), in discussing sulfur dioxide as an airway irritant, pointed out that the bronchomotor response to any given concentration of an irritant is dependent on a great number of factors. They are, among others, the level of the bronchial reactivity of the airways, the minute ventilation (level of exercise), the distribution of airflow through the nose and mouth, the temperature and humidity of the inhaled air, the recent history of exposure to the irritant, and the presence of other pollutant gases or particles in the atmosphere.

Nitrogen dioxide is usually present in a mixture with other air pollutants in real-life exposures. There are a number of reasons to believe that interactions with other environmental factors take place that may enhance the effects of nitrogen dioxide. For example, (i) nitrogen dioxide may interfere with the macrophage activity in the lung so that bacterial or viral infections are more likely to be established (compare the synergistic effects observed in the studies of laboratory-induced respiratory infections); (ii) nitrogen dioxide may affect other defense mechanisms of the respiratory tract, like mucociliary transport (compare the findings of reduced pulmonary clearance of inhaled microbes in animals), and cause increased particulate retention as shown by the inhalation of soot; (iii) nitrogen dioxide may be transported more easily to the lungs by absorption to particulates of adequate size; and (iv) nitrogen dioxide may interact with other sensory irritants in stimulating sensory receptors throughout the respiratory tract.

The additivity of effects between nitrogen dioxide and ozone exposures demonstrated with animal infectivity models (27) suggests that serious consideration should be given to the presence of pollutant mixtures in the establishment of air quality standards. It should be noted that such interactive irritation does not necessarily include chemical irritants only. Physical stimulation (like cold air) and reflex-mediated stimulation from other sensory organs may also sometimes be of importance.

The epidemiologic study by Mostardi et al (103, 104) suggests that fairly low annual average concentrations of nitrogen dioxide may have adverse health effects

when the compound appears together with moderate levels of sulfur dioxide (and accompanying pollutants). But the study results need confirmation, and the etiologic role of nitrogen dioxide remains unclear until supporting evidence from other studies is obtained.

It is obvious that we know too little of the detailed etiology behind many of the effects observed after nitrogen dioxide exposure. The great number of possible interactions between nitrogen dioxide and other environmental variables makes it easier, however, to accept the sometimes large discrepancies in results between laboratory studies and epidemiologic investigations of real-life exposures. Furthermore, it is easy to understand that even controlled studies of respiratory effects of nitrogen dioxide may be difficult to reproduce because of the large number of intervening variables that may count in such studies. On the other hand, false positive results may be observed for the same reason as well.

The high probability of interactions between nitrogen dioxide and other pollutants makes it necessary not only to determine limit values for nitrogen dioxide based on its own power to elicit effects, but to determine what proportion of the permissible total irritant pollution can be attributed to nitrogen dioxide. For instance, indoors, nitrogen dioxide may compete with formaldehyde and other organic irritants. This problem cannot be solved on the basis of the scientific facts available at present. However the mere existence of the problem requires that a considerable safety factor be used in the setting of limit values for nitrogen dioxide.

In conclusion, it would seem that, on the basis of current knowledge, the minimum adverse effect level for short-term exposure to nitrogen dioxide should be $900 \mu\text{g}/\text{m}^3$; for sensitive persons it should possibly be even lower. A large safety factor should be added to this value to protect public health.

Specific effects of ozone and oxidants

The health effects of photochemical oxidants, and specifically of ozone, have been reviewed by the US National Academy of Sciences (156), a task group of WHO (170), Ferris (38), and the US Environmental Protection Agency (153). Ozone has long been used as an indicator of photochemical oxidant concentrations, and most studies deal with the health effects of ozone only. The information available does not necessarily reflect the full impact of photochemical oxidants; for instance, only a few studies consider the effects of peroxyacetyl nitrates.

Studies on animals, tissues, and cells

Similar to nitrogen dioxide, ozone can exert a harmful effect on many enzyme systems in cells, as shown in many reports (eg, references 10, 86, 99, 105). On

the other hand, ozone may increase the activity of the enzyme systems which protect against cellular oxidation (14). Some of the toxic effects of ozone are attributed to lipid peroxidation (58), which ultimately leads to cytotoxic breakdown products. Ozone may also release endogenous histamine (1).

Subcellular organelles like mitochondria are affected by ozone exposure and have been used as a sensitive test system for detecting the toxicity of ozone (109). Chromosome damage in hamsters and man have been reported following ozone exposure of around 400–1 000 $\mu\text{g}/\text{m}^3$, but the results are contradictory (60, 93, 100, 173).

The primary target of ozone is the lung. Morphologically the picture following short-term exposure to high levels of ozone is that of acute inflammatory reactions and pulmonary edema. Prolonged exposure to lower levels of ozone produces emphysema, bronchopneumonia, and fibrosis (46). Morphological changes in animals have been observed after short- and long-term exposures at around 400–2 000 $\mu\text{g}/\text{m}^3$ and above. Stephens et al (140) found degeneration and destruction of alveolar cells in rats after short-term exposure to 400 $\mu\text{g}/\text{m}^3$. The renewal rate of alveolar cells in mice was found to increase after short-term exposure to 1 000 $\mu\text{g}/\text{m}^3$ (33) and after long-term exposure to synthetic air pollution containing ozone at around concentrations of 600–800 $\mu\text{g}/\text{m}^3$ (91).

Short-term exposure of small rodents to ozone at $\geq 600 \mu\text{g}/\text{m}^3$ can cause slight pulmonary edema, which is an adverse effect in itself but which, also in some cases, may produce tolerance in the animals towards subsequent higher exposures to ozone or bacterial infections (141). On the other hand, a number of studies on animals have shown that ozone exposure, even at fairly low levels, can increase the sensitivity of the organism to respiratory infections. For instance, Coffin & Gardner (15) and Gardner et al (53) demonstrated a decreased tolerance to laboratory-induced infections in mice after short-term exposures to 160–600 $\mu\text{g}/\text{m}^3$. Many factors may be responsible for this synergism, eg, dysfunction of the alveolar macrophages and inactivation of protective enzyme systems.

The additivity of effects in an animal infectivity model has recently been demonstrated by Ehrlich (27). The most pronounced increases in mortalities from streptococcal pneumonia were observed in mice continuously exposed to a low background concentration level of nitrogen dioxide (380 $\mu\text{g}/\text{m}^3$) with superimposed daily peaks containing mixtures of nitrogen dioxide (1 880 $\mu\text{g}/\text{m}^3$) and ozone (200 $\mu\text{g}/\text{m}^3$).

A main effect of ozone exposure is changes in pulmonary function. Short- and long-term exposures of animals at levels of about 400–600 $\mu\text{g}/\text{m}^3$ produce an increase in respiration rate and airway resistance or a decrease in lung elasticity (3, 143). At present it is not possible to determine the exact mechanism of environment-induced bronchospastic responses. A model sug-

gested by Nadel (110) describes how an inflammatory stimulus such as ozone leads to hyperresponsiveness of the airway smooth muscles. Ozone may initially interact with airway epithelial cells causing these cells to generate and release chemotactic factors (eg, leukotriene 84). These factors mediate the infiltration of neutrophils from the tissue microcirculation into the airway epithelium. The neutrophils are believed to release lipid factors that act on the smooth muscles and their nerves to cause increased contractile responsiveness.

In animals the most sensitive indication of ozone toxicity on behavioral performance is a reduction in spontaneous activity. Reduced motor activity has been found in rodents after short-term exposure to ozone at 400–1 000 $\mu\text{g}/\text{m}^3$ and above (81, 107, 146).

Controlled studies on humans

Pulmonary function. In resting man increased airway resistance has been demonstrated after short-term exposure to ozone at 1 200 to 2 000 $\mu\text{g}/\text{m}^3$ and above (57, 172). However, the impact of ozone exposure becomes more evident during exercise. Many studies show that airway resistance and other pulmonary function effects increase during exercise after short-term exposure at concentrations around 200 to 500 $\mu\text{g}/\text{m}^3$ (24, 76, 88, 114, 133). In contrast, Linn et al (89) did not find any changes in pulmonary function at 400 $\mu\text{g}/\text{m}^3$ in a controlled study of asthmatic patients during short-term exposure, exercise, and heat stress. DeLucia et al (25), studying the effects of ozone and carbon monoxide on exercising healthy humans, found that 1-h exposure to 600 $\mu\text{g}/\text{m}^3$ elicited symptoms of discomfort and 10–15 % decreases in performance in spirometric tests. The combination of ozone and carbon monoxide affected the subjects similarly, whereas exposure to filtered air or carbon monoxide alone did not cause any deterioration in pulmonary function. In three other studies airway resistance was shown to increase after short-term exposure to ozone at 740 $\mu\text{g}/\text{m}^3$ during exercise (43, 61, 66).

Immediately after ozone exposure there is an increased sensitivity to histamine which results in bronchoconstriction (56, 71). The threshold level of ozone causing increased bronchial reactivity to histamine in healthy resting subjects was found to be between 400 and 800 $\mu\text{g}/\text{m}^3$ (7).

The large divergencies in results between investigations indicate that the sensitivity among subjects exposed to low levels of ozone may differ considerably. It appears that most normal nonsmokers who react to ozone at 800 $\mu\text{g}/\text{m}^3$ fall into one of two clearly defined groups, either a very sensitive group or a just slightly sensitive group (34). Linn et al (88), studying the respiratory effect of heavy exercise on 60 subjects in oxidant-polluted ambient air, found significant effects on forced expiration from 1-h exposure to ambient air with ozone levels above 240 $\mu\text{g}/\text{m}^3$ in comparison

to conditions with ozone below that level. A further analysis of the results revealed that some people appear to experience marked physiological decrement without consistent accompanying symptoms and without relationship to a priori physical or clinical status. Thus it is unclear why some individuals are susceptible to oxidant effects and others are not. This is in contrast with the situation concerning sulfur dioxide, where reactivity appears to be greater in asthmatics than in normal persons (87).

It is a well-known phenomenon that repeated exposure to ozone causes adaptation resulting in less pulmonary function change with time (35, 42). Tolerance has been shown to develop to pulmonary effects of ozone at 400–800 $\mu\text{g}/\text{m}^3$, as well as at 1 000 $\mu\text{g}/\text{m}^3$ (7, 73, 82). The number of consecutive days of ozone exposure that was required to produce adaptation varied from 2 to 5. More sensitive persons required more sequential exposures in order to adapt. Adaptation lasted, on the average, for less than two weeks (7–20 d). As proposed by Folinsbee et al (42), the mechanism for adaptation to ozone may be decreased reflex bronchoconstriction by diminished receptor sensitivity or an increased production of mucus in the airways.

Effects on the nervous system. Ozone affects the nervous system in a number of ways. The odor detection threshold for ozone has been determined by Henschler et al (69) to be 40 $\mu\text{g}/\text{m}^3$. Prolonged ozone inhalation at 400 $\mu\text{g}/\text{m}^3$ or above may influence visual parameters in humans, like visual acuity and night vision (84).

One of the early symptoms of exposure to photochemical air pollution is eye irritation, which has been recognized in epidemiologic studies when ozone concentrations exceed 200 $\mu\text{g}/\text{m}^3$ (63). Probably compounds other than ozone are responsible for most of the eye irritation effect. Other complaints evoked by exposure to photochemical smog, and to controlled laboratory exposures of ozone, are headache, dizziness, and irritation of the nose, throat and chest (146).

Epidemiologic studies

Except for some occupational health studies there is no epidemiologic study of the health effects of ozone alone. The studies have primarily concerned the impact of photochemical air pollution, in which ozone is just one compound of many. Although the exact levels of ozone are uncertain, it appears from two studies that photochemical air pollution may impair pulmonary function in patients with chronic respiratory disease at ozone concentrations of about 200–300 $\mu\text{g}/\text{m}^3$ and cause cough and chest discomfort in healthy humans at about 600 $\mu\text{g}/\text{m}^3$ (63, 105). Epidemiologic data by Wayne et al (164), according to which the performance of long-distance runners was affected

by photochemical pollution at ozone levels of above 200–300 $\mu\text{g}/\text{m}^3$, have been questioned. However, their data are given some support by later laboratory studies on the influence of exercise on the impact of ozone.

In Japan a number of epidemiologic studies have been conducted on the relationships between photochemical air pollution and health effects. The Japanese experiences are reviewed in the report of the WHO Task Group (170). According to the review, subjective complaints have frequently been reported among schoolchildren when photochemical oxidant concentrations exceed short-term values of 200–400 $\mu\text{g}/\text{m}^3$. Symptoms include, eg, eye and respiratory irritation. Kagawa & Toyama (77) also reported a correlation between the ambient ozone concentration and airway resistance in schoolchildren over the concentration range of 0–560 $\mu\text{g}/\text{m}^3$.

In the United States an ambient peak 1-h ozone exposure of 200 $\mu\text{g}/\text{m}^3$ was recently found to be associated with a slightly diminished forced vital capacity and forced expiratory volume among healthy schoolchildren in comparison with a peak concentration of less than 160 $\mu\text{g}/\text{m}^3$ (90). It should be noted that the levels of other pollutants (particulate matters, sulfuric acid) were low.

Evaluation of reported effects of ozone and oxidants

Most researchers now seem to agree that adverse short-term effects can occur in some people at the highest ambient ozone concentrations. An expert committee of WHO (168) recommended, already in 1972, a 1-h maximum limit value of 120 $\mu\text{g}/\text{m}^3$ and an 8-h average value of 60 $\mu\text{g}/\text{m}^3$. These recommendations refer to photochemical oxidants as measured by the potassium iodide (KI) method, expressed as ozone, and the recommendations were regarded as long-term goals.

A thorough review and evaluation of the health effects of photochemical oxidants was made in 1977 by another task group of WHO (170). Considering oxidants and ozone together, the group arrived at a number of conclusions which are, in summary, the following: (i) lung function in healthy humans is affected by short-term exposure to ozone at 700–800 $\mu\text{g}/\text{m}^3$ and maybe already at 200 $\mu\text{g}/\text{m}^3$; (ii) some population studies suggest that short-term oxidant levels at ozone concentrations of 200–500 $\mu\text{g}/\text{m}^3$ may affect lung function in children, increase the frequency of asthma, cause more frequent eye irritation, and reduce athletic performance; (iii) short-term oxidant levels at 400–1 400 $\mu\text{g}/\text{m}^3$ may exert additional stress on patients with chronic pulmonary disease; (iv) animal data generally support the results of the human studies, although certain adverse effects of ozone at about 200 $\mu\text{g}/\text{m}^3$ or even less have been observed in animals

only; and (v) the role of ozone and other photochemical oxidants in the etiology of cancer is not clear but should be kept under continual surveillance.

In the opinion of the WHO Task Group (170) a 1-h exposure limit for ozone of 100–200 $\mu\text{g}/\text{m}^3$ would protect public health. The best single value estimate of the exposure limit for oxidants in the ambient air was suggested to be 120 $\mu\text{g}/\text{m}^3$. This value is approximately the same as the highest natural background concentration of oxidants, which precludes the use of any safety factor.

The US national ambient air quality standard for ozone is 240 $\mu\text{g}/\text{m}^3$ as a 1-h average, not to be exceeded more than once per year. Ferris (38) reviewed the literature on this compound and argued that many of the earlier studies may be biased by a significant underestimation of oxidant levels due to errors in the chemical method used (the KI method). However, Ferris supported the earlier (before 1978) short-term US standard (160 $\mu\text{g}/\text{m}^3$) and found no reason for a change until more valid data were collected. According to Ferris there is to date no evidence of health effects from chronic (long-term) exposure to those oxidants that currently occur in Los Angeles. Thorough epidemiologic studies on the long-term health effects of photochemical oxidants are, however, strongly needed.

In conclusion, it would seem that on the basis of current knowledge the minimum adverse effect level for short-term exposure to photochemical oxidants as represented by ozone should be 200 $\mu\text{g}/\text{m}^3$. Since the sometimes high background levels of ozone preclude the use of a large safety factor to protect public health, extra precautions should be prescribed to insure that the minimum adverse effect level is not exceeded.

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