

9. Health risk evaluation and recommended guideline values

Evaluation of health effects

Nitrogen dioxide

Numerous toxicologic, epidemiologic, and controlled human studies have been performed with nitrogen dioxide (NO_2).

Upon inhalation, approximately 80-90% of NO_2 is absorbed and converted to nitrite and nitrate in the blood. Some systemic effects have been observed, such as an influence on the immune system and changes in blood cell counts and serum proteins. However, these effects are less well documented than local effects on the lung, and they seem to be less important in an overall risk assessment.

NO_2 and nitrite are genotoxic *in vitro*. The *in vivo* genotoxicity of NO_2 seems to be low, and it is restricted to lung tissue. There is no clear evidence of a carcinogenic potential of NO_2 , although lung adenomas have been induced in a susceptible strain of mice. Possible secondary risks are imposed by the formation of carcinogenic nitrosamines and the like after the inhalation of NO_2 and the atmospheric formation of mutagenic products of reaction with polycyclic aromatic hydrocarbons and alkenes. Neither quantitative nor qualitative cancer risk estimates can be made for NO_2 exposure. Thus the risk assessment of NO_2 is based on general toxic effects on the lungs and airways.

Upon inhalation, NO_2 penetrates deep into the lung. The primary targets for toxic action are the terminal conducting airways, the alveolar ducts, and the alveoli.

Being a free radical, NO_2 can oxidize polysaturated fatty acids in cell membranes, as well as functional groups of proteins. In animal experiments, lipid peroxidation has been demonstrated after chronic exposure to as low an NO_2 concentration as $75 \mu\text{g}\cdot\text{m}^{-3}$. Generally, however, biochemical changes have been found at considerably higher exposure levels. Around $800 \mu\text{g}\cdot\text{m}^{-3}$ is required for significant morphological changes after subacute and chronic exposure. In one study, $640 \mu\text{g}\cdot\text{m}^{-3}$ for six weeks caused alveolar type II cell hypertrophy and hyperplasia, which is the lowest effect level reported for morphological effects.

NO_2 affects host defense mechanisms. In subacute or chronic animal inhalation studies, effects on ciliated epithelial cells, such as loss of cilia, have been seen at $940 \mu\text{g}\cdot\text{m}^{-3}$, however, without affecting muco-

ciliary clearance. Other demonstrated effects are an impaired function of alveolar macrophages at concentrations down to $560 \mu\text{g}\cdot\text{m}^{-3}$ and an increased susceptibility towards infections provoked by bacteria or viruses (lowest reported effect levels $940 \mu\text{g}\cdot\text{m}^{-3}$ or $370 \mu\text{g}\cdot\text{m}^{-3}$ with daily peaks of $1500 \mu\text{g}\cdot\text{m}^{-3}$).

Prolonged exposure to NO_2 causes decreased pulmonary function in mice and rats, seen as a decrease in lung dynamic compliance and respiratory capacity. These functional effects coincide with morphological changes and have been demonstrated after chronic exposure to concentrations as low as $380 \mu\text{g}\cdot\text{m}^{-3}$ with daily peaks of $1500 \mu\text{g}\cdot\text{m}^{-3}$. In guinea pigs, an increased airway responsiveness to inhaled histamine has been demonstrated after short-term exposure to much higher concentrations of NO_2 ($7500 \mu\text{g}\cdot\text{m}^{-3}$).

The increased airway responsiveness in experimental animal studies is interesting in light of the results from controlled studies on humans. In such studies, NO_2 causes an acute and transient increase in bronchial responsiveness towards histamine or other airway challenges leading to bronchoconstriction. Studies with low doses have shown conflicting results, but a meta-analysis of all studies indicates a lowest effect level of $200 \mu\text{g}\cdot\text{m}^{-3}$ for asthmatics and $2000 \mu\text{g}\cdot\text{m}^{-3}$ for normal subjects. It has also been shown that the inhalation of NO_2 for 0.5-2 h can cause bronchoconstriction (without histamine challenge) in normal subjects (lowest effect level around $4000 \mu\text{g}\cdot\text{m}^{-3}$), patients with chronic obstructive bronchitis and asthmatics (lowest reported effect level $560 \mu\text{g}\cdot\text{m}^{-3}$). The acute lung function effects in humans probably reflect different mechanisms of action when compared with the lung function decrements seen in chronic animal studies.

Different health effects from both short-term and long-term exposures have been observed in epidemiologic studies. Most of the studies concerning acute effects provide some evidence of association with ambient air pollution contaminated by NO_2 in urban and industrialized areas. The long-term average concentrations in the studies ranged from about 10 to $50 \mu\text{g}\cdot\text{m}^{-3}$, with maximum hourly concentrations up to several hundred micrograms of NO_2 per cubic meter of air. The specific role of NO_2 is difficult to define in complex ambient air exposure situations. Furthermore, the reporting of results has

often been based on regression or correlation coefficients and therefore does not permit a determination of threshold or lowest effect levels. Reported effects include annoyance reactions and symptoms from the respiratory tract. Studies on pulmonary function have shown inconsistent results, but asthmatics have been investigated only to a limited extent. Only one epidemiologic study is available on bronchial hyperreactivity, and it showed an increased prevalence among urban children exposed to a long-term average NO_2 concentration of $36 \mu\text{g}\cdot\text{m}^{-3}$. Although the specific role of NO_2 cannot be determined, the result is of particular interest in view of the increased bronchial responsiveness found after controlled exposure to NO_2 .

The evidence most useful for risk assessment concerning the long-term effects of NO_2 comes from a series of about 15 studies on symptoms and diseases of the lower respiratory tract (bronchitis, asthma, pneumonia) in children living in houses with gas appliances. The average NO_2 concentrations measured in such residences (excluding kitchens) range from about 40 to $80 \mu\text{g}\cdot\text{m}^{-3}$, but short-term peaks in kitchens can exceed $1000 \mu\text{g}\cdot\text{m}^{-3}$. A meta-analysis of the studies showed a statistically significant increase in risk of about 20% for lower respiratory tract illness associated with gas appliances, which contributed an average of about $30 \mu\text{g}\cdot\text{m}^{-3}$ to the indoor NO_2 levels. The prevalence of lower respiratory symptoms in adults was related to gas cooking in two of three investigations. Studies on pulmonary function in adults and children from homes with gas appliances provide inconsistent results.

There are also some studies on respiratory symptoms and diseases related to outdoor NO_2 exposure, but these studies are difficult to interpret because of the complex exposure environments. One study on children living near a trinitrotoluene plant and exposed to average levels of about $40\text{--}90 \mu\text{g}\cdot\text{m}^{-3}$ and two studies in urban areas with average concentrations of about $30 \mu\text{g}\cdot\text{m}^{-3}$ indicate increased rates of lower respiratory illness. An increased prevalence of respiratory symptoms among nonsmoking adults was seen in four of six studies with average NO_2 concentrations of about $30\text{--}100 \mu\text{g}\cdot\text{m}^{-3}$.

The epidemiologic evidence of an association between prolonged NO_2 exposure and respiratory diseases is strengthened by the findings of animal studies (ie, that NO_2 affects the respiratory host defense systems), although the NO_2 concentrations used in animal experiments are generally higher than human exposure levels.

Nitric oxide

Vasodilation seems to be one of the most sensitive target mechanisms for nitric oxide (NO) action. The effect occurs *in vitro* at nanomolar or subnanomolar concentrations. In anesthetized sheep and in awake humans significant lung vasodilator effects of NO

at 5 and 10 ppm (6150 and $12\,300 \mu\text{g}\cdot\text{m}^{-3}$), respectively, in inhaled air have been observed, and in guinea pigs bronchodilation occurs at 5 ppm. The value 5 ppm can be regarded as established for acute vascular effects in animals, and 10 ppm can be considered the corresponding value for effects in humans. Animal experiments with inhibitors of endogenous NO formation suggest that pulmonary vasodilator effects of NO at 0.15 ppm ($185 \mu\text{g}\cdot\text{m}^{-3}$) might be expected if individuals with depressed endogenous NO formation exist. It is not clear whether the pulmonary vasodilator effects are to be regarded as adverse or favorable.

Another very sensitive parameter seems to be resistance to infection upon bacterial aerosol exposure, for which impairment of resistance in female mice has been found at an NO level of 2 ppm ($2460 \mu\text{g}\cdot\text{m}^{-3}$). Effects of NO exposure on blood parameters, including leucocytosis, have occurred in mice in chronic NO exposure at 2.4 ppm ($2950 \mu\text{g}\cdot\text{m}^{-3}$).

Whether these effects occur via NO itself or after conversion to NO_2 might have to be reconsidered in the future, since endogenous NO seems to have beneficial effects in defense against infections.

Recommended guideline values

Nitrogen dioxide

A 1-h guideline value for NO_2 ambient air should be based on controlled studies on human subjects, since acute studies with laboratory animals use much higher concentrations. The effect of main concern is the increase of bronchial responsiveness in asthmatics. Although the studies are not consistent, $200 \mu\text{g}\cdot\text{m}^{-3}$ is judged to be the lowest effect level. The effect is small and transient. Still, a safety margin should be applied since the most sensitive subjects (persons with severe asthma) have probably not been studied, delayed effects are not included, and interactions with other pollutants and low temperatures are not included. A 1-h guideline of $100 \mu\text{g}\cdot\text{m}^{-3}$ is recommended. This value also provides a safety margin for the lowest effect level for increased airway resistance in asthmatics, $560 \mu\text{g}\cdot\text{m}^{-3}$. From a public health point of view, a guideline value of $100 \mu\text{g}\cdot\text{m}^{-3}$ does not necessarily have to be treated as a maximum value (never to be exceeded), but could be expressed as, for example, the 99th percentile (can be exceeded 88 h during a year).

The epidemiologic studies on daily rates of annoyance reactions and symptoms from the respiratory tract are inconclusive concerning the specific role of NO_2 , and they are not recommended for use as the basis for a 24-h guideline.

Concerning health effects of long-term exposure

to NO_2 , the studies on children living in homes with gas stoves suggest an increased risk of lower respiratory illness at average indoor concentrations of about $40\text{--}80\ \mu\text{g}\cdot\text{m}^{-3}$, with short-term peaks exceeding $1000\ \mu\text{g}\cdot\text{m}^{-3}$. The epidemiologic studies focusing on outdoor exposure provide some evidence of increased respiratory disease rates in children and nonsmoking adults living in areas with long-term average NO_2 concentrations of $30\text{--}100\ \mu\text{g}\cdot\text{m}^{-3}$; however, the specific role of NO_2 is not clear. The epidemiologic evidence is not considered sufficient as a basis for a long-term guideline for NO_2 .

Data on the distribution of NO_2 concentrations indicate that the recommended 1-h guideline of $100\ \mu\text{g}\cdot\text{m}^{-3}$ (99th percentile) would correspond to a long-term (half-year mean) NO_2 level of about $40\ \mu\text{g}\cdot\text{m}^{-3}$. An outdoor level of $40\ \mu\text{g}\cdot\text{m}^{-3}$ corresponds to an indoor concentration of about $20\text{--}25\ \mu\text{g}\cdot\text{m}^{-3}$ if no indoor sources are present. This value lies below the levels at which effects have been reported after exposure to indoor sources of NO_2 , these effects constituting the most useful evidence for the risk assessment.

In summary, we recommend a short-term (1-h)

health-based guideline value of $100\ \mu\text{g}\cdot\text{m}^{-3}$, which would correspond to a long-term average (half-year mean) of about $40\ \mu\text{g}\cdot\text{m}^{-3}$. The epidemiologic evidence is not considered sufficient as a basis for a long-term guideline for NO_2 . The data are consistent, though, with an excess risk of lower respiratory tract disease among children exposed to long-term average NO_2 concentrations of about 40 to $80\ \mu\text{g}\cdot\text{m}^{-3}$ in homes with gas appliances. The importance of the longer exposure time indoors, as compared with outdoors, and of short-term high exposures for the reported health effects is not clear. In conjunction with some evidence focusing on outdoor NO_2 exposure, it is suggested that a long-term average level of $40\ \mu\text{g}\cdot\text{m}^{-3}$ may only provide a small or no margin of safety.

Nitric oxide

Considering that there are relatively few reports on adverse effects from the inhalation of NO and that it is unclear whether these effects are caused by NO or by NO that has been oxidized to NO_2 , we do not consider it meaningful to suggest a health-based guideline value for NO .