COMMISSION OF THE EUROPEAN COMMUNITIES

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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S u m m a r y

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

Nitric oxide (NO) and nitrogen dioxide (NO_2)

All other nitrogen oxides (N_2O_3, N_2O_4, N_2O_5, etc.) do not occur in appreciable quantities in ambient air, or as in the case of nitrous oxide (N_2O) 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.

CONTENTS

P R E F A C E

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.

P. RECHT
Director of Health Protection
Commission of the European Communities

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The Commission of the European Communities wishes to acknowledge the help given by the scientific experts and consultants who assisted the Health Protection Directorate in drawing up this report.

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A PREPARATORY STUDY FOR ESTABLISHING CRITERIA

(DOSE/EFFECT RELATIONSHIPS)FOR NITROGEN OXIDES

1. INTRODUCTION

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

Nitric oxide (NO) and nitrogen dioxide (NO_2)

All other nitrogen oxides (N_2O_3, N_2O_4, N_2O_5, etc.) do not occur in appreciable quantities in ambient air, or as in the case of nitrous oxide (N_2O) 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.

A short survey of this complex pattern of direct and indirect action of NO_x 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 re-
search which places special emphasis on those results that
in the opinion of the rapporteur are of decisive significance
is presented unter "Health Effects Summary" in the chapter
"HEALTH EFFECTS of NO_x".

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

As the NO_x-problem is also a "photochemical smog" problem, a
short review of this aspect of NO_x-pollution is given in the
chapter "THE PHOTOCHEMICAL SMOG SYSTEM".

Conversion factors :

The concentrations for NO and NO_2 are given in ppm with the
equivalent $\mu g/m^3$ or mg/m^3 value in brackets. The conversion
factor is temperature dependent, however in almost all cases
the values for $25^{o}C$ are used :

$$1 \text{ ppm NO } = 1.23 \text{ mg/m}^3 \quad (1230 \text{ } \mu g/m^3)$$

$$1 \text{ ppm NO}_2 = 1.88 \text{ mg/m}^3 \quad (1880 \text{ } \mu g/m^3)$$

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_x on Man :

Due to their extreme aggressiveness, the nitrogen oxides (NO and NO_2) react immediately upon contact with the surface of the respiratory tract.

Neither NO nor NO_2 as such reach the capillaries. Only the metabolites nitrite (NO_2^-) and nitrate (NO_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 NO$_x$ on man
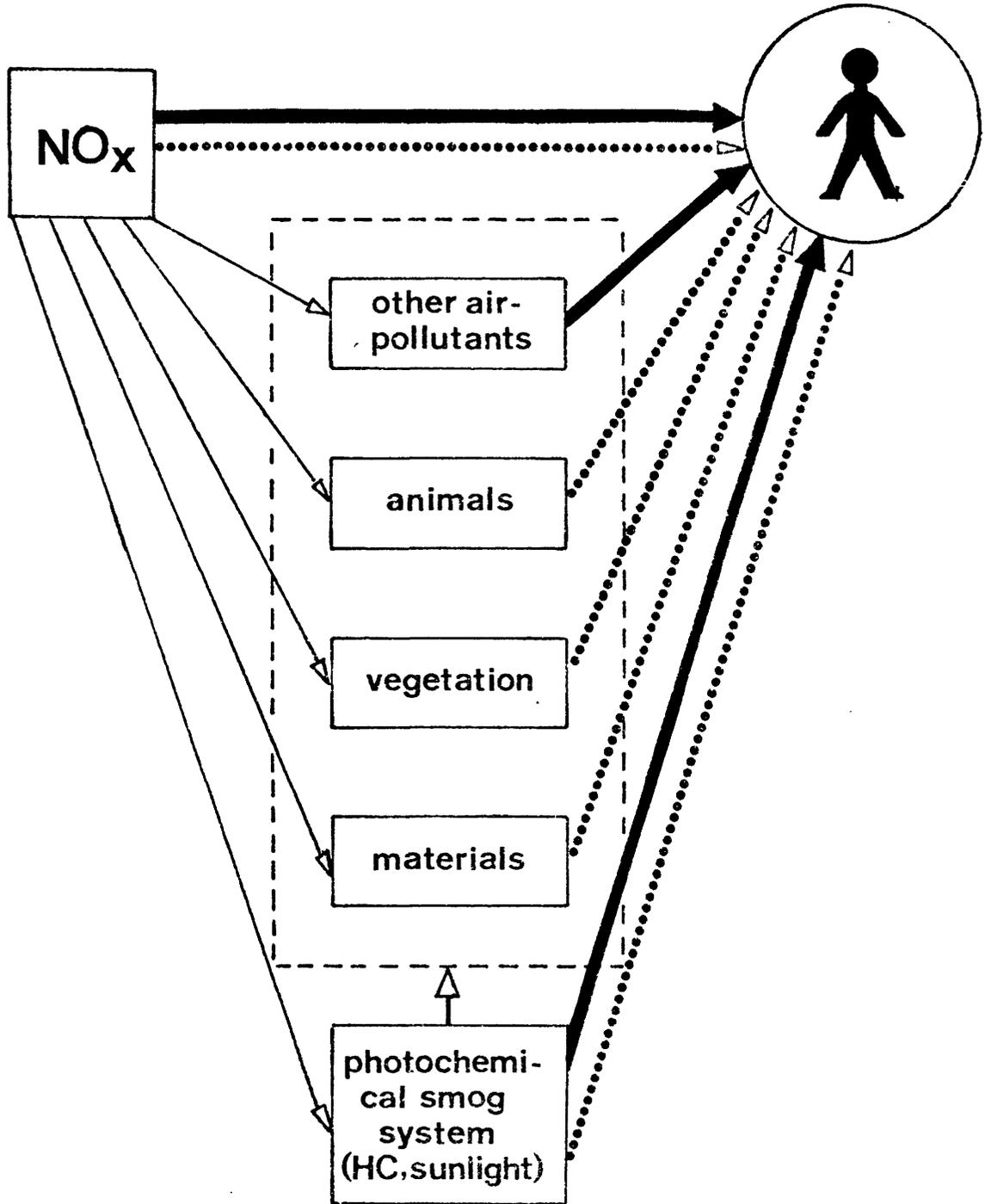
direct detrimental effect on human health

indirect effect on human well-being (psychol. stress, economic losses, etc.)

direct effect on plants, animals, material, etc.

fig.1

2.2   <u>Indirect Effect of NO$_x$</u>   (Reduction and Visibility)

Nitrogen dioxide absorbes light in the blue region
leading to yellow to reddish-brown coloration of the sky
and a weakening of the intensity of sunlight. The si-
multaneous 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$_x$ may also exist.

2.3   <u>Effects of NO$_x$ on other Systems</u> :

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 prod-
ucts on human health have not been studied. Also the
simultaneous reactions of NO$_2$ 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 live-
stock, no accumulation of nitrogen oxides or their meta-
bolites nitrite (NO$_2$-) or nitrate (NO$_3$-) takes place
in the animal organism. Ambient concentrations of NO$_x$,

even in the vicinity of industrial sources, have never
reached a level where acute intoxications have been re-
ported. 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 in-
direct (through economic losses), can be ruled out.

2.3.3   Effects on Vegetation :

The phytotoxicity of nitrogen oxides is not very pro-
nounced. Compared to sulfur dioxide (SO_2), nitrogen
dioxide (NO_2) 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 NO_2
(800 μg NO_2/m^3)   (see Chapter 5 "EFFECTS OF NO_x ON
VEGETATION").

2.3.4   Effect on Materials:

Nitrogen oxides have a detrimental effect upon the quali-
ty of dyes, fabrics, and certain alloys in use for
electrical appliances, leading to sizeable economic los-
ses (s. Chapter 6   "EFFECTS OF NO_x ON MATERIALS").

2.3.5   The "Photochemical Smog" Problem

The photochemical reaction, leading to the air pollu-
tion complex termed "photochemical" or "Los Angeles
Type" smog is directly induced by NO_x . NO_x 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 con-
centration, 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 NO_x by bacterial transformation of
nitrite (JUNGE, 1963) and other biological processes by
far exceed the man-made production of NO_x from anthro-
pogenic sources which stems mainly from the combustion
of fossil fuel : Approximately 450 x 10^6 metric tons
(MT) originate from natural, 45 x 10^6 from man-made
emissions (ROBINSON, 1970).

Man-made 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 NO_x levels in urban atmospheres are 10 to 100 times
higher than in non-urban regions (EPA, 1971). The ratio
of NO to NO_2 is dependent upon the type of source and
the meteorological conditions (see under 3.6).

In 1970 21 x 10^6 MT, nearly 50 % of the world's total
anthropogenic emissions of 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 x 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 x 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 x 10^6 MT in 1966
to 21 x 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 suc-
cessful in specific fields has not been able to cope
with the constant over-all rise in man-made NO_x emis-
sions.

The various techniques of emission control for station-
ary and mobile sources are reviewed in two recent publi-
cations 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

Estimated Emissions for 1980 (from: REPORT PAC 1972)

Country	NO_x in 10^6 metric tons MT	
	Year: 1968	Year: 1980
Finland	0.119	0.208
Sweden	0.103	0.224
Norway	0.027	0.038
Denmark	0.088	0.148
Total:	0.337	0.618
United Kingdom	1.065	1.19
The Netherlands	0.220	0.374
Germany	1.262	1.942
Belgium	0.177	0.232
France	0.494	0.588
Total:	3.218	4.324
Switzerland	0.035	0.054
Austria	0.078	0.098
Total:	0.113	0.152
Spain	0.210	0.518
Italy	0.418	1.124
Greece	0.035	0.116
Turkey	0.137	0.317
Total:	0.800	2.075
United States	9.02	16.01
Canada	0.31	0.59
Total:	9.33	16.60
Japan	0.97	3.36
Grand total:	14.8	27.1

a Mean of range.

of decisive influence on NO_x generation from chemical
processes (DÜMMLER, 1974).

Unfortunately control measures for the reduction of car-
bon monoxide (CO) and hydrocarbons (HC) in motor vehicle
exhaust have led to an increase on NO_x emissions due to
higher combustion temperatures in the cylinders and after-
burners. Reduction catalysts converting NO_x into nitro-
gen (N_2) have been reported functioning at the labora-
tory 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 vehi-
cles with the guarantee of functional stability
(KLIMISCH, 1972; MEGUERIAN, 1971; OBLAENDER, 1972).

In other words, a change in the current trend of con-
stantly rising man-made NO_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_x does not accumulate in the atmosphere. The
natural removal from ambient air occurs in several ways :
by washout (rain), surface reaction (physical and chemic-
al adsorption), microbiological degradation (biological
absorption), particulate nitrate formation (after oxi-
dation and reaction with H_2O), scavenging by hydrocar-
bons (in "photochemical smog" reaction) (ABELES,1971;
MILLER, 1958; RIPPERTON, 1970; ROBINSON, 1970).

The elimination of NO_2 by soil is usually underestimated:
ABELES et al, (1971),calculated from the results of
laboratory experiments, that the yearly uptake of NO_2
by soil in the USA is 6 x 10^8 tons, a capacity large
enough to absorb the whole U.S. annual production of NO_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_x concentrations are lower - the ratio changes in favour of higher NO_2-concentrations.

Apart from being determined by the type of source - in emissions from nitric acid plants the NO to NO_2 ratio is 0.33 to 0.5 (HEW 1966)—the varying relation of NO to NO_2 in ambient air is due to the fact that oxidation of NO to NO_2 takes time.

At higher concentrations NO reacts with oxygen in the atmosphere almost instantaneously to form NO_2 :

$$2\ NO + O_2 \ \text{------}\!\!\rightarrow\ \ 2\ NO_2$$
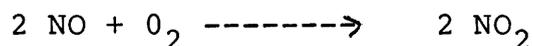
This conversion, however, is extremely slow at ambient concentrations : at 1 ppm the oxidation of 50 % of the NO to NO_2 takes 100 hours (STERN, 1968). In the presence of reactive hydrocarbons and sunlight the reaction can be greatly accelerated owing to photochemical reactions and the intermediate formation 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_2 requires a definite time, the "photochemical age" of an air parcel can be estimated from the ratio of nitrogen dioxide (NO_2) to total NO_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 $NO:NO_2$ ratio can be seen from the comparative measurements of NO and NO_2 in summer and autumn which show the general tendency that NO_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_x levels - not
caused by meteorological factors - depends on the type
of NO_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 pro-
file is shown in the figure "Daily concentration pat-
terns of motor vehicle exhaust pollutants" in Chapter 7
("PHOTOCHEMICAL SMOG SYSTEM", fig. 6).

Regions with high industrial and household emissions of-
ten show a pronounced higher NO_x-level during the night,
due to meteorological "less favorable to dispersion" con-
ditions, 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_2 vary
greatly due to the above mentioned factors.The inform-
ation gained from a recent study of NO_x-levels in the
European Community (JOST, 1974c) shows the monthly
averages for NO_x or NO_2 to rarely exceed 56.5 ppb
$(100 \ \mu g/m^3)$.

---

*) The NO_2 peak in the morning hours occurs later than NO
because oxidation is slow.
In the evening only a slight rise of the NO_2 level is
evident, because no photochemically catalized oxidation
takes place.

However, peak levels (24 hr. mean values) of 522 ppb
(940 $/ug/m^3$) occurred in Torino, Italy.

Yearly averages for total NO_x (expressed as NO_2) in
Frankfurt (FRG) were 117 ppb (210 $/ug/m^3$) in the center
of the city and reached 139 ppb (25o $/ug/m^3$)when mea-
sured in traffic. In the outskirts of town concentra-
tions 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) :

	ppb HO_2	$/ug\ NO_2/m^3$
Denver	42	75
Munich *	459	827 *
Rome	17	30
Rotterdam	25	45
Vlaardingen	22	39
Washington	52	94

* 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.
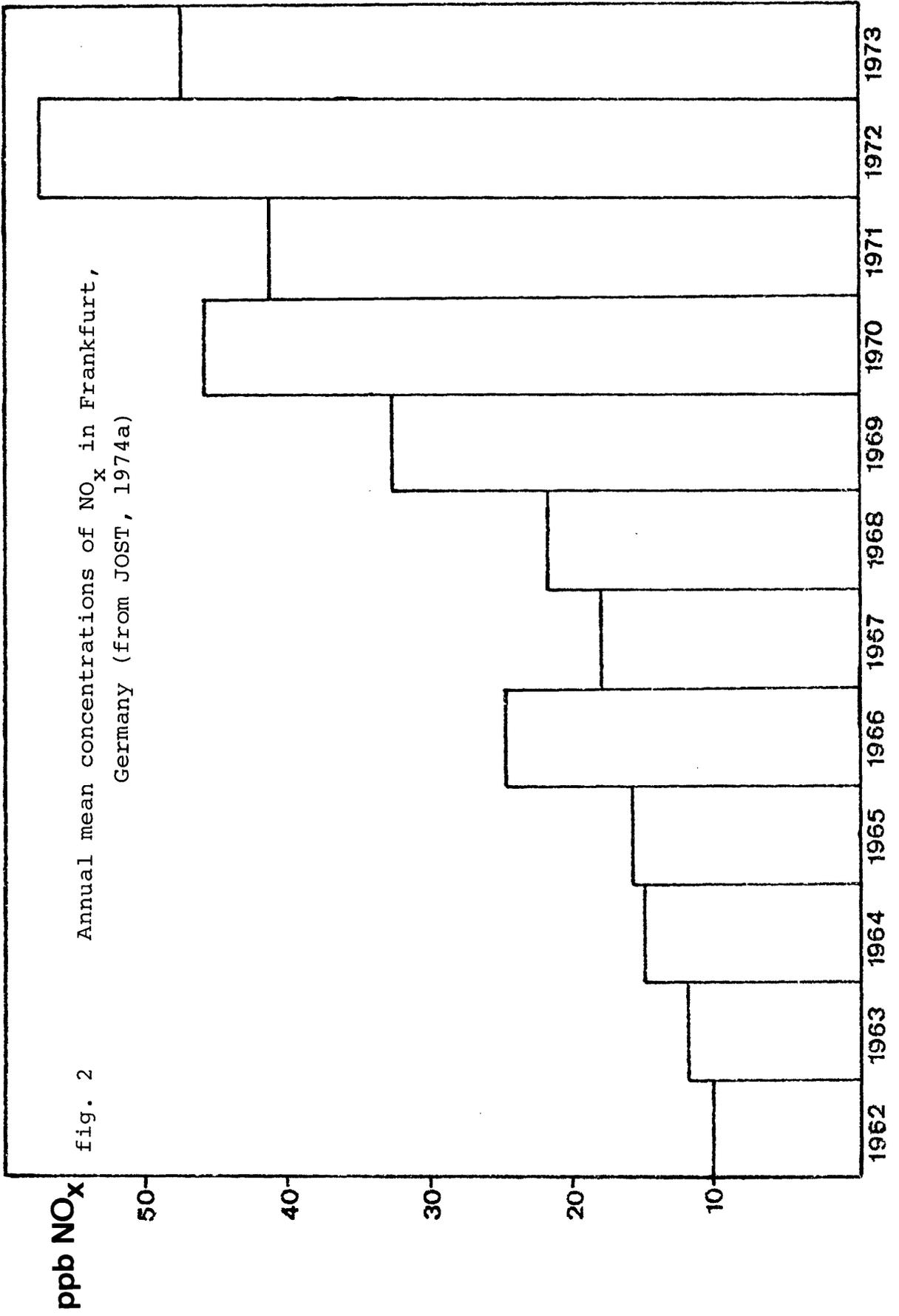
fig. 2   Annual mean concentrations of NO_x in Frankfurt, Germany (from JOST, 1974a)

3.7.1   Occupational Exposure :

Exposure to NO_x is encountered during welding proces-
ses. Here, intoxications still frequently occur.

Average concentrations of 84 ppm NO_x (158 mg/m^3) with
maximum values of 93 ppm NO_x (175 mg/m^3) have been re-
ported (McCORD, 1941; HARROLD, 1940). Although these
concentrations occur only under unfavourable conditions
(insufficient ventilation) other authors have also re-
ported levels in this range (PRESS, 1974; 1975;
NORWOOD, 1966). Other occupation groups for which expo-
sure to elevated NO_x levels is common are miners, silo
fillers, and workers in nitric acid plants.

3.7.2   Household Exposures :

Exposure to NO_x in the home due to use of gas-burning
household appliances is usually underestimated. The re-
cent expansion in the use of natural gas has increased
this exposure.

Owing to the higher flame-temperature of natural gas the
amount of NO_x produced is higher by a factor of 1.5 to
2 (MOURIK, 1967; SCHWARZBACH, 1974).

Measurements conducted by SCHWARZBACH (1974) regarding
NO_x formation by household gas-burning appliances (heat-
ers, boilers, stoves) showed that the use of natural gas
led to a marked increase of indoor NO_x - levels : in nose-
height in the direct proximity of the cooking stove
concentrations up to 1 ppm NO_2 (1.9 mg/m^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_x from tobacco smoke. The nitrogen oxide con-
tents of tobacco smoke is very high : BOKHOVEN (1961)
reported a total NO_x- content of 170 to 210 ppm in
direct cigarette smoke. Of this,100 ppm was the more
aggressive NO_2, NO_x (NO + NO_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_2
reaches occupational levels during smoking. Non-smokers
are also affected by "indirect smoking" (HARKE, 1972).

3.8   Problems Regarding Analysis of NO_x :

3.8.1 The Problem :

As a recent review of the NO_x-measurements in several
countries of the European Community has shown (JOST,
1974c), intercomparability of the data is rendered ex-
tremely 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 mea-
suring 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_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_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 nitro-
gen dioxide (NO_2), not for nitric oxide (NO). Before a
determination of total NO_x (i.e. NO plus NO_2) can be
made, NO must be oxidized to NO_2. 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 (NO_x) values.

3.8.4   Automated Procedure :

The automated instruments using physical or physico-
chemical procedures (photoluminescence, coulumetry),
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
NO_x-analysis: the lack of suffiently simple and re-
liable 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 ef-
forts still have to be undertaken, before NO_x -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 en-
tirely 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 (NO_2).

Nitrous oxide (N_2O) which is also found in the atmo-
sphere (at concentrations of approximately 0.25 ppm)
is considered to be non-toxic. It is used in high con-
centrations (up to 80 %) as an anaesthetic in medicine.
Harmful effects have been reported only after pro-
longed exposure to extreme concentrations (LASSEN, 1956;
SHEPARD, 1967).

All other nitrogen oxides virtually do not occur in am-
bient 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 pol-
lutants 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 simult-
aneous 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 ef-
fect 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). How-
ever, also other noxious agents were also present at

high concentrations : carbon monoxide 40.000 ppm
(45,9 g/m^3) and hydrocyanic acid (HCN) 5.400 ppm
(6 g/m^3) 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 respons-
ible 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 NO$_2$, 24 hr. ambient air analyses
of suspended particular 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 do-
minated the whole area, was a trinitrotoluene (TNT)
plant of very high capacity. The main pollutant emit-
ted by this factory was NO$_2$.

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 NO_2-exposure,

2) an area with high levels of suspended particulates with relatively low NO_2-concentrations,

3) a control area containing both low NO_2 and low suspended particulate level, and

4) a second control area with the same qualifications.

The annual arithmetic mean for the high NO_2-exposure areas was 0.08 - 0.15 ppm (150-282 $\mu g/m^3$), for the control region 0.03 ppm (56 $\mu g/m^3$) NO_2. The 90th percentile values were 0.15-0.5 ppm (282-940 $\mu g/m^3$) for the high, and 0.05 (94 $\mu g/m^3$) 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 in-dicator for the determination of an influence of air pollutants. The ventilatory performance of the children in the high NO_2 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 $(FEV_{0,75})$.

The respiratory illness rates showed a higher incidence in the families from the high NO_2 and high particulate areas. The relative excess was 18.8 % in the high NO_2 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 NO_2-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 NO_2 in that area. By comparison with studies conducted parallel by the U.S. Forces in the same area corrections regarding the concentrations of NO_2 were necessary.

The conclusion is that an annual average concentration of about 0.08 to 0.15 ppm (150 to 282 $\mu g/m^3$) 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 NO_2 concentrations of 0.15 ppm to 0.50 ppm (282 to 940 $\mu g/m^3$) (SHY, 1973).

4.2.3 Czeckoslovakian Study :

PETR (1967) conducted comparative studies of Czechoslovakian children living in three towns with different air pollutant patterns. In one town SO_2 predominated, with concentrations ranging from 0.01 to 0.12 ppm (30 to 320 $\mu g/m^3$), NO_x also being present but at a

much lower concentration 5 to 50 $\mu g/m^3$ (for an un-
defined 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 pol-
lutant the ambient NO_x concentration ranged from
20 to 70 $\mu g/m^3$. The mean SO_2-level in this area was
0.005 ppm (12 $\mu g/m^3$).

Finally a control town was selected with virtually no
sizeable air pollution sources. The parameters studied
in the children were erythrocyte fragility, Met-hemo-
globin 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 child-
ren 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_2 levels in the house-
holds of the families using gas was significantly higher
than in the compared group. The peak NO_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 de-
tection of chronic respiratory impairment. Forced
vital capacity and 0.75 sec forced expiratory volume
were measured.

The concentration range for NO_2 in the homes using gas
was 5 to 110 ppb (9.5 - 209 $\mu g/m^3$), for NO 10 to
410 ppb (12 - 492 $\mu g/m^3$). In the homes with electric
cooking 0 to 60 ppb (0 - 114 $\mu g/m^3$) for NO_2 and 0
to 340 ppb (0 - 408 $\mu g/m^3$) for NO. At the same time
the outdoor levels ranged from 15 to 50 ppb (2.9 -
95 $\mu g/m^3$) for NO_2 and 50 to 220 ppb (60 - 264 $\mu g/m^3$)
for No.

The result of the study showed no significant differ-
ence 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 concen-
trations 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 concen-
trations 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 $\cdot$ 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 $\cdot$ l^{-1}. sec)
Alveolar oxygen partial pressure (P$_{A_{O_2}}$) 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 NO_2 (188 to 1.880 mg/m^3) cause death in most animal species (GRAY, 1954).

4.4.1 Human Experimental Exposures :

4.4.1.1 Effect of NO_2 on the Human Respiratory Tract :

Studies of the acute effects of NO_2 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 NO_2 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 O_2 and CO_2 pressure (PaO_2) ($PaCO_2$) and the arterial hydrogen-ion-concentration (pHa).

2) The end expiratory O_2 and CO_2 gas partial pressures (P_AO_2) and (P_ACO_2).

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 O_2 and CO_2 gas exchange before, during, and after inhalation of NO_2 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_2O/L/sec before and after NO_2 inhalation a
   dependency of the relative R_t increase upon the
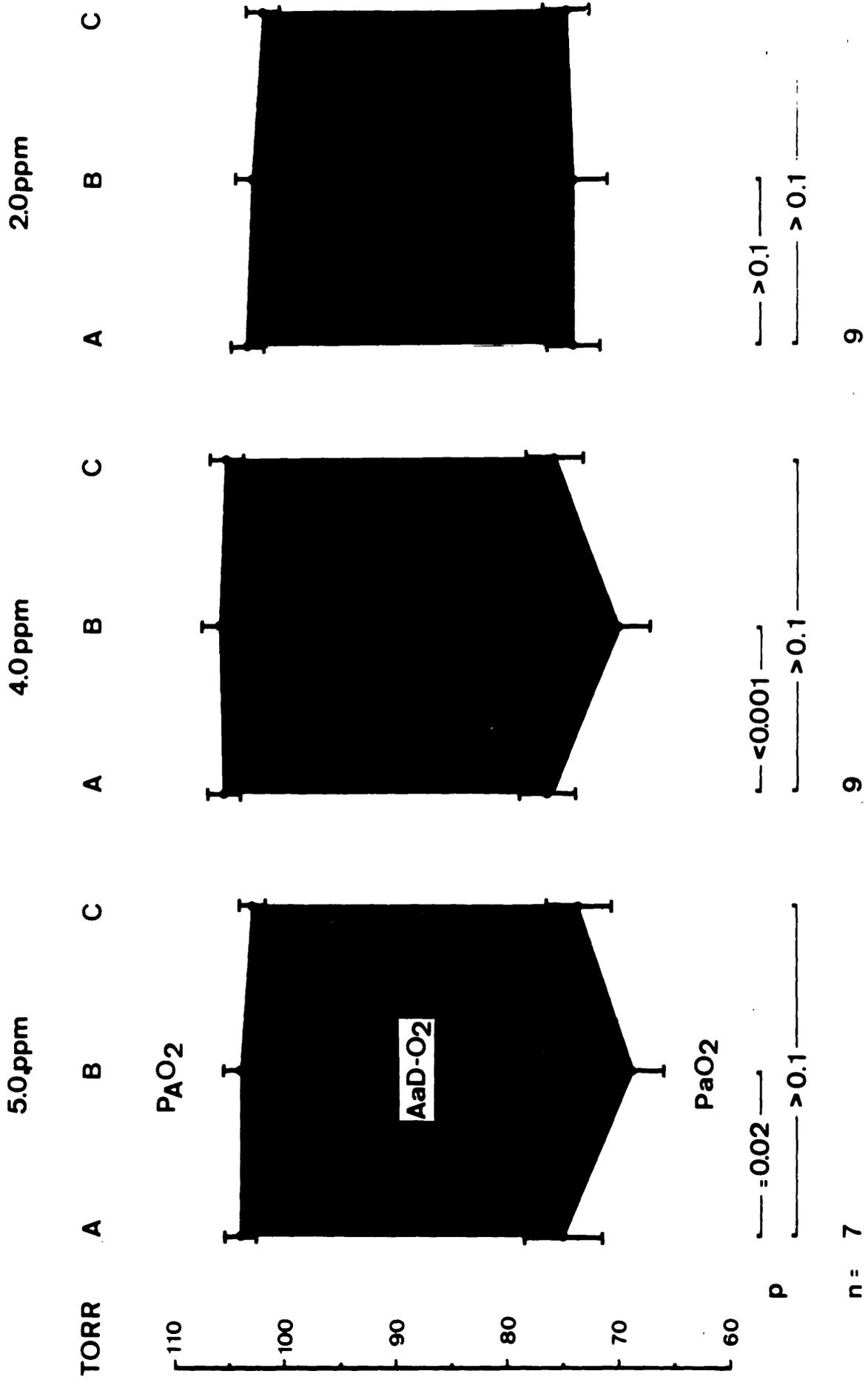
fig.3
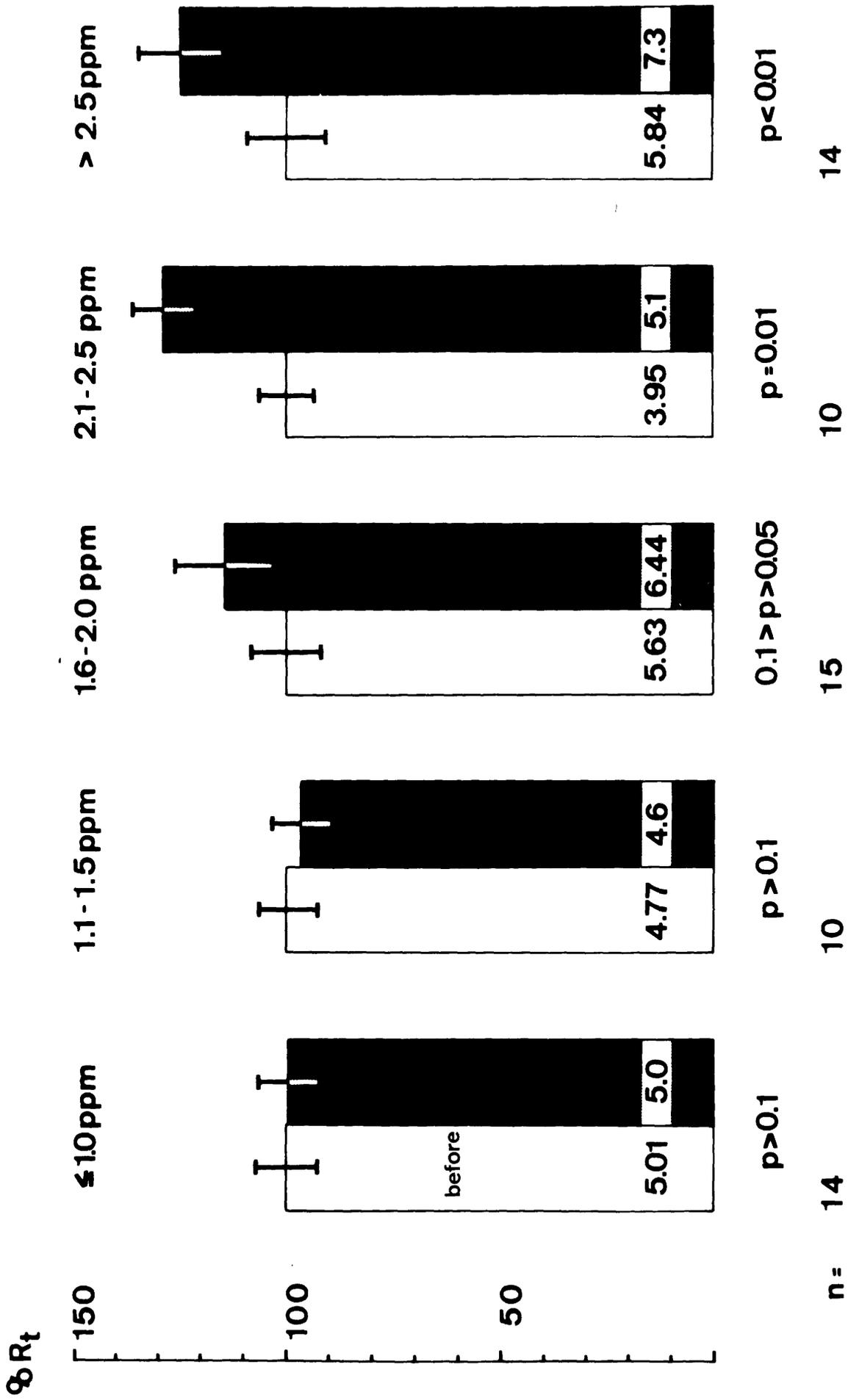
fig.4

NO_2 concentration appears to be present. There
seems to be no effect in concentrations between
1.0 and 1.5 ppm NO_2. At a range between 1.6 and
2.0 ppm, a slight but significant effect on air-
way 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 concen-
trations corresponding to the German MAC-value
of 5 ppm NO_2 (DEUTSCHE FORSCHUNGSGEMEINSCHAFT,
1972) and below. The decrease of the arterial
oxygen partial pressure seen, may be attributed to
various functional mechanisms, as pulmonary dif-
fusion, 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 NO_2 and NO concentrations are
inhaled. The fact that even a prolongation of NO_2
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 mechan-
isms are triggered, which minimize the further NO_2
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_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_2 (18.8 mg/m^3) caused no measurable increase of Met-hemoglobin in volunteers. Inhalation of air containing 20 ppm NO_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_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_2 depends very much on the mode of applying the NO_2-containing air mixture to the test person. A very slow but continuous rise of the NO_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^3), 61% at a level of 0.22 ppm (415 ug/m^3) and 100 % at a concentration of 0.42 ppm (0.835 mg/m^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 con-
tradictory. Simultaneously with nitrogen oxides usual-
ly 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 bronchi-
tis and other symptoms were seen. There was evidence
indicating the possibility of the formation of pulmon-
ary 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 attrib-
uted 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 di-
oxide levels of 100 to 1000 ppm (188 to 1880 mg/m^3)
are lethal to most animals (GRAY, 1954).

4.4.3.2 The Effect of NO_2 on Pulmonary Function in Animals :

The respiratory tract of animals studied in laborat-
ory experiments seems to be relatively resistant
towards low concentrations of NO_2. Several authors
have described no effect in concentrations ranging
from 5 ppm (9.4 mg/m^3) on guinea pigs (BALCHUM, 1965),
from 1 to 5 ppm NO_2 (1.88-9.4 mg/m^3) (WAGNER, 1965)
in rabbits and beagles exposed to 0.5 to 2 ppm (0.94-
3.8 mg/m^3) 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/m^3) for 4 hrs showed no
impairment of pulmonary function (MURPHY, 1964).

Using the O_2 partial pressure (P_{O_2}) in brain tissue of
rats as an indirect indicator of lung function im-
pairment (ZORN, 1975) showed that an exposure of 6-8
hrs in the concentration range of 0.5 - 20 ppm NO_2
(0.94 - 37.6 mg/m^3) resulted in a decrease of P_{O_2}.
The lowest concentration of NO_2 showing a statis-
tically significant decrease of P_{O_2} 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 $\mu g/m^3$) 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 NO_2. In his experiment, however, far higher concentrations were used (40 ppm NO_2), i.e. 76 mg/m^3).

The reaction at the cellular level upon the exposure to NO_2 can also be seen in changes of cell population. Continuous exposure to 2 ppm (3,8 mg/m^3) of NO_2 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/m^3) and 5 ppm NO_2 (9,4 ppm mg/m^3) 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 $\mu g/m^3$) 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 NO_2 (1.88 - 56.4 mg/m^3) 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 phenomen-
on of increased lipid peroxidation. Extracts of the
lipids from the lungs of rats previously exposed to
1 ppm (1,9 mg/m^3) of NO_2 for 4 hrs.showed evidence of
peroxidation of lipids. The values increased when the
exposure was repeated for 6 days at the same con-
centration giving an indication of a cumulative ef-
fect (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 NO_2. The effects occur at
concentrations as low as 0.5 ppm (0.9 /ug/m^3).

After acute or chronic pre-exposure to NO_2 at various
levels from 0.5 to 25 ppm (0.9 - 45 mg/m^3) 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/m^3) NO_2

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 reduct-
ion 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 NO_2
(14.5 mg/m^3) 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/m^3) NO_2. 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 signi-
ficant after 12 months and increased with continuing
exposure.

A similar rise in cholesterol levels occurred in guinea
pigs after exposure to 1 ppm NO_x (NO + NO_2) for 8
hours daily for 180 days. The exact level of NO_2 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/m^3) to 12 ppm (22.6 mg/m^3) NO_2 (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/m^3) to 25 ppm (47.5 mg/m^3)NO_2 or

mixtures of NO_2 and NO (EHRLICH, 1968; STEPHENS,
1970; WAGNER, 1965; WAGNER, 1975).

4.4.3.11 Immunological Effects :

Nitrogen dioxide when applied chronically over sever-
al months in concentrations of 5 ppm (9 mg/m^3) 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/m^3) NO_2
occurred with lung protein extracts of control
animals (BALCHUM, 1965).

Normal immunological response to antigens (fresh
chicken albumen plus Freud's adjuvans) was not in-
fluenced by exposure to 5.5 ppm (10 mg/m^3) NO_2 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/m^3) 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 NO_2 might influence the level of urinary
protein excretion is indicated by the findings of
SHERWIN (1974) : guinea pigs exposed to 0.5 ppm NO_2
(0.94 mg/m^3) for 7 - 14 days all showed consistently

higher levels of urinary albumins, α- and β-glob-
ulins, and γ-globulins than control animals. This
phenomenon occurred even when the exposure was re-
duced to 4 hours per day (for 5 - 14 days).

4.4.3.13 Combination Effects (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 expo-
sure 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 irrever-
sible 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 in-
dicate 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 concen-
trations 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 NO_2 at peak ambient con-
centrations (highest concentrations were NO_2 = 2.5
ppm (4.7 mg/m^3), ozone = 0.25 ppm (0.49 mg/m^3) 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 : NO_2 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 bron-
chial portions of the terminal bronchiolar epithelium,
the entire alveolar duct and the immediately as-
sociated 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 for-
mation of emphysema and chronic obstructive pulmonary
disease (FREEMAN, 1974).

Motor Vehicle Exhaust :

Chronic exposure to motor vehicle exhaust with dif-
ferent concentrations of NO_x showed a marked effect
on rats only in the high NO_x group. The mean NO_2 con-
centration was 0.92 ppm (1.7 mg/m^3), the NO level
22.54 ppm (27.7 mg/m^3). The effects were : decrease
of body weight, diminution of the sound avoiding
reflexes, and increase of spontaneous tumors (STUPFEL,
1973).

Sulfur dioxide (SO_2) and soot :

Rats and mice were exposed up to 5 months to combi-
nations of 3 ppm (5.6 mg/m^3) NO_2 with 5 - 6 ppm
SO_2 (13 - 15.6 mg/m^3), and of NO_2, SO_2 and 7 mg/m^3 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 ery-
throcyte 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 con-
sidered 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 Nitrates :

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 par-
ticipation 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$_2$ them-
selves have antigenic properties, it cannot be exclud-
ed 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 per-
formance (Chapter 4.3.4.8), and the elevation of

serum cholesterol levels in rats after long-term
exposures to 5 ppm (9 mg/m^3) of NO_2 could be evidence
of humoral responses to the action of NO_x on the
organism.

4.5.9   Combined Toxicity :

The impairment of ciliar and lung macrophage ac-
tivity and general damage to the lining cells of the
respiratory tract due to the action of NO_2 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 hydro-
carbons, 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 NO_2 and ozone, or NO_2 and
SO_2 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 nitros-
amines in the lung by the reaction of NO or NO_2 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 nitros-
amine 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 1970 b) has shown, nitrite is
formed upon contact of NO_x with the lung. Nitros-
amines, however, could only be detected in vitro,
not in vivo.

HENSCHLER (1966), and ROSS (1968) in investigating
the DRUCKREY hypothesis conducted 2 long-term ex-
posure experiments, in which they exposed mice and in
a later project hamsters to high concentrations of
NO_2 for over a year.

In spite of the length of the exposure time and the
high concentrations (40 ppm NO_2, 76 mg/m^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_x
exposures with laboratory animals at lower con-
centrations report any increased tumor rates amongst
the groups of animals under exposure. Only in combi-
nation with motor vehicle exhaust an increase in the
number of spontaneous tumors with increasing NO_x
levels was observed (STUPFEL, 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-carcino-
genic 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 possi-
bility 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 form-
ation 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 high-
ly 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_x Standards :

In the setting of standards all information available
should incorporated. This would infer, in the case
of the nitrogen oxides (NO and NO_2), that the com-
parative 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 (NO₂)

100 $\mu g/m^3$ (0.05 ppm)	arithmetic mean annual values;
	based on half hour mean values (IW 1).
300 $\mu g/m^3$ (0.16 ppm)	95 % value of the cumulative frequency distribution, based on half hour mean values (IW 2).

Nitrogen monoxide (NO)

200 $\mu g/m^3$ (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 cumu-
                             lative frequency distrib-
                             ution, 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 stan-
dards 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 deter-
                             minations (EPA 1973)

USSR :
   0.049 ppm (0.085 mg/m^3) daily average (KETTNER,
                             1972).

5. EFFECT OF NO_x ON VEGETATION

The phytotoxicity of nitrogen oxides is not very pronounced.
It is less toxic to plants than sulfur dioxide (SO_2) and
ranges far below such phytotoxicants as "photochemical oxid-
ants", 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_x (NO and NO_2) are usually
attributed to nitrogen dioxide (NO_2).

While Van HAUT and STRATMAN used a 1 : 1 mixture of NO_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_2 on vegetation. The parameter measured
was the reduction of "apparent photosynthesis", which occurred
at concentrations of 0.6 ppm NO (700 $\mu g/m^3$) and 0.6 ppm NO_2
(1100 $\mu g/m^3$).

Continuous exposures to 0.25 ppm NO_2 (450 $\mu g/m^3$) 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_2 and
SO_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_2 (188 $\mu g/m^3$) and 0.1 ppm SO_2 (260 $\mu g/$
m^3) The damage caused by these low exposures strongly suggests
a synergistic mechanism.

Summarizing it can be said that although NO_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_x emissions on vegetation has been found.

The threshold limit for medium sensitive plants is considered
to be 0.43 ppm NO_2 (800 $\mu g/m^3$) (VAN HAUT, 1967).

Standards proposed for NO_2 considering phytotoxicity alone
are 0.19 ppm (0.35 mg/m^3) as a mean concentration for a semi-
annual vegetation period and a 30 minutes' mean value of
0.43 ppm NO_2 (0.80 mg/m^3) (VAN HAUT, 1975).

Much greater significance regarding plant damage than the
injury caused by the direct effect of NO_x is the nitrogen
oxide induced formation of photochemical smog. These re-
action products have a far greater phytotoxicity than NO and
NO_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_2 in ambient air.

6. EFFECT OF NO$_x$ 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$_x$ (0.6 - 2 ppm,
respectively 1100 - 3700 $\mu g/m^3$, expressed as NO$_2$) McLENDON,
1965), still cause sizeable financial losses.

The component held mainly responsible for the damage is
nitrogen dioxide (NO$_2$) (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$_2$ (BELOIN, 1973; BELOIN, 1972).

Another effect attributed to NO$_x$ 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$_x$ 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$_3$-)-ions on the metals, occur
when humidity is high (>50 %) and particulate nitrate content
of the air exceeds concentrations of 2.4 μg NO$_3$-/m^3
(HERMANCE, 1966; McKINNEY, 1967; HERMANCE, 1971).

Since nitrate formation is strongly enhanced by photochemical
reactions of NO$_x$ with hydrocarbons, this, too, exemplifies
the necessity of taking into consideration side-reactions of
NO$_x$ in the atmosphere.

7. THE PHOTOCHEMICAL SMOG SYSTEM

(Interaction of NO_x with Hydrocarbons (HC) and Sunlight)

The interaction of NO and NO_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_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_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_2 and the subsequent photolysis of the latter leading to formation of ozone (O_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_3 is a far more aggressive pollutant than NO_x, the photochemical smog inducing capacity of

the nitrogen oxides can be considered to be one of its pro-
perties 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 ana-
lytical procedure used for the monitoring of NO_x concentrations
was not sufficiently reliable to permit a correlation between
observed effects and exact NO_x concentrations. It was by mere
coincidence that alternate NO_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_x levels
in Europe by the European Commission has shown that the great
variations in analytical procedures, site choosing, cali-
bration methods lead to a very insufficient intercomparability
of NO_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_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_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_x and photochemical smog, in addition other areas with
predominant NO_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 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 popu-
lated area are normally seen as a simple sum of all the com-
ponents 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
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 pol-
lutants are known to be present.

Recommendation:

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

A model region in Europe could be selected, where 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 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 aggres-
sive gaseous pollutants can be a real hazard to human health.

Recommendation :

A discussion should be initiated whether ambient air stan-
dards, usually considering yearly, 24 hour, and 1 hour mean
values should not, in the case of highly aggressive sub-
stances, 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
quantitive differential analysis of organic and inorganic
nitrates suited for routine use.

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