environment and quality of life

A PREPARATORY STUDY FOR ESTABLISHING CRITERIA (DOSE/EFFECT RELATIONSHIPS) FOR NITROGEN OXIDES
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A PREPARATORY STUDY FOR ESTABLISHING CRITERIA (DOSE/EFFECT RELATIONSHIPS) FOR NITROGEN OXIDES

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Summary

This report restricts itself to the two hygienically significant nitrogen oxides:

Nitric oxide (NO) and nitrogen dioxide (NO$_2$)

All other nitrogen oxides (N$_2$O$_3$, N$_2$O$_4$, N$_2$O$_5$, etc.) do not occur in appreciable quantities in ambient air, or as in the case of nitrous oxide (N$_2$O) do not have any known negative effect upon man and his environment except under extreme conditions. Furthermore only data regarding the effect of ambient concentrations or slightly higher levels encountered in occupational exposures are considered.

It is the aim of this paper to point out the complexity of the problem when trying to assess the health effect of NO and NO$_2$: i.e. not only to describe the direct effect of NO$_x$ on man, but also to show the interdependence of the two nitrogen oxides with other systems, resulting in direct or indirect detrimental effects on human health.
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The Programme of Action of the European Communities on the Environment requires that an objective evaluation of the risks to human health and the environment from pollution is carried out. This necessitates the compilation of as complete a bibliography as possible on the effects of the pollutants under consideration and a critical analysis of this information so that criteria (dose/effect relationships) can be determined.

In this Programme of Action nitrogen oxides were chosen for priority investigation on the grounds both of their toxicity and of the current state of knowledge of their significance in the health and ecological fields.

This work has been undertaken by the Health Protection Directorate of the Directorate General for Social Affairs. Meetings of the group of experts directed by the Health Protection Directorate have discussed this report and agreed its contents.

This report, for which the rapporteur was Dr. H.-M. Wagner, is therefore the reference document from which criteria have subsequently been selected.

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Director of Health Protection
Commission of the European Communities
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1) Meeting of 18 February 1975  
2) Meeting of 15, 16 & 17 July 1975  
3) Meeting of 9 & 10 October 1975
1. INTRODUCTION

This report restricts itself to the two hygienically significant nitrogen oxides:

Nitric oxide (NO) and nitrogen dioxide (NO₂)

All other nitrogen oxides (N₂O₃, N₂O₄, N₂O₅, etc.) do not occur in appreciable quantities in ambient air, or as in the case of nitrous oxide (N₂O) do not have any known negative effect upon man and his environment except under extreme conditions. Furthermore only data regarding the effect of ambient concentrations or slightly higher levels encountered in occupational exposures are considered.

It is the aim of this paper to point out the complexity of the problem when trying to assess the health effect of NO and NO₂: i.e. not only to describe the direct effect of NOₓ on man, but also to show the interdependence of the two nitrogen oxides with other systems, resulting in direct or indirect detrimental effects on human health.

A short survey of this complex pattern of direct and indirect action of NOₓ on man is given in the chapter "THE PROBLEM".
In the chapter "EXPOSURE" the attempt is made to demonstrate the extent and intensity in which man is exposed to these two air pollutants.

A condensed evaluation of the findings on health effects research which places special emphasis on those results that in the opinion of the rapporteur are of decisive significance is presented under "Health Effects Summary" in the chapter "HEALTH EFFECTS of NO\textsubscript{x}".

This is followed by a chapter termed "CONCLUSION AND RECOMMENDATION" in which suggestions for future research and measures are made.

As the NO\textsubscript{x}-problem is also a "photochemical smog" problem, a short review of this aspect of NO\textsubscript{x}-pollution is given in the chapter "THE PHOTOCHEMICAL SMOG SYSTEM".

Conversion factors:

The concentrations for NO and NO\textsubscript{2} are given in ppm with the equivalent $\mu$g/m\textsuperscript{3} or mg/m\textsuperscript{3} value in brackets. The conversion factor is temperature dependent, however in almost all cases the values for 25°C are used:

\[ 1 \text{ ppm NO} = 1.23 \text{ mg/m}^3 \quad (1230 \text{ \(\mu\text{g/m}^3\})} \]
\[ 1 \text{ ppm NO}_2 = 1.88 \text{ mg/m}^3 \quad (1880 \text{ \(\mu\text{g/m}^3\})} \]
2. THE PROBLEM

Adverse effects of a pollutant depend on the concentrations reached and the length of time they persist. The priority accorded to any one pollutant depends on how frequently and how closely the known combinations of concentrations and time of persistence approach those at which harmful effects have been demonstrated, and on whether the prevalence of the pollutant is increasing or decreasing in Man's environment.

An appraisal of the hygienic significance of an air pollutant often considers only the direct effect of the compound on human health and often overlooks the fact, that through atmospheric interactions, combinations or new reaction products can be formed, which may be of higher toxicity than the initial pollutant. This latter phenomenon is especially true of the chemically highly aggressive nitrogen oxides.

In fig. 1 the attempt is made to demonstrate the many possibilities in which the nitrogen oxides, directly and indirectly, might affect human health:

2.1. Direct Effect of NO\textsubscript{x} on Man:

Due to their extreme aggressiveness, the nitrogen oxides (NO and NO\textsubscript{2}) react immediately upon contact with the surface of the respiratory tract.

Neither NO nor NO\textsubscript{2} as such reach the capillaries. Only the metabolites nitrite (NO\textsubscript{2}^-) and nitrate (NO\textsubscript{3}^-) are found in the blood. In this they differ from chemically more inert pollutants like lead (Pb) and carbon monoxide (CO) neither of which react as vehemently with the alveolar tissue.
action of $\text{NO}_x$ on man

- $\text{NO}_x$
- other air pollutants
- animals
- vegetation
- materials
- photochemical smog system (HC,sunlight)

- $\Rightarrow$ direct detrimental effect on human health
- $\Rightarrow\Rightarrow\Rightarrow$ indirect effect on human well-being (psychol. stress, economic losses, etc.)
- $\Rightarrow\Rightarrow\Rightarrow$ direct effect on plants, animals, materials, etc.

fig.1
2.2 **Indirect Effect of NO\textsubscript{x} (Reduction and Visibility)**

Nitrogen dioxide absorbs light in the blue region leading to yellow to reddish-brown coloration of the sky and a weakening of the intensity of sunlight. The simultaneous induction of a photochemical smog reaction further enhances the reduction of visibility (STERN, 1968). The possibility of a weakening of the ozone shield in the stratosphere through interaction of ozone with NO\textsubscript{x} may also exist.

2.3 **Effects of NO\textsubscript{x} on other Systems** :

2.3.1 **Combined Effects** :

Nitrogen oxides can combine with other pollutants in the air to form non-photochemical combination products, nitric and nitrous acid, and particulate nitrates. The combined effect to these addition and degradation products on human health have not been studied. Also the simultaneous reactions of NO\textsubscript{2} and other particulate and gaseous pollutants present in the atmosphere on the human respiratory tract are as yet little known.

However, the synergistic and antagonistic effects of air pollutants has been proven for other compounds by many authors (AMDUR, 1954 and 1959; DAUTREBANDE, 1951; LA BELLE, 1955; PATTLE, 1957; STOKINGER, 1957; Van OETTINGEN, 1944).

2.3.2 **Effects on Animals** :

Unlike other air pollutants like lead or fluoride that can cause extensive economic losses by damage to livestock, no accumulation of nitrogen oxides or their metabolites nitrite (NO\textsubscript{2}^-) or nitrate (NO\textsubscript{3}^-) takes place in the animal organism. Ambient concentrations of NO\textsubscript{x},
even in the vicinity of industrial sources, have never reached a level where acute intoxications have been reported. Thus, at the moment, any negative consequences, direct (through ingestion of contaminated meat or other animal products as in the case of heavy metals) or indirect (through economic losses), can be ruled out.

2.3.3 Effects on Vegetation:

The phytotoxicity of nitrogen oxides is not very pronounced. Compared to sulfur dioxide (SO₂), nitrogen dioxide (NO₂) is 2 - 5 times less toxic depending on the plant species tested (VAN HAUT and STRATMANN, 1967, 1975). The authors consider the threshold limit for damage to medium sensitive plants to be 0.43 ppm NO₂ (800 mg NO₂/m³) (see Chapter 5 "EFFECTS OF NOₓ ON VEGETATION").

2.3.4 Effect on Materials:

Nitrogen oxides have a detrimental effect upon the quality of dyes, fabrics, and certain alloys in use for electrical appliances, leading to sizeable economic losses (s. Chapter 6 "EFFECTS OF NOₓ ON MATERIALS").

2.3.5 The "Photochemical Smog" Problem

The photochemical reaction, leading to the air pollution complex termed "photochemical" or "Los Angeles Type" smog is directly induced by NOₓ. NOₓ not only catalyzes, but also takes part in the reaction forming organic and inorganic nitrates and nitrites, peroxides, hydroperoxides, and peroxyacetyl derivates, which are strong irritants.

This "photochemical smog" is considered by many to be
the more serious consequence of NO$_x$-pollution than the effect of NO$_x$ itself.

When considering the toxicity of NO$_x$ on man and his environment, it is imperative to include the phenomenon "photochemical smog" in the evaluation. In chapter 7 "PHOTOCHEMICAL SMOG SYSTEM" a short review of the effects of this air pollutant system is given.
3. EXPOSURE

The hygienic significance of an air pollution depends not only on its initial toxicity, but also on the concentration, the frequency and the time of persistence to which man is exposed to the pollutant, and on the fact whether it is on the increase or decrease in man's environment.

3.1. Sources:

Natural emissions of $\text{NO}_x$ by bacterial transformation of nitrite (JUNGE, 1963) and other biological processes by far exceed the man-made production of $\text{NO}_x$ from anthropogenic sources which stems mainly from the combustion of fossil fuel: Approximately $450 \times 10^6$ metric tons (MT) originate from natural, $45 \times 10^6$ from man-made emissions (ROBINSON, 1970).

Man-made $\text{NO}_x$, however, is emitted in relatively small densely populated areas leading to high concentrations of nitrogen oxides in the direct vicinity of man. Thus the $\text{NO}_x$ levels in urban atmospheres are 10 to 100 times higher than in non-urban regions (EPA, 1971). The ratio of NO to $\text{NO}_2$ is dependent upon the type of source and the meteorological conditions (see under 3.6).

In 1970 $21 \times 10^6$ MT, nearly 50% of the world's total anthropogenic emissions of $\text{NO}_x$ were produced in the United States (DATA FILE OF NATIONWIDE EMISSIONS, 1972).

The emission figures of other countries are far lower. In the Federal Republic of Germany the estimation for the year 1969 was $2 \times 10^6$ MT. Of these 45% derive from transportation emissions, 45% from other combustion processes, and less than 10% are emitted in the course
of chemical processes (BUNDESMINISTER DES INNERN, 1971).

A survey exists giving the 1968 emission data of various countries for stationary emissions only (see Table 1) (REPORT PAC, 1972). The total NO$_x$ emission figure for the EC countries is $3.7 \times 10^6$ MT.

3.2 Total Emission Tendency:

The table also includes a list of estimated emission for the year 1980 indicating the magnitude of the problem regarding the control of NO$_x$ in the future. Owing to the increasing consumption of fossil fuels, NO$_x$ production is rising steadily: In the U.S., for instance, man-made emissions have increased from $15 \times 10^6$ MT in 1966 to $21 \times 10^6$ MT in 1970 (DATA FILE, 1972).

This tendency also manifests itself in a continuous rise of ambient air NO$_x$ levels during the last few years as can be seen from measurements in the Frankfurt area (see under 3.6.3, fig. 2) (JOST, 1974a).

3.3 Emission Control:

Emission control technology, although relatively successful in specific fields has not been able to cope with the constant over-all rise in man-made NO$_x$ emissions.

The various techniques of emission control for stationary and mobile sources are reviewed in two recent publications by the U.S. National Air Pollution Control Administration (NAPCA 1970a, 1970b).

Combustion temperature and fuel/oxygen ratio are the main variables determining NO$_x$ emissions from fossil-fuel burning (BIENSTOCK, 1966; CHAIKIVSKY, 1965; MAY, 1967). Pressure, acid concentration, and temperature are
Table 1

Total Emissions of NO\(_x\) from Stationary Sources in the Year 1968 and

<table>
<thead>
<tr>
<th>Country</th>
<th>NO(_x) in 10(^6) metric tons MT</th>
<th>Year: 1968</th>
<th>Year: 1980</th>
</tr>
</thead>
<tbody>
<tr>
<td>Finland</td>
<td>0.119</td>
<td>0.263</td>
<td></td>
</tr>
<tr>
<td>Sweden</td>
<td>0.105</td>
<td>0.224</td>
<td></td>
</tr>
<tr>
<td>Norway</td>
<td>0.027</td>
<td>0.038</td>
<td></td>
</tr>
<tr>
<td>Denmark</td>
<td>0.056</td>
<td>0.148</td>
<td></td>
</tr>
<tr>
<td>Total:</td>
<td>0.337</td>
<td>0.618</td>
<td></td>
</tr>
<tr>
<td>United Kingdom</td>
<td>1.065</td>
<td>1.19</td>
<td></td>
</tr>
<tr>
<td>The Netherlands</td>
<td>0.220</td>
<td>0.374</td>
<td></td>
</tr>
<tr>
<td>Germany</td>
<td>1.252</td>
<td>1.942</td>
<td></td>
</tr>
<tr>
<td>Belgium</td>
<td>0.177</td>
<td>0.232</td>
<td></td>
</tr>
<tr>
<td>France</td>
<td>0.494</td>
<td>0.533</td>
<td></td>
</tr>
<tr>
<td>Total:</td>
<td>3.216</td>
<td>4.324</td>
<td></td>
</tr>
<tr>
<td>Switzerland</td>
<td>0.035</td>
<td>0.054</td>
<td></td>
</tr>
<tr>
<td>Austria</td>
<td>0.073</td>
<td>0.083</td>
<td></td>
</tr>
<tr>
<td>Total:</td>
<td>0.113</td>
<td>0.132</td>
<td></td>
</tr>
<tr>
<td>Spain</td>
<td>0.210</td>
<td>0.518</td>
<td></td>
</tr>
<tr>
<td>Italy</td>
<td>0.416</td>
<td>1.124</td>
<td></td>
</tr>
<tr>
<td>Greece</td>
<td>0.035</td>
<td>0.116</td>
<td></td>
</tr>
<tr>
<td>Turkey</td>
<td>0.137</td>
<td>0.317</td>
<td></td>
</tr>
<tr>
<td>Total:</td>
<td>0.860</td>
<td>2.075</td>
<td></td>
</tr>
<tr>
<td>United States</td>
<td>9.02</td>
<td>16.61</td>
<td></td>
</tr>
<tr>
<td>Canada</td>
<td>0.31</td>
<td>6.59</td>
<td></td>
</tr>
<tr>
<td>Total:</td>
<td>9.33</td>
<td>16.60</td>
<td></td>
</tr>
<tr>
<td>Japan</td>
<td>0.97</td>
<td>3.36</td>
<td></td>
</tr>
<tr>
<td>Grand total:</td>
<td>14.3</td>
<td>27.1</td>
<td></td>
</tr>
</tbody>
</table>

*Mean of range.*
of decisive influence on NO\textsubscript{\text{x}} generation from chemical processes (DUMMLER, 1974).

Unfortunately control measures for the reduction of carbon monoxide (CO) and hydrocarbons (HC) in motor vehicle exhaust have led to an increase on NO\textsubscript{\text{x}} emissions due to higher combustion temperatures in the cylinders and afterburners. Reduction catalysts converting NO\textsubscript{x} into nitrogen (N\textsubscript{2}) have been reported functioning at the laboratory stage and in limited road tests, but none have as yet attained the stage of technical "maturity" that permits mass production and routine use in motor vehicles with the guarantee of functional stability (KLIMISCH, 1972; MEGUERIAN, 1971; OBLAENDER, 1972).

In other words, a change in the current trend of constantly rising man-made NO\textsubscript{\text{x}} emissions and ambient air concentrations in urban areas is not to be expected in the near future.

3.4 **Elimination from the Atmosphere**

In spite of this marked increase of man-made nitrogen oxides, NO\textsubscript{x} does not accumulate in the atmosphere. The natural removal from ambient air occurs in several ways: by washout (rain), surface reaction (physical and chemical adsorption), microbiological degradation (biological absorption), particulate nitrate formation (after oxidation and reaction with H\textsubscript{2}O), scavenging by hydrocarbons (in "photochemical smog" reaction) (ABELES, 1971; MILLER, 1958; RIPPERTON, 1970; ROBINSON, 1970).

The elimination of NO\textsubscript{2} by soil is usually underestimated: ABELES et al. (1971), calculated from the results of laboratory experiments, that the yearly uptake of NO\textsubscript{2} by soil in the USA is 6 x 10\textsuperscript{8} tons, a capacity large enough to absorb the whole U.S. annual production of NO\textsubscript{x}.
Considering all the removal processes, the residence time of NO and NO\(_2\) is estimated to be 3 - 5 days (JOST, 1974a, ROBINSON, 1970). This indicates, that the elimination is not rapid enough to prevent concentration buildups in densely populated and industrialized areas, but that a global accumulation of atmospheric NO\(_x\) is not to be expected.

3.5 Background Levels of NO\(_x\):

The background concentrations are low:
In remote areas on the European Continent the NO\(_x\) levels vary from 1 to 3 ppb (1.9 to 5.6 \(\mu g/m^3\) calculated as NO\(_2\)) (GEORGII, 1962, 1967), for the North American Continent an average level of about 4 ppb (7.5 \(\mu g/m^3\)) NO\(_2\) and 2 ppb (2.5 \(\mu g/m^3\)) NO was calculated (ROBINSON, 1970).

3.6 Urban Levels:

The highest concentrations on NO\(_x\) in urban atmospheres will be found in streets with dense traffic. Here, in the direct proximity of the emission source, the motor vehicle, the far less toxic nitric oxide (NO) is the predominant nitrogen oxide. The ratio of relative NO to NO\(_2\) concentration in motor vehicle exhaust is 20 : 1 to 10 : 1 (RECAT Report 1972). This is due to the fact that initially during the combustion process NO is produced almost exclusively. The NO\(_2\) measured in ambient air is the reaction product of NO with atmospheric oxygen.

3.6.1 Ratio of NO to NO\(_2\)

Thus, when measured in streets with dense traffic, over 80 % of the total NO\(_x\) will be nitrogen monoxide. In some cases the ratio of NO to NO\(_2\) can even reach 20 to 1
(WALLER, et al., 1961; WAGNER, 1975; REED and BARRET, 1965), at sites further away from traffic — where the absolute NO\textsubscript{x} concentrations are lower — the ratio changes in favour of higher NO\textsubscript{2}-concentrations.

Apart from being determined by the type of source — in emissions from nitric acid plants the NO to NO\textsubscript{2} ratio is 0.33 to 0.5 (HEW 1966)—the varying relation of NO to NO\textsubscript{2} in ambient air is due to the fact that oxidation of NO to NO\textsubscript{2} takes time.

At higher concentrations NO reacts with oxygen in the atmosphere almost instantaneously to form NO\textsubscript{2}:

\[
2 \text{NO} + \text{O}_2 \rightarrow 2 \text{NO}_2
\]

This conversion, however, is extremely slow at ambient concentrations: at 1 ppm the oxidation of 50\% of the NO to NO\textsubscript{2} takes 100 hours (STERN, 1968). In the presence of reactive hydrocarbons and sunlight the reaction can be greatly accelerated owing to photochemical reactions and the intermediate formation of ozone. Under these oxidative conditions the half life of NO at a concentration of 1 ppm is only 1.8 seconds.

Considering the fact, that the conversion of NO to NO\textsubscript{2} requires a definite time, the "photochemical age" of an air parcel can be estimated from the ratio of nitrogen dioxide (NO\textsubscript{2}) to total NO\textsubscript{x}. This is of special interest, when, owing to meteorological conditions (i.e. inversion and a prevailing wind flow from one direction) the air parcel is transported into distant regions. This can aid in tracing the pollutants to their origin (MOSHER, 1970). The direct influence of the light-intensity on the NO:NO\textsubscript{2} ratio can be seen from the comparative measurements of NO and NO\textsubscript{2} in summer and autumn which show the general tendency that NO\textsubscript{2} predom-
inates in summer whereas NO concentrations are highest in the winter months (JOST, 1974b; CCMS Report 1973).

3.6.2 Diurnal Variation Pattern:

The extent of diurnal fluctuations of NO\textsubscript{\text{x}} levels - not caused by meteorological factors - depends on the type of NO\textsubscript{\text{x}} sources dominant in that area.

Motor vehicle emission concentrations vary with traffic density, causing NO concentration peaks to occur in the early morning hours and in the evening with constantly low levels at night. *) A schematic concentration profile is shown in the figure "Daily concentration patterns of motor vehicle exhaust pollutants" in Chapter 7 ("PHOTOCHEMICAL SMOG SYSTEM", fig. 6).

Regions with high industrial and household emissions often show a pronounced higher NO\textsubscript{\text{x}}-level during the night, due to meteorological conditions, i.e. low wind speeds and little turbulence (EMISSIONSKATASTER KÖLN, 1972).

3.6.3 Actual Ambient Concentration Levels:

The urban ambient air concentrations of NO and NO\textsubscript{2} vary greatly due to the above mentioned factors. The information gained from a recent study of NO\textsubscript{\text{x}}-levels in the European Community (JOST, 1974c) shows the monthly averages for NO\textsubscript{\text{x}} or NO\textsubscript{2} to rarely exceed 56.5 ppb (100 μg/m\textsuperscript{3}).

*) The NO\textsubscript{2} peak in the morning hours occurs later than NO because oxidation is slow. In the evening only a slight rise of the NO\textsubscript{\text{x}} level is evident, because no photochemically catalized oxidation takes place.
However, peak levels (24 hr. mean values) of 522 ppb (940 $\mu$g/m$^3$) occurred in Torino, Italy.

Yearly averages for total NO$_x$ (expressed as NO$_2$) in Frankfurt (FRG) were 117 ppb (210 $\mu$g/m$^3$) in the center of the city and reached 139 ppb (250 $\mu$g/m$^3$) when measured in traffic. In the outskirts of town concentrations dropped to less than half of the values obtained.

The annual average concentration of nitrogen dioxide in some European and American cities for the year 1970 are shown in the following table (CCMS REPORT, 1973):

<table>
<thead>
<tr>
<th>City</th>
<th>NO$_2$ ppm</th>
<th>NO$_2$ $\mu$g/m$^3$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Denver</td>
<td>42</td>
<td>75</td>
</tr>
<tr>
<td>Munich *</td>
<td>459</td>
<td>827</td>
</tr>
<tr>
<td>Rome</td>
<td>17</td>
<td>30</td>
</tr>
<tr>
<td>Rotterdam</td>
<td>25</td>
<td>45</td>
</tr>
<tr>
<td>Vlaardingen</td>
<td>22</td>
<td>39</td>
</tr>
<tr>
<td>Washington</td>
<td>52</td>
<td>94</td>
</tr>
</tbody>
</table>

- measured at sites with high motor vehicle traffic density.

The steady increase in emissions (see Chapter 3.2) in the course of recent years is mirrored in the constant rise of ambient levels. Fig. 2 shows a comparison of yearly average NO$_x$-values measured in the city of Frankfurt, Germany (JOST, 1974a):

3.7 Additional Exposures:

Since nitrogen oxides are formed in all combustion processes man is exposed daily to these pollutants not only from the sources mentioned above, but also through occupational contact, and from household fuel consumption and tobacco smoke.
fig. 2 Annual mean concentrations of NO$_x$ in Frankfurt, Germany (from JOST, 1974a)
3.7.1 Occupational Exposure:

Exposure to NO\textsubscript{X} is encountered during welding processes. Here, intoxications still frequently occur.

Average concentrations of 84 ppm NO\textsubscript{X} (158 mg/m\textsuperscript{3}) with maximum values of 93 ppm NO\textsubscript{X} (175 mg/m\textsuperscript{3}) have been reported (MCCORD, 1941; HARROLD, 1940). Although these concentrations occur only under unfavourable conditions (insufficient ventilation) other authors have also reported levels in this range (PRESS, 1974; 1975; NORWOOD, 1966). Other occupation groups for which exposure to elevated NO\textsubscript{x} levels is common are miners, silo fillers, and workers in nitric acid plants.

3.7.2 Household Exposures:

Exposure to NO\textsubscript{X} in the home due to use of gas-burning household appliances is usually underestimated. The recent expansion in the use of natural gas has increased this exposure.

Owing to the higher flame-temperature of natural gas the amount of NO\textsubscript{x} produced is higher by a factor of 1.5 to 2 (MOURIK, 1967; SCHWARZBACH, 1974).

Measurements conducted by SCHWARZBACH (1974) regarding NO\textsubscript{x} formation by household gas-burning appliances (heaters, boilers, stoves) showed that the use of natural gas led to a marked increase of indoor NO\textsubscript{x} levels: in nose-height in the direct proximity of the cooking stove concentrations up to 1 ppm NO\textsubscript{2} (1.9 mg/m\textsuperscript{3}) were measured (see also Chapter 4.3.1.4).

3.7.3 Exposure to Tobacco Smoke:

Special mention must be made of the intense exposure of
man to NO\textsubscript{x} from tobacco smoke. The nitrogen oxide contents of tobacco smoke is very high: BOKHOVEN (1961) reported a total NO\textsubscript{x} content of 170 to 210 ppm in direct cigarette smoke. Of this, 100 ppm was the more aggressive NO\textsubscript{2}, NO\textsubscript{x} (NO + NO\textsubscript{2}), concentrations of over 600 ppm in cigarette and over 1000 ppm in cigar and pipe smoke were measured by HAAGEN-SMIT (1959). Even taking into account the facts that upon inhalation, these mixtures of nitrogen oxides are strongly diluted in the lumen of the lung, the exposure to NO and NO\textsubscript{2} reaches occupational levels during smoking. Non-smokers are also affected by "indirect smoking" (HARKE, 1972).

3.8 Problems Regarding Analysis of NO\textsubscript{x}:

3.8.1 The Problem:

As a recent review of the NO\textsubscript{x}-measurements in several countries of the European Community has shown (JOST, 1974c), intercomparability of the data is rendered extremely difficult by the lack of uniform or standardized analytical procedures. As the report states "there are apparently no site types for which more than two measuring locations are available in different countries using the same analytical technique and sampling time". Furthermore there were great differences in the methods of calibration.

In the U.S. the results of an epidemiological project, the Chattanooga Study (SHY, 1970a; 1970b; PEARLMAN, 1971), were questioned because the reliability of the analytical technique*originally used in the project had been shown to be insufficient (KNELSON, 1975). Only through a fortunate coincidence monitoring data gained with a more reliable analytical procedure, the *) the Jacobs-Hochheiser Method (JACOBS, 1958)
SALTZMAN-method (SALTZMAN, 1954), were available for the Chattanooga area.

These two examples indicate that there is a great need for harmonization and standardization in this field.

3.8.2 The Analytical Methods:

The analytical methods predominantly in use today are:

1. The colorimetric method by SALTZMAN (1954) which can be used for manual as well as continuous analysis.

2. Coulometric determination: These are small, compact, and relatively inexpensive instruments suited for continuous monitoring of 1 component (BREUER, 1970).

3. The photoluminescence procedure: Very expensive, but versatile instruments with two component analysis (NO and NO\textsubscript{x}) in one instrument. Also suited for continuous automatic analysis (FONTIJN, 1970; GUICHERIT, 1972).

3.8.3 Manual Procedures:

The problem lies in the unreliability of some of the manual methods when applied in the field, and the lack of stable commercially available gas mixtures suited for calibration purposes.

Even the most widely used photometric method for the determination of nitrogen oxides, the SALTZMAN method, has been under scrutiny owing to discrepancies regarding the conversion factor of NO\textsubscript{2} into nitrite which is needed for the calculation of the results. It seems that at low ambient concentrations this factor is close to 1. At higher (occupational) levels the factor seems to be approximately 0.75 (BUCK, 1967; FORWERG, 1974; HARTKAMP, 1969; NIETRUCH, 1969).
An additional problem is the fact that the Saltzman procedure is only suited for the determination of nitrogen dioxide (NO₂), not for nitric oxide (NO). Before a determination of total NOₓ (i.e. NO plus NO₂) can be made, NO must be oxidized to NO₂. The oxidizing agents, usually permanganate or chromate, may work (BUCK, 1967; CALHOUN, 1965; FORWERG, 1968; THOMAS, 1956; WILSON, 1968) well under ideal laboratory conditions and within a narrow concentration range, but under field conditions and in routine application, the oxidation efficiency is very often far below 100 % (REPLEY, 1964; ICAC, 1965) resulting in too low total nitrogen oxides (NOₓ) values.

3.8.4 Automated Procedure:

The automated instruments using physical or physico-chemical procedures (photoluminescence, coulometry), although far easier to operate than the instruments based on wet-chemical reactions, are also open to criticism.

They, too, have inherited the principle weakness of NOₓ-analysis: the lack of sufficiently simple and reliable calibration procedures. Only mixtures of nitric oxide (NO) in nitrogen can be considered relatively stable over a short period of time. The permeation tube type instruments, being relatively new, are not yet sufficiently reliable.

Although, with the new type of automated analytical instruments (coulometric and photoluminescence) faults in analysis have been greatly reduced and continuous monitoring rendered simple and reliable, further efforts still have to be undertaken, before NOₓ-analysis can reach a stage of reliability that enables inter-comparison of date as in the case of carbon monoxide (CO).
4. HEALTH EFFECTS OF NITROGEN OXIDES

4.1. Introduction:

In this chapter findings are presented that deal with the effect of low concentrations of nitrogen oxides on humans and experimental animals. The injury caused by exposure to ambient and occupational levels is entirely different from the damage that results from acute intoxication with high concentrations of nitrogen oxides (FLURY, 1931; SCHULTZ, 1930).

The material is also restricted to the effects of the two nitrogen oxides known to be of hygienic significance, nitrogen monoxide (NO) and nitrogen dioxide (NO₂).

Nitrous oxide (N₂O) which is also found in the atmosphere (at concentrations of approximately 0.25 ppm) is considered to be non-toxic. It is used in high concentrations (up to 80 %) as an anaesthetic in medicine. Harmful effects have been reported only after prolonged exposure to extreme concentrations (LASSEN, 1956; SHEPARD, 1967).

All other nitrogen oxides virtually do not occur in ambient air or are present only in traces as shortlived intermediary reaction products.

Recently preliminary results of studies conducted in the United States have become known that seem to indicate that particulate nitrates play a role in the exacerbation of asthma (KNELSON, 1975).

At the present too little is known of this phenomenon to include it into this report.
The two nitrogen oxides, NO and NO$_2$, owing to their slight solubility in water, penetrate deeper into the respiratory tract than other water-soluble gaseous pollutants that are mainly held back in the upper airways (STUPFEL, 1974). Over 80% of the nitrogen oxides are retained in the respiratory tract (WAGNER, 1970).

4.2 Epidemiological Studies:

As mentioned previously, a long term effect of nitrogen oxide exposure is very difficult to prove. The simultaneous presence of other pollutants and the lack both of any specific type of injury and of metabolites of NO$_x$ renders the epidemiological assessment of NO$_x$ induced health effects especially difficult. Essentially there are 4 epidemiological studies which were conducted especially under the aspect of an elevated NO$_x$-exposure to persons. These are: The Cleveland Clinic Study (GREGORY, 1969), The Chattanooga Study (SHY, 1970 a), 1970 b), PEARLMAN, 1971), a Czechoslovakian Study (PETR, 1967) and a recent household survey of the incidence of respiratory disease in relation to environmental pollution (MITCHELL, 1974, in press). Of these, the last 3 are studies of the effect of chronic exposures.

4.2.1 The Cleveland Clinic Study (1929):

The Cleveland Clinic Study (GREGORY, 1969) concerned a short acute exposure with high concentrations due to an accident in the X-ray department of the clinic in which 50,000 nitrocellulose films were ignited. The fumes contained concentrations of nitric oxide (NO) at an estimated concentration of 51.500 ppm (63.3 g/m$^3$). However, also other noxious agents were also present at
high concentrations: carbon monoxide 40,000 ppm (45.9 g/m³) and hydrocyanic acid (HCN) 5,400 ppm (6 g/m³). The latter two noxious agents caused death within two hours (for 97 persons).

The death of 26 additional individuals who died in the course of a month following the incidence and in 92 other non-fatal cases nitrogen oxides were held responsible for the effects.

An epidemiological study was conducted in 1965 to see where the survival rates and expected survival rates of these persons having been exposed to high concentration of nitrogen oxides for short duration were in any way affected. No statistical difference could be found between the exposed and unexposed groups.

4.2.2 The Chattanooga Study:

This very elaborate study took into consideration not only nitrogen oxides but also other air pollutants in the area (SHY, 1970a; SHY, 1970b; PEARLMAN, 1971). Besides measurements of NO₂, 24 hr. ambient air analyses of suspended particulate matter, suspended nitrates, suspended sulfates, were performed. These measurements were conducted intermittently over the years 1968 to 1969. The pollutant source, the emissions of which dominated the whole area, was a trinitrotoluene (TNT) plant of very high capacity. The main pollutant emitted by this factory was NO₂.

The investigators took into consideration 3 possible health effects:

1) Impaired ventilatory function in elementary school children.

2) Increased frequency of acute respiratory illness.
3) Impaired host resistance during epidemic influenza.

For the study the area was divided into 4 parts:

1) An area with high NO₂-exposure,
2) an area with high levels of suspended particulates with relatively low NO₂-concentrations,
3) a control area containing both low NO₂ and low suspended particulate level, and
4) a second control area with the same qualifications.

The annual arithmetic mean for the high NO₂-exposure areas was 0.08 - 0.15 ppm (150-282 µg/m³), for the control region 0.03 ppm (56 µg/m³) NO₂. The 90th percentile values were 0.15-0.5 ppm (282-940 µg/m³) for the high, and 0.05 (94 µg/m³) for the low exposure area.

At a later date PEARLMAN (1971) conducted a follow-up study, in which he included the prevalence of acute lower respiratory illness among children in 3 of the above mentioned areas. The results of the study show that the lung function parameters are a suitable indicator for the determination of an influence of air pollutants. The ventilatory performance of the children in the high NO₂ area was significantly less than that of children in the control areas. For this part of the study 987 children took part in the measurements of forced expiratory volume in 0.75 sec (FEV₀,₇₅).

The respiratory illness rates showed a higher incidence in the families from the high NO₂ and high particulate areas. The relative excess was 18.8 % in the high NO₂ area and 10.4 % in the high particulate area. This study encompassed a total of 4,043 individuals in 871 families.
The retrospective study regarding acute lower respiratory illness among children, in which approximately 3,000 participated, also showed a highly interesting result. The parameters studied were a frequency of croup, bronchitis, pneumonia, and asthma during the 3-year-period from July 1966 through June 1969. In the area with high NO₂-exposure a significant increase in acute bronchitis was obvious. Croup, pneumonia, and hospitalizations for acute lower respiratory illness did not show significant area differences.

The Chattanooga Study was re-evaluated recently due to discrepancies regarding the analytical procedure used for the determination of NO₂ in that area. By comparison with studies conducted parallel by the U.S. Forces in the same area corrections regarding the concentrations of NO₂ were necessary.

The conclusion is that an annual average concentration of about 0.08 to 0.15 ppm (150 to 282 μg/m³) was associated with adverse health effects in Chattanooga. Since increasing emphasis is placed on the significance of peak level exposure, regarding health impairment, hourly concentration peaks were calculated over one year. From these data lung function impairment would result from exposure to repeated 2 - 3 hr daily peak NO₂ concentrations of 0.15 ppm to 0.50 ppm (282 to 940 μg/m³) (SHY, 1973).

4.2.3 Czeckoslovakian Study:

PETR (1967) conducted comparative studies of Czeckoslovakian children living in three towns with different air pollutant patterns. In one town SO₂ predominated, with concentrations ranging from 0.01 to 0.12 ppm (30 to 320 μg/m³), NOₓ also being present but at a
much lower concentration 5 to 50 μg/m$^3$ (for an undefined mixture of NO and NO$_2$ it is not possible to express the value in ppm).

In the other town in which NO$_x$ was the main air pollutant the ambient NO$_x$ concentration ranged from 20 to 70 μg/m$^3$. The mean SO$_2$-level in this area was 0.005 ppm (12 μg/m$^3$).

Finally a control town was selected with virtually no sizeable air pollution sources. The parameters studied in the children were erythrocyte fragility, Met-hemoglobin levels, and blood cell counts in the smears of peripheral blood.

The researchers observed an increase in resistance of erythrocytes to hemolysis and an increase in number of immature red blood cells in the children from the high NO$_2$ area, and also from the high SO$_2$ area, as compared to the children from the control. This was interpreted as the compensatory response of the children to the pollutants in their environment.

The findings were confirmed by animal experiments with mixtures of interrelated ambient gases containing NO$_2$ (SCHLIPKOETER, 1973).

The Met-hemoglobin levels in the high NO$_2$ area were significantly higher (2.5 % Met-hemoglobin) than in the blood from the children of the control area (0.86 %). This difference was significant, however, a possible effect from high nitrate content of drinking water must be taken into account. A follow-up study at a later date, after the high NO$_2$ emissions had been reduced, showed no increase of Met-hemoglobin level in the same group of children.
4.2.4 Household Survey:

The household survey was conducted recently to study possible effects of nitrogen oxides and other pollutants in families cooking by gas as compared to those using electricity (MITCHELL, 1974). It included 441 families divided into two groups. The NO\textsubscript{2} levels in the households of the families using gas was significantly higher than in the compared group. The peak NO\textsubscript{2} levels in gas cooking mode households while cooking by gas were generally 8 times higher than the 24 hr average. In some cases the values exceeded 1 ppm. The participants were contacted by telephone every 2 weeks to obtain records of respiratory illness among members of the household during that period. Furthermore, pulmonary function screening tests were conducted for the detection of chronic respiratory impairment. Forced vital capacity and 0.75 sec forced expiratory volume were measured.

The concentration range for NO\textsubscript{2} in the homes using gas was 5 to 110 ppb (9.5 - 209 \(\mu\text{g}/\text{m}^3\)), for NO 10 to 410 ppb (12 - 492 \(\mu\text{g}/\text{m}^3\)). In the homes with electric cooking 0 to 60 ppb (0 - 114 \(\mu\text{g}/\text{m}^3\)) for NO\textsubscript{2} and 0 to 340 ppb (0 - 408 \(\mu\text{g}/\text{m}^3\)) for NO. At the same time the outdoor levels ranged from 15 to 50 ppb (2.9 - 95 \(\mu\text{g}/\text{m}^3\)) for NO\textsubscript{2} and 50 to 220 ppb (60 - 264 \(\mu\text{g}/\text{m}^3\)) for NO.

The result of the study showed no significant difference in reported respiratory illness frequency between household members cooking with gas and those cooking with electricity. A comparison of lower respiratory illness also showed no significant difference between the two groups.
This study, however, does not take into account that the increasing use of natural gas is accompanied with a production of nitrogen oxides during combustion of this gas (see Chapter 3.7.2). Thus, in households where natural gas is used for cooking, higher concentrations of nitrogen oxides would result.
4.3 Health Effect of Nitric Oxide (NO)

Due to the almost instantaneous conversion of NO to NO$_2$ in high concentrations (see Chapter 3.6.1), it is very difficult to expose man or experimental animals to controlled atmospheres containing only NO. This is the reason why very little data exist on the effect of pure NO.

In spite of a high affinity of NO for hemoglobin, as can be seen from in vitro experiments, no NO.Hb or NO. methemoglobin could be detected in vivo even after rats were exposed to concentrations of 10 ppm NO for up to 9 days (SANCIER, 1962).

An elevation of methemoglobin-levels becomes detectable in blood of humans only after exposure to NO concentrations of 15 - 20 ppm (18.5 - 24.6 mg/m$^3$) (NIEDING, 1973a). In rats this threshold lies between 5 and 10 ppm (6.2 - 12.3 mg/m$^3$) (WAGNER, 1975) (see also Chapter 4.4.2).

An experiment with very high concentrations conducted by FLURY (1931) demonstrates the very important feature of NO. After an exposure of several minutes to 2500 ppm (3075 mg/m$^3$) death occurred in mice within 12 minutes. If the exposure was interrupted after 7 minutes the animals recovered without showing any prolonged effects. This indicates that NO itself has almost no irritant quality in the sense of destructive surface reactions with the linings of the respiratory tract.

4.3.1 Human Exposures:

In an experiment conducted by NIEDING, (1973a) a total of 191 healthy subjects was exposed to NO at concen-
trations up to 40 ppm (49 mg/m$^3$). Due to the experimental set-up only traces of NO$_2$ (as an average 1 to 2% of the NO concentration) were present in the inhaled mixture. The duration of exposure to the NO/air mixtures was 15 minutes.

Measurements of breathing mechanics were performed by means of whole body plethysmography. Furthermore alveolar oxygen and carbon dioxide partial pressures, and the blood gases were measured. Finally the diffusion capacity of the lung for CO and the Met-hemoglobin level of venous blood was determined.

No influence on arterial oxygen partial pressure could be detected upon inhalation of air containing NO-concentration below 15 ppm (18.5 mg/m$^3$). At concentrations between 15 and 19.9 ppm (18.5 and 24.5 mg/m$^3$) a mean partial pressure of oxygen in arterial blood decrease of 7 Torr (mm mercury) occurred. This decrease reached a value of 8 Torr when the concentration was raised to 20.0 till 29.9 ppm (24.6 - 36.8 mg/m$^3$).

The alveolar-arterial $O_2$-pressure difference showed an increase only at concentrations above 15 ppm. At all NO-concentrations used, neither the values for CO$_2$ gas exchange nor the pH showed any significant change due to NO-exposure.

The diffusion capacity of the lung for CO ($D_{LCO}$) did not decrease even at concentrations ranging from 20 to 39 ppm (24.6 - 48 mg/m$^3$). After exposure to concentrations over 30 ppm (37 mg/m$^3$) the $D_{LCO}$ decreased as an average by 0.4 ml · min$^{-1}$ · Torr$^{-1}$; this, however, was not statistically significant.

Airway resistance as measured before and after a 15
minutes' exposure to NO at concentrations above 20.0 ppm (24.6 mg/m$^3$) showed a statistically significant increase, the mean value being more than 0.5 cm H$_2$O/L/sec. The TGV, however, did not change at all concentrations studied.

The Met-hemoglobin concentration was measured before, during, and after the 15 min' inhalation of the nitrogen oxide-air mixture. At concentrations between 10.0 up to 14.9 ppm (12.3 - 18.3 mg/m$^3$) NO a slight but statistically not significant Met-hemoglobin increase is noticeable. At concentrations above 15.0 ppm (18.5 mg/m$^3$) this increase becomes significant. There is a direct relationship between the NO concentration of the inhaled air and Met-hemoglobin formation: the mean increase of the met-hemoglobin in blood at a NO concentration of 15.0 to 19.9 ppm (18.5 - 24.5 mg/m$^3$) was 0.22 % Met-hemoglobin, the mean Met-hemoglobin value prior to inhalation being 0.84 %. At concentrations of 20.0 to 29.9 ppm (24.6 - 36.8 mg/m$^3$) the increase was 0.52 % (the initial mean value was 0.72 %).

Note:

Airway resistance ($R_t$) in (cm H$_2$O · l$^{-1}$ · sec)
Alveolar oxygen partial pressure ($P_{A02}$) in Torr
Diffusion Capacity for CO ($D_{LCO}$) in ml. min$^{-1}$. Torr$^{-1}$
Interthoracic gas volume (GV)

4.4 Effects of Nitrogen Dioxide on Man and Experimental Animals:

Nitrogen dioxide is an extremely aggressive gas. Its chemical aggressiveness causes it to combine almost
instantaneously with most substances it comes into contact with. On inhalation it reacts vehemently with the lining cells of the respiratory tract and the alveoli leading to strong irritation, and, in high concentrations, to edema of the lung and death by congestion (FLURY, 1931; SCHULTZ, 1930).

Concentrations of 100 to 1000 ppm NO₂ (188 to 1.880 mg/m³) cause death in most animal species (GRAY, 1954).

4.4.1 Human Experimental Exposures:

4.4.1.1 Effect of NO₂ on the Human Respiratory Tract:

Studies of the acute effects of NO₂ on lung function, i.e. the influence on diffusion, perfusion, and ventilation of the lungs were conducted by NIEDING et al. (1970, 1971, 1973b). 55 healthy male subjects and 48 male patients suffering from chronic bronchitis were investigated upon their reaction to NO₂ exposure over 15 min and in some cases to an exposure up to 60 min from concentrations up to 5 ppm. The parameters measured were:

1) the arterial O₂ and CO₂ pressure (PaO₂) (PaCO₂) and the arterial hydrogen-ion-concentration (pHₐ).

2) The end expiratory O₂ and CO₂ gas partial pressures (PₐO₂) and (PₐCO₂).

3) In 13 healthy individuals, the mixed-venous pH, the cardiac output, heart rate, stroke volume, and systolic pressure in the pulmonary artery by means of a venous catheter.

4) In 14 patients the respiratory O₂ and CO₂ gas exchange before, during, and after inhalation of NO₂ over 60 min (as compared to the normal 15 min' exposure) were measured.
The result of the study was:

1. **CO diffusing capacity**: The diffusing capacity for CO of the lungs decreased significantly in the healthy subjects by an average of 3.8 ml min$^{-1}$ Torr$^{-1}$ (from 20.6 to 16.8 following an inhalation of 5 ppm NO$_2$ over 15 min.

2. **Respiratory gas exchange**: When the alveolar partial pressure before, during, and after NO$_2$ inhalations were compared the mean values for the chronic bronchitis patients tested did not show any changes that could be statistically confirmed. Accordingly, the alveolar O$_2$ partial pressure remained practically unchanged during all 3 test phases. The arterial O$_2$ partial pressure, however, decreased from an average of 76.5 to 71.3 Torr during the first 15 min of NO$_2$ inhalation and did not change significantly during the continued inhalation of NO$_2$.

Accordingly, the alveolo-arterial O$_2$ pressure gradients increased significantly from an average of 25.7 to 32.3 Torr (Fig. 3). A comparison of the alveolar-arterial O$_2$ pressure gradients after 15 min of NO$_2$ exposure and after 60 min exposure did not reveal any significant disturbances of respiratory gas exchange beyond the extent of those observed after 15 min of NO$_2$ exposure. For CO$_2$ gas exchange and pH no significant changes could be observed.

3. **Air-way resistance (R$_t$)**: When comparing the individual resistance values for cases of chronic bronchitis (initial values between 3.5 and 10.0 cm H$_2$O/L/sec before and after NO$_2$ inhalation a dependency of the relative R$_t$ increase upon the
The diagram shows the distribution of values in different ppm ranges:

- **> 2.5 ppm**
  - Value: 5.84
  - p-value: < 0.001
  - n = 14

- **2.1 - 2.5 ppm**
  - Value: 3.95
  - p-value: > 0.01
  - n = 10

- **1.6 - 2.0 ppm**
  - Value: 5.63
  - p-value: > 0.05
  - n = 15

- **1.1 - 1.5 ppm**
  - Value: 4.77
  - p-value: > 0.1
  - n = 10

- **≤ 1.0 ppm**
  - Value: 5.01
  - p-value: > 0.1
  - n = 14

The x-axis represents the ppm values, and the y-axis represents the number of measurements (n).
NO₂ concentration appears to be present. There seems to be no effect in concentrations between 1.0 and 1.5 ppm NO₂. At a range between 1.6 and 2.0 ppm, a slight but significant effect on airway resistance is noticeable. Above 2 ppm the increase becomes more significant (Fig. 4).

It has been demonstrated by the present and preceding studies (NIEDING, 1970, 1971, 1973b) that concentrations of 5 ppm and less will clearly affect cardiopulmonary functions even after short-term-inhalation. These findings are at concentrations corresponding to the German MAC-value of 5 ppm NO₂ (DEUTSCHE FORSCHUNGSGEMEINSCHAFT, 1972) and below. The decrease of the arterial oxygen partial pressure seen, may be attributed to various functional mechanisms, as pulmonary diffusion, perfusion, or ventilation. The impaired diffusion for CO, previously demonstrated in animal experiments by HENSCHLER (1964a) occurred in healthy human subjects after acute exposure to MAC-value concentrations.

These MAC-concentrations are even exceeded by the levels occurring in tobacco smoke. Here, for short periods even higher NO₂ and NO concentrations are inhaled. The fact that even a prolongation of NO₂ exposure (Chap. 3.7.3) up to 60 min does not lead to a further decrease of arterial oxygen partial pressure must be interpreted in this way, that possibly mechanisms are triggered, which minimize the further NO₂ effect. It is possible that after the first few minutes of exposure the protective mechanism described for irritant gases by STOKINGER (1956) and HENSCHLER (1964 a, 1964 b) is induced.
Summarizing the results there is a complex reaction of all partial functions of the lungs to NO\textsubscript{2} inhalations comprising changes in the distribution of the ventilation, ventilation-perfusion, and the ventilation-diffusion ratio.

4.4.1.2 Met-hemoglobin Formation:

As with nitric oxide (NO) (see Chapter 4.2.2) nitrogen dioxide inhalation is associated with Met-hemoglobin formation. The concentrations necessary to effect this phenomenon, however, are quite high.

An exposure from 2 to 6 hrs to 10 ppm NO\textsubscript{2} (18.8 mg/m\textsuperscript{3}) caused no measurable increase of Met-hemoglobin in volunteers. Inhalation of air containing 20 ppm NO\textsubscript{2} over 2 hrs resulted in a mean increase of 0.95 % Met-hemoglobin. Exposures at these concentrations of longer duration or to higher NO\textsubscript{2} levels were considered detrimental to health by the author (HENSCHLER, 1963).

4.4.1.3 Odour Perception

The threshold for odour perception in NO\textsubscript{2} depends very much on the mode of applying the NO\textsubscript{2}-containing air mixture to the test person. A very slow but continuous rise of the NO\textsubscript{2} concentration will cause the moment of odour perception to be much later than in the case of an sudden exposure to a given concentration.

HENSCHLER (1960) in experiments with healthy male volunteers determined the olfactory threshold: 35 % of the individuals perceived the odour at a concentration of 0.12 ppm (225 ug/m\textsuperscript{3}), 61 % at a level of 0.22 ppm (415 ug/m\textsuperscript{3}) and 100 % at a concentration of 0.42 ppm (0.835 mg/m\textsuperscript{3}). The author describes, how-
ever, that virtually no odour perception took place when the concentration was raised slowly within 15 min from 0 ppm to approximately 15 ppm (47 mg/m$^3$) due to adaptation.

4.4.2. Occupational Exposure:

Data regarding occupational exposures to NO$_x$ is contradictory. Simultaneously with nitrogen oxides usually high concentrations of other gaseous and particulate pollutants are present (as in welding, mining, etc.).

VIGDORTSCHIK (1937) describes effects of NO$_x$ after a 3 to 5 years' exposure to concentrations of about 2.5 ppm (4.7 mg/NO$_2$/m$^3$). Emphysema, chronic bronchitis and other symptoms were seen. There was evidence indicating the possibility of the formation of pulmonary fibrosis by the chronic inhalation of nitrogen oxides.

This was corroborated by the findings of KOSMIDER (1972) who also found elevated urinary hydroxyproline levels amongst workers chronically exposed to NO$_2$ levels of 0.4 to 2.7 ppm NO$_2$ (0.75 - 5.1 mg/m$^3$).

PATTY (1963) found no symptoms which could be attributed to the continuous exposure to nitrogen oxides in spite of the fact that the workers examined had been exposed for 18 months to daily concentrations ranging from 5 to 30 ppm (9.4 - 56.6 mg/NO$_2$/m$^3$), the mean concentration being 10 to 20 ppm (16.8 - 37 mg/m$^3$). Other authors also reported negative findings (COLLEN, 1944; BAETJER, 1950).

4.4.3 Effect of Nitrogen Dioxide on Animals:
4.4.3.1 Lethal Concentrations:

Depending on the duration of exposure nitrogen dioxide levels of 100 to 1000 ppm (188 to 1880 mg/m³) are lethal to most animals (GRAY, 1954).

4.4.3.2 The Effect of NO₂ on Pulmonary Function in Animals:

The respiratory tract of animals studied in laboratory experiments seems to be relatively resistant towards low concentrations of NO₂. Several authors have described no effect in concentrations ranging from 5 ppm (9.4 mg/m³) on guinea pigs (BALCHUM, 1965), from 1 to 5 ppm NO₂ (1.88-9.4 mg/m³) (WAGNER, 1965) in rabbits and beagles exposed to 0.5 to 2 ppm (0.94-3.8 mg/m³) with the simultaneous presence of 0.2 ppm NO (VAUGHAN, 1969). All of these experiments were conducted over a relatively long time and can be termed as "Chronic or Semichronic Experiments".

Acute exposures only resulted in reversible changes in respiratory rates and tidal volumes (MURPHY, 1964; HENRY, 1969). Guinea pigs exposed to concentrations of 16 to 50 ppm (19.7 - 94.0 mg/m³) for 4 hrs showed no impairment of pulmonary function (MURPHY, 1964).

Using the O₂ partial pressure (P₀₂) in brain tissue of rats as an indirect indicator of lung function impairment (ZORN, 1975) showed that an exposure of 6-8 hrs in the concentration range of 0.5 - 20 ppm NO₂ (0.94 - 37.6 mg/m³) resulted in a decrease of P₀₂. The lowest concentration of NO₂ showing a statistically significant decrease of P₀₂ was 0.5 pp.

4.4.3.3 Emphysematous Lesions:

The chronic exposure to nitrogen oxides leads to pre-
emphysematous lesions indicative of the later development of emphysema. This effect could be seen at concentrations as low as 0.5 ppm (940 μg/m$^3$) in mice. The duration of exposure ranged from 3 – 12 months (BLAIR, 1969). The continuous exposure of young rats to concentrations of 10 to 25 ppm (18.8 to 47.0 mg/m$^3$) after several months of exposure showed gross pathological changes resembling emphysema. A loss of cilia, distended peripheral alveoli and changes in collagen and elastic tissue particularly in the regions of the alveolar ducts (FREEMAN, 1964, 1968a, 1968b, 1969a; HAYDON, 1965).

Part of the effects seen were reversible. The hypertrophic epithelium of the lungs receded and cilia re-appeared. However, the previously exposed rats had lungs of excessive weight as compared with controls of the same age (FREEMAN, 1969b).

Morphometry by FREEMAN (1968b) showed that detrimental effects caused by 15 ppm NO$_2$ (28.2 mg/m$^3$) reduced the total number of air spaces in the entire lung as much as 50% compared with controls and that the reduction in alveolar surface area is approximately 25%. Thus the biologic reactive surface of the lung, necessary for optimal gas exchange is reduced by more than a quarter. Similar changes in collagen of rat lungs occurred with exposures of approximately the same concentrations when the experiments were conducted over the whole life time of the rats (STEPHENS, 1971).

4.4.3.4 Cellular Reaction in the Respiratory Tract:

The continuous exposure to 17 ppm of NO$_2$ (32.0 mg/m$^3$) induced cell hyperplasia of terminal bronchiolar and type 2 pneumocyte cells and macrophage in rat lung (EVANS, 1971). This effect, in spite of continued
exposure, began to decline following a peak after 24 hrs. The tissue returned to normal within a week.

HENSCHLER (1966) also showed cell proliferation in the terminal bronchioli due to continuous exposure to NO₂. In his experiment, however, far higher concentrations were used (40 ppm NO₂), i.e. 76 mg/m³).

The reaction at the cellular level upon the exposure to NO₂ can also be seen in changes of cell population. Continuous exposure to 2 ppm (3.8 mg/m³) of NO₂ for 3 days caused alterations in the terminal bronchiolar epithelium of rats. This change of type 1 pneumocytes into the more cuboidal type 2 can be considered as a protective measure of the organism, because the diffusion distance for toxic agents is greater in the enlarged cuboidal cells. Furthermore ciliary cells did not develop normally (FREEMAN, 1968a, 1968b, 1972; SHERWIN, 1972; STEPHENS, 1971).

4.4.3.5 Alterations of Proteins:

Rabbits exposed for 1 hr. to 1 ppm (1.9 mg/m³) and 5 ppm NO₂ (9.4 ppm mg/m³) led to a configuration change in collagen and elastin. This denaturation of collagen and elastin was shown to be reversible when the animals were sacrificed 24 hrs. after determination of exposure (BUELL, 1966). An exposure of rabbits to lower concentrations, 0.25 ppm (470 μg/m³) for 4 hrs. per day for 6 days showed irreversible structural changes in lung collagen as determined by electron microscopy (MUELLER, 1969).

Owing to increased collagen and elastin catabolism in the lung the hydroxyproline excretion is also increased in rats exposed to concentrations of 1 - 30
ppm NO₂ (1.88 - 56.4 mg/m³) for 6 to 8 hours (LINDNER, 1975).

4.4.3.6 Lipid Peroxidation:

An effect that might be explained with the radio-mimetic properties of nitrogen oxide is the phenomenon of increased lipid peroxidation. Extracts of the lipids from the lungs of rats previously exposed to 1 ppm (1.9 mg/m³) of NO₂ for 4 hours showed evidence of peroxidation of lipids. The values increased when the exposure was repeated for 6 days at the same concentration giving an indication of a cumulative effect (THOMAS, 1968; ROEHM, 1970).

4.4.3.7 Impaired Resistance to Infection:

An enhanced susceptibility of the respiratory tract to infections is noticeable when animals are acutely or chronically exposed to NO₂. The effects occur at concentrations as low as 0.5 ppm (0.9 μg/m³).

After acute or chronic pre-exposure to NO₂ at various levels from 0.5 to 25 ppm (0.9 - 45 mg/m³) the animals (mice, hamsters, squirrel monkeys) were challenged with respiratory pathogens (Klebsiella pneumonia, influenza virus). As compared to the controls which were exposed to the pathogens only, the mortality increased significantly. The rate of clearance of bacteria from the lung was reduced, and the pulmonary macrophages functionally impaired (EHRLICH, 1966; 1968; HENRY, 1969, 1970; GARDNER, 1969; GOLDSTEIN, 1973).

4.4.3.8 Reduction of Physical Performance:

If rats are acutely exposed to 5 ppm (9 mg/m³) NO₂
during swimming their physical performance is reduced markedly when compared with unexposed controls. An adaptation does not take place. Chronic exposure to the same concentration also led to significant reduction in swimming performance of the exposed group after 6 months (TUSL, 1973; WAGNER, 1975).

The voluntary running activity of mice is also reduced by acute exposures to concentrations of 7.7 ppm NO₂ (14.5 mg/m³) or higher (MURPHY, 1964).

4.4.3.9 Serum Cholesterol Levels:

Serum cholesterol levels in rats increased after long-term exposure to 5 ppm (9 mg/m³) NO₂. The controls also showed an age-induced rise of serum cholesterol, however, the increase in the exposed rats was greater (WAGNER, 1972). The effect became statistically significant after 12 months and increased with continuing exposure.

A similar rise in cholesterol levels occurred in guinea pigs after exposure to 1 ppm NOₓ (NO + NO₂) for 8 hours daily for 180 days. The exact level of NO₂ was not given (KOSMIDER, 1973).

4.4.3.10 Weight Loss:

Regarding weight loss the findings are contradictory. While some authors describe a marked reduction in the rate of weight gain in rats and rabbits after chronic exposure to concentrations in the range of 3 ppm (3.6 mg/m³) to 12 ppm (22.6 mg/m³) NO₂ (MITINA, 1962; FREEMAN, 1968a), other authors find no such an effect in mice, rabbits, guinea pigs, rats, hamsters, or dogs under chronic exposure at various concentrations from 0.5 ppm (0.95 mg/m³) to 25 ppm (47.5 mg/m³)NO₂ or

4.4.3.11 Immunological Effects:

Nitrogen dioxide when applied chronically over several months in concentrations of 5 ppm (9 mg/m³) seem to induce an immunobiological response in guinea pigs. A direct in vitro reaction of antibody from animals exposed one year to 15 ppm (27 mg/m³) NO₂ occurred with lung protein extracts of control animals (BALCHUM, 1965).

Normal immunological response to antigens (fresh chicken albumen plus Freud's adjuvans) was not influenced by exposure to 5.5 ppm (10 mg/m³) NO₂ for 33 days (ANTWEILER, 1975).

4.4.3.12 Other Effects:

Tissue changes: HENRY (1969) describes tissue changes in different organs not immediately exposed to the gas after acute inhalation of various concentrations of nitrogen oxides. These organs were: kidneys, liver, and heart of squirrel monkeys. At an exposure level of 15 ppm (28.2 mg/m³) tubular erosions appeared in the kidneys; also liver cells showed marked changes. At higher concentrations (35 ppm and 50 ppm) heart, kidney, and liver tissues showed even greater signs of a detrimental effect (interstitial fibrosis, interstitial edema, and infiltration by lymphocytes in kidney and the lung).

The fact that NO₂ might influence the level of urinary protein excretion is indicated by the findings of SHERWIN (1974): guinea pigs exposed to 0.5 ppm NO₂ (0.94 mg/m³) for 7 - 14 days all showed consistently
higher levels of urinary albumins, $\alpha$- and $\beta$-globulins, and $\gamma$-globulins than control animals. This phenomenon occurred even when the exposure was reduced to 4 hours per day (for 5 - 14 days).

4.4.3.13 Combination Effects ($\text{NO}_x$ Combined with Other Pollutants):

Tobacco Smoke:

Tobacco smoke and NO$_2$ effects on hamster lungs were compared. The NO$_2$ concentration was 15 ppm (28.2 mg/m$^3$), the tobacco smoke was 3% by volume. The exposure which lasted 2 hrs. in the case of NO$_2$ and 1 hr. in the case of tobacco smoke left no marked effects on the hamster lungs. However, when NO$_2$ exposure followed tobacco smoke exposure marked and irreversible changes in lung surface structure occurred. A loss of cilia was noted 2 days after the exposure and the structure of the mucus-secreting cells was altered. These changes were not reversible. 7 days after exposure even greater lesions regarding the surface structure were observed. These results indicate that NO$_2$ and tobacco smoke act synergistically on the bronchial epithelium. The pathological changes of the combined pollutants are much greater than those caused by the individual pollutant (HENRY, 1972).

Ozone:

No synergistic effect occurred when NO$_2$ was applied in combination with O$_3$. The pulmonary resistance to infection with aerosols of staphylococcus aureus in mice showed a degree of impairment that would be expected from each individual pollutant. The concentrations used in the experiment were 1.5 - 7.3 ppm NO$_2$ (2.8 - 13.7 mg/m$^3$) and 0.11 - 0.4 ppm O$_3$ (0.2 - 0.78 mg/m$^3$), exposure time was 17 hours or 4 hours.
(GOLDSTEIN, 1974). When rats were exposed for several weeks to mixtures of ozone and NO₂ at peak ambient concentrations (highest concentrations were NO₂ = 2.5 ppm (4.7 mg/m³), ozone = 0.25 ppm (0.49 mg/m³)) this led to comparable morphological responses. The main damage was within the small airways. The sites of the major effect, however, were different for the two gases: NO₂ affected the epithelium of the entire bronchiole and of the alveolar duct adjacent to its juncture with the respiratory bronchiole; with ozone the damage was in the distal and respiratory bronchial portions of the terminal bronchiolar epithelium, the entire alveolar duct and the immediately associated alveoli. The preliminary results seem to suggest that the combined exposure to both gases - as would be the case in smokers residing in areas with photochemical smog - could lead to enhanced formation of emphysema and chronic obstructive pulmonary disease (FREEMAN, 1974).

Motor Vehicle Exhaust:

Chronic exposure to motor vehicle exhaust with different concentrations of NOₓ showed a marked effect on rats only in the high NOₓ group. The mean NO₂ concentration was 0.92 ppm (1.7 mg/m³), the NO level 22.54 ppm (27.7 mg/m³). The effects were: decrease of body weight, diminution of the sound avoiding reflexes, and increase of spontaneous tumors (STUPFEL, 1973).

Sulfur dioxide (SO₂) and soot:

Rats and mice were exposed up to 5 months to combinations of 3 ppm (5.6 mg/m³) NO₂ with 5 - 6 ppm SO₂ (13 - 15.6 mg/m³), and of NO₂, SO₂ and 7 mg/m³ soot.
Additive effects of the components were evident, the NO$_2$/SO$_2$/soot combination showing the greatest effects: there was a significant decrease in erythrocyte fragility, thrombocyte count, and bacterial clearance (SCHLIPKOETER, 1973).

4.5. Health Effects Summary and Discussion:

In the following chapter the findings are summarized and a few points are discussed that, in the opinion of the rapporteur, are of significance.

4.5.1 Comparing the Toxicity of NO and NO$_2$

NO$_2$ is far more irritant than NO. When an attempt is made at quantization, the parameters for comparison of toxicity show different values (NIEDING, 1975):

1) Considering the Met-hemoglobin formation then NO and NO$_2$ are equally toxic.

2) If the airway resistance is compared NO$_2$ is 10 times more toxic than NO.

3) The arterial oxygen partial pressure shows NO$_2$ to be 4 times as noxious as NO.

4) If nitrite formation in tissue is regarded both NO and NO$_2$ seem to have the same capacity.

4.5.2 Met-hemoglobin formation:

An increase of Met-hemoglobin formation was long considered to be a suitable and sensitive indicator for an NO exposure. This is not the case because:

(1) at ambient and the usual occupational exposures no Met.Hb increase is measurable,
(2) it is not specific, since all chemical substances with the necessary oxidation potential can oxidize the Fe (II) to Fe (III) in the hemoglobin molecule,

(3) NO$_2$ has an approximately equal Met.Hb formation capacity.

The threshold-level of NO$_x$ for a detectable Met.Hb-increase in humans is a concentration range of 15 - 20 ppm NO (NIEDING, 1973a) or NO$_2$ (HENSCHLER, 1963).

These levels will not occur in ambient air and only under extreme conditions of occupational exposure (PRESS, 1974, 1975). Therefore elevated Met.Hb.levels can only be used as an assay for NO$_x$ exposure at toxic levels. Owing to its lack of specificity, however, even here its value as evidence for NO$_x$ exposure is limited.

The origin for the overemphasis of Met.Hb as an indicator for nitrogen monoxide (NO) exposure is historical.

In intoxications by the highly irritant NO$_2$, other acute detrimental effects (edema, extreme irritation of the respiratory tract, congestion) are far more noticeable and occur at lower concentrations than with the far less irritant NO.

4.5.3 Resistance to Bacterial Infection:

A very important factor is the reduced capacity of the respiratory tract to resist infection by respiratory pathogens after exposure to NO$_2$.

The results of the animal experiments (see Chapter 4.3.4.7) suggest, that by preparing the respiratory tract for infection, nitrogen oxides contribute to
the formation of respiratory diseases.

The results of the Chattanooga Study clearly indicate that nitrogen oxides are an aggravating factor in this regard.

4.5.4 Particulate Nitrites:

A re-evaluation of the data from the Chattanooga Study, made necessary by unreliability of aerometric measurements, revealed that respirable particulate nitrates seem to be of significance regarding detrimental effects on human health.

This seems to be corroborated by preliminary data from a study being conducted in several U.S. cities. The role of these particulate nitrates which stem from NO and NO$_2$ is not yet clear.

4.5.5 Development of Tolerance:

The development of tolerance to nitrogen dioxide, pertaining to survival in animals and to the odour threshold and irritation in man, has been described by HENSCHLER (1960, 1964a, 1964b). The changes in cell population in the lung (from pneumocyte type 1 to type 2 in animals) can also be seen as an adaptive mechanism of the organism (see Chapter 4.3.4.4).

4.5.6 Histamine Depletion:

The pronounced effect of NO$_2$ on airway resistance and other lung function parameters resembles the action of ozone on the respiratory tract. There is an indication that histamine liberation might play a role in triggering these effects.

THOMAS (1967) has shown mast cell degranulation in rat lung tissue after acute exposure to low con-
centrations (0.5 - 1 ppm; 0.9 - 1.9 mg/m$^3$) of NO$_2$.

NIEDING (1971b) demonstrated a marked protective action of histamine suppressing agents (Meclastine) on lung function in volunteers exposed to 5 - 8 ppm NO$_2$ (9 - 15 mg/m$^3$) for 15 min. Atropine had not such an effect.

Thus there seems to be strong evidence of a participation of histamine in the very sensitive reaction of the respiratory tract to nitrogen oxides.

4.5.7 Immunologic Effect:

The evidence as to possible immunologic responses to NO$_x$ exposure is scant. Only one publication (BALCHUM, 1965) has shown in vitro reaction of antibody from chronic exposed rats with lung tissue extract of control animals.

Although it is highly improbable that NO or NO$_2$ themselves have antigenic properties, it cannot be excluded that the reaction of nitrogen oxides with lung tissue leads to altered proteins which could then act as antigens.

This very interesting aspect will have to be subject of further study, however.

4.5.8 Stress:

Nitrogen oxides, apart from causing specific damage to the respiratory tract may also play a role as an unspecific environmental stressor.

Whole body reactions, like the systemic effects (Chapter 4.3.4.13), the reduction of physical performance (Chapter 4.3.4.8), and the elevation of
serum cholesterol levels in rats after long-term exposures to 5 ppm (9 mg/m³) of NO₂ could be evidence of humoral responses to the action of NOₓ on the organism.

4.5.9 Combined Toxicity:

The impairment of ciliar and lung macrophage activity and general damage to the lining cells of the respiratory tract due to the action of NO₂ renders the elimination of inhaled particles (by transport, lysis, absorption or detoxication) less effective.

This would mean that particulate inorganic (heavy metals, oxides, sulfates, nitrates, soot) and organic material (allergenic substances, polynuclear hydrocarbons, viable particles) would have a far greater detrimental effect on the tissue of the lung due to an increased residence time.

Furthermore, inhalation of interdependent ambient gases and particulates (as NO₂ and ozone, or NO₂ and SO₂ and soot) clearly leads to experiments (see Chapter 4.4.3.13).

4.5.10 Possible Carcinogenic Action of Nitrogen Oxides:

Possible carcinogenic action of nitrogen oxides on the respiratory tract has been under discussion since DRUCKREY (1962) postulated the formation of nitrosamines in the lung by the reaction of NO or NO₂ with biogenic amines. The production of nitrosamines in the digestive tract by interactions of nitrite and amine has been shown (SANDER, 1971). This reaction, however, takes place in an acidic medium. A nitrosamine formation in neutral pH-medium has not been proven.
However, not only the indirect carcinogenic action of nitrogen oxides by formation of nitrosamine must be regarded as a potential hazard, but also the direct mutagenic effect of nitrite: In vitro, nitrite is used as a highly potent mutagen for experimental processes (WATSON, 1965; ZIMMERMANN, 1967; MAHLER, 1967; DRAKE, 1970).

As KAUT (1970a and 1970b) has shown, nitrite is formed upon contact of NO\textsubscript{x} with the lung. Nitrosamines, however, could only be detected in vitro, not in vivo.

HENSCHLER (1966), and ROSS (1968) in investigating the DRUCKREY hypothesis conducted 2 long-term exposure experiments, in which they exposed mice and in a later project hamsters to high concentrations of NO\textsubscript{2} for over a year.

In spite of the length of the exposure time and the high concentrations (40 ppm NO\textsubscript{2}, 76 mg/m\textsuperscript{3}) applied no increase of tumor frequency could be detected in exposed groups. However, cell proliferation in the terminal bronchioli was present in all exposed animals.

Neither did other authors in their long-term NO\textsubscript{x} exposures with laboratory animals at lower concentrations report any increased tumor rates amongst the groups of animals under exposure. Only in combination with motor vehicle exhaust an increase in the number of spontaneous tumors with increasing NO\textsubscript{x} levels was observed (STUFFEL, 1973) (see under 4.4.3.13).

To this point it can be stated that the nitrogen oxides have no proven carcinogenic or co-carcino-
genic effect on the tissue of the respiratory tract.

In spite of these negative results of the experiments the question of a possible carcinogenic or co-carcinogenic effect of nitrogen oxides should be studied in the future. There are two main reasons for this:

(1) The positive evidence of nitrosamine formation by nitrite and biogenic amines in the digestive tract gives an indication of possible endogenous formation of nitrosamines in the human organism. This possibility should be experimentally excluded before a final statement regarding the subject can be made.

(2) The fact that nitrogen oxides are counted into the group of radiomimetic substances like ozone. Substances with radiomimetic properties are able to form free radicals upon their reaction with tissue. These free radicals play a great role in the formation of tumors as they will interact with cell membranes and the DNA.

4.5.11 Photochemical Smog Induction:

In assessing the health hazards of nitrogen oxides NO$_x$-induced photochemical smog formation must be considered to be a significant part of the action pattern of NO$_x$ on man and his environment.

The photochemical products by the reaction are highly irritating to the conjunctiva and mucosa and seem to be a significant factor in the aggravation of respiratory diseases. Great economic losses due to damage to vegetation and materials are also caused by this form of air pollution (see Chapter 7).
4.5.12 Ambient Air NO<sub>x</sub> Standards:

In the setting of standards all information available should be incorporated. This would infer, in the case of the nitrogen oxides (NO and NO<sub>2</sub>), that the comparative actual toxicities and the potential hazard (for instance, regarding photochemical smog formation) would have to be taken into consideration.

An ambient air standard of nitrogen dioxide alone would only be of value in areas, where neither high intensity of sunlight nor elevated hydrocarbon levels in the atmosphere, nor unfavourable geographic and meteorologic conditions leading to inversions would occur.

The ambient air standards recently released by the Interior Ministry of the Federal German Republic try to pay regard to these facts (TAL, 1974):

**Nitrogen dioxide (NO<sub>2</sub>)**

- 100 µg/m<sup>3</sup> (0.05 ppm) arithmetic mean annual values; based on half hour mean values (IW 1).
- 300 µg/m<sup>3</sup> (0.16 ppm) 95 % value of the cumulative frequency distribution, based on half hour mean values (IW 2).

**Nitrogen monoxide (NO)**

- 200 µg/m<sup>3</sup> (0.17 ppm) arithmetic mean annual value; based on half hour mean values (IW 1).
600 $\mu g/m^3$ (0.50 ppm) 95% value of the cumulative frequency distribution, based on half hour mean values (IW 2).

In other countries no standards have been set for nitrogen monoxide (NO). However, permissible oxidant levels are sometimes used in combination with standards for nitrogen dioxide (NO$_2$), as in Japan (SHODA, 1973).

For nitrogen dioxide (NO$_2$) the following standards have been established:

Japan:
- 0.02 ppm (0.038 mg/m$^3$) daily recommended level; based on hourly mean values (SHODA, 1973)

Netherlands:
- 0.05 ppm (0.09 mg/m$^3$) daily average; based on hourly mean values (HAMANAKA, 1973)

USA:
- 0.05 ppm (0.09 mg/m$^3$) annual average
- 0.12 ppm (0.23 mg/m$^3$) 24 hour maximum, not to be exceeded more than once a year; based on hourly determinations (EPA 1973)

USSR:
- 0.049 ppm (0.085 mg/m$^3$) daily average (KETTNER, 1972).
5. **EFFECT OF NO\textsubscript{x} ON VEGETATION**

The phytotoxicity of nitrogen oxides is not very pronounced. It is less toxic to plants than sulfur dioxide (SO\textsubscript{2}) and ranges far below such phytotoxicants as "photochemical oxidants", fluoride, and certain hydrocarbons, notably ethylene. Reviews dealing with damage to vegetation caused by nitrogen oxides were published recently (VAN HAUT, 1967, 1975; JACOBSON, 1970).

The plant injuries caused by NO\textsubscript{x} (NO and NO\textsubscript{2}) are usually attributed to nitrogen dioxide (NO\textsubscript{2}).

While Van HAUT and STRATMAN used a 1 : 1 mixture of NO\textsubscript{2} and NO for their experiments but considered the contribution of NO to plant damage to be negligible, HILL and BENNETT (1970) demonstrated an additive physiological (not detrimental) effect of NO and NO\textsubscript{2} on vegetation. The parameter measured was the reduction of "apparent photosynthesis", which occurred at concentrations of 0.6 ppm NO (700 μg/m\textsuperscript{3}) and 0.6 ppm NO\textsubscript{2} (1100 μg/m\textsuperscript{3}).

Continuous exposures to 0.25 ppm NO\textsubscript{2} (450 μg/m\textsuperscript{3}) over most of the growing season reduced the yields of tomatoes (SPIERINGS, 1971; THOMPSON, 1970).

There seems to be evidence of a synergistic effect of NO\textsubscript{2} and SO\textsubscript{2} : DUNNING et al. (1970) and TINGEY et al. (1971) found leaf injury in tobacco after a four hours' exposure to a mixture of 0.1 ppm NO\textsubscript{2} (188 μg/m\textsuperscript{3}) and 0.1 ppm SO\textsubscript{2} (260 μg/m\textsuperscript{3}) The damage caused by these low exposures strongly suggests a synergistic mechanism.

Summarizing it can be said that although NO\textsubscript{x} is a moderate phytotoxicant which can lead to decreased crop yields in
certain plants, it is very difficult to assess the actual damage to vegetation caused directly by nitrogen oxides due to other pollutants usually present in the atmosphere. Only in the vicinity of nitric-acid-plants evidence of a direct effect of NO\textsubscript{x} emissions on vegetation has been found.

The threshold limit for medium sensitive plants is considered to be 0.43 ppm NO\textsubscript{2} (800 \mu g/m\textsuperscript{3}) (VAN HAUT, 1967).

Standards proposed for NO\textsubscript{2} considering phytotoxicity alone are 0.19 ppm (0.35 mg/m\textsuperscript{3}) as a mean concentration for a semi-annual vegetation period and a 30 minutes' mean value of 0.43 ppm NO\textsubscript{2} (0.80 mg/m\textsuperscript{3}) (VAN HAUT, 1975).

Much greater significance regarding plant damage than the injury caused by the direct effect of NO\textsubscript{x} is the nitrogen oxide induced formation of photochemical smog. These reaction products have a far greater phytotoxicity than NO and NO\textsubscript{2} themselves.

This is a perfect example for the necessity of taking into consideration also the interaction of one pollutant with other pollutant systems. The extensive damage to horticultural and agronomic crops caused by photochemical oxidants is directly dependent on the initial concentrations of NO and NO\textsubscript{2} in ambient air.
6. **EFFECT OF NO\textsubscript{x} ON MATERIALS**

Nitrogen oxides have a deteriorative effect upon the quality of fabrics and dyes, causing bleaching, discoloration, or characteristic yellowing of the fibers, depending on the type of material. This phenomenon is well-known and processes like the "gas fume fading" or "gas fading" of acetate materials (MORLEY, 1967; ANON., 1966; ANON., 1962), or cotton fading in gas-dryers which occurs at low levels of NO\textsubscript{x} (0.6 - 2 ppm, respectively 1100 - 3700 µg/m\textsuperscript{3}, expressed as NO\textsubscript{2}) McLENDON, 1965), still cause sizeable financial losses.

The component held mainly responsible for the damage is nitrogen dioxide (NO\textsubscript{2}) (GILES, 1966; SALVIN et al., 1952; BELOIN, 1973). Field and laboratory studies in which a great number of different fabrics were exposed to ambient air or laboratory-controlled environments demonstrated the phytotoxic quality of NO\textsubscript{2} (BELOIN, 1973; BELOIN, 1972).

Another effect attributed to NO\textsubscript{x} is a marked loss in breaking strength of cotton yarn (MORRIS, 1964) and damage to nylon stockings (ANON., 1964; TRAVNICEK, 1966).

A very specific form of damage caused by NO\textsubscript{x} or its derivatives is the breakage of nickel-brass wire spring and components, and nickel-palladium contacts of switch bars from telephone relays and other electrical appliances. The effects, which are surface reactions of nitrate (NO\textsubscript{3}-)-ions on the metals, occur when humidity is high (>50 %) and particulate nitrate content of the air exceeds concentrations of 2.4 µg NO\textsubscript{3}-/m\textsuperscript{3} (HERMANCE, 1966; MCKINNEY, 1967; HERMANCE, 1971).

Since nitrate formation is strongly enhanced by photochemical reactions of NO\textsubscript{x} with hydrocarbons, this, too, exemplifies the necessity of taking into consideration side-reactions of NO\textsubscript{x} in the atmosphere.
7. THE PHOTOCHEMICAL SMOG SYSTEM

(Interaction of NO\textsubscript{x} with Hydrocarbons (HC) and Sunlight)

The interaction of NO and NO\textsubscript{2} with hydrocarbons in the presence of sunlight leads to the formation of "photochemical smog". This complex system of pollutants is known for its strong irritant quality on the conjunctiva and the respiratory tract in man, its high phytotoxicity and its damaging affects on materials (textiles, rubber, plastics).

In the frame work of this report it is not possible to bring a detailed presentation of the effects of photochemical smog formation and the effects on man and his environment.

In the following section a short review, however, is given dealing with theoretic background of the photochemical smog reaction:

The simultaneous presence of nitrogen oxides (NO or NO\textsubscript{2}), reactive hydrocarbons (olefins or certain aromatics), and sunlight are a prerequisite for photochemical smog formation. The reaction is triggered by the photolysis of NO\textsubscript{2} by which highly reactive atomic oxygen is liberated which in turn initiates a series of reactions with reactive hydrocarbons and oxygen to the formation of "oxidants".

The time lapse between the oxidation of NO to NO\textsubscript{2} and the subsequent photolysis of the latter leading to formation of ozone (O\textsubscript{3}), can be demonstrated in a simplified, schematic graph of daily ambient air concentration patterns of motor vehicle pollutants (Fig.5).

Ozone is the main component of the "total oxidants", usually constituting over 90%. As O\textsubscript{3} is a far more aggressive pollutant than NO\textsubscript{x}, the photochemical smog inducing capacity of
the nitrogen oxides can be considered to be one of its properties most harmful to human health.

Thus the problem of health effects of nitrogen oxides embraces that of a photochemical smog. Any attempt at setting of ambient air standards for NO should also take this fact into consideration.
8. CONCLUSIONS AND RECOMMENDATIONS

Reliability of Analytical Data:

The Chattanooga children study demanded great financial means and numerous manhours in furnishing the researchers with the information. These data were used as a basis for the setting of the ambient air standard for nitrogen dioxide by the United States Federal Government.

Soon thereafter, however, it became evident that the analytical procedure used for the monitoring of NO\textsubscript{x} concentrations was not sufficiently reliable to permit a correlation between observed effects and exact NO\textsubscript{x} concentrations. It was by mere coincidence that alternate NO\textsubscript{x} data were available for the same area. Even then, the results of the Chattanooga school children study had to be reevaluated and corrected.

This example as well as the preliminary survey of NO\textsubscript{x} levels in Europe by the European Commission has shown that the great variations in analytical procedures, site choosing, calibration methods lead to a very insufficient intercomparability of NO\textsubscript{x} analytical data.

Recommendation:

Epidemiological studies and estimation of a health hazard can only be as good as the quality of the analytical techniques used to gain exposure data. Harmonization of the analytical methods, standardization of calibration procedures, and the introduction of reference methods seem to be the most important initial steps towards a better evaluation of the NO\textsubscript{x} situation.

This could be effected by initiating working groups dealing with the following subjects:
1) Intercomparison of various analytical procedures now in use.

2) The selection of a reference method.

3) Agreement on the modes of calibration.

4) Sampling techniques and site selection.
Epidemiological and Field Studies

Since the problem of NO\textsubscript{x} as a health hazard is so intricately linked to photochemical smog formation, these two complexes should be investigated simultaneously in areas where, owing to the nature of the emission, this form of air pollution occurs. As the Chattanooga study is the only epidemiological project as yet conducted, the verification of the findings, especially since they constitute the basis of U.S. ambient air standards, is necessary.

Recommendation:

An epidemiological appraisal and the setting up of a field laboratory for the measurement of respiratory parameters in the population should be envisaged or initiated. Regions especially suited for such projects would be Rotterdam in the Netherlands, Torino in Italy for pollution complexes of NO\textsubscript{x} and photochemical smog, in addition other areas with predominant NO\textsubscript{x} pollution without the photochemical component would have to be selected.
Susceptibility to Bacterial Infections:

If, as the results of animal studies indicate, nitrogen oxide weakens the resistance to bacterial infections owing to damage to alveolar macrophages and to lining cells in the respiratory tract, population groups exposed to elevated nitrogen oxide levels (welders, workers in nitric acid plants, smokers) should show an increased incidence of infectious respiratory illness.

Recommendation:

An epidemiological study should be initiated regarding the prevalence of respiratory illness in individuals exposed to high concentrations of nitrogen oxides.
Tolerance:

Several authors have described the development of tolerance to \( \text{NO}_2 \) in animals. This includes cell-reaction of the lung tissue as well as survival of the animals when exposed to high concentrations.

Occupationally exposed groups (welders, nitric acid plant workers) and cigarette smokers are constantly exposed to high concentrations of nitrogen oxides. If tolerance develops, these persons should show a different reaction regarding their lung function and circulation parameters than non-exposed individuals.

Recommendation:

Studies should be undertaken to investigate possible tolerance development in occupationally exposed groups and in smokers.
Carcinogenic or Co-carcinogenic Action of $NO_x$:

Carcinogenic effect of nitrogen monoxide (NO) or nitrogen dioxide ($NO_2$) have not been proven. Owing to the possible formation of nitrosamines and the certain formation of nitrites in lung tissue after the inhalation of $NO_x$ the possibility of carcinogenic, co-carcinogenic, or syncarcinogenic action cannot be excluded.

Recommendation:

Experiments of the type that HENSCHLER conducted with mice and hamsters should be performed with other animal species. Also the co- and syncarcinogenic character should be excluded by two-phase experiments with pre- or post-treatment of $NO_x$ exposed animals with carcinogens and co-carcinogens.
Combined Toxicity:

Data on experimental studies with human volunteers and animals regarding the direct effect of NO$_2$ or NO exist. However, little information is available in respect to the synergistic or antagonistic action of nitrogen oxide acting in combination with other gaseous or particulate pollutants.

Recommendation:

Since nitrogen oxides almost never occur alone in urban atmospheres, the effect of typical pollutant combinations with NO$_x$ upon man and experimental animals should be studied with high priority.
Emission Control and Inventories:

The pollutants in the air of an industrial or densely populated area are normally seen as a simple sum of all the components emitted into the atmosphere in that region. Certain combinations, however, trigger the formation of entirely new pollutant systems. These interactions leading to additional irritants can only be reduced when emission planning prevents new industrial or other sources of a reactive component like \( \text{NO}_x \) (or hydrocarbons) to settle in an area where numerous emission sources of the other reactant are already present.

The prerequisite of emission planning and zoning is the setting up of emission inventories for all greater industrial or densely populated areas where specific interreacting pollutants are known to be present.

Recommendation:

The problem of setting up emission inventories as a preparatory measure for emission planning and zoning should be awarded high priority.

A model region in Europe could be selected, where \( \text{NO}_x \) and hydrocarbon emissions are dominant and photochemical smog formation is known to occur. A study group would then carry out a situation analysis. An example region suited for such a study - from the pollutant aspect - would be the Rotterdam area.
"Tracing" of Air Pollutants:

The ratio of NO to NO$_2$ is determined by the presence of hydrocarbons and sunlight. It is a time-dependent reaction and gives an indication of the age of an air parcel. If the factors influencing the ratio are known the latter can be used to "trace" the air pollution parcel to its source. This is of interest when a prevailing wind direction transports the pollutant parcel into other areas, where damage to crop, material, and detrimental effects to human health can occur.

Recommendation:

A seminar dealing with the possibilities and value of this phenomenon would probably be of interest. It would help to clarify the problems arising from air pollution damage caused through transport of industrial or other emissions across national boundaries.
Peak Level Exposure:

Owing to the aggressive nature of $\text{NO}_x$, short exposures to very high concentrations of this air pollutant can cause acute damage and irritation to the respiratory tract. In contrast to noxious agents like lead and other heavy metals, where a short exposure to peak concentrations are of far less severe consequences owing to the time dependent absorptive mechanisms in the lung, short peak exposures to very aggressive gaseous pollutants can be a real hazard to human health.

Recommendation:

A discussion should be initiated whether ambient air standards, usually considering yearly, 24 hour, and 1 hour mean values should not, in the case of highly aggressive substances, include peak levels which in no case should be exceeded.
Particulate Nitrates:

Lately there has been indication that particulate nitrates are of hygienic significance as air pollutants. Before the role of particulate nitrates can be assessed, however, the problem of analysis of organic and inorganic nitrates should be dealt with.

Recommendation:

A working group should be set up, dealing with the quantitative differential analysis of organic and inorganic nitrates suited for routine use.
9. REFERENCES
Fate of air pollutants: Removal of ethylene, sulfur dioxide, and nitrogen dioxide by soil.
Science 173 (1971) 914-916

AMDUR, M.O. (1954)
Effect of a combination of \( \text{SO}_2 \) and \( \text{H}_2\text{SO}_4 \) on guinea pigs.
Public Health Report (U.S.), 69 (1954) 503

AMDUR, M.O. (1959)
The physiologic response of guinea pigs to atmospheric pollutants.
Intern. J. Air Pollution 1, (1959) 170

ANON. (1962)
Gas fume fading.
Dyer, Text. Printer, 128 (1962) 89-90

ANON. (1964)
City finds nylon culprit: Blasting gas.
The New York Times, March 11, 1964

ANON. (1966)
Fume fading.

ANON. (1972)
Energy Policy in the European Community
OECD-Observer, June 1972, p. 36-39

ANTWEILER, J.; KOMPCH, K.-H.; BROCKHAUS, A. (1975)
Investigations on the influence of \( \text{NO}_2 \) and \( \text{SO}_2 \) as well as a combination of the two gases on the production of precipitating antibodies in guinea-pigs.
BAETJER, A.M. (1950)
Chronic exposure to air pollutants and acute infectious respiratory diseases.
Arch. Industr. Hyg. 2 (1950) 400-406

Nitrogen dioxide inhalation and lung antibodies.
Arch. Environ. Health 10 (1965) 274-277

BELOIN, N.J. (1972)
Fading of dyed fabrics by air pollution: A field study.
Text. Chem. Color. 4 (1972) 43-48

BELOIN, N.J. (1973)
Fading of dyed fabrics by air pollution: A chamber study.
Text. Chem. Color. 5 (1973) 128-133

Formation of oxides of nitrogen in pulverized coal combustion.

Chronic toxicity of nitrogen dioxide: II. Effects on histopathology of lung tissue.
Arch. Environ. Health 18 (1969) 186-192

BOKHOVEN, C. and NIESSEN, H.J. (1961)
Amounts of oxides of nitrogen and carbon monoxide in cigarette smoke, with and without inhalation.
Nature 192 (1961) 458-459

Eine Neuentwicklung zur automatischen Analyse gasförmiger Luftverunreinigungen
Die Messung von Stickstoffmonoxid neben Stickstoffdioxid in der Atmosphäre.  
Staub 27 (1967) 265-268

BUELL, G.C.; TOKIWA, Y.; MUELLER, P.K. (1966)  
Lung collagen and elastin denaturation in vivo following inhalation of nitrogen dioxide.  

BUNDESMINISTER DES INNERN (1971)  
Materialien zum Umweltprogramm der Bundesregierung 1971

CALHOUN, J.D.; BROOKS, C.R. (1965)  
A solid oxidant for oxides of nitrogen analyzer.  

CCMS REPORT (1973)  
"Air quality criteria for nitrogen oxides".  
Committee on the Challenges of Modern Society, NATO, June 1973

CHAIKIVSKY, M. and SIEGMUND, C.W. (1965)  
Low-excess-air combustion of heavy fuel – high temperature deposits and corrosion.  
J. Engr. Power 87 (1965) 379-388

COLLEN, M.F.; DYBAHL, G.L.; O'BRIEN, G.F. (1944)  
A study of pneumonia in the shipbuilding industry.  
J. Ind. Hyg. 26 (1944) 1-7
DATA FILE OF NATIONWIDE EMISSIONS (1972)
On File: U.S. Environmental Protection Agency, Office of Air and Water Programs, Division of Applied Technology, Research Triangle Park, North Carolina, July 1972

DAUTREBANDE, L.; SHAVER, J.; CAPPS J. (1951)
Studies on aerosols. XI Influence of particulate matter on eye irritation produced by volatile irritants.
Arch. Intern. Pharmacodyn. 85 (1951) 17

DEUTSCHE FORSCHUNGSGEMEINSCHAFT (1972)
Maximale Arbeitsplatzkonzentrationen gesundheits-schädlicher Arbeitsstoffe (MAK-Werte)
Mitteilung VIII der Kommission zur Prüfung gesundheitsschädlicher Arbeitsstoffe vom 27. Juni 1972

The molecular basis of mutation.

DRUCKREY, H. and PREUSSMANN, R. (1962)
Zur Entstehung carcinogener Nitrosamine am Beispiel des Tabakrauches.
Naturwissenschaften 49 (1962) 498

DÜMMLER, F.(1974)
Gegenwärtige Entwicklungstendenzen zur Verringerung der Abluftprobleme bei Salpetersäure- und Volldünger-Erzeugungsanlagen.

Nitrogen dioxide and sulfur dioxide interact to injure horticultural and agronomic crops.
Hort. Sci. 5 (1970) 333
EHRlich, R. (1966)
Effect of nitrogen dioxide on resistance to respiratory infection.

EHRlich, R., HENRY, M.C. (1968)
Chronic toxicity of nitrogen dioxide: I. Effects on resistance to bacterial pneumonia.
Arch. Environ. Health 17 (1968) 860-865

EHRlich, R. and HENRY, M.C. (1968)
Chronic toxicity of nitrogen dioxide: I. Effects on resistance to bacterial pneumonia.
Arch. Environ. Health 17 (1968) 860-865

EMISSIONSKATASTER KÖLN (1972)
Minister für Arbeit, Gesundheit und Soziales des Landes Nordrhein-Westfalen:
Emissionskataster Köln.
Verlag TÜV-Rheinland GmbH, Köln 1972

(EPA) ENVIRONMENTAL PROTECTION AGENCY (1971)
Air quality criteria for nitrogen oxides.

(EPA) ENVIRONMENTAL PROTECTION AGENCY (1973)
Regulations on National Primary and Secondary Ambient Air Quality Standards.
EPA. 40 C FR 50; 36 FR 22384, Nov. 25, 1971, as amended by 38 FR 25678, September 14, 1973

EVANS, M.J., STEPHENS, R.J., FREEMAN, G. (1971)
Effects of nitrogen dioxide on cell renewal in the rat lung.
Arch. Intern. Med. 128 (1971) 57-60
FLURY, F. and ZERNIK, F. (1931)
Schädliche Gase.
J. Springer Verlag, Berlin (1931)

Homogenous chemiluminescent measurement of nitric oxide with ozone.

FORWERG, W. and CRECELIUS, H.-J. (1968)
Zur Bestimmung des Stickstoffmonoxids in atmosphärischer Luft.
Staub 28 (1968) 514-516

Messen von Emissionen und Immissionen der Stickstoffoxide

FREEMAN, G., HAYDON, G.B. (1964)
Emphysema after low-level exposure to NO₂.
Arch. Environ. Health 8 (1964) 125-128

FREEMAN, G., CRANE, S.C., STEPHENS, R.J., FURIOSI, N.J. (1968a)
Environmental factors in emphysema and a model system with NO₂
YALE J. Biol. Med. 40 (1968) 566-575

FREEMAN, G., CRANE, S.C., STEPHENS, R.J. (1968b)
Pathogenesis of the nitrogen dioxide-induced lesion in the rat lung: A review and presentation of new observations.
Amer. Rev. Resp. Dis. 98 (1968) 429-443
FREEMAN, G., CRANE, S.C., STEPHENS, R.J., FURIOSI, N.J. (1969a)
The subacute nitrogen dioxide-induced lesions in the rat lung.
Arch. Environ. Health 18 (1969) 609-612

FREEMAN, G., CRANE, S.C., FURIOSI, N.J. (1969b)
Healing in rat lung after subacute exposure to nitrogen dioxide.
Amer. Rev. Resp. Dis. 100 (1969) 662-676

Covert reduction in ventilatory surface in rats during prolonged exposure to subacute nitrogen dioxide.

Pathology of pulmonary disease from exposure to interdependent ambient gases (nitrogen dioxide and ozone).

Effects of nitrogen dioxide on pulmonary cell population.
J. Bacteriol. 98 (1969) 1041-1043

GEORGII, H.W. and WEBER, E. (1962)

GEORGII, H.W. (1967)
Experientia. Suppl. No. 13 (1967) 14-20

The fading of colouring matter.
J. Appl. Chem. 15 (1966) 541-550
GOLDSTEIN, E., EAGLE, M.C., HOEPRICH, P.D. (1973)
Effect of nitrogen dioxide on pulmonary bacterial defense mechanisms.
Arch. Environ. Health 26 (1973) 202-204

GOLDSTEIN, E., WARSHAUER, D., LIPPERT, W., and TARKINGTON, B. (1974)
Ozone and nitrogen dioxide exposure, murine pulmonary defense mechanisms.

Toxicity of the oxides of nitrogen
AMA Arch. Ind. Hyg. Occup. Toxicol. 23 (1941) 129-133

Cleveland Clinic Fire : Survivorship study 1925-1965
Arch. Environ. Health 18 (1969) 508-515

GUICHERIT, R. (1972)
Indirect determination of NO by a chemiluminescence technique.
Atmos. Environ. 6 (1972) 807-814

HAAGEN-SMIT, A.J., BRUNELLE, M.F., HARA, J. (1959)
Nitrogen oxide content of smokes from different types of tobacco.
Arch. Ind. Health 20 (1959) 53/399-54/400

HAMANAKA, H. (1973)
The environmental standard for nitrogen dioxide and photochemical oxidant.
PPM (Japan) 4 (1973) 67-73
HARKE, H.-P., BAARS, A., FRAHM, B., PETERS, H., SCHULTZ, Ch. (1972)
Zum Problem des Passivrauchens.
Int. Arch. Arbeitsmed. 29 (1972) 323-339

HARROLD, G.C., MEEK, S.F., McCORD, C.P. (1940)
A chemical and physical investigation of electric arc welding: Bare, washed welding rods.
J. Ind. Hyg. Toxicol. 22 (1940) 347-378

Untersuchungen zur Stöchiometrie der Umsetzung zwischen gasförmigem Stickstoffdioxid und Saltzman-Reagens.
Staub 29 (1969) 447-451

HAYDON, G.B., FREEMAN, G., FURIOSI, N.J. (1965)
Covert pathogenesis of NO₂-induced emphysema in the rat.
Arch. Environ. Health 11 (1965) 776-783

Effect of nitrogen dioxide on resistance of squirrel monkeys to Klebsiella pneumoniae infection.
Arch. Environ. Health 18 (1969) 580-587

Chronic toxicity of NO₂ in squirrel monkeys.
III Effect of resistance to bacterial and viral infection.
Arch. Environmental Health 20 (1970) 566-570

HENRY, M.C., ARANYI, C., EHRlich, R. (1972)
Scanning electron microscopic observations of the effects of atmospheric pollutants and infectious agents.
Presented at the 4th International Symp. on Aerobiology, Enschede, The Netherlands, Sept. 3-7, 1972
Combating the effects of smog on wire-spring relays.

HERMANCE, H.W., RUSSEL, C.A., BAUER, E.J.,
EGAN, T.F., WADLOW, H.V. (1971)
Relation of air borne nitrate to telephone equipment damage.

Geruchsschwellen einiger wichtiger Reizgase (Schwefeldioxid, Ozon, Stickstoffdioxid) und Erscheinungen bei der Einwirkung geringer Konzentrationen auf den Menschen.
Arch. Gewerbepath. Gewerbehyg. 17 (1960) 547-570

Methämoglobinbildung durch Einatmen niederer Konzentrationen nitroser Gase.

HENSCHLER, D., HAHN, E., HEYMANN, H., WUNDER, H. (1964a)
Mechanismus einer Toleranzsteigerung bei wiederholter Einatmung von Lungenödem erzeugenden Gasen.
Naunyn-Schmiedebergs Arch. exp. Path., Pharmak. 249 (1964) 343-356

HENSCHLER, D., HAHN, E., ASSMANN, W. (1964b)
Wirkungbedingungen einer Toleranzsteigerung bei wiederholter Einatmung von Lungenödem erzeugenden Reizgasen.
Naunyn-Schmiedebergs Arch. exp. Path. Pharmak. 249 (1964) 249-342

Zur Frage einer cancerogenen Wirkung inhalierter Stickstoffoxide.
Naunyn-Schmiedebergs Arch. exp. Path. u. Pharmak. 253 (1966) 495-507
"Atmospheric Emissions from Nitric Acid Manufacturing Processes".
Public Health Service Publication No. 999 - AP - 27.
PHS, NCAPC, Cincinnati, Ohio, (1966)

Inhibition of apparent photosynthesis by nitrogen oxides.
Atmos. Environ. 4 (1970) 341-348

(ICAC) Interbranch Chemical Advisory Committee (1965)
Selected methods for the measurement of air pollutants.
Public Health Service, Cincinnati, Publ. No. 999-AP-11, 1965

JACOBSON, J.S., HILL, A.C. (1970)
Recognition of air pollution injury to vegetation:
A pictorial atlas.

JAKOBS, M.B., HOCHHEISER, S. (1958)
Continuous sampling and ultra-microdetermination of
nitrogen dioxide in air.
Anal. Chem. 30 (1958) 426-428

JOST, D. (1974a)
Kohlenmonoxid- und Stickstoffdioxid-Messungen in der
Frankfurter Innenstadt.

JOST, D. (1974b)
NO/NO2-Konzentrationen in der Bundesrepublik Deutschland.
Vortrag: VDI-Kolloquium "Stickoxide", Düsseldorf (BRD),
12.-13.9.1974
VDI-Berichte 247, Düsseldorf, FRG (1975)
JOST, D. (1974c)
Community report on the levels of nitrogen oxides in the atmosphere monitored in the Member States in 1971/72.
Commission of the European Communities, Directorate-General for Social Affairs, Doc.No. 4819/1/73e, Luxembourg, 14 - 15 Jan., 1974

JUNGE, C.E. (1963)
Air chemistry and radioactivity.

KAUT, V., SVORCOVA, S., TUSL, M. (1970a)
(Determination of nitrite-ions in the lungs and in the blood of animals after inhalation of low concentrations of nitrogen oxides) Czech.
Supplementum Sborniku vedeckych prací Lékarská fakulty KU v Hradci Králově (Supplement of a collection of scientific works of the faculty of medicine, Charles University at Hradec Králové) 13 (1970) 213-218

KAUT, V. (1970b)
(contribution to the problem of nitrosamine formation after inhalation of nitrogen oxides) Czech.

KETTNER, H. (1972)
Schadstoff-Normierung der Aussenluft in der Sowjetunion.

KLIMISCH, R.L. and BARNES, G.J. (1972)
Chemistry of catalytic nitrogen oxide reduction in automotive exhaust gas.
Env. Sci. Technol. 6 (1972) 543-548

KNELSON, J.H., FRENCH, J.G., SHY, C.M. (1975)
Health effects basis for the U.S. air quality standard for nitrogen dioxide.
Staub-Reinhaltung der Luft 35 (1975) 178-184
KOSMIDER, S., LUDYGA, K., MISIEWICZ, A., DROZDZ, M., SAGAN, J. (1972)

KOSMIDER, S., MISIEWICZ, A. (1973)
Experimental and epidemiological investigation on the effect of nitrogen oxides on lipid metabolism. Int. Arch. Arbeitsmed. 31 (1973) 249-256

LA BELLE, C.W., LONG, J.E., CHRISTOFANO, E.E. (1955)
Synergistic effects of aerosols. Arch. Ind. Health 11 (1955) 297

Treatment of tetanus. Severe bone-marrow depression after prolonged nitrous-oxide anaesthesia. Lancet 1 (1956) 527-528

LINDNER, J. and ZORN, H. (1975)
Das Hydroxyprolin im Urin als Mass für die NO₂-bedingte Kollagenschädigung der Atmungsorgane. Staub – Reinhaltung der Luft 35 (1975) 166-169

MAHLER and CORDES (1967)

MAY, H. and SCHULZ, H. (1967)
Benzineinspritzung bei Kraftwagenmotoren. Motortech. Z. 28 (1967)
McCORD, C.P., HARROLD, G.C., MEEEK, S.F. (1941)
A chemical and physiological investigation of electric arc welding: III Coated welding rods.
J. Ind. Hyg. Toxicol. 23 (1941) 200 - 215

Stress corrosion cracking rates of a nickel brass alloy under applied potential stress corrosion testing.

McLENDON, V., RICHARDSON, P. (1965)
Oxides of nitrogen as a factor in color changes of used and laundered cotton articles.
Amer. Dyest. Rep. 54 (1965) 305-311

MEGUERIAN, G.H. and LANG, G.R. (1971)
NO reduction catalysts for vehicle emission control.
Presented at the SAE (Society of Automotive Engineers) Congress, Detroit, Michigan 1971

MILLER, L.E. (1958)
The chemistry of oxides of nitrogen in the upper atmosphere.

Household survey of the incidence of respiratory disease in relation to environmental pollutants.

MITINA, L.S. (1962)
The combined effect of small concentrations of nitrogen dioxide and sulfur dioxide upon an organism.
Gig. Sanit. 27 (1962) 3 - 8

MORLEY, D.J. (1967)
Upholstery fabric fading by impurities present in the air.
MORRIS, M.A., YOUNG, M.A., MOLVING, T. (1964)
The effect of air pollutants on cotton.
Test. Res. 34 (1964) 563-64

MOSHER, J.C., MACBETH, W.G., LEONARD, J.J.,
The distribution of contaminants in the Los Angeles Basin
resulting from atmospheric reactions and transport.

MOURIK, J.H. (1967)

Air quality criteria - Toxicological appraisal for oxidants,
nitrogen oxides, and hydrocarbons.

MURPHY, S.D., ULRICH, C.E., FRANKOWITZ, S.H.,
XINTARAS, C. (1964)
Altered function in animals inhaling low concentrations
of ozone and nitrogen dioxide.
Amer. Ind. Hyg. Assoc. J. 25 (1964) 246-253

NAPCA (1970a)
Control techniques for nitrogen oxides from stationary
sources.
US Dept. Health, Education an Welfare, PHS,

NAPCA (1970 b)
Control techniques for carbon monoxide, nitrogen oxide,
and hydrocarbon emissions from mobile sources.
US Dept. Health, Education, and Welfare, PHS,
NIEDING, G. von, KREKELER, H. (1971b)
Pharmakologische Beeinflussung der akuten NO₂-Wirkung auf die Lungenfunktion von Gesunden und Kranken mit einer chronischen Bronchitis.
Int. Arch. Arbeitsmed. 29 (1971) 55-63

Absorption of NO₂ in low concentrations in the respiratory tract and its acute effects on lung function and circulation.

Grenzwertbestimmung der akuten NO₂-Wirkung auf den respiratorischen Gasaustausch und die Atemwegswiderstände des chronisch lungenkranken Menschen.
Int. Arch. Arbeitsmed. 27 (1971) 338-348

NIEDING, G. von, WAGNER, H.M., KREKELER, H. (1973a)
Investigation of the acute effects of nitrogen monoxide on lung function in man.
Proc. 3rd Int. Clean Air Congr., Düsseldorf (BRD), 1973, A 14 - A 16

Studies of the acute effects of NO₂ on lung function: Influence on diffusion, perfusion, and ventilation in the lungs.
Int. Arch. Arbeitsmed. 31 (1973) 61-72

NIEDING, G. von, WAGNER, H.M. (1975)
Vergleich der Wirkung von Stickstoffdioxid und Stickstoffmonoxid auf die Lungenfunktion des Menschen.
Staub - Reinhaltung der Luft 35 (1975) 175-178
NIETRUCH, F., PRESCHER, K.-E. (1969)
Dosierung kleiner Stickstoffdioxid-Mengen und Bestimmung des "Saltzman-Faktors".

NORWOOD, W.D. (1966)
Nitrogen dioxide poisoning due to metal cutting with oxyacetylene torch.
J. Occup. Med. 8 (1966) 201-305

OBLAENDER, K., and ABTHOFF, J. (1972)
Entwicklungsstand der thermischen und katalytischen Nachverbrennung bei Ottomotoren.
Motortech. Z. 33 (1972) 206-213

PATTLE, R.E., BURGESS, F. (1957)
Toxic effects of mixtures of SO₂ and smoke.
J. Pathol. Bacteriol. 73 (1957) 411

PATTY, F.A. (1963)
Industrial Hygiene and Toxicology. Vol. II : Toxicology
Interscience Publishers, New York, 1963

PEARLMAN, M.E. et al. (1971)
Nitrogen dioxide and lower respiratory illness.
Pediatrics 47 (1971) 391-398

PETR, B. and SCHMIDT, P. (1967)
The influence of an atmosphere contaminated with sulfur dioxide and nitrous gases on the health of children.
Z. Gesamte Hg. Grenzgebiete 13 (1967) 34-48
Umweltschutz beim Schweissen - Untersuchungen der Stick-
oxidbildung bei einer Brenngas-Sauerstoff-Flamme.
Verbindungstechnik 6 (1974) 61-64

PRESS, H. (1975)
Schadstoffkonzentration beim vollmechanischen Plasmaschneiden.
Schweissen und Schneiden 27 (1975) 165-168

RECAT Report (1972)
Cumulative Regulatory Effects on the Costs of Automotive Transportation (RECAT).
Final Report of the Ad hoc Committee, Office of Science and Technology, Feb. 28, 1972

REED, L.E., BARRETT, C.F. (1965)
"Air pollution from road traffic-measurements in Archway Road, London".
Int. J. Air Wat. Poll., 2 (1965) 357-365

REPORT PAC (1972)
Report on Joint Ad hoc Group on Air Pollution from Fuel Combustion in Stationary Sources.
Organization of Economic Co-operation and Development (OECD), Paris, Report PAC/70.7., May 1972

Continuous determination of nitrogen oxides in air and exhaust gases.
Air/Water Pollution 8 (1964) 455-463

Nitrogen dioxide and nitric oxide in non-urban air.
Gaseous nitrogen compound pollutants from urban and natural sources.

Antioxidants versus lung disease.
Presented at the 10th Annual Hanford Biology Symp., Richland, Wash., June 2 - 5, 1970

ROSS, W. and HENSCHEL, D. (1968)
Fehlen einer cancerogenen Wirkung von nitrosen Gasen beim Goldhamster.
Experientia 24 (1968) 55

SALTZMAN, B.E. (1954)
Colorimetric microdetermination of nitrogen dioxide in the atmosphere.

SALVIN, V.S., PAIST, W.D., MYLES, W.J. (1952)
Advances in theoretical and practical studies of gas fading.

Electron spin resonance of nitric oxide hemoglobin complexes in solutions.
Science 137 (1962) 752-754

 SANDER, J., BÜRKLE, G., FLOHE, L., AEIKENS, B. (1971)
Untersuchungen in vitro über die Möglichkeit einer Bildung cancerogener Nitrosamide im Magen.
Arzneimittelforschung (Drug.-Res.) 21 (1971) 411-414
SCHLIPKOETER, H.-W., FODOR, G.G., GHELERTER, L.,
DOLGNER, R. (1973)
Tierexperimentelle Befunde zur Kombinationswirkung.
Proc. 3rd Int. Clean Air Congr., Düsseldorf (FRG),
1973, A 26 - A 30

SCHULTZ-BRAUNS, O. (1930)
Die tödlichen Vergiftungen durch gasförmige Stickoxyde
(Nitrose-Gase) beim Arbeiten mit Salpetersäure.
Arch. Path. Anat. 277 (1930) 174-220

SCHWARZBACH, E. (1974)
Zur Frage der Entstehung von Stickstoffoxiden bei
Erdgasfeuerungen.
Vortrag: VDI-Kolloquium "Stickoxide", Düsseldorf (BRD)
VDI-Berichte 247, Düsseldorf, FRG (1975)

SHEPARD, T.H., FINK, B.R. (1967)
Teratogenic activity of nitrous oxide in rats.
Toxicity Anesthetics Proc. Symp. Seattle, Wash.,
(1967) p. 308-323

SHERWIN, R.P., DIBBLE, J., WEINER, J. (1972)
Alveolar wall cells of the guinea pig, increase in
response to 2 ppm nitrogen dioxide.
Arch. Environ. Health 24 (1972) 43-47

Proteinuria in guinea pigs exposed to 0.5 ppm
nitrogen oxide.

SHODA, Y. (1973)
On establishment of environmental standards concerning
nitrogen dioxide.
Sangyo to Kankyo (Ind. Environ.) 2 (1973) 14-20
The Chattanooga school study: Effects of community exposure to nitrogen dioxide.
I. Methods, description of pollutant exposure, and results of ventilatory function testing.

SHY, C.M. et al. (1970b)
The Chattanooga school study: Effects of community exposure to nitrogen dioxide.
II. Incidence of acute respiratory illness.

SHY, C.M., NIEMEYER, L., TRUPPI, L., ENGLISH, T. (1973)
Re-evaluation of the Chattanooga school children studies and the health criteria for NO$_2$ exposure.
In-house technical report, National environmental Research Center, EPA, Research Triangle Park, N.C., March 1973

SPIERINGS, F.H.F.G. (1971)
Influence of fumigation with NO$_2$ on growth and yield of tomato plants.
Neth. J. Plant Path. 77 (1971) 194-200

STEPHENS, R.S., FREEMAN, G., EVANS, M.J. (1970)
Connective Tissue changes in lungs of rats exposed to NO$_2$.

STEPHENS, R.S., FREEMAN, G., EVANS, M.J. (1971)
Ultrastructural changes in connective tissue in lungs of rats exposed to NO$_2$.
Arch. Internal Med. 127 (1971) 873-883

STERN, A.C. (1968)
STOKINGER, H.E. (1957)
Evaluation of the acute hazards of O₃ and oxides of nitrogen.
A.M.A. Arch. Ind. Health 15 (1957) 181

STUPFEL, M., MAGNIER, M., ROMARY, F., TRAN, M., MOUTET, J. (1973)
Lifelong exposure of SPF rats to automotive exhaust gas.
Arch. Environ. Health 26 (1973) 264-269

Penetration of pollutants in the airways.

TAL - Technische Anleitung zur Reinhaltung der Luft (1974)
Bundesministerium des Innern, Bonn, Germany
(4. September 1974)

Automatic apparatus for determination of nitric oxide and nitrogen dioxide in the atmosphere.
Anal. Chem. 28 (1956) 1810-1816

THOMAS, H.V., MUELLER, P.K., WRIGHT, R. (1967)
Response of rat lung mast cells to nitrogen dioxide inhalation.

THOMAS, H.V., MUELLER, P.K., LYMAN, R.L. (1968)
Lipidperoxidation of lung lipids in rats exposed to nitrogen dioxide.
Science 159 (1968) 532-534
THOMPSON, C.R. et al. (1970)
Effects of continuous exposure of navel oranges to NO₂.
Atmos. Environ. 4 (1970) 349-355

Vegetation injury from the interaction of NO₂ and SO₂
Phytopath. 61 (1971) 1506-1511

TRAVNICEK, Z. (1966)
Effects of air pollution on textiles, especially synthetic fibers.

TUSL, M., STOLIN, V., WAGNER, M., AST, D. (1973)
Physical exertion (swimming) in rats under the effect of chemical agents.

VAN HAUT, H., STRATMANN, H. (1967)
Experimentelle Untersuchungen über die Wirkung von Stickstoffdioxid auf Pflanzen.

VAN HAUT, H. (1975)
Kurzzeitversuche zur Ermittlung der relativen Phytotoxizität von Stickstoffdioxid.
Staub - Reinhaltung der Luft 35 (1975) 187-193

Long-term exposure to low levels of air pollutants. Effects on pulmonary function in the beagle.
Arch. Environ. Health 19 (1969) 45-50
The symptomatology of chronic poisoning with oxides of nitrogen.
J. Ind. Hyg. 19 (1937) 469-473

VON OETTINGEN, W.F. (1944)
Carbon monoxide, its hazards and its mechanism of action.
U.S. Public Health Serv., Public Health Bull. 290 (1944)

WAGNER, H.M. (1970)
Absorption von NO und NO₂ in MIK- und MAK-Konzentrationen bei der Inhalation.
Staub 30 (1970) 380-381

WAGNER, H.M. (1975)
Arbeiten über die Wirkung von Stickoxiden.
Bericht des Instituts für Wasser-, Boden- u. Lufthygiene 1975 (in Vorbereitung)

WAGNER, H.M. (1972)
Wirkungen von Einzelkomponenten aus Kraftfahrzeug-Abgasen auf Mensch und Tier.

Experimental study of threshold limit of NO₂.
Arch. Environ. Health 10 (1965) 455-466

WALLER, R.E., COMMINS, B.T., LAWTHER, P.J. (1961)
Air pollution in road tunnels.
WATSON, J.D. (1965)
Molecular biology of the gene.
Benjamin Publ., (1965)

WILSON D., KOPCZYNSKI, S.L. (1968)
Laboratory experiences in analysis of nitric oxide with "dichromate" paper.
J. Air Poll. Contr. Assoc. 18 (1968) 160

ZIMMERMANN, F.K. and SCHWAIER, R. (1967)
Induction of mitotic gene conversion with nitrous acid, 1-methyl-3-nitro-1-nitrosoguanidine and other alkylating agents in Saccharomyces cerevisiae.
Molec. gen. Genet. 100 (1967) 63-76

ZORN, H. (1975)
Die alveolo-arterielle Sauerstoff-Spannungs differenz und der Gewebe-Sauerstoffpartialdruck bei NO₂-Belastung.
Staub - Reinhal tung der Luft 35 (1975) 170-175