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Quantification of Health Effects Related to SO_2, NO_2, O_3 and Particulate Matter Exposure

Report from the Nordic Expert Meeting Oslo, 15-17 October, 1995

Edited by J. Clench-Aas, NILU and M. Krzyzanowski, WHO

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WHO Regional Office for Europe,
European Centre for Environment and Health, Bilthoven, The Netherlands

Abstract

Estimates of exposure–response relationships are needed to assess the health impact of environmental factors. Based on available research evidence, the relationships for the common air pollutants – particulate matter, sulphur dioxide (SO_2), ozone (O_3) and nitrogen dioxide (NO_2) – were reviewed by the Nordic Expert Meeting. The Meeting was organized by the Norwegian Institute for Air Research in collaboration with the WHO European Centre for Environment and Health, and with the financial support of the Nordic Council of Ministers. The report of the Meeting summarizes the discussion and the working papers that provide the background to the discussion. The limitations of current data and restrictions on their application are also addressed.

The Meeting concluded by quantifying exposure–response relationships for particulate matter, SO_2 and ozone; the relationship for NO_2 was not quantified. The Meeting also identified other exposure–response relationships that were felt to be substantiated, but for which the available data did not provide sufficient background to quantify the risk. The reported concentration–response associations relate to short-term changes in risk due to changes in levels of pollutants. For chronic effects of prolonged exposures the data were judged to be insufficient for quantification.

More research is necessary on the chronic and other effects identified but not quantifiable. Work needs to be done on health outcomes that give an early warning of a disease process. Greater comparability in definition of health outcomes and in research methods, as well as better reporting of study results, are necessary to allow general conclusions to be drawn.

European health for all target 21: air quality

By the year 2000, air quality in all countries should be improved to a point at which recognized air pollutants do not pose a threat to public health.

Keywords

- ENVIRONMENTAL EXPOSURE
- AIR POLLUTANTS
- SULPHUR DIOXIDE – adverse effects
- NITROGEN DIOXIDE – adverse effects
- OZONE – adverse effects
- EUROPE

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Preface

European countries, the European Community and the World Health Organisation are in the process of reviewing their air quality guidelines. This process entails a shift from giving a single value under which there is considered to be no effect, to giving a more complete assessment, including a dose-response function. Environmental and health administrators need the assistance of scientific experts to synthesise the available research on the health effects of exposure to the various pollutants, with the aim of quantifying the effects. As a link in this process the Nordic Council of Ministers funded a workshop of European and Nordic experts (project 2.5.19) to assess the current literature and develop dose-response functions for the criteria air quality indicators of SO_2, NO_2, O_3 and particulate matter. The workshop, organised by the Norwegian Institute of Air Research and the World Health Organisation, European Centre for Environment and Health, was held in Oslo, (Lysebu) October 15-17, 1995.

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Background

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Quantification of Health Effects Related to SO_2, NO_2, O_3 and Particulate Matter Exposure

1. Introduction

The body of knowledge concerning the health effects of air pollution is increasing and should be used by public health administrators. To make the scientific data available for the administrators, the scientific community's own assessment of the epidemiological work that has been done is necessary. This assessment serves in the development of air quality guidelines and the establishment of preventive regulatory measures to diminish the possible adverse effects of reduced air quality.

The European Centre for Environment and Health of the WHO (WHO-ECEH) is currently updating the air quality guidelines published first in 1987 (WHO 1987, 1994). Among the other air pollutants, the revision includes sulphur dioxide (SO_2), nitrogen dioxide (NO_2), particulate matter (PM), and ozone (O_3). The current state of knowledge concerning the health effects of these compounds, including their mechanisms of action, has been evaluated and the air quality guidelines have been recommended with the aim to protect populations from the adverse effects of the pollution (WHO, 1994). However, in various locations in Europe, ambient air concentrations of all considered here "classical" pollutants reach levels at which certain health effects are observed in epidemiological studies. To support decisions on the public health protection, to facilitate selection of problems of the highest priority and to optimize the risk management strategies, the quantitative assessment of these impacts is necessary. Besides identification of the hazardous substances in the air and quantification of population exposure, this assessment needs information about the extent of health response associated with a certain exposure level (Harrison, 1994; Möller et al., 1994).

Motivated by the desire to promote and facilitate the risk assessment process in Europe, the Nordic Expert Meeting on the Estimation of Potential Health Effects from Air Pollution Exposure on a Regional Scale was organized by the Norwegian Institute for Air Research in collaboration with the European Centre for Environment and Health of the World Health Organization. The meeting was sponsored by the Nordic Council of Ministers and was held at the Lysebu Hotel, Oslo, Norway 15-17 October 1995.

The participants were divided into two working groups, one for the discussion of NO_2 and O_3 and one for the discussion of SO_2 and particulate matter. Both groups met regularly for plenary discussion and evaluation. The meeting consensus is summarized in this report. The results of the discussions should provide an important input to the risk assessment of the four commonly referred to air quality indicators. The group is aware that with the growing body of scientific evidence, the more precise and specific estimates can be proposed. Therefore a systematic update of the work will be necessary in the future.

2. Aim of the meeting

The aim of the expert meeting was to provide estimates of exposure - response relationships for both acute and chronic health effects of exposure to O_3, NO_2, SO_2 and PM. A quantification of these relationships was to be provided where the consensus was that it is relatively certain (Group A effects). In addition, a second list of health effects was to be provided where the indications were convincing that there was a pollutant effect, but where it was felt that based on the current knowledge, the ability to quantify this effect was so far limited (Group B effects).

3. Methods of quantification

To provide a background for the discussion, each session leader prepared a literature survey prior to the meeting. This was used as the basis of the quantification. Further, the draft evaluations prepared for the update and revision of the Air Quality Guidelines were available to the meeting participants and were considered in the discussion. In this report, the focus is on the quantitative combined estimate of the effect emerging from the available studies with very brief reference to the individual studies. Most of the discussion of these studies is available in the background material.

A set of common rules was agreed upon to make the quantified relationships as comparable as possible. References used were principally to papers published after 1985. As far as possible, results of studies conducted in Europe were used, and the American results were provided as a comparison. In addition, some major literature reviews were used (Holgate and Anderson, 1995; Holgate and Waller, 1995).

The discussion for each compound has included both acute and chronic health effects. Information from animal research, clinical studies and epidemiological studies has been integrated in the final assessment.

It has been recognized that individual pollutants considered in epidemiological studies may represent a mix of various pollutants, and the health effects attributed to this indicator component of the mix may, to some extent, result from the impact of the other, not measured, components. For example, PM_{10} is a mix containing particles of various size and chemical composition. However, the meeting has agreed to quantify the associations of the "indicator components" with health effects assuming that even such information is useful for health impact assessment and management in the absence of more specific relationships.

4. Limitations

Much of the research reviewed at this report is quite recent and the analysis of the data considered here is still progressing. In addition, the individual studies are not performed with a complex regional assessment as their main goal. It is therefore important to specify the limitations, known and discussed during the meeting, that underlie the derived quantifications. Much of these limitations are common to

various reviews and are described in major review articles (Brunekreef et al., 1995; Holgate and Anderson, 1995; Holgate and Waller, 1995; Möller et al., 1994).

4.1 Air pollution exposure

An important limitation for combined analysis of results from various studies is the great diversity in methods of air pollution exposure assessment used in the studies cited. Exposure is a function of ambient pollution, of indoor concentrations both due to penetration of outdoor pollutants and indoor sources, and of the movements of the individuals from one micro-environment to another. Often only a limited number of outdoor monitoring sites provides estimates of exposure. Differences occur due to placement and number of outdoor measuring stations and reliability of measured data. Representativity of the stations for exposure of the population is not well described. This is illustrated by a recent overview of air quality and its monitoring in Europe (Sluyter, 1995).

Each monitored compound must be considered as an air quality indicator. The pollution mixture that the indicator represents, varies by season, time of day and region due to differences in relative importance of vehicular traffic, and of industrial, energy and home emissions sources. In many regions the compounds in themselves are strongly correlated, both due to a few sources emitting several compounds simultaneously and to the impact of meteorological conditions. This makes it difficult to separate and quantify the relative impact of each compound. The problem becomes worse as the averaging time becomes longer, such that research on chronic effects of air pollution where air pollution exposure to each compound over a lifetime tends to be strongly correlated (Tattersfield, 1995). The pollution profile can vary over time, due to changes in pollution sources. This aspect is often not recognized in epidemiological studies.

Further, the methods of air pollution monitoring restrict possibilities for the comparisons of studies using routine monitoring data. Particulate matter is measured and monitored as total suspended particles (TSP), PM_{10}, $PM_{2.5}$, black smoke (BS) or haze. The black smoke method has been used for many years in Europe, whereas technology has made PM_{10} and $PM_{2.5}$ measurements more often available in the later years. These different measures of particulate matter represent different features. The use of standard conversion factors between TSP and PM, based on data from American studies (Dockery and Pope, 1994), has important limitations when applied in European situations.

Outdoor air pollution concentrations correspond to personal exposure to a limited extent only, and differently in various societies. Cultural differences in lifestyle may influence both permeation of pollution into buildings, time spent outdoors and factors influencing indoor exposure. Indoor exposure may modify total personal exposure significantly and to various extent in various populations, since for example the use of gas in cooking and heating varies by countries. Cultural differences in smoking habits also contribute to regional differences in pollution exposure.

4.2 Health effect endpoints

The choice of endpoints was based on those where research has recently focused. These endpoints include mortality (total and by organ system), morbidity as measured by hospital admissions, lung function measurements, medication use and symptom reporting. In studies using routinely collected mortality or morbidity data, the differences in the health care systems, and in systems of case reporting, restrict possibilities for comparison and extrapolation of the study results. This is particularly true in relation to the data on hospital or emergency room admissions. Symptoms of reduced health were also recognized as important indicators of the effect of air pollution, however, the methods for the symptoms assessment are not standardized enough to allow combination of the results obtained by various research teams. The results of major collaborative studies, such as the PEACE study (a multinational European series of panel studies of children with symptoms of recent airway disease) are expected to overcome some of these shortcomings.

4.3 Establishing a relationship

The attempt to quantify the dose-response relationship is done in full recognition that many limitations are inherent in the final risk assessment. These include: the shape of the relationship, limitations in combining results derived in regionally and otherwise different populations, effects of pollutant mixtures and diversity in definitions of particular health endpoints.

Discussion on the shape of the exposure - effect curve have focused on the concentration range where the relation can be considered to be linear, on the existence of a threshold pollution level below which the effects do not exist and on the relationship at higher exposure levels. In attempting to address the entire range of concentration of the individual compounds for Europe, it was necessary to compile research results from many different countries. Regions in Europe are relatively stable in the concentration of pollutants, therefore, the risk quantification for the high and low end of the exposure scale is based on specific geographic regions. Potentially, this is a source of bias since the health effects may be related to different susceptibility and to confounding by factors characteristic for different populations.

Even though there is evidence that the compounds can interact in a synergistic fashion to produce health effects, it was not possible to account for this in this paper. It is therefore, extremely important to realize that the quantitative relationships reported in this paper cannot be considered additive or synergistically related to exposure to the other compounds. This is very important in the possible use of these relationships by public health authorities. One cannot assume that measures that reduce exposure of a given population to both PM_{10} and SO_2 (for example reduction of emissions from sulphur containing coal) will reduce the health effects by the sum of the estimated impacts of each of the compounds reported here. However, it should be safe to use the higher of the two estimated impacts as the most likely indicator of the overall effect.

4.4 Description of susceptible population

One of the tasks of the meeting was to provide a quantitative estimate for different population subgroups that can be considered to be susceptible and may react differently to pollution. This was discussed where information was available, but current research often does not allow such quantifications. Where possible, the population subgroup used for the estimate is mentioned. However, differences in baseline health status in various countries and regions may result in populations, especially for the elderly, that are not totally comparable.

4.5 Confounding factors

When comparing research from different regions, many confounding factors should be accounted for that were not always considered in the individual studies. These may include differences in culture, lifestyles and climate. Other air pollutants such as pollen and other aeroallergens may also correlate with both climate and the pollutants considered here. As mentioned before, cultural factors may introduce differences in exposure patterns, and the cultural variations may also differentially affect population subgroups.

In an attempt to reduce the impact of these limitations, it was decided to restrict the quantification to the Western European countries where most of the European research data have been generated until now. The quantitative results acquired in recent studies seem less applicable to the Eastern European countries. More work needs to be done before well founded conclusions for this part of Europe can be drawn.

4.6 Data analysis methods

Derivation of the quantitative estimates of effect in the environmental epidemiology studies often requires application of highly refined statistical methods able to account for the complex and only generally described structure in the data. Many of the data analysis methods that are required are still in the process of development. Therefore, much attention was placed on what type of data analysis method was used when selecting papers for the review. Most of the quantitative information on short term impacts of air pollution is based on temporal studies with geographically aggregated data (Schwartz et al., 1996). Other study designs and data analyses methods are necessary to confirm the results of those studies and to facilitate their interpretation.

5. Applications

The consensus achieved in this meeting should be useful in assessment of health impacts of air pollution in various populations. This will support public health administrators in decision making related to the need for regulatory measures to reduce the impacts and in estimation of the expected effects of these measures. In addition, the missing relationships should provide an incentive to both administrators and research groups to undertake the necessary studies to enable quantifying these relationships.

There are two kinds of essential limitations of any further use of the results. One is connected to the "health effect", where we have to bear in mind all the limitations connected to the extrapolating from one population, often limited in size, to a general situation. The other major limitation is connected to the air quality data to be used. In regional assessments, data are going to be used that are collected and reported through different kinds of networks. The process that the information undergoes from the measurement to the final use of the results, may differ between regions. Different measurement protocols may exist, different considerations for station placement, different criteria for acceptability of the data, and indeed a selection process for what data to report. In addition, there may be different measuring intervals and periods, and different kinds of sites. For regional assessments, we are dependent on good quality and comparability of the data available in the interactional data bases. It is therefore, important to work constructively for the harmonization of data collection, processing and storage.

To predict effects of changes in emission patterns due to economic development and/or to pollution control measures, model estimates of the air pollution concentrations are used. These may vary in their time and space validity and applicability in health impact predictions.

6. Summary of conclusions in this meeting

Taking into account all the limitations that this procedure entails, the workshop concluded with the quantified relationships summarized in the Table 1 (group A effects). In addition, the workshop identified other dose-response relationships that were felt to be substantiated but the available data do not provide sufficient background to quantify the risk (group B effects). The latter group is documented in the sections for each individual compound.

As is seen from the table, quantifications are reported for particles, SO_2 and ozone, as opposed to no quantification for NO_2. The latter may not reflect the seriousness of the effects associated with the individual compounds and is due to the available body of research. Until now, more studies have concentrated on the compounds related to fossil fuel combustion for industry and heating. The source composition and pollution emissions have changed in the recent years, due to regulatory processes and changes in lifestyle. Today, traffic is an important pollution source, with subsequent high emissions of nitrogen compounds. This affects the NO_2 and O_3 concentrations. Quantification of health effects associated with these changes are of utmost importance, however, the research are is new and the available results sparse.

The reported concentration-response associations relate to the short-term changes in risk due to the changes in daily levels of the pollutants. For chronic effects of prolonged exposures the data were judged to be not sufficient for quantification; the identified effects of individual pollutants are discussed further. Table 1 presents the "best guess" estimate whenever the European data have indicated such value. The values in brackets present the range of the reported results if more studies were available for the review. For PM, the upper limit was usually based on American studies.

Table 1: Percent change of risk of a health endpoint associated with an increased exposure to air pollution component for Western European conditions.

Health Endpoint	PM_{10} [1,2]	Black Smoke[1]	SO_2 [1]	O_3[3]	NO_2[4]
Total Mortality	0.6 (0.3 - 1.5)	0.6 (0.4 - 0.8)	0.6 (0.3 - 1.5)	(1-4)	
Respiratory Mortality	1.2 (0.8 - 3.7)	0.9	1.2 (0.3 - 3.3)		
Cardiovascular Mortality	0.8 (0.8 - 1.8)	0.7	0.6 (0.3 - 1.5)		
Hospital/Emergency Room Admissions (respiratory dis.)	0.5 (2)		0.5[5] (0.1-0.9)	6 (2-10)	
Bronchodilator use[6]	2 (12)				
Upper Respiratory Symptoms	1.2 (7)				
Lower Respiratory Symptoms	1.3 (5)				
Cough	1.3 (8)				
Symptom Exacerbation among asthmatics	5				
Pulmonary Function change (% change in the mean level)	-0.1 (-0.25)			-1.5 (-1- -2) (FEV_1)	

1) Per 10 µg/m³ 24-hour mean PM_{10}, black smoke or SO_2
2) Conversion used: PM_{10} = 0.55 TSP
3) Per 100 µg/m³ of maximum daily 1-hour mean
4) No quantification available
5) In age of 65+ years
6) In asthmatics

7. Recommendations

As is evident in this paper much work remains before a quantified risk identification and quantification can be considered as effective. Air pollution exposure estimates must be improved and made more comparable from region to region and from individual to the other individual. More work needs to be done especially for the chronic effects and other effects presented as Group B results (identified but not quantified) to allow them to be quantifiable.

More work needs to be done on health endpoints that give an early warning of a disease process, such as symptom reporting. This work needs to be done such that there is a greater comparability in choice of symptoms and general research methods. Different population subgroups need to be identified and investigated. More comparable data-analysis methods need to be used. Multicenter, international studies using the same research protocol (such as APHEA and PEACE) may be the most effective method to improve our knowledge and provide us with a better basis for impact assessment.

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Particulate Matter

Evaluation of Particulate Matter at Nordic Expert Meeting

Quantifiable relationships

The estimates of effects will be based on estimates for Western Europe. Extrapolation to Eastern Europe should be done with caution. Epidemiological studies which are still in progress suggest differences in the relationships between the regions, possibly due to different background mortality, socio-economic and environmental conditions. The estimates are proposed for TSP, PM_{10}, and Black Smoke. The latter was considered as an indicator for particulate pollution due to its wide use in European monitoring networks and in many European studies. However, the limitations in the extrapolation of the BS data must be recognized.

Short-term effects

The evaluation is mostly based on recent time-series and panel studies conducted in the United States and in Europe. Possible differences in the effects have been recognized, both due to the differences in the methods of the pollution measurements as well as due to real differences in the (size and chemical) composition of the particulate matter mix. A uniform conversion of TSP to PM_{10} was used here: PM_{10} = 0.55 * TSP. However, different ratios of respirable dust may be present in different locations. A separate estimate was derived for the black smoke (BS) based on several European studies where BS was measured; possible variations of the meaning of that indicator of particulate pollution in different locations must be kept in mind as well.

Mortality

The majority of the relationships described in this section originate in the APHEA studies and the North American studies. (Dab et al., 1996; Dockery et al., 1992; Dockery and Pope, 1994; Dockery and Schwartz, 1995; Ito et al., 1995; Kinney et al., 1995; Moolkavkar et al., 1995; Ponce de Leon et al., 1996; Samet et al., 1995; Schwartz, 1991, 1993, 1994a, 1996; Schwartz and Dockery, 1992a,b; Touloumi et al., 1996; Verhoeff et al., 1996; Vigotti et al., 1996; Wietlisbach et al., 1996; Wojtyniak and Piekarski, 1996; Zmirou et al., 1996).

In those studies, the relation between the number of deaths during a day and the pollution level in the same, or previous, day, is estimated. The APHEA study is still under analysis and additional information related to the departures of the association from the linearity, as well as the consistency of the estimates between the various locations providing the data to the analysis may be expected. Available data suggest that the effects increase linearly with the concentration of particulate pollution up to 200 $\mu g/m^3$ of PM_{10} (24h average). The estimates presented below relate to that range of concentrations which is the most common in European cities. In higher concentrations the increase of the effects is less steep.

Total mortality is estimated to increase by 0.3% per 10 μg/m³ of TSP (range: 0.2 -0.7%). This corresponds to a 0.6% increase per 10 μg/m³ of PM_{10} (range 0.3%-1.5%). The best estimate is based on the European studies with the American results lying at the upper end of the range. For the BS, the estimated 0.6% increase in total mortality per 10 μg/m³ (range 0.5%-0.8%) is based on European data.

In some of the studies, cause-specific mortality has been analyzed. However, small daily number of deaths due to a certain cause increases random variation of the estimated effect of pollution (even though the effect may be more specific). The mortality due to *respiratory system diseases* is estimated to increase by 0.8% per 10 μg/m³ of TSP (range 0.4% - 1.8%), and by 1.2% per 10 μg/m³ of PM_{10} (range 0.8%-3.7%), with the upper limit coming from the study in Utah Valley (Pope et al., 1992). For the black smoke, a 0.9% increase per 10 μg/m³ BS can be estimated based on good consistency between the studies, but not enough data is available to give estimates for the range of effect. Deaths caused by *cardiovascular diseases* increase by 0.8% per 10 μg/m³ of PM_{10} (range 0.5%-1.8%). This estimate is based on a joint evidence from studies where TSP and PM_{10} was measured; American data remain close to the upper limit. For the BS, an estimated effect is 0.7%. It is based on the data from Barcelona (0.9%) and cardiovascular deaths as a proportion of total deaths.

Hospital admissions

The relation of the number of admissions to hospitals and emergency room visits for respiratory conditions with the particulate pollution level was a subject of several studies. The majority of data suitable for the effects quantification stems from the APHEA project and the North American studies (Dab et al., 1996; Ponce de Leon et al., 1996; Samet et al., 1981; Schwartz et al., 1993; Schwartz, 1994b, c, d, 1996; Thurston et al., 1994).

A 0.5% increase per 10 μg/m³ of PM_{10} (or BS) is estimated but there is not enough data for the estimation of a range. A reasonable upper limit is 2% as observed for COPD admissions in Barcelona. American studies give higher values but it may be due to differences in morbidity registration.

Symptoms

The following estimates related to symptoms are based on several studies conducted in Europe and in USA, the variability of the results is high, however. Estimates are only provided for change in the symptom incidence per 10 μg/m³ of 24h average PM_{10}).

Bronchodilator usage in asthmatics: A 2% increase is suggested, however, various observations have suggested a wide range of the estimate, up to 12% (Pope et al., 1991; Roemer et al., 1993).

Symptoms exacerbation among asthmatics: A 5% increase is indicated by both Dutch and an American study (Pope and Dockery, 1992; Roemer et al., 1993).

Upper Respiratory Symptoms: A 1.2% increase with an upper limit of 7% suggested by American studies (Hoek and Brunekreef, 1993, 1994; Pope and Dockery, 1992).

Lower Respiratory Symptoms: A 1.3% increase with an upper limit of 5%, although 15% has been estimated in an American Six Cities Study (Hoek and Brunekreef, 1993, 1994; Pope and Dockery, 1992).

Cough: A 1.3% increase with an upper limit of 8%, although 28% has been estimated in one study in USA (Union town) (Hoek and Brunekreef, 1994; Pope and Dockery, 1992).

Change in lung function

A reduction of Peak Expiratory Flow by 0.1% with an upper limit of 0.25% (Pope and Dockery, 1992; Pope et al., 1991; Roemer et al., 1993) per 10 $\mu g/m^3$ of 24 hour mean PM_{10}. Preliminary analysis of the data from the PEACE study does not confirm the relationship (Roerner et al., 1996).

Measurable effects of PM that are as yet non-quantifiable

Short-term effects

Activity restrictions (disability days, school/work absenteeism) are well established (see Ostro and Rothschild, 1989; Ransom and Pope, 1992) and are of significant socio-economic impact. However, the results of the studies are difficult to be generalized in a quantitative way due to cultural and other differences.

In *hospital admissions*, an increase in COPD admissions in the age group over 65 on days with increased PM levels has been observed as well as an increase in asthma in the 0 to 14 year old group has been noted. However, more data is needed to derive a quantitative estimate of the effect.

Long-term (chronic) effects

Risk of death over a prolonged period of time

Two cohort studies are available from the USA showing clear effects of particulate matter (PM_{10}, $PM_{2.5}$ and sulphates) on mortality over the period of many years. The estimate for PM_{10} is available for one study only showing the increase in the death rate by 9% per 10 $\mu g/m^3$ (annual average) for total mortality (95% CI from 3 to 17%). Relatively the best pronounced relationship was observed for deaths caused by cardio-pulmonary diseases (Dockery et al., 1993; Pope et al., 1995).

European studies (from the 1980s) support qualitative conclusion of the American observations, but the characterization of exposure available in those studies is not sufficient for quantitative risk estimation. Considering the (ecological) type of the American studies and the possibility for alternative explanations for the between-population differences, no quantitative risk estimates are proposed at present (though they are badly needed). Although the short-term changes in mortality are

not comparable directly with the long-term changes, the available estimates would suggest that the effects predicted by the time series studies underestimate the total impact of the pollution on life expectancy (e.g. through the over-adjustment for seasonality).

Decrements in pulmonary function

Lower than expected pulmonary function level in children and adults living in more polluted environments is well established in qualitative terms conducted both in American and European studies since the 1970s. Most of the studies are of cross-sectional design and the exposure characterization does not allow quantitative risk estimation. For example exposure is given as mean pollution level for the area, there is no separation of particulate pollution and SO_2 or other pollution in the comparison of urban (or industrial) and rural populations. There is often a strong confounding by socio-economic or indoor environmental factors.

Prevalence of respiratory symptoms and illnesses in children and adults

The Six Cities study in USA has indicated an 11% increase in cough and bronchitis rates in children for each 10 $\mu g/m^3$ in long-term TSP concentration. In adults, a California cohort study indicated a relative risk of 1.36 per 1000 hours per year when a concentration of 200 $\mu g/m^3$ was exceeded for developing definite symptoms of airway obstructive disease. An increased risk of COPD has been observed in Athens (Hatzakis et al., 1986). However, for both children and adults no quantitative estimates are available from other studies.

Lung Cancer

Air pollution with higher levels of PM have been suggested to be correlated with an increased risk of lung cancer also in studies conducted in Europe. However, the results are not fully consistent (Barbone et al., 1995; Jedrychowski et al., 1990; Katsouyanni et al., 1991). Two cohort studies in USA provided further evidence of the association. Quantitative risk assessment is restricted by the difficulties in retrospective exposure estimation, both in relation to the composition of the pollution and to the levels of its individual components.

The estimation of potential health effects from particulate matter exposure

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1. Introduction

There has been a growing number of studies published recently on the adverse health effects of particulate air pollution. Although it was known from studies conducted during or after air pollution episodes in the beginning or mid of this century, that high levels of air pollution could result in adverse health effects including increased mortality among the exposed population, recently there has been a number of epidemiologic studies published with suggestive evidence that also at low air pollution concentrations, even below the WHO Air Quality Guidelines, adverse health effects were demonstrated. This is especially true for particulate matter in ambient air, which has been shown to be associated with a number of health outcomes.

In this working document a brief review of the main results from these studies will be given. This working document is not meant as a comprehensive literature review, because these already exist (Brunekreef et al., 1995, Dockery and Pope, 1994; Pope et al., 1995; Schwartz, 1994e-g), but it will focus on the risk estimates that can be derived from the published studies, and the method that can be used to assess the implications for Europe, based on these risk estimates and exposure data.

In epidemiologic studies several health outcomes have been looked at. Most of the studies investigated the acute effect of particulate matter on daily mortality, daily respiratory symptoms and effects on daily peak flow, less on the acute effect on hospital admissions and/or emergency room visits, medication use and spirometry.

In this working paper a grouping based on these health effects has been used to express the associations between health effects and particulate air pollution. Overall, the results from the original papers indicate that there appears to exist good evidence for a particulate matter effect on human health in the population. There is some evidence that the effect is larger in the elderly and in people suffering from diseases; the associations are stronger for the respiratory and cardiovascular deaths than for total mortality. The associations seem to be independent of weather factors and other pollutants.

In Table 1 a summary is given of the studies in which PM_{10}, $PM_{2.5}$ and TSP is measured and the average concentration-response for the different health outcomes based on the studies. The review of the studies is not meant to be comprehensive; more studies have been published on the health effects of particulate matter (in the appendix a number of studies are summarized). For the purpose of this paper however, only studies in which concentrations-response could be calculated from the published results are considered. This excluded f.e. studies in which "high" pollution days were compared with "low" pollution days, or high exposed populations were compared with low exposed populations.

Table 1: Summary of studies in which PM_{10}, $PM_{2.5}$ and TSP is measured and the average concentration-response for the different health outcomes.

MORTALITY	Total	Cardiovasc	Resp
TSP			
Schwartz 1991 Detroit	0.6	na	na
Schwartz/Dockery 1992 Philadelphia	0.7	0.9	1.8
Schwartz/Dockery 1992 Steubenville	0.4	na	na
Schwartz 1994 Cincinnati	0.6	0.8	1.5
PM_{10}			
Pope 1992 Utah Valley	1.6	1.8	3.7
Dockery 1992 St. Louis	1.5	na	na
Dockery 1992 Kingston	1.6	na	na
Schwartz 1993 Birmingham, Alabama	1.0	1.6	1.5
Ito, 1995	0.4		
Kinney 1995	0.5		
$PM_{2.5}$			
Dockery 1992 St. Louis	1.7	na	na
HOSPITAL ADMISSIONS			
PM_{10}			
COPD in elderly:			
Schwartz, 1994 Birmingham, Alabama	2.6		
Schwartz, 1994 Minneapolis	5.0		
Schwartz, 1994 Detroit	2.2		
$PM_{2.5}$			
Asthma			
Thurston, 1994, Toronto	3.5		
All			
Thurston, 1994, Toronto	5.7		
Emergency room visits asthma < 65 years			
Schwartz, 1993 Seattle	3.4		
TSP			
Samet, 1981	0.3		
BS COPD			
Sunyer, 1993 Barcelona	2.3		

Table 1 (cont.).

MEDICATION	Total		
PM_{10}			
Bronchodilator			
Pope, 1991 Resp. Health Utah Valley	12.0%		
Roemer, 1993 Bennekom	2.3%		
Symptom exacerbations amongst asthmatics			
Pope, 1992 Acute health Utah Valley	5%		
Roemer, 1993 Bennekom	5%		
RESP. SYMPTOMS	Upper	Lower	Cough
PM_{10}			
Pope, 1991 Resp. Health,	3.7	5.1	
Pope, 1992 Acute health	-0.2	2.4	3.4
Hoek, 1993 Acute effects	2.6	1.2	
Hoek, 1993 Effects of low	-0.2	1.5	1.3
PEF:			
PM_{10}			
Pope, Resp Health	0.25		
Pope, Acute	0.05		
Roemer	0.09		

2. Exposure measures for particulate matter

Instead of gaseous air pollutants like SO_2, NO_2 or O_3, particulate matter can not be characterized by one representation, but is characterized by the size of the particles that has been measured in the air pollution mixture.

In general, particulate matter can be divided into two classes: the coarse fraction and the fine particulate fraction. The coarse fraction has an aerodynamic diameter of the particles of 2.5 μm or more, while the fine fraction has an aerodynamic diameter of less than 2.5 μm. The coarse fraction contains, in general, particles originating from mechanical activities like industrial processes, resuspension of road dust etc., while the fine fraction contains, in general, particles originating from combustion processes. Unfortunately there is no unique measurement technique applied to measure the coarse or the fine fraction. In contrast, particulate matter has been measured with different measurement methods, which makes comparability between measurements sites and between studies difficult.

The most common techniques applied are the measurements of the 'Total Suspended Particles' (TSP) which measures particles with sizes of less than 100 μm, 'Black Smoke' (BS) which represents the darkness of a white filter through which air has been passed, and 'PM_{10}', particles with an aerodynamic diameter of less than 10 μm, which is also referred to as the 'Thoracic Particles' (TP) indicating that this fraction is able to enter the thoracic area (in the US also PM_{15} has been measured).

The size of the particles determines the probability of the particle to reach the lower airways. TSP for instance contains also particles which are not able to enter the lower airways and is therefore less informative about the health relevance of the air pollution mixture. PM_{10} is therefore a better indicator for health-related particles. Black smoke was developed during the sixties and is specifically applicable for the air pollution mixture in the sixties; nevertheless this method is still used, although the air pollution mixture has changed from coal burning into natural gas burning and traffic related emissions.

In a recent paper by Dockery and Pope (1994) suggestions have been made for "conversion factors" between the different size fractions. They propose the following relations:

$PM_{10} = 0.55 * TSP$
$PM_{10} = PM15$
$PM_{2.5} = 0.60 * PM_{10}$
$Sulphate = 0.25 * PM_{10}$
$PM_{10} = BS$

These were calculations based on the American database of air pollution measurements, and some caution should be used when applying these conversion equations in other countries and in specific situations: recently a paper on air pollution levels in US-Canadian cities has shown that within the US/Canada the ratio of fine particles to PM_{10} varied from 0.30 to 0.70, depending on the location of measurement (Spengler et al., 1996).

However, these conversion formulas can be used as a tool to compare the outcomes of different studies with different size fraction measurements into a uniform relationship. In the aforementioned paper the associations were used to standardize the outcomes from different epidemiologic studies into PM_{10} relationships. By converting the concentration-response relationships with the appropriate conversion factors, the associations between exposure and health outcome were 'standardized' into a PM_{10} relation.

In the remainder of this paper, the health outcomes examined, and the concentration-response relationships will be described briefly.

3. Acute health effects of particulate matter

Mortality

The association between particulate air pollution and increased daily mortality has been described in several papers (Schwartz, 1994e). In general, in the studies the daily variations in air pollution are associated retrospectively with daily variations in mortality for a period of 1 or several years. Health outcomes under study are the total daily mortality and in addition in several studies also cause-specific outcomes like respiratory mortality and cardiovascular mortality.

Most of the papers have reported on the association between PM_{10} (Dockery et al., 1992; Ito et al., 1995; Kinney et al., 1995; Pope et al., 1992; Schwartz, 1993) as the particle size fraction under study, however, also some papers have reported on the association between particulate matter expressed as $PM_{2.5}$ (Dockery et al., 1992), TSP (Schwartz, 1991; Schwartz and Dockery, 1992a, 1992b; Schwartz, J., 1994d) and BS and increased mortality. As mentioned before, TSP is probably, because of the particle size measured, less informative for the health effects, because it also measured the fraction which is not able to enter the lower airways; BS is troublesome because its dependence on the contribution of the darkness of the mixture which might be unrelated to the thoracic fraction. $PM_{2.5}$, representing the finer fraction is, on the other hand, probably more informative of the health effects of particulate matter.

The results from the mortality studies are very consistent in the way that overall a positive association has been found between daily mortality and particulate air pollution, although a factor of 3-4 occurs between estimated effect sizes between the studies. On average, total mortality increases by 1.1% per 10 $\mu g/m^3$ increase in PM_{10}, with a range varying from 0.4% to 1.6%. The concentration-effect estimates for the studies in which TSP and $PM_{2.5}$ have been measured correspond with the PM_{10} estimates when using the conversion factors proposed by Dockery and Pope (1994). The estimated effects were larger for respiratory and cardiovascular mortality.

Several of the studies have been performed at very low levels of exposure. It has been suggested that from the current data base no threshold level can be derived and that the association between particulate air pollution and mortality is continuous over a wide concentration range (0-200 $\mu g/m^3$).

However, there are indications that at higher concentrations this is not the case anymore and that there is a flattening of the concentration-response curve at higher levels. Therefore the use of these estimates in higher concentration ranges is questionable. Preliminary results from a European study on the effects of air pollution on mortality/morbidity indicate that estimates from this study for mortality are smaller (ca. 50%) than previously published (mainly US) estimates. In addition, estimates from Eastern and Western European countries seem to be smaller than estimates from Western European countries. Implications of this result might be that smaller concentration-response associations should be applied when quantifying the health risk of particulate air pollution in Europe.

Hospital admissions and Emergency room visits

Studies on hospital admissions and emergency room visits have investigated several different outcomes and are therefore less comparable than studies on mortality. Sometimes all respiratory admissions are considered, sometimes only specific admissions (asthma, COPD, cardiovascular, cardiopulminar). The elderly population (> 65 years) and people suffering from diseases are considered to be more at risk than the younger population. Therefore recently several studies have focused on the effects on hospital admissions among the elderly (Schwartz, 1994a; 1994b, 1994c). Overall, respiratory admissions, are associated with particulate air pollution; the estimated percent increase is ca. 3% per 10 $\mu g/m^3$ PM_{10}.

Only 2 studies on emergency room visits have been considered in this overview. A third existing study, performed in Barcelona (Sunyer et al., 1993), has reported on a positive association between emergency room visits for Chronic Obstructive Pulmonary Diseases and Black Smoke (relative risk 2.3% per 10 μg/m³ Black Smoke).

Table 2: Percentage change in daily mortality per 10 μg/m³ increase in concentration (references are noted in parentheses).

	TSP	PM_{10}	$PM_{2.5}$
Total daily mortality	0.6 (1,2,3,4)	1.1 (5,6,7,8,9)	1.7 (6)
Respiratory mortality	1.7 (2,4)	2.6 (5,7)	
Cardiovascular mortality	0.9 (2,4)	1.7 (5,7)	
Hospital admissions all	-	-	5.7 (13)
Hospital admissions asthma	-	-	3.5 (13)
Hospital admissions COPD in elderly	-	3.3 (10,11,12)	-
Emergency room visits	0.3 (15)	3.4 (14)	
Bronchodilator use among asthmatics	-	7 (16,17)	-
Symptom exacerbations among asthmatics	-	5 (17,18)	-
Upper respiratory symptoms	-	1.5 (18,19,20)	-
Lower respiratory symptoms	-	2.6 (18,19,20)	-
Cough symptoms	-	2.4 (18,20)	-
Peak expiratory flow	-	-0.13 (16,17,18)	-

1) Schwartz, 1991
2) Schwartz and Dockery, 1992
3) Schwartz, 1994
4) Brunekreef et al., 1995
5) Pope et al., 1992
6) Dockery et al., 1992
7) Schwartz, 1993
8) Ito et al., (1995)
9) Kinney et al., 1995
10) Schwartz, 1994
11) Schwartz, 1994
12) Schwartz, 1994
13) Thurston et al., 1994
14) Schwartz et al., 1993
15) Samet et al., 1981
16) Pope et al., 1991
17) Roemer et al., 1993
18) Pope and Dockery, 1992
19) Hoek and Brunekreef, 1993
20) Hoek and Brunekreef, 1994

Bronchodilator use and symptom exacerbations among asthmatics

A few studies have been conducted on the association between particulate matter and bronchodilator use and children with respiratory symptoms (Pope et al., 1991; Roemer et al., 1993). In these studies, the children use a diary to register their daily medication use and other daily respiratory symptoms. The daily prevalence of bronchodilator use was positively associated with an increase in particulate matter. Per 10 $\mu g/m^3$ increase in PM_{10} the daily prevalence of bronchodilator use increased with 7% (range 2.3%-12.0%). It should be mentioned that this estimate is based on a selection of the total population: children with respiratory symptoms.

In the same studies, the association between PM_{10} and symptom exacerbations among asthmatics have been studied (Roemer et al., 1993; Pope and Dockery, 1992). Overall, a 10 $\mu g/m^3$ increase in PM_{10} was associated with a 5% increase in symptom exacerbation.

Prevalence of respiratory symptoms

Several studies have assessed the association between daily prevalence of respiratory symptoms and ambient particulate air pollution (Hoek and Brunekreef, 1993; Hoek and Brunekreef, 1994; Pope and Dockery, 1992). The daily prevalence is assessed with diaries in which the participants (children) fill in whether they had a respiratory symptom during the day or not. In the analyses, individual symptoms are aggregated into 3 main categories: upper respiratory symptoms defined by nose and throat symptoms; lower respiratory symptoms, defined by wheeze, shortness of breath, asthma attacks and phlegm; and cough as an individual symptom. Positive associations between the daily prevalence of symptoms and PM_{10} have been reported; on average an increase in PM_{10} with 10 $\mu g/m^3$ was associated with an 1.5%, 2.6% and 2.4% increase in the daily prevalence of upper, lower respiratory symptoms and cough respectively.

Peak expiratory flow

Measurements of peak flow variability in relation to particulate matter have been conducted in several studies (Pope and Dockery, 1992; Pope et al., 1991; Roemer et al., 1993). Peak flow measurements are used as an objective measure for health effects of air pollution. The measurements are performed on a daily basis by the participants. A small negative association between peak flow and PM_{10} has been reported with an average decrease in PEF of 0.13% per 10 $\mu g/m^3$ increase in PM_{10}. In a large European study conducted in the winter of 93/94 in 14 centres in Europe, the relation between PM_{10} and PEF was studied. Preliminary results presented recently at 2 international meetings (ISEE/ISEA and ERS) indicate that previously reported associations between PM_{10} and PEF could not be reproduced (Roemer et al., 1996). Further analyses will be performed on this dataset.

4. Chronic effects on mortality of particulate air pollution

Mortality

A few studies have reported on the chronic effects of particulate matter on mortality, indicating that there is suggesting evidence for an association between mortality and chronic exposure to particulate air pollution. However, several of the studies were 'ecological' in design, in that they compare aggregate data on mortality with aggregate data on pollution. In 2 studies a cohort design has been used; one advantage of this design compared with ecological studies is that they use individual data on possible confounders (Dockery et al., 1993; Pope et al., 1995). These two studies, both from the US, found a positive association between chronic exposure to particulate matter and mortality. On average the increase in total mortality was 9% for an increase in of 10 $\mu g/m^3$ of long-term PM_{10} exposure and an 11% increase in total mortality per 10 $\mu g/m^3$ increase in $PM_{2.5}$.

Lung function and respiratory symptoms

A few studies have reported on the association between lung function or respiratory symptoms and long-term exposure to particulate air pollution. Positive associations between decreased FVC and TSP levels were reported (Chestnut et al., 1991), and an increase of 11% in cough and bronchitis rates for a 10 $\mu g/m^3$ increase in the annual average TSP concentration (Ware et al., 1986).

5. Concluding remarks

In this review the overall effect estimates of several size fractions for several health outcomes have been presented. This review was not meant to be conclusive, but merely meant as a document to initiate the discussions during the expert meeting in Oslo. There is good evidence from the published literature for a particular health effect in the population.

This has been extensively demonstrated for acute effects, however recently published studies also showed health effects from chronic exposure to particulate air pollution. Although there is good evidence for an association, it remains unclear what the causal agent is; some studies indicate that effects may be more associated with fine particles, strong aerosol acidity or sulphates, however also gaseous components, correlated with particles, can not be excluded yet. On the other hand however, comparable results have been found between studies conducted in different areas, both different in air pollution mixture (urban, rural, wood-burning) and different in climatic conditions (arid climate, humid, high temperature, low temperature), indicating that particulate mass is of relevance.

Some attempts have been made to 'standardize' results between different studies into 'PM_{10}' effects. It has been shown that applying such a uniform conversion factor might result into serious under- or over-estimation of health effects. This might be especially true for European conditions, in which there is historically a difference in the air pollution mixture between Western Europe (traffic, local industry) and Central and Eastern Europe (home heating, brown coal, local industry). It is therefore plausible to assume that TSP- PM_{10} conversion factors are

smaller for Eastern/Central Europe (PM_{10} << 0.55*TSP) than for Western Europe and the US. Before applying risk estimates to these parts of Europe more insight in this association is needed.

Other differences within Europe might have influences on the risk estimates. Due to difference in nutrition, smoking habits, health care etc. some caution is needed when applying 'western study results' to the whole of Europe.

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Table 3: Summary and results of epidemiologic studies on Particulate Matter.

A. Studies on mortality

LOCATION	DESIGN	POPULATION	CONCENTRATION ($\mu g/m^3$)	EFFECTS	REMARKS	AUTHOR(S)
St. Louis and Kingston/Harriman September 1985-August 1986	Analysis of registration of daily mortality; mortality as a result of accidents and deaths outside the region excluded	Population in 1980: St. Louis 2.356.460 Kingston/Harriman 640.887	Distribution over the period of study: St. Louis: PM_{10} average 27.6 ± 14.9 (1-97); Maximum daily average 97 Kingston/Harriman: PM_{10} average 30 ± 12.1 (4-67); Maximum daily average 67	Number of deaths per day: St. Louis 56.0 ± 8.2 Kingston/Harriman 15.5 ± 4.2 Relation between mortality and PM_{10} is significant only in St. Louis: 16% increase of mortality for 100 $\mu g/m^3$ increase of PM_{10}	Adjusted for weather conditions and season Temperature: St. Louis 57.8 ± 20.0 (°F) Kingston/Harriman 59.8 ± 17.2 (°F) Humidity St. Louis 45.0 ± 19.4 (°F) Kingston/Harriman 47.9 ± 17.8 (°F)	Dockery et al. (1992)
Kingston/Harriman, St. Louis, Steubenville, Portage, Topeka and Watertown (US)	Prospective cohort research on effects of air pollution on mortality with a follow-up period of 14-16 years (= 111076 person years)	8111 white adults from 6 cities in the US between 24-74 years of age ☺ = 52-56%	Distribution over the 6 cities: Total dust: 34.1-89.1 PM_{10}: 18.2-46.5 $PM_{2.5}$: 11.0-29.6	Number of deaths per person years 9.68-10.73 Mortality ratios between most and least polluted city: Total dust 1.26 (95% CI: 1.08-1.47) PM_{10} 1.27 (95% CI: 1.08-1.48) $PM_{2.5}$ 1.26 (95% CI: 1.08-1.47) Cause-specific mortality ratios: Lung cancer 1.37 (95% CI: 0.81-2.31) Cardiopulmonary diseases 1.37 (95% CI: 1.11-1.68)	Adjusted for smoking habits, age, sex, weight, height, education, occupational exposure and medical history	Dockery et al. (1993)

Table 3: Summary and results of epidemiologic studies on Particulate Matter.

A. Studies on mortality (cont.)

LOCATION	DESIGN	POPULATION	CONCENTRATION ($\mu g/m^3$)	EFFECTS	REMARKS	AUTHOR(S)
Los Angeles, CA county/ Cook, IL county 1985-1990	Analysis of registration of daily mortality	Population LA county = 8.3 million, Cook county = 5.3 million	PM_{10} concentrations graphically presented; PM_{10} levels are generally lower in Cook County	RR for mortality = 1.06 (95% CI = 1.01-1.10)	Several different exposure estimates were used, study shows that choice of PM_{10} sites and sampling frequency can make difference.	Ito et al. (1995)
151 US metropolitan areas 1982-1989	Analysis of mortality using data from a large cohort drawn from many study areas	Population cohort of 552.138 aged 30+	FP: mean 18.2 ug/m3 (range 9.0 - 33.5 ug/m3) SO4: mean 11.0 ug/m3 (range 3.6-23.5 ug/m3)	PM2.5 per 10 ug/m^3 $RR_{all\ causes}$ =1.07 (95% CI = 1.04 - 1.11) $RR_{lung\ cancer}$ = 1.01 (95% CI = 0.92 - 1.13) $RR_{cardiopulmonary}$ = 1.13 (95% CI = 1.07 - 1.19) SO4 per 10 ug/m3 $RR_{all\ causes}$ =1.08 (95% CI = 1.05 - 1.11) RR lung cancer = 1.18 (95% CI = 0.90 - 1.36) $RR_{cardiopulmonary}$ = 1.13 (95% CI = 1.08 - 1.19)	Study on long term exposure Adjustment for individual confounders	Pope et al. (1995)

Table 3: Summary and results of epidemiologic studies on Particulate Matter.

A. Studies on mortality (cont.)

LOCATION	DESIGN	POPULATION	CONCENTRATION ($\mu g/m^3$)	EFFECTS	REMARKS	AUTHOR(S)
Utah County April 1985- December 1989	Analysis of registration of daily mortality; mortality as a result of accidents and deaths outside the region excluded	Population in 1988 = 260.000 5.5% of adults smoke	Distributions over the period of study: PM_{10} daily average 47 ± 38 (1-365); PM_{10} 5-day average 47 ± 34 (11-297); Maximum daily average 365; Maximum 5-day average 297	Number of deaths per day = 2.7 ± 1.7 Significant relation between mortality and PM_{10}; strongest relation for 5-day average: RR = 1.16 for 100 $\mu g/m^3$ increase of PM_{10}	Strongest relation with respiratory diseases, then with cardiovascular diseases and then with other diseases Adjusted for time trends, season and humidity Temperature = 40 ± 15 (°F) Humidity = 30 ± 14 (°F)	Pope et al. (1992)
Detroit 1973-1982	Analysis of registration of daily mortality; mortality as a result of accidents and deaths outside the city excluded	No further details	Distribution over the period of study: TSP average 87: 5% percentile 46: 95% percentile 137	Average number of deaths per day = 53 5% percentile = 39 95% percentile = 68 RR for mortality = 1.06 (95% CI: 1.03-1.09) for 100 $\mu g/m^3$ increase TSP	Adjusted for season, weather conditions, time trends, overdispersion and serial correlation Average temperature = 49°F Dew point = 39°F Effects noticeable at concentrations <137 $\mu g/m^3$	Schwartz (1991)

Table 3: Summary and results of epidemiologic studies on Particulate Matter.

A. Studies on mortality (cont.)

LOCATION	DESIGN	POPULATION	CONCENTRATION ($\mu g/m^3$)	EFFECTS	REMARKS	AUTHOR(S)
Birmingham/ Alabama 1985-1988	Analysis of registration of daily mortality; mortality as a result of accidents and deaths outside the region excluded	Population in 1980 = 884.000	Distribution over the period of study: PM_{10} average 47.9; 10% percentile 21; 90% percentile 80; maximum 163	Average number of deaths per day = 17.1 RR for mortality = 1.11 (95% CI: 1.02-1.20) for 100 $\mu g/m^3$ increase of PM_{10} Cause-specific mortality: $RR_{chronic\ pulmonary\ diseases}$ = 1.16 (95% CI: 0.77-1.75); $RR_{cardiovascular}$ = 1.17 (95% CI: 1.04-1.31); RR_{other} = 1.06 (95% CI: 0.94-1.18)	Temperature has a significantly protective effect on mortality: RR = 0.98 (95% BI: 0.96-0.996) for an increase of 5°C Adjusted for time trends, day of the week, year of study, long-term patterns and weather conditions Temperature = 62.6 °F Dew point = 50.8°F	Schwartz (1993)
Cincinnati 1977-1982	Analysis of registration of daily mortality, age-specific (older 65), cause-specific	Population in 1980 = 873.224	TSP: 76 ug/m3 ± 31 25% perc. 53; 75% perc. 93	RR for mortality = 1.06 (95% CI = 1.03-1.10) age > 65: RR=1.09 (95% CI = 1.05-1.14) cause specific: $RR_{pneumonia}$ = 1.09 (95% CI = 0.95-1.42) $RR_{cardiovasc.}$ = 1.08 (95% CI = 1.03-1.14)	Several different Poisson models, Analysis with and without extreme temperatures, adjusted for T, season, month	Schwartz (1994d)

Table 3: Summary and results of epidemiologic studies on Particulate Matter.

A. Studies on mortality (cont.)

LOCATION	DESIGN	POPULATION	CONCENTRATION ($\mu g/m^3$)	EFFECTS	REMARKS	AUTHOR(S)
Philadelphia 1973-1980	Analysis of registration of mortality on 5% of the days with highest and 5% of the days with lowest TSP-concentrations (total 284 days); accidents excluded	Average age of deceased during days with high concentrations 65.86 Average age of deceased during days with low concentrations 65.25 Ratio ☹/☺ deceased during days with high concentration 1.17 Ratio ☹/☺ deceased during days with low concentration 1.18	Average TSP during days with high concentrations 141 Average TSP during days with low concentrations 47	Number of deaths during days with high concentrations = 7915 Number of deaths during days with low concentrations = 7337 RR for mortality = 1.08 Cause-specific mortality: $RR_{\text{chronic pulmonary diseases}} = 1.25$ $RR_{\text{pneumonia}} = 1.13$ $RR_{\text{cardiovascular}} = 1.09$ $RR_{\text{lung cancer}} = 1.19$ $RR_{\text{cerebrovascular}} = 1.15$	Adjusted for year of, study season, temperature and humidity Temperature: High-concentration days 57°F Low-concentration days 55°F Dew point: High-concentration-days 46°F Low-concentration days 47°F	Schwartz (1994f)

Table 3: Summary and results of epidemiologic studies on Particulate Matter.

A. Studies on mortality (cont.)

LOCATION	DESIGN	POPULATION	CONCENTRATION ($\mu g/m^3$)	EFFECTS	REMARKS	AUTHOR(S)
Philadelphia 1973-1980	Analysis of registration of daily mortality; mortality as a result of accidents and deaths outside the city excluded	Population in 1980 = 1.688.710	Distribution over the period of study: TSP average 77.2; 5% percentile 37; 95% percentile 132; maximum daily average 222	Average number of deaths per day = 48.2 RR for mortality = 1.07 (95% CI: 1.04-1.10) for 100 $\mu g/m^3$ increase TSP Cause-specific mortality: RR_{COPD} = 1.19 (95% CI: 0.0-1.42); $RR_{pneumonia}$ = 1.11 (95% CI: 1.03-1.27); $RR_{cardiovascular}$ = 1.10 (95% CI: 1.06-1.14)	Effect is greater in persons >65 years than in persons <65 years (10% and 3% increase of total mortality respectively) Adjusted for year of study, season, temperature and humidity Temperature = 54.8°F Dew point = 42.8°F	Schwartz/Dockery (1992a)
Steubenville, Ohio 1974-1984	Analysis of registration of daily mortality; mortality as a result of accidents and deaths outside the city excluded	No further details	Distribution over the period of study: TSP average 111; 10% percentile 36; 90% percentile 209	Average number of deaths per day = 3.07 10% percentile = 1 90% percentile = 5 (number of days = 4018) RR for mortality = 1.04 (95% CI: 1.02-1.06) for 100 $\mu g/m^3$ increase TSP	Adjusted for season and temperature Average temperature = 10.1°C Dew point = 3.6°C	Schwartz/Dockery (1992b)
London 1958-1972	Analysis of registration of daily mortality during winter months; non-traumatic cases only	No further details	Annual average concentrations of black smoke varied from 59 to 536 during the years of the study	Strong relation between mortality and black smoke	Adjusted for temperature and humidity	Schwartz/Marcus (1990)

Table 3: Summary and results of epidemiologic studies on Particulate Matter.

A. Studies on mortality (cont.)

LOCATION	DESIGN	POPULATION	CONCENTRATION ($\mu g/m^3$)	EFFECTS	REMARKS	AUTHOR(S)
Nordrhein-Westfalen 1985	Study of number of hospital admissions, visits to general practitioners and mortality as a result of air pollution episode	Population: 6 million	TSP: Maximum 24-hour average in polluted area 0.6 $\mu g/m^3$ Average 24-hour concentration in polluted area 0.44 $\mu g/m^3$ Maximum 24-hour average in control area 0.19 $\mu g/m^3$	Increases in polluted vs control area: Mortality 8% vs 2% Hospital admissions 15% vs 3% Visits to doctor -2% vs -4% Transport by ambulance 28% vs not known Cause-specific mortality: cardiovascular 6% vs 8% Respiratory 3% vs -5% combination Cardiovascular and respiratory 9% vs 2% Cause-specific hospital admissions: Cardiovascular 19% vs 5% Respiratory 7% vs 0% Cerebrovascular 57% vs 0% Arrhythmia 49% vs -8% Chronic bronchitis 39% vs 6%	Adjusted for weather conditions Temperature in polluted area -4- -12°C	Wichmann et al. (1989)

Table 3: Summary and results of epidemiologic studies on Particulate Matter.

B. Studies of hospital and emergency room admissions

LOCATION	DESIGN	POPULATION	CONCENTRATION ($\mu g/m^3$)	EFFECTS	REMARKS	AUTHOR(S)
Brabant 1987	Measurements of pulmonary function before and after an episode of air pollution; reference values were measured three months before the episode	191 children aged 6-12 years; average age is 9.01	Concentration of black smoke is highest in the middle of the episode (maximum 24-hour value = 110); the concentration TSP is highest at the end of the episode (maximum 24-hour value = 280)	A decrease in FVC, FEV_1 and PEF is seen immediately and two weeks after the episode: after 3½ weeks FVC and FEV_1 are still low	Adjusted for age 24-hour average of - temperature varied from 2.1-8.8	Brunekreef et al. (1989)
Watertown, St. Louis, Portage, Kingston/Harriman, Steubenville, Topeka 1980-1981	Cross-section study of relation between air pollution and chronic respiratory health in children	5422 white children aged 10-12 years	Distribution of annual averages over the cities: TSP 34.1-80.0 PM_{15} 20.1-58.8 $PM_{2.5}$ 11.8-36.7 FSO_4 3.2-13.9	Chronic coughing, bronchitis and 'chest illness' are related to concentrations of TSP, PM_{15}, $PM_{2.5}$ and FSO_4 only in the case of PM_{15} the relation with bronchitis is significant: OR = 2.5 (95% CI: 1.1-6.1)	Adjusted for sex, age, education of parents, smoking habits parents, city and presence of gas oven in the house	Dockery et al. (1989)

Table 3: Summary and results of epidemiologic studies on Particulate Matter.

B. Studies of hospital and emergency room admissions (cont.)

LOCATION	DESIGN	POPULATION	CONCENTRATION ($\mu g/m^3$)	EFFECTS	REMARKS	AUTHOR(S)
California 1976-1981	Analysis of data on acute respiratory morbidity in HIS- database (Health Interview Survey) Indicators for morbidity are: RRAD = respiratory- Related restricted activity days MRAD = minor restricted activity days	Working adults from urban area aged 18-65 years; average age is 38.1 ☺ = 58.8%	Two-week averages $PM_{2.5}$ per year of study: 1976: 22.27 ± 10.23 1977: 21.85 ± 10.92 1978: 22.59 ± 9.43 1979: 22.02 ± 8.38 1980: 20.73 ± 8.78 1981: 21.33 ± 7.17	1 $\mu g/m^3$ change in PM_{10} is related to an increase by 1.58% ± 0.35% in RRAD 1 $\mu g/m^3$ change in $PM_{2.5}$ is related to an increase by 0.82% ± 0.18% in MRAD	RRAD is defined as a day on which the normal activity of persons is disrupted and when there are acute respiratory symptoms MRAD is defined as a day which does <u>not</u> result in absenteeism from work and thus has less influence on daily activity	Ostro/Rothschild (1989)

Table 3: Summary and results of epidemiologic studies on Particulate Matter.

B. Studies of hospital and emergency room admissions (cont.)

LOCATION	DESIGN	POPULATION	CONCENTRATION ($\mu g/m^3$)	EFFECTS	REMARKS	AUTHOR(S)
Utah Valley April 1985-February 1988	Analysis of registration of hospital admissions for respiratory symptoms in 4 hospitals	Population in 1987: 258.000 5.5% of adults smoke Population is divided into two cohorts: 0-17 years and >18 years	Average PM_{10}-concentration during 35 months: 45.8 ± 4.3 Average maximum PM_{10}-concentration during 35 months: 94.7 ± 11.9	Relation between hospital admissions for pneumonia, bronchitis, asthma and 'pleurisy' During months with PM_{10}>150 $\mu g/m^3$ (24-hour) admissions of children are 3 x as high: for adults an increase of 44% can be seen During months with PM_{10} ≥50 $\mu g/m^3$ (24-hour) an increase by 89% can be seen in children: in adults 47%	Adjusted for weather conditions	Pope (1989)

Table 3: Summary and results of epidemiologic studies on Particulate Matter.

B. Studies of hospital and emergency room admissions (cont.)

LOCATION	DESIGN	POPULATION	CONCENTRATION ($\mu g/m^3$)	EFFECTS	REMARKS	AUTHOR(S)
Utah Valley, Salt Lake Valley, Cache - Valley April 1985 March 1989	Analysis of registration of hospital admissions	Population: Utah Valley 188.000 Salt Lake Valley 780.000 Cache Valley 72.500 Number of smokers (≥18 years): Utah Valley 6% Salt Lake Valley 18% Cache Valley 10%	Annual averages PM_{10}: Utah Valley 53 Salt Lake Valley 55 Cache Valley <40 Maximum daily averages PM_{10}: Utah Valley 365 Salt Lake Valley 194 Cache Valley <150 Winter averages PM_{10}: Utah Valley 95 Salt Lake Valley 71 Cache Valley <60	Number of admissions for Utah, Salt Lake and Cache Valley respectively: Pneumonia: 1697, 714 and 600 Bronchitis: 2389, 779 and 1175 Asthma: 656, 142 and 139 Regression analysis shows a significant relation between average monthly concentration PM_{10} and hospital admissions as a result of respiratory diseases in Utah and Salt Lake Valley Strong relation particularly in children <5 years	Winter temperature: Utah Valley 21.1°F Salt Lake Valley 21.3°F Cache Valley 12.6°F	Pope (1991)

Table 3: Summary and results of epidemiologic studies on Particulate Matter.

B. Studies of hospital and emergency room admissions (cont.)

LOCATION	DESIGN	POPULATION	CONCENTRATION ($\mu g/m^3$)	EFFECTS	REMARKS	AUTHOR(S)
Utah Valley December 1989-March 1990	Study of relation between PM_{10} and changes in pulmonary function on the basis of measurements of pulmonary function and registration of acute respiratory symptoms in diaries	34 healthy children aged 9-11 years and 21 asthma patients aged 8-72 years Healthy children: ☺ = 38% Asthma patients: ☺ = 52%	Daily average PM_{10}-concentration 46 (11-195) 2 x exceedance of 150	Increased PM_{10}- concentrations of 150 $\mu g/m^3$ lead to: A decrease of PEF (3-6%) in both populations An increase in respiratory symptoms (significant in children only); complaints about upper and lower bronchi were 1.5 and 2.1 x higher, respectively, during high-concentration--days (195 $\mu g/m^3$) than during low-concentration-days (11 $\mu g/m^3$) An increase in use of medicine in both populations (6.2 x higher during high-concentration days)	Adjusted for weather conditions	Pope et al. (1991)

Table 3: Summary and results of epidemiologic studies on Particulate Matter.

B. Studies of hospital and emergency room admissions (cont.)

LOCATION	DESIGN	POPULATION	CONCENTRATION ($\mu g/m^3$)	EFFECTS	REMARKS	AUTHOR(S)
Helsinki 1987-1989	Analysis of registration of hospital admissions for asthma attacks during 3 years	Population Helsinki: 1987: 488604 1988: 491148 1989: 491777	Annual average TSP-concentration over 3 years: 76.3 ± 51.6 (6-414) Average concentration during low-concentration days = 42.3 Average concentration during high-concentration days = 93.1	Average number of admissions per day = 3.84; number of admissions per age category: 0-14 years: 1359 15-64 years: 1685 65^{+}: 1165 Significant relation between hospital admissions and weekly average concentrations of TSP; the number of admissions increased by 18% on high-concentration days	Relations are strongest in persons aged 15-64 years, then in persons >65 years and then in children 0-14 years Temperature= 4.7±9.3(°C) Humidity = 82.9±12.0(%)	Pönkä (1991)
Utah Valley 1985-1990	Analysis of registration of school absenteeism of children who were followed for 6 years	6700-6900 school children	Weekly average PM_{10} 50 28-day average PM_{10} 51 maximum daily average 365 10 x per year exceedance of 150	An increase of the 28-day average of PM_{10} by 100 $\mu g/m^3$ is related to an increase of the total absence by 40%	Adjusted for weather conditions, month of the year, day of the week, holidays and weekends	Ransom/Pope (1992)

Table 3: Summary and results of epidemiologic studies on Particulate Matter.

B. Studies of hospital and emergency room admissions (cont.)

LOCATION	DESIGN	POPULATION	CONCENTRATION ($\mu g/m^3$)	EFFECTS	REMARKS	AUTHOR(S)
Steubenville 1974-1977	Analysis of emergency room visits during March, April, October, November	Population = 31.000 inhabitants, industrial (steel)	TSP 156 ug/m3, SD = 123 ug/m3 (range: 14 - 696)	TSP increase 100 ug/m3: RR = 1.03	Months chosen because of contrasting air pollution and meteorology Analysis less sophisticated than later papers	Samet et al. (1981)
Birmingham, Al 1986-1989	Analysis of daily counts of hospital admissions for pneumonia and COPD for persons aged 65 and older	Population = 884.000	PM_{10} daily average 45 ug/m^3 10% perc. 19 ug/m^3 90% perc. 77 ug/m^3	$RR_{pneumonia}$ = 1.19 (95% CI = 1.07-1.32) RR_{COPD} = 1.27 (95% CI = 1.08-1.50)	Several different models were calculated, results were not sensitive to model; test for nonlinearity were not significant ; no evidence for threshold	Schwartz (1994a)
Minneapolis-St.Paul, MI 1986-1989	Analysis of daily counts of hospital admissions for pneumonia and COPD for persons aged 65 and older		PM_{10} daily average 36 ug/m3 10% perc. 18 ug/m3 90% perc. 58 ug/m3	$RR_{pneumonia}$ = 1.17 (95% CI = 1.02-1.33) RR_{COPD} = 1.57 (95% CI = 1.20-2.06)	Several different models were calculated, results were not sensitive to model	Schwartz (1994b)
Detroit, MI 1986-1989	Analysis of daily counts of hospital admissions for pneumonia, COPD and asthma for persons aged 65 and older	Population 4.382.000 of whom = 517.000 were 65 yr or older	PM_{10} daily average 48 ug/m3 10% perc. 22 ug/m3 90% perc. 82 ug/m3	$RR_{pneumonia}$ = 1.12 (95% CI = 1.04-1.19) RR_{COPD} = 1.20 (95% CI =1.09-1.32) No association with asthma	Results were not changed when ozone was in or out model	Schwartz (1994c)

Table 3: Summary and results of epidemiologic studies on Particulate Matter.

B. Studies of hospital and emergency room admissions (cont.)

LOCATION	DESIGN	POPULATION	CONCENTRATION ($\mu g/m^3$)	EFFECTS	REMARKS	AUTHOR(S)
53 urban areas in US	Analysis of registration of cases of chronic respiratory disease	6138 persons from 53 urban areas aged 30-74 years; average age is 51.7	Annual average TSP 85.5 5% percentile 47.6 95% percentile 130.8	Annual average TSP is related to an increase of the risk of bronchitis and respiratory diagnosis by a doctor: OR = 1.07 (95% CI: 1.02-1.12) and OR = 1.06 (95% CI: 1.02-1.11) for an increase by 10 $\mu g/m^3$ of TSP	Relations are stronger in non-smokers: OR = 1.11 (95% CI: 1.02-1.21) and OR = 1.07 (95% CI: 0.996-1.15) Adjusted for age, sex, race and smoking habits	Schwartz (1994g)
Duisburg, Cologne, Stuttgart, Tübingen, Freudenstadt January 1986-December 1987	Analysis of registration of daily cases of croup and bronchitis by physicians and hospitals during two years	Children aged 0-2 years	24-hour averages TSP: 10% percentile 5-34 50% percentile 17-56 90% percentile 41-118	6330 cases of croup 4755 cases of bronchitis An increase in TSP by 10-70 $\mu g/m^3$ is related to an increase in cases of croup by 27%	Adjusted for weather conditions, season and time trends	Schwartz et al. (1991)
Seattle September 1989-September 1990	Analysis of registration of hospital visits for asthma in 8 hospitals; hospital visits for gastroenteritis used as a control group	39% of the asthma patients <20 years; analyses are limited to persons <65 years	Distribution over the period of study: PM_{10} 29.6 ± 18 (6-103)	Number of hospital visits for asthma = 2955 (7.1 ± 3.2) RR for an increase by 30 $\mu g/m^3$ of PM_{10} is 1.12 (95% CI: 1.04-1.20)	Effects noticeable at a concentration of 24 $\mu g/m^3$ Adjusted for weather conditions, season, time trends, age, hospital and day of the week Temperature = 7.9°C Humidity = 73%	Schwartz et al. (1993)

Table 3: Summary and results of epidemiologic studies on Particulate Matter.

B. Studies of hospital and emergency room admissions (cont.)

LOCATION	DESIGN	POPULATION	CONCENTRATION ($\mu g/m^3$)	EFFECTS	REMARKS	AUTHOR(S)
Barcelona 1985-1986	Analysis of registration in hospitals of acute outpatient treatment for deterioration of COPD	Population= 1.7. mill Age >14 years 99.4% >35 years	Annual average concentration of black smoke 72.9 ± 38.7 (39-310)	Number of admissions for COPD per day = 11.9± 5.6 Daily cases of acute treatments for COPD increase by 0.01 per $\mu g/m^3$ black smoke	By COPD is understood: chronic bronchitis, emphysema, chronic airway obstruction, 'cor pulmonary' and secondary effects Adjusted for weather conditions, season and time trends Temperature = 11.7-20.1°C Relative humidity = 66.7%	Sunyer et al. (1991)
Barcelona 1985-1989	Analysis of registration of daily emergency cases of COPD in 4 hospitals	Age: 96% >45 years 70% >65 years	Concentration range of black smoke over the period of study: 39-310	Average number of cases per day: 15.8 (3-34) in winter 8.3 (1-24) in summer An increase by 25 $\mu g/m^3$ of black smoke is related to an increase by 6-9% of hospital admissions for COPD during winter; in summer the effect is less strong	Adjusted for weather conditions, day of the week and year of study	Sunyer et al. (1993)

Table 3: Summary and results of epidemiologic studies on Particulate Matter.

B. Studies of hospital and emergency room admissions (cont.)

LOCATION	DESIGN	POPULATION	CONCENTRATION ($\mu g/m^3$)	EFFECTS	REMARKS	AUTHOR(S)
Toronto 1986-1988	Analysis of daily hospital admissions for respiratory causes (total respiratory and asthma) during July and August	Population= 2.4. mill	SO4, H+, O3, FP, CP, PM10, TSP, TSP-PM10, SO2, NO2 during 3 summer seasons (July-August)	SO4 per 10 ug/m3: $RR_{total\ respiratory}$ = 1.12 (95% CI = 1.00 - 1.23) RR_{asthma} = 1.11 (95% CI = 0.99 - 1.23) $PM_{2.5}$ per 100 ug/m3: $RR_{total\ respiratory}$ = 1.59 (95% CI = 1.07 - 2.10) RR_{asthma} = 1.35 (95% CI = 0.85 - 1.85) PM_{10} per 100 ug/m3: $RR_{total\ respiratory}$ = 1.46 (95% CI = 1.05 - 1.86) RR_{asthma} = 1.20 (95% CI = 0.99 - 1.42)	In the various model the relative particle metric strenghts of association with admissions were generally H+ > SO_4 > $PM_{2.5}$ > TSP	Thurston (1994)
6 cities in US 1976-1977	Analysis of lung function and respiratory symptoms and long-term exposure	8327 preadolescent children (7-10 yrs)	Distribution of annual averages over the cities: TSP:32.0 - 163.0 SO2: 2.9 - 184 SO4 in TSP: 4.4 - 19.3	TSP per 10 ug/m3: OR_{cough} = 1.11 (1.07-1.15) $OR_{bronchitis}$ = 1.11 (1.01-1.21) No associations with pulmonary function	Study suggest association between air pollution and increased risk for bronchitis and other respiratory disorders, but not with pulmonary function	Ware (1986)

Table 3: Summary and results of epidemiologic studies on Particulate Matter.

C. Studies of pulmonary function and/or symptoms

LOCATION	DESIGN	POPULATION	CONCENTRATION ($\mu g/m^3$)	EFFECTS	REMARKS	AUTHOR(S)
Zurich, Basel November 1985- November 1986	Analysis of registration of acute respiratory symptoms in diaries during 6 weeks in children	625 children aged 0-5 years ☺ = 52.2% 😐 = 47.8%	Median concentration TSP 43 75% percentile 66 range 30-117	6-week average concentration TSP significantly related to coughing incidences: RR= 1.16 (95% CI: 1.07-1.26) for an increase by 20 $\mu g/m^3$ Concentration TSP of previous day is related to symptoms of the upper bronchi: RR = 1.12 (95% CI: 1.00-1.24) for an increase by 20 $\mu g/m^3$ Relative risks for the duration of the complaints (RD): RD_{total} = 1.12 (95% CI: 1.004-1.24) $RD_{coughing}$ = 1.06 (95% CI: 0.99-1.14) $RR_{difficult\ breathing}$ = 1.37 (95% CI: 0.96-1.96) $RR_{upper\ bronchi}$ = 1.04 (95% CI: 0.97-1.11)	Adjusted for temperature and season Zurich: Average day temperature 8.5°C (-12-27.1) Humidity 76.5% (52.3-95.8) Basel: Average day temperature 7.5°C (-12.8-24.8) Humidity 82.6% (45.0-97.9)	Braun-Fahrländer et al. (1992)

Table 3: Summary and results of epidemiologic studies on Particulate Matter.

C. Studies of pulmonary function and/or symptoms (cont.)

LOCATION	DESIGN	POPULATION	CONCENTRATION ($\mu g/m^3$)	EFFECTS	REMARKS	AUTHOR(S)
49 locations in US NHANES 1	Analysis of relationship between pulmonary function and quarterly levels of TSP	Subsample from NHANES1 25-75 yrs	TSP range 40-160µg/m^3	1 standard deviation increase (about 34 ug/m3) in TSP from sample mean (84 ug/m3) was associated with an average decrease of 2.2% in FVC	Suggestion of threshold level (appr. 60 ug/m3, quarterly average)	Chestnut et al. (1991)
Piteå, Sweden	Study of relation between asthma symptoms and air pollution on the basis of registration of symptoms in diaries	31 asthma patients aged 9-71 years 4 persons <15 years 6 persons ≥65 years Number of men = 18 number of women = 13 Divided into classes: Total group Variable group (= at least one day with 5 or more attacks of shortness of breath)	24-hour average black smoke measured over 55 days: 7.1 (1.0-21.4) Divided into classes: high: 12.2 medium: 6.8 low: 3.9	Shortness of breath: $OR_{medium,\ total\ group}$ = 1.5 (90% BI: 0.7-2.9) $OR_{medium,\ variable\ group}$ = 2.2 (90% BI: 0.9-5.6) $OR_{high,\ total\ group}$ = 1.8 (90% BI: 0.8-4.0) $OR_{high,\ variable\ group}$ = 3.3 (90% BI: 1.1-10.0)	Adjusted for weather conditions temperature: -4.5°C (-22.4-6.2) humidity: 73% (42-96)	Forsberg et al. (1993)

Table 3: Summary and results of epidemiologic studies on Particulate Matter.

C. Studies of pulmonary function and/or symptoms (cont.)

LOCATION	DESIGN	POPULATION	CONCENTRATION ($\mu g/m^3$)	EFFECTS	REMARKS	AUTHOR(S)
Wageningen 1990-1991	Study of effects of air pollution episode during winter on the basis of measurements of pulmonary function and registration of acute respiratory symptoms in diaries	112 children aged 7-12 years	PM_{10}-concentration 1x above 110 and 1x above 150; maximum concentration 171 concentrations on days of measurements of pulmonary function 30-144 Daily average black smoke 2-120	During the episode especially FVC and FEV_1 are significantly low Regression analysis shows that per 100 $\mu g/m^3$ PM_{10} the FVC, FEV_1 and MMEF decrease by ± 3%; the decrease in PEF (1.5%) is not significant	Adjusted for low temperature	Hoek/Brunekreef (1993)
Deurne, Enkhuizen, Venlo and Nijmegen 1987-1988	Study of effects of air pollution in winter on the basis of measurements of pulmonary function and registration of acute respiratory symptoms in diaries	1000 children aged 7-11 years from a non-industrial area	24-hour averages of PM_{10} 14.1-126.1 24-hour average on the day before measurements of pulmonary function 44.9 ± 23.3	Slight negative relation between pulmonary function (FVC, FEV_1, PEF and MMEF) and PM_{10} despite the low concentr.; changes for concentr. of the same day (N = 782) and conc. of the previous day (N = 759) resp. ΔFVC = 0.26% and 0.31% (not signif.) ΔFEV_{10} = 0.29% and 0.39% (not signif.) ΔPEF = 0.62% and 0.72% ΔMMEF = 0.70% and 0.86% No relations with acute respir. symptoms found	Adjusted for temperature	Hoek/Brunekreef (1994)

Table 3: Summary and results of epidemiologic studies on Particulate Matter.

C. Studies of pulmonary function and/or symptoms (cont.)

LOCATION	DESIGN	POPULATION	CONCENTRATION ($\mu g/m^3$)	EFFECTS	REMARKS	AUTHOR(S)
Utah Valley 1990-1991	Study of daily change of pulmonary function on the basis of measurements of pulmonary function and registration of acute respiratory symptoms in diaries	79 children aged 10-12 years, 39 of whom with and 40 without respiratory complaints Children with respiratory complaints: ☺ = 46% Children without respiratory complaints: ☺ = 68%	Daily average PM_{10}-concentrations varied from 7-251 average = 76 14 x exceedance of 150 Division into quartiles: Q_1 = 25 Q_2 = 55 Q_3 = 89 Q_4 = 141	Pulmonary function: significant negative relation between decrease in pulmonary function and 5-day average PM_{10}-concentration for both groups of children: Increased levels of PM_{10} by 150 $\mu g/m^3$ lead to a reduction of PEF by 1.8% and 1.3% Acute respiratory symptoms in comparison of highest and lowest concentration-quartile: In symptomatic children symptoms of lower and upper bronchi and coughing have increased by 57, 82 and 100% respectively; in asymptomatic children, a connection has only been observed with the 5-day average: symptoms of lower bronchi and coughing have increased by 40 and 78%	Adjusted for weather conditions average day temperature 20°F (-16-46)	Pope/Dockery (1992)

Table 3: Summary and results of epidemiologic studies on Particulate Matter.

C. Studies of pulmonary function and/or symptoms (cont.)

LOCATION	DESIGN	POPULATION	CONCENTRATION ($\mu g/m^3$)	EFFECTS	REMARKS	AUTHOR(S)
Salt Lake City and Utah	Study of effects of PM_{10} on pulmonary function in smokers with mild form of COPD; cross-section study in which measurements were taken 2x with an intervening period of 10-90 days	624 smokers (≥10 cigarettes per day) with mild form of COPD ($FEV_1/FVC \leq 0.70$)	24-hour averages of PM_{10} varied from 1-181; during the study the average concentration was 55	Slight negative relations between ΔFEV_1 and PM_{10} and $\Delta FEV_1/FVC$ and PM_{10}; these relations are stronger in men than in women 100 $\mu g/m^3$ increase of PM_{10} is related to an average decrease of FEV_1 by ca. 2%	Temperature = 39°F (7-72)	Pope/Kanner (1993)
Wageningen, Bennekom December 1990-March 1991	Study of the influence of winter smog episodes on bronchi in children on the basis of measurements of pulmonary function and registration of acute respiratory effects in diaries	73 children aged 6-12 years with chronic respiratory symptoms; average age 9.3 ± 1.7 ☺ = 45%	Maximum daily average PM_{10}-concentration: 175 on 6 days >110	PEF decreased by 1-2% per 100 $\mu g/m^3$ PM_{10} At higher concentra-tions the prevalence of respiratory symptoms and use of medicine increased: RR_{asthma} = 1.48 and 1.74 for PM_{10} concentration of previous day and average concentration of previous week respectively; $RR_{wheezing}$ = 1.33, 1.41 and 1.50 for concentration on the same day, concentra-tion previous day and average concentration of previous week;	The results for PM_{10} are <u>not</u> independent of concentrations of SO_2 and black smoke Adjusted for temperature, time trends (time series analysis)	Roemer et al. (1993)

Table 3: Summary and results of epidemiologic studies on Particulate Matter.

C. Studies of pulmonary function and/or symptoms (cont.)

LOCATION	DESIGN	POPULATION	CONCENTRATION ($\mu g/m^3$)	EFFECTS	REMARKS	AUTHOR(S)
Wageningen, Bennekom December 1990-March 1991 (cont.)				$RR_{runny\ nose}$ = 1.09 and 1.31 for concentra-tion on the same day and average concentration of previous week; $RR_{use\ of\ medicine}$ = 1.26, 1.22 and 1.38 for concentration on the same day, concentration of the previous day and average concentration of previous week		Roemer et al. (1993) (cont.)

Sulphur Dioxide

Evaluation of Sulphur Dioxide at the Nordic Expert Meeting

There are much fewer studies focusing on health effects of SO_2 than the studies analyzing the impacts of particulate matter. In many, mostly American, studies, the particulate matter seems to be the component responsible for the health effect of the pollution mix containing both SO_2 and PM. However, some recent results indicate that SO_2 has independent, additional, adverse health effect. In this evaluation, those independent effects were the main focus of discussion but the ideal separation of the impacts of both pollutants may not always be possible, and the effects attributed to SO_2 may be, infact due to a mixture of pollutants for which SO_2 is an indicator. Therefore, a caution should be used in the extrapolation of the presented results.

Quantifiable relationships

Short-term effects

Similarly as the studies of the impacts of particulate matter, most studies are the temporal studies using aggregated data and time series analysis. Daily number of events is associated with the 24-hour mean SO_2 concentration in the preceding day(s). Most of the recent European analyses are conducted within the framework of the APHEA study.

Mortality

Total daily mortality is estimated to increase by 6% per 100 µg/m^3 SO_2 (range 3%-15%). The studies available do not indicate a threshold. However, it may be prudent to consider the above estimate of effect applicable for SO_2-concentrations above 50 µg/m^3. Mortality due to *respiratory* diseases increases by 9% per 100 µg/m^3 SO_2 (range: 3%-33%), while the results for the *cardiovascular mortality* are similar to the estimated effect on total mortality.

Hospital admissions

Based on a limited data from a few cities participating in the APHEA study, the estimate of 5% for increments for 100 µg/m^3 SO_2 is given for all respiratory admissions for the age group over 65 years. The estimates varied between the cities and seasons, indicating a range from 1% to 9%.

Measurable effects of SO_2 that are as yet non quantifiable

The list of the effects requiring further study is similar to that for the particulate pollution. One of the principal reason for limitations of the use of the many existing studies where SO_2 effects are reported is possible confounding by the particulate matter. Strong correlation of both pollutants in many locations make separation of the effects very difficult in the absence of very refined exposure estimates.

Sulphur dioxide exposure and health

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1. Introduction

Sulphur dioxide is among the first pollutants to be considered for causing adverse health effects. Its levels in Europe and North America have been reduced during the last three decades so that annual mean concentrations are generally below 100 $\mu g/m^3$. A description of the chemistry, sources, exposure and a historical account are given in the 1987 WHO "Air quality guidelines for Europe".

2. Studies on short-term health effects

This review will only consider epidemiologic studies published after 1985 concerning the health effects of pollutants, including SO_2. The majority of these are temporal studies using aggregated data investigating short-term health effects (Katsouyanni et al., 1993). The reviewed studies are generally assessing the health effects of moderate or low SO_2 pollution levels (below the WHO 1987 criteria for the levels of pollution) (WHO, 1987).

The emphasis given in the United States on the adverse health effects of particulate matter and the debate surrounding that issue has resulted in many studies which have only considered, or are greatly focused, on the health effects of particulate matter, which are thus now better understood. However, some recent results indicate that SO_2 has independent (from other measured pollutants) acute adverse health effects. This is also reflected in the WHO "Update and revision of the Air Quality Guidelines for Europe" (WHO, 1994) where guidelines are given for the first time for SO_2 levels independently of particulate matter.

The health effects considered are usually either total or cause-specific (respiratory, cardiovascular) daily number of deaths and hospital admissions mainly for respiratory causes (specifically for COPD or asthma) or cardiovascular causes.

In the Table these recent studies are described along with several done within the European multicenter study APHEA (Air pollution and health: a European approach) (Katsouyanni et al., 1994; Katsouyanni et al., 1996; Schwartz et al., 1996). The first 3 papers (Derrienic et al., 1989; Hatzakis et al., 1986; Katsouyanni et al., 1990) present the first "new generation" studies which have been published in Europe and both indicate an SO_2 effect on mortality but no

particulate matter effect. However, the analysis employed either do not lead to epidemiologically interpretable results or apply analysis which may now be considered partly outdated. Among the next 5 papers which investigate mortality, one (Verhoeff et al., 1996) does not find any SO_2 effect, two (Spix et al., 1993; Wietlisbach et al., 1996) find an SO_2 effect but may pose doubts as to the extent that this effect is independent of particle levels and two (Xu et al., 1994; Touloumi et al., 1994) find a clear SO_2 effect (in fact stronger than the investigated particle effect).

Among the two following studies on hospital admissions (Schwartz and Morris, 1995; Sunyer et al., 1993) the first found an SO_2 effect on cardiovascular admissions between the elderly which became non-significant in a two pollutant model including also PM_{10}, while the second, from Barcelona, has reported a clear SO_2 effect on emergency COPD admissions.

The next study included in the Table is the mortality time-series study in Philadelphia, USA (Schwartz and Dockery, 1992) which is the location among those studied in the U.S. with SO_2 data and moderately elevated SO_2 levels. This data set has raised discussions and was considered extensively in the H.E.I. study done by Samet et al. (1995). One of the points of concern is whether the SO_2 coefficient remains or does not remain statistically significant in a model in which TSP is also included.

The next pages in the Table present results from the APHEA project. The individual cities results (Spix and Wichmann, 1996; Sunyer et al., 1996; Dab et al., 1996; Zmirou et al., 1996; Ponce de Leon et al., 1996; Touloumi et al., 1996; Vigotti et al., 1996; Anderson et al., 1996) have recently been published. However, the combined results reported are still under preparation. The available results for the Central and Eastern European APHEA cities (Bacharova, 1996; Wojtyniak and Piekarski, 1996) are not presented as they are less consistent. For total mortality a very statistically significant effect of SO_2 is noted with significant heterogeneity between the cities included.

The range of estimates is between 3% and 15% increase associated with 100 $\mu g/m^3$ increase in total daily number of deaths. This range could lead to a combined estimate of about 6%. Similarly, the range for respiratory mortality is between 3% and 33% and could be summarized by a figure of about 9%. Cardiovascular mortality follows generally the same pattern as total mortality. Based on the limited APHEA and other studies morbidity data an estimate of 5% increase for all respiratory admissions for the elderly (65+ years) associated with 100 $\mu g/m^3$ increase in SO_2 could be inferred.

The above results seem to indicate that there are short-term effects of moderate and low SO_2 levels on health but are probably not adequate for quantifying this association for most of the health outcomes considered. An important issue which should be addressed in this context is the relative importance of one and more-pollutant models taking into consideration the collinearity of the pollutant variables, their measurement error and how accurately each measurement represents true population exposure.

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Mortality

Studies on SO_2 health effects

Location/Time	Lyons, Marseilles / France / 1969-1972.
Study design	Temporal study using aggregated data.
Method of data analysis	Multiple regression analysis on deseasonalized series.
	Time series analysis (controlling for autocorrelation)
Population/sample size	
Level of pollution	SO_2 (µg/m³) =65.0 in Lyons, =50.7 in Marseilles
	TSP(µg/m³) =86.8 in Lyons, =124.4 in Marseilles
Health outcome	Daily number of deaths from respiratory and cardiac causes.
Effect estimates	- Coefficients from the regression models are given but are not directly interpretable. However, the association of SO_2 and deaths from respiratory causes in the elderly is statistically very significant; and it is significant with cardiovascular deaths only in Marseilles.
Special conditions	TSP was not significantly associated with any outcome.
Confounders	Season, temperature.
Comments	This paper adopts a more traditional time-series approach which yields estimates not adjusted to epidemiologic interpretation.
Reference	Derrienic et al., 1989

Mortality

Studies on SO_2 health effects

Location/Time	Athens, Greece /1975-82
Study design	Temporal study using aggregated data(1) and a contrast of high and low pollution days (2)
Method of data analysis	Multiple regression analysis (1) and ANOVA for randomized blocks (2)
Population/sample size	Part of the Athens population 1,700,000
Level of pollution	SO_2 (μg/m³) geometric mean of 5 monitors = 85.7, max: 936 Black smoke (μg/m³) geometric mean of 5 monitors = 56.6, max: 790
Health outcome	Total daily number of deaths (1) and cardiac, respiratory and "other" deaths(2)
Effect estimates	- An increase of 100 μg/m³ in SO_2 levels is associated with 3% increase in mortality. - The RR of dying on a "high" pollution day vs a "low" was 1.16 for respiratory deaths among the elderly (>75 yrs) and 1.11 for all ages.
Special conditions	Black Smoke was not significantly associated with mortality.
Confounders	Season, Long-term trend, day of week, temperature, humidity, holidays.
Comments	
Reference	(1) Hatzakis et al., 1986 (2) Katsouyanni et al., 1990

Mortality

Studies on SO_2 health effects

Location/Time	Erfurt, Germany / 1980-89
Study design	Temporal study using aggregated data.
Method of data analysis	Poisson regression (allowing for overdispersion and controlling for autocorrelation)
Population/sample size	Inhabitants of Erfurt 217,000
Level of pollution	SO_2 (µg/m³) 5% = 27, 50% = 197, 95% = 952, max = 3569 Suspended particles (µg/m³) 5% = 30, 50% = 106, 95% = 390, max = 650
Health outcome	Total daily number of deaths.
Effect estimates	- For change of 906 µg/m³ in SO_2 (95% vs 5%) RR 1.10 (lag 2) - In 1988-89 only, in a two pollutant model (+TSP), the SO_2 effect was small (RR 1.02) and not statistically significant.
Special conditions	TSP was also considered for two out of ten years.
Confounders	Influenza epidemics, trend, season, temperature, precipitation.
Comments	
Reference	Spix et al., 1993

Mortality

Studies on SO_2 health effects

Location/Time	Amsterdam / 1986-1992
Study design	Temporal study using aggregated data.
Method of data analysis	Poisson regression controlling for autocorrelation and allowing for overdispersion.
Population/sample size	Population of Amsterdam 713,000
Level of pollution	SO_2 ($\mu g/m^3$) =13, 10%=4, 50%=11, 90%=25
Health outcome	Total daily number of deaths
Effect estimates	- The SO_2 mortality association was not statistically significant.
Special conditions	Black smoke, PM_{10}, CO, O_3 were also considered. Significant associations reported with particles
Confounders	Temperature, humidity, seasonality, long-term trends, day of week, influenza epidemics.
Comments	
Reference	Verhoeff et al., 1996.

Mortality

Studies on SO_2 health effects

Location/Time	Two areas in Beijing, China, representing 25% of urban population of Beijing / 1989
Study design	Temporal study using aggregated data
Method of data analysis	Poisson regression (controlling for autocorrelation)
Population/sample size	Inhabitants of the area 1,419,123
Level of pollution	SO_2 (µg/m³) = 102.3, 10% = 6, 50% = 40, 90% = 291 TSP(µg/m³) = 375.0, 10% = 184, 50% = 336, 90% = 616
Health outcome	Total and cause specific daily death counts
Effect estimates	- (Log transformations of pollutants were used) - Doubling the level of SO_2 was associated with 11% (95% CI 5%-16%) increase in total number of deaths. For deaths from COPD the corresponding figure was 29%, for pulmonary heart disease 19%, for CVD 11%, for all non-malignant causes 8% and 2% for cancer.
Special conditions	TSP was only associated significantly with deaths from COPD
Confounders	Temperature, humidity, day of week (Sunday), season.
Comments	The effects were stronger in the summer. Main source of pollution are coal stoves used for heating and cooking.
Reference	Xu et al., 1994.

Mortality

Studies on SO_2 health effects

Location/Time	Athens, Greece / 1984-88.
Study design	Temporal study using aggregated data.
Method of data analysis	Time-series analysis
Population/sample size	Part of the population of the Athens area 1,700,000
Level of pollution	SO_2 (µg/m³) = 44.92 SD = 30.16 median = 37.00 Black Smoke(µg/m³)= 82.93 SD = 44.70 median = 70.38
Health outcome	Total daily number of deaths
Effect estimates	- Doubling the levels of SO_2 is associated with 4% increase in the total daily number of deaths. An increase from 20 µg/m³ to 80 µg/m³ (4 fold) implies a 9% increase in mortality. - In a multi-pollutant model (including also BS and CO) the corresponding estimates are 3% and 6% respectively.
Special conditions	Black smoke and carbon monoxide were also considered.
Confounders	Seasonality, temperature, humidity, day of week, long term trend.
Comments	Pollutants were log-transformed in the models.
Reference	Touloumi et al., 1994.

Mortality

Studies on SO_2 health effects

Location/Time	Zurich, Basel, Geneva, Switzerland / 1984-1989
Study design	Temporal study using aggregated data.
Method of data analysis	Poisson regression (allowing for autocorrelation and overdispersion) and non-parametric models.
Population/sample size	Zurich: 706,000; Basle: 365,000; Geneva: 335,000
Level of pollution	Zurich SO_2 (µg/m³) = 35.4, max = 397 Basel " " = 26.5, max = 282 Geneva " " = 40.2, max = 219
Health outcome	Total mortality, mortality of persons 65 yrs or older, respiratory mortality and cardiovascular mortality.
Effect estimates	- For 100 µg/m³ increase in SO_2, associated increase in total mortality: Basle=15%, Geneva=13%, Zurich=3% N.S., for mortality in the elderly: Basle=17%, Geneva=15%, Zurich=N.S., for respiratory mortality: Zurich=12%, Basle=8% N.S., Geneva=33%; for cardiovascular mortality: Zurich=1%N.S., Basle=24%, Geneva=13
Special conditions	TSP, Ozone, NO_2, CO were also considered.
Confounders	Seasonality, day of week, long-term trends, temperature, humidity
Comments	
Reference	Wietlisbach et al., 1996.

Hospital admissions

Studies on SO_2 health effects

Location/Time	Detroit, Michigan, USA metropolitan statistical area 1986-1989.
Study design	Temporal study using aggregated data.
Method of data analysis	Poisson regression (autocorrelation)
Population/sample size	Population >65 years : 517,000
Level of pollution	SO_2 (µg/m³) =68.7, 10%=29.7, 50%=62.2, 90%=119.0 PM_{10} = 48 µg/m³, CO = 2.77 µg/m³, O_3 = 82 µg/m³
Health outcome	Admissions to hospitals for cardiovascular disease of persons>65 years old
Effect estimates	- IHD RR for increase 48.7 µg/m³ (interquartile range) SO_2 =1.014 95% C.I.:1.003-1.026 in single pollutant model - RR became 1.009, not statistically significant when PM_{10} was included in the model. - The estimated RR were not significant for congestive heart failure or dysrhythmias.
Special conditions	PM_{10}, Ozone and Carbon monoxide were considered
Confounders	Seasonality (dummy variables for each month of the study period) Long term trends, temperature, dew point temperature, day of week.
Comments	Sensitivity analysis was performed
Reference	Schwartz and Morris, 1995.

Hospital admissions

Studies on SO_2 health effects

Location/Time	Barcelona, Spain / 1985-89
Study design	Temporal study using aggregated data.
Method of data analysis	Autoregressive linear regression.
Population/sample size	All the inhabitants of Barcelona over 14 years old. Population of Barcelona: 1,700,000.
Level of pollution	SO_2 (µg/m³) = 56.5, SD = 22.5, 98% = 114.5, range 17-160 Black Smoke (µg/m³) = 72.9, SD = 38.7, 98% = 181.1, range 39-310
Health outcome	Emergency hospital admissions for COPD.
Effect estimates	- Increase of 25 µg/m³ of SO_2 was associated with: - 6% increase in admissions in the winter & 9% in the summer - 2% increase in admissions in the winter and 4% in the summer, when both SO_2 and black smoke were included in the same model.
Special conditions	Ozone, nitrogen dioxide and sulphates were taken into account without changing the results.
Confounders	Temperature, day of week (Monday), year (1987) Autocorrelation was also controlled for.
Comments	The health outcome register was specially set by the researchers and gave more accurate data than routine statistics.
Reference	Sunyer et al., 1991, 1993.

Mortality

Studies on SO_2 health effects

Location/Time	Philadelphia, USA /1973-1988.
Study design	Temporal study using aggregated data.
Method of data analysis	Time-series and novel approaches addressing autocorrelation, overdispersion and other issues and arguments.
Population/sample size	1,688,710
Level of pollution	SO_2 (µg/m³ 24h) =57, 5%=16, 95%=124
Health outcome	Total daily number of deaths.
Effect estimates	- Schwartz and Dockery reported a significant increase in mortality associated with SO_2 in single pollutant models (14% increase for 100 µg/m³ change in SO_2) This dropped to a non-significant 6% in a model with both TSP and SO_2. However, Samet and Zeger find SO_2 still significant in 2-pollutant models with different control of long-term trends.
Special conditions	TSP was also considered.
Confounders	
Comments	The Samet & Zeger report was the result of Phase I of a Health Effects Institute project on the validation of some U.S. time-series studies on PM & daily mortality.
Reference	Schwartz & Dockery, 1992 Samet et al., 1995.

Mortality

Studies on SO_2 health effects

Location/Time	Köln, Germany / 1975-1985
Study design	Temporal study using aggregated data.
Method of data analysis	Poisson regression controlling for autocorrelation and allowing for overdispersion.
Population/sample size	Population of K ln 977,000
Level of pollution	SO_2 (μg/m³) =44, median=66, max=401 in the winter
Health outcome	Total daily number of deaths.
Effect estimates	- An increase of 100 μg/m³ in SO_2 resulted in a 3% increase in the total daily number of deaths.
Special conditions	NO_2, TSP, PM_7 also considered.
Confounders	Long-term trends, seasonality and other cyclical patterns, day of week, holidays, temperature, humidity, influenza epidemics.
Comments	Part of the APHEA project.
Reference	Spix and Wichmann., 1996.

Mortality

Studies on SO_2 health effects

Location/Time	Barcelona, Spain / 1985-91.
Study design	Temporal study using aggregated data.
Method of data analysis	Poisson regression controlling for autocorrelation and allowing for overdispersion.
Population/sample size	Population/sample size Population of Barcelona 1,700,000.
Level of pollution	SO_2 (µg/m³) winter = 51, summer = 40, Ozone(µg/m³) winter = 60, summer = 88 BS (µg/m³) winter = 51, summer = 38, TSP(µg/m³) winter = 128, summer = 164 NO_2 (µg/m³) winter = 54, summer = 53
Health outcome	Total, cardiovascular and respiratory mortality and mortality of persons older than 70 years.
Effect estimates	- For 10 µg/m³ increase in SO_2 the total daily number of deaths increased by 1.4% in the winter and 1% in the summer. - The corresponding figures for cardiovascular mortality were 1.4% and 1.3% and for respirating there was no statistically significant effect in the winter but the increase in the summer was 2.2%. For the mortality in the elderly a 1.6% increase was observed in the winter and 0.9% in the summer.
Special conditions	TSP, BS, NO_2, Ozone also considered
Confounders	Long-term trends, seasonality and other cyclical patterns, day of week, holidays, temperature, humidity, influenza epidemics.
Comments	Part of the APHEA project
Reference	Sunyer et al., 1996.

Studies on SO_2 health effects

Location/Time	Paris, France / 1987-92.
Study design	Temporal study using aggregated data
Method of data analysis	Poisson regression controlling for autocorrelation and allowing for overdispersion.
Population/sample size	6,140,000 inhabitants of the Paris area.
Level of pollution	SO_2 (µg/m³) = 30, median =23, 5% = 7, 99% = 125 NO_2 (µg/m³ 1-h=74 BS (µg/m³) = 32, median = 26, 5% = 11, 99% = 123 O_3 (µg/m³) =45 PM_{13} (µg/m³) = 51, median = 47, 5% = 19, 99% = 137
Health outcome	Mortality and daily number of hospital stays for respiratory causes.
Effect estimates	- An increase of 100 µg/m³ in SO_2 24-h is associated with 8% increase in the daily number of respiratory deaths but is not statistically significant. A similar increase in SO_2 1-h is associated with 9% in the outcome and is statistically significant. The RR for 24-h SO_2 and hospital stays for respiratory diseases, COPD and asthma is 1.04, 1.10, 1.07 respectively ($P<0.05$)
Special conditions	BS, PM_{13}, NO_2 and ozone were taken into account.
Confounders	Long-term trends, seasonality and other cyclical patterns, day of week, holidays, temperature, humidity, influenza epidemics.
Comments	Part of the APHEA project.
Reference	Dab et al., 1996.

Mortality

Studies on SO_2 health effects

Location/Time	Lyon, France / 1985-1990.
Study design	Temporal study using aggregated data.
Method of data analysis	Poisson regression controlling for autocorrelation and allowing for overdispersion.
Population/sample size	Population of Lyon 410,000.
Level of pollution	SO_2 ($\mu g/m^3$ 24-h) = 47, range = 2-315, NO_2 ($\mu g/m^3$ 1-h) = 133, range = 10-737 PM_{13} ($\mu g/m^3$ 24-h) = 38, range = 3-180, Ozone ($\mu g/m^3$ 1-h) = 15, range = 0-152
Health outcome	Total, respiratory, cardiovascular and digestive mortality.
Effect estimates	- A 50 $\mu g/m^3$ increase in 24-h SO_2 was associated with 6% increase in total mortality, 5% in respiratory, 8% in cardiovascular and no increase in digestive mortality.
Special conditions	PM_{13}, NO_2, and ozone were also considered. Ozone levels are from a monitor in the city center.
Confounders	Long-term trends, seasonality and other cyclical patterns, day of week, holidays, temperature, humidity, influenza epidemics.
Comments	Part of the APHEA project.
Reference	Zmirou et al., 1996.

Morbidity

Studies on SO_2 health effects

Location/Time	London, U.K. / 1987-88 & 1991-92.
Study design	Temporal study using aggregated data.
Method of data analysis	Poisson regression controlling for autocorrelation and allowing for overdispersion.
Population/sample size	7,300,000.
Level of pollution	SO_2 (µg/m³ 24-h) = 32, 5% = 15, 95% = 54 NO_2 (µg/m³ 1-h) = 57, 5% = 33, 95% = 102 BS (µg/m³ 24-h) = 15, 5% = 6, 95% = 27 O_3 (µg/m³ 1-h) = 21, 5% = 2, 95% = 46
Health outcome	Daily number of respiratory admissions: total and by age groups.
Effect estimates	- The SO_2 effects were not statistically significant in most instances.
Special conditions	BS, NO_2 and ozone were also considered. The most consistent results were found by ozone.
Confounders	Long-term trends, seasonality and other cyclical patterns, day of week, holidays, temperature, humidity, influenza epidemics.
Comments	Part of the APHEA project
Reference	Ponce de Leon et al., 1996.

Mortality

Studies on SO_2 health effects

Location/Time	Athens, Greece / 1987-91.
Study design	Temporal study using aggregated data.
Method of data analysis	Poisson regression controlling for autocorrelation and allowing for overdispersion.
Population/sample size	Approximately 2,000,000 inhabitants of the Athens area.
Level of pollution	SO_2 (µg/m³ 24-h) = 51, median = 45, range = 6-361, CO (mg/m³ 8-h) = 7, median = 6, range=1-25 BS (µg/m³ 24-h) = 84, median = 73, range = 9-333
Health outcome	Total daily number of deaths.
Effect estimates	- An increase of 100 µg/m³ in 24-h SO_2 levels is associated with 12% increase in mortality.
Special conditions	BS, CO, NO_2 and ozone were also taken into account.
Confounders	Long-term trends, seasonality and other cyclical patterns, day of week, holidays, temperature, humidity, influenza epidemics.
Comments	Part of the APHEA project.
Reference	Touloumi et al., 1996.

Mortality

Studies on SO_2 health effects

Location/Time	London / 1987-92			
Study design	See APHEA protocol			
Method of data analysis	See APHEA protocol			
Population/sample size	7,200,000			
Level of pollution	Mean (µg/m³) SO_2 = 32.0	BS = 14.6	NO_2 (1h) = 57.2	O_3 (1h) = 20.6
	Median µg/m³) SO_2 = 31	BS = 13	NO_2 (1h) = 52	O_3 (1h) = 20
Health outcome	All cause, cardiovascular and respiratory mortality			
Effect estimates	RR = 1.0152 for change in SO_2 from 18 to 43 µg/m³			
Special conditions	Statistically significant associations were found for O_3 and BS			
Confounders	Long-term trends, seasonality and other cyclical patterns, day of week, holidays, temperature, humidity, influenza epidemics.			
Comments	Part of the APHEA project			
Reference	Anderson et al., BMJ 1996.			

Mortality and Morbidity

Studies on SO_2 health effects

Location/Time	Milano/ 1980-89
Study design	See APHEA protocol
Method of data analysis	See APHEA protocol
Population/sample size	1,600,000
Level of pollution	Mean SO_2 = 117.7 µg/m³ TSP = 139 µg/m³ Median SO_2 = 65,5 µg/m³ TSP = 119.5 µg/m³
Health outcome	Deaths and hospital admissions for respiratory causes
Effect estimates	RR for respiratory number of deaths, SO_2 and TSP change from 25 to 125 µg/m³ = 1.05 RR for hospital admissions for respiratory diseases for persons aged 65+ years, for SO_2 = 1.05 and for TSP = 1.05
Special conditions	-
Confounders	Long-term trends, seasonality and other cyclical patterns, day of week, holidays, temperature, humidity, influenza epidemics.
Comments	Part of the APHEA project
Reference	Vigotti et al., JECH 1996.

Ozone

Evaluation of Ozone at the Nordic Expert Meeting

Quantifiable relationships

Available data has allowed to quantify associations of changes in ozone levels in ambient air with changes in the daily rates of hospital admissions and mortality as well as decrements in lung function. Data from Western Europe and the United States are included in the estimates. As exposure indicator, the maximum daily 1 and 8 hour mean O_3 concentration as well as such averages have been used.

Short term effects

Lung function decrements is the best studied parameter of ozone effects, but exposure response relationships based on recent time series and panel studies have also been reported for hospital admissions and mortality.

Lung function decrements

The data used for the quantification of the relationship come from controlled human exposure studies and from epidemiologic studies of the general population or children in summer camps.

In controlled exposure studies it has been observed that the magnitude of decrease in lung function measured as forced expiratory volume in one second (FEV_1) is a function of ozone concentration, exposure time and the volume of inhaled air during the exposure period. This volume is determined by the exercise level during the study. Concentration is a stronger predictor of change in FEV_1 than time or inhaled volume. Large differences in intrinsic responsiveness result in considerable inter-subject variation in spirometric responses, yet individual responses are highly reproducible (McDonnell et al., 1985). It has been estimated that 10% of the population have a responsiveness twice as high as the median value. The responsiveness to ozone may be diminishing with age, the most responsive individuals are likely to be less than 25 years of age. Less changes were seen in the elderly and even smokers (Adams et al., 1981; Avol et al., 1984; Colluci, 1983; Drechsler-Parks et al., 1987; Folinsbee et al., 1988; Hazucha, 1987; Hazucha et al., 1992; Highfill and Costa, 1995; Hoek et al, 1993; Horstmann et al., 1990; Kleinman et al., 1989; Marra, 1995; McDonnell et al., 1983; 1985a, b; 1991; 1993; McDonnell and Smith, 1994; Reisenauer et al., 1988; Thurston et al., 1992; Whitfield et al., 1995;).

Different mathematical models have been used to describe the dose/response relationships. Highfill and Costa (1995) compared these different types of models. They concluded that the models performed well with both FEV_1 and broncho-alveolar lavage (BAL) protein, and that in the exponential model the two changes in response were equal for concentrations less than 800 $\mu g/m^3$. Changes in the BAL-fluid constituents indicate inflammatory responses in the lung, possibly neurologically mediated.

The changes in FEV_1 may seem small, but for persons with an already compromised respiratory function additional reductions may have serious consequences. In children a 1.5% reduction in FEV_1 per 100 µg/m³ daily maximum 1 hour value of ozone has been indicated by the meta analysis of the summer camp studies in Eastern US (Kinney et al., 1993)(95% C.I.,1-2%). This analysis was considered appropriate to compare with many European regions, because the levels of ozone in general were lower than in South Western US studies. In people constantly exposed to higher levels of ozone an attenuation of some effects of ozone may be observed, implying that people in low ozone areas tend to be more responsive during an ozone episode. In Europe, a Dutch study has estimated a smaller effect with a 1% change in FEV_1 per 100 µg/m³ (Hoek et al., 1993). The difference may be due to the more intensive activities, and therefore a greater ozone intake, of the children in the summer camps than of the Dutch children, who were studied under normal conditions.

Morbidity

An exposure-response relationship for hospital admission is reported by Thurston et al. (1992). They have reported the excess daily respiratory related hospital admissions being associated with elevated daily maximum 1 h O_3 levels during the O_3 season in some New York state cities. The regression coefficient in New York city is 0.6 admissions/100 µg/m³ O_3/10^6 people and a standard error of 0.2 admissions/100 µg/m³ O_3/10^6 people. This regression coefficient and its standard error were used by EPA to define a probabilistic concentration-response relationship (see Figure 2). For the quantitative assessment of risk based on exposure-response relationships from epidemiological studies less elaborate information of population exposure is needed. Mostly a combination of daily maximum 1 or 8 h O_3 concentration with population density is sufficient. This type of risk assessment will result in a "bench" risk which is the probability that a certain percentage of the population will exhibit a particular health effect.

Schwartz (1994) performed a meta analysis on the available data, resulting in a central estimate of 6% increase in the daily number of admissions for respiratory disease with an increase of 100 µg/m³ in daily maximum 1 hour value of ozone (range 2 to 10% corresponding to 95% CI). Analysis of the APHEA data (Air Pollution and Health: a European Approach) showed that an increase in the maximum 1 hour daily ozone levels of 100 µg/m³ was associated with responses of 1% (Rotterdam), 3% (Paris), 7% (Amsterdam) and 19% (London) increase for respiratory emergency admissions for the elderly (<65 years). Only the London results were significant at the 95% level (Touloumi, 1996).

If the exposure-response relationships are not linear functions, being steeper at higher levels, the proposed estimates are likely to overestimate effects at lower levels and underestimate at higher levels. The ozone effects on hospital admissions tend to be independent of the effects of other pollutants.

Mortality

Various studies have been reported from North America and these have been reviewed by Schwartz (1994). In addition data are available from a number of European studies in the APHEA series (Dab et al., 1996; Katsouyanni et al., 1996; Ponce de Leon et al., 1996; Touloumi et al., 1996; Verhoeff et al., 1996; Wietlisbach et al., 1996). The proposed estimate here is an increase in daily mortality of 1 to 4% per 100 µg/m^3 increase in daily maximum 1 hour value of ozone. The lower level comes from the American studies, the higher from the European investigations. Analysis of the APHEA data indicates increase in daily total number of deaths of 5% (Athens and Barcelona), 8% (Lyon) and 18% (London) for increases of 100 µg/m^3 of maximum daily 1 hour levels. The only non-significant relationships (at the 95% level) were for the results from Lyon. The increases for respiratory deaths in Lyon, Paris, London and Barcelona were 2, 4, 24 and 7% respectively. However, only the London data was significant at the 95% level (Touloumi, 1996).

Population groups at increased risk

In general, children are found to be more sensitive than older people to low ozone level exposure as mentioned above, together with active people engaged in outdoor activities with increased exposure to ozone. Pre-existing respiratory disease also modifies the response to ozone exposure and these individuals are considered to be at higher risk than other groups of the population. Whether the increased sensitivity of a subgroup of the population (see above) is related to gender or ethnicity or some other factor remains unresolved.

Measurable effects that are as yet non quantifiable

Short term effects

Symptoms

Increased incidence of cough and other symptoms of airway irritation in days with higher ozone concentrations have also been reported by epidemiological studies, but did not provide a basis for quantification. These relationships are often found in panel studies. More information is needed.

Long-term effects

The data on chronic effects of cumultive exposure of ozone is limited and not sufficient for quantification of the effects. Studies have indicated an effect on asthma incidence and seriousness of the disease.

Quantitative exposure-response relationships for ozone

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1. Introduction

Ozone (O_3) is generally regarded as the most toxic component of photochemical oxidant air pollution. Although other components may contribute to the observed health effects, the acute-exposure chamber, field and epidemiological human health data raises concern especially for O_3 at levels of photochemical oxidants commonly reported in ambient air. (EPA, 1995a). For the purpose of this working paper O_3 is taken as the indicator to characterise the seriousness of the photochemical oxidant air pollution mixture. Further, deriving quantitative exposure-response relationships will be based on results of controlled human studies (O_3 alone), and on field and epidemiological studies (O_3 as indicator).

The occurrence of O_3 in the air is described briefly. Thereafter health effects of O_3 are summarised. Since most quantitative health effects data have been described for single short-term exposures, these will be dealt with in this paper. Factors modifying acute response and sensitive population groups are mentioned before describing some examples of quantitative exposure-response relationships and methodological issues concerning their derivation. In the discussion the limitations of health risk assessments for population exposure to O_3 are considered and recommendations for the further development of exposure assessment are made.

2. Occurrence in the air

O_3 and other photochemical oxidants are formed by the action of short-wavelength radiation from the sun on nitrogen dioxide. In the presence of volatile organic compounds, carbon monoxide and methane, the equilibrium favours the formation of higher concentrations of O_3. One-hour background levels of O_3, mainly from anthropogenic origin, range from 40-70 $\mu g/m^3$, but can be as high as 120-140 $\mu g/m^3$ during stratospheric incursions. In Europe, maximum hourly O_3 concentrations may exceed 350 $\mu g/m^3$ on rare occasions (WHO, 1987). In urban areas, levels are somewhat lower than in suburban and rural areas due to scavenging by nitrogenmonoxide. Sub-maximal levels of 90-80% of the maximum generally occur for 8-12 h/day (Rombout et al., 1986). Since photochemical oxidant air pollution is highly dependent on the intensity and duration of sunlight and the emission of O_3 precursors for a summer season is

rather constant, its occurrence is wholly dependent on season and meteorology. Thus it occurs mainly during spring and summer and episodes characterised by increased O_3 levels may last many consecutive days and may occur several times per summer season.

3. Health effects of ozone

A wide array of health effects has been attributed to short-term (1-3 h), prolonged (6-8 h or longer), and long-term (months - years) exposures to O_3 (EPAa, 1995). Acute health effects induced by 1-3 h exposures to O_3 concentrations as low as 240 µg/m^3 while engaged in heavy exercise, include: transient pulmonary function responses, transient respiratory symptoms and effects on exercise performance, increased airway responsiveness, transient pulmonary inflammation, increased susceptibility to respiratory infection, and increased hospital admissions and emergency- room visits. Similar health effects have been observed following 6-8 h exposures to O_3, at concentrations of O_3 as low as 160 µg/m^3 and at lower levels of exercise (moderate) than for 1-3 h exposures. Effects of chronic exposure such as structural damage to pulmonary tissue, premature mortality, carcinogenicity, and genotoxicity have been investigated in a substantial number of laboratory animal studies. However, these effects have and/or could not be(en) adequately established in human populations to draw clear conclusions at this time.

4. Factors modifying acute human response to ozone

For the purpose of quantitatively assessing human health effects caused by exposure to O_3, it is important to know that there are several factors which have been identified as potentially affecting human susceptibility to O_3 exposure (exposure is characterised by O_3 concentration and duration (EPA, 1995a)). The most significant of these factors are exertion (e.g. exercise, manual labour), pre-existing disease, age, gender, ethnicity/race, smoking status, environmental factors. Most of these factors have not been addressed adequately, in clinical or field studies, to draw definitive conclusions. Some preliminary observations regarding each of these potential modifiers of response will be mentioned.

1) Exertion

Exertion resulting in an increased minute ventilation (VE) is a factor which increases O_3 sensitivity of most humans at any elevated O_3 concentration. This is partly due to the increased O_3 dose received by the lungs but also to the deeper penetration of O_3 into more peripheral regions of the lungs, which are more sensitive to acute O_3 response and injury. Furthermore, respiratory effects are observed at lower O_3 concentrations if the level of exertion is increased and/or the duration of exertion is extended. An increased level of exertion can cause an individual, who has a respiratory system which is highly responsive to O_3, to experience lung function impairment and symptoms sufficient to curtail activity, even though the individual is otherwise healthy.

2) Pre-existing disease

Controlled studies on mild asthmatics suggest that they have similar lung volume responses but greater airway resistance to O_3 exposures than non-asthmatics. Limited data from moderate asthmatics suggest that they may have greater lung volume responses than non-asthmatics. Daily life studies reporting exacerbation of asthma and decrease in peak respiratory flow rates, particularly in asthmatic children, appear to support the observations from the controlled studies. In addition, field studies of summertime daily hospital admissions for respiratory causes show a consistent relationship between hospital admissions for asthmatics and ambient levels of O_3.

Other population groups with pre-existing limitations in pulmonary function and exercise capacity may experience health effects with greater clinical significance due to O_3 exposure than comparable changes in healthy individuals.

3) Age

A growing body of evidence suggests that age plays a role in determining sensitivity to O_3. Children appear to respond to low-level O_3 exposures in a manner comparable to that of young adults, albeit without symptoms, whereas older persons exhibit a decreased sensitivity relative to young adults.

4) Gender and ethnicity

The question as to whether there is a difference in the respiratory susceptibility to O_3 between males and females or between individuals with ethnic differences is as yet unresolved. The limited data available on this topic have not provided evidence for the existence of these susceptibility modifying factors.

5) Smoking status

Results of several studies suggest that smokers are less responsive to O_3 than non-smokers. Cessation of smoking leads to improved baseline pulmonary functions and possibly a return to O_3 susceptibility as is indicated by some recent studies.

6) Interaction with other pollutants

In general, controlled human studies of O_3 mixed with other pollutants show no more than an additive response with symptoms and spirometry as an endpoint. At the levels of co-pollutants used in these studies, the responses can be attributed mainly to O_3. The data from toxicological studies support a hypothesis that co-exposure to pollutants, each at innocuous or low-effect level, may result in effects of significance. However, current results of field and epidemiological studies do not allow a firm or let alone a quantitative

conclusion whether additional or synergistic effects occur due to the exposure of a mixture of O_3, irritant gases and (acid) aerosol.

5. Population groups at increased risk

Although preliminary data indicate the importance of the antioxidant levels and genetically predisposing factors for the identification of subpopulations at increased risk, it is most practical for the purpose of this paper to identify the following groups at increased risk to O_3 induced health effects: 1) Those individuals who are exposed most to O_3, 2) those individuals who are intrinsically more susceptible to O_3, and 3) those individuals with pre-existing pulmonary disease.

1) Active individuals

Healthy children, adolescents and adults who are actively engaged in outdoor activities during maximum diurnal O_3 levels most often in the afternoon, are at risk due to their increased exposure to O_3 and the consequent increased inhaled O_3 dose and dose-rate.

2) Individuals with increased intrinsic sensitivity

Controlled human exposure studies and field and epidemiological studies have clearly demonstrated a wide variability among otherwise healthy subjects in sensitivity to O_3. Some 10% of the population may respond as much as twice the response of the median of the population. These so-called "responders" respond consistently stronger than the rest of the population.

3) Individuals with pre-existing respiratory disease

As mentioned earlier, pre-existing respiratory disease modifies the susceptibility to O_3 exposure. These individuals constitute therefore a subpopulation that is potentially at increased risk to O_3.

6. Quantitative exposure-response relationships

The population is exposed to O_3 episodically during a number of consecutive days and during a number of episodes with varying (recovery) intervals for a summer season during dozens of years. Irrespective of this fact, the available data allow only for the construction of exposure-response relationships for some acute health effects for a single exposure. Since O_3 is considered to be the most important single air pollutant of photochemical oxidant air pollution, these exposure-response relationships may be based on human controlled studies with O_3 in addition to epidemiological studies. In this paper a few examples of quantitative exposure-response relationships will be presented, together with some methodological issues. A more thorough analysis will need a considerable effort.

Developing quantitative exposure-response relationships involves a number of steps. The first step is to choose the investigation to be used in the analysis and evaluate the "observations" for systematic bias, making corrections, interpolating data etc. (EPA, 1995b; COST, 1994). The second step is to fit the data via regression techniques which allows for the estimation of response rates at exposures differing from those at which O_3 investigational data are available. In step 3 credibility intervals have to be developed around the fitted response rate at O_3 exposures needed for the risk assessment calculations.

1) Human controlled studies - Lung function

In principle, acute response data from human controlled studies appear to be available to establish quantitative exposure-response relationships for lung function decrements, symptoms, and pulmonary inflammation. Hereafter some examples will be given for the decrement of the forced respiratory volume in 1 second (FEV_1) with inhaled O_3 dose as the estimator of exposure. This analysis was performed by Marra (1995) as part of ozone risk-assessment activities at RIVM. Single exposure of humans - mainly healthy Caucasian young adults - to ozone resulted in changes in lung function parameters measured immediately after exposure, such as a decrease in FEV_1. This effect diminishes rapidly after exposure has ceased. The magnitude of the decrease in FEV_1 is a function of ozone concentration (C), exposure time (T), and the inhaled volume of air during the exposure period. This volume is determined by the exercise level expressed commonly as the mean minute volume (V_E). The studies were performed with concentrations of ozone ranging between 160 and 800 $\mu g/m^3$ for 0.5 to 8 h durations, with exercise levels equivalent to minute volumes ranging from 20 to 90 dm_3 (Adams et al., 1981; Avol et al., 1984; Folinsbee et al., 1988; Hazucha, 1987; Hazucha et al., 1992; Horstman et al., 1990; McDonnell et al., 1983, 1991).

Large differences in intrinsic responsiveness result in considerable inter-subject variation in spirometric responses, yet individual responses are highly reproducible (McDonnell et al., 1985a). McDonnell et al. (1993) identified, among others, age as a predictor of individual differences in acute FEV_1 responses. They suggested that responsiveness to ozone is already diminishing by age 30, and that the most responsive individuals are likely to be less than 25 years of age. One study with 8 to 11 years old children demonstrated small decrements in FEV_1 which are - expressed as a percentage of the initial FEV_1 - equivalent to those found under similar exposure conditions in adults (McDonnell et al., 1985b). No changes in FEV_1 were seen in healthy individuals aged 55 or more after exposure to ozone at exposure conditions that caused no or just marginal changes in young adults in other studies (Reisenauer, C.S. et al., 1988). In a study with 50-80 year old men and women, significantly smaller FEV_1 responses in the older subjects than in the younger subjects were found (Drechsler-Parks et al., 1987)

The FEV_1 decrement after a single exposure to ozone has been described as a mathematical function of the exposure variables C, T, and V_E by a number of investigators. Linear relationships between effect and the total inhaled dose D ($C \times T \times V_E$) or the dose rate ($C \times V_E$) have been observed (Adams et al., 1981;

Colluci, 1983). Utilization of multiple regression equations showed that C is a stronger predictor for FEV_1 decrements than V_E or T (Adams et al., 1981; Folinsbee et al., 1988).

Hazucha (1987) proposed quadratic concentration-response relationships for 5 classes of exercise based on 39 human-clinical studies with short-term (approximately 2 hour) exposures.

After exposures for short-duration (≤2.5 hour) the response has been demonstrated to be exponentially increasing with increasing exposure (Adams et al., 1981, Avol et al., 1984; Hazucha, 1987; Horstman et al., 1990; McDonnell et al., 1983). At high concentrations with heavy exercise or at longer exposure times, the response tends to level to a plateau of maximum FEV_1-decrease (Adams et al., 1981; Hazucha et al., 1992; McDonnell et al., 1983).

McDonnell et al. (1993) and McDonnell and Smith (1994) analyzed the data from five different studies, all conducted at the same laboratory. They identified a sigmoid-shaped mathematical model that described the mean FEV_1 decrement as a logistic function of inhaled dose and dose-rate or, by defining V_E a constant based on the limited variation in V_E within these studies, a function of C×T and C.

Highfill and Costa (1995) compared these different types of mathematical models in which C and T were incorporated as variables and V_E was defined a constant. They used FEV_1 decrements obtained from human studies as well as protein in bronchoalveolar lavage fluid (BAL) obtained from studies of laboratory animals. Their analysis led to the conclusion that the models, perform well with both kind of responses and that the changes in response with concentration in the exponential model of FEV_1 and BAL protein were equal for $C \leq 800$ µg/m³.

Table 1 summarizes the logistic and exponential models. The coefficients were adjusted to represent the response as the fractional change in FEV_1 as a function of inhaled dose D (mg) and - in 2 cases - of dose-rate $C \times V_E$. The quadratic models and the majority of the logistic models are derived from data of studies with a maximum exposure duration of approximately 2 hour. One of the logistic models and the exponential model are derived from one study with an exposure duration of 6.6 hour. Whitfield et al. (1995) performed a probabilistic exposure-response analysis for longer exposure times (6 - 8 h) based on three studies. The result is shown in Figure 2. Kleinman et al. (1989) reported that inhaled O_3 dose per kg body weight is a good predictor for FEV_1 decrement and for a number of respiratory and non-respiratory symptoms.

For the final risk assessment process it is necessary to describe population exposure in terms of the probability that an individual (of a sub-population) will inhale a certain dose during a certain exposure period. When this information is available it is possible to calculate "head count" risk, this is the percentage of the population experiencing a defined health effect from, in this case, a single O_3 exposure day.

2) Epidemiological studies

A large number of epidemiological studies have shown associations between daily 1 or 8 h maximum O_3 concentrations and lung function decrements, respiratory and non-respiratory symptoms, exacerbation of asthma, increased hospital admissions for respiratory disease and daily mortality. We will present examples for exposure-response relationships for FEV_1 decrements and for hospital admissions. Kinney et al. (1993) performed a meta-analysis on six so-called "summercamp" studies. In these summercamps the lung function of children without respiratory complaints is measured daily during a period of 1 or 2 weeks. These measurements are then correlated with the maximum daily O_3 concentration measured in or nearby the camp. In general, the children are outdoors most of the day and are physically active. Linear regression revealed an overall effect on FEV_1 of 32 ml per 100 $\mu g/m^3$ O_3 ($\beta = 0.32 \pm 0.09$ (SE) ml $\mu g/m^3$. The O_3 concentration was expressed as the daily maximum 1 h value on the day preceding the lung function measurement. In The Netherlands, Hoek et al. (1993), performed a study among 533 schoolchildren, age 7-11. In this study the FEV_1 decrement attributed to the daily maximum 1 h O_3 concentration was 21 ml (1.04%) per 100 $\mu g/m^3$ ($\beta = -0.21 \pm 0.921$ (SE) ml/$\mu g/m^3$). The effect in this study is smaller than the effect found in the summercamp studies, partly because of the difference in the amount of time spent outdoors and the level of physical exercise. Since children and young adults respond similar to O_3 exposure in human controlled studies, the percentile FEV_1 decrement from the above mentioned studies may perhaps also be applied to the adult population.

Morbidity - Hospital admissions

An exposure-response relationship for hospital admission is reported by Thurston et al. (1992). They have reported the excess daily respiratory related hospital admissions being associated with elevated daily maximum 1 h O_3 levels during the O_3 season in some New York state cities. The regression coefficient in New York city is 0.6 admissions/100 $\mu g/m^3$ $O_3/10^6$ people and a standard error of 0.2 admissions/100 $\mu g/m^3$ $O_3/10^6$ people. This regression coefficient and its standard error were used by EPA to define a probabilistic concentration-response relationship (see Figure 2). For the quantitative assessment of risk based on exposure-response relationships from epidemiological studies less elaborate information of population exposure is needed. Mostly a combination of daily maximum 1 or 8 h O_3 concentration with population density is sufficient. This type of risk assessment will result in a "bench" risk which is the probability that a certain percentage of the population will exhibit a particular health effect.

Schwartz (1994) performed a meta analysis on the available data, resulting in a central estimate of 6% increase in the daily number of admissions for respiratory disease with an increase of 100 $\mu g/m^3$ in daily maximum 1 hour value of ozone (range 2 to 10% corresponding to 95% CI). Analysis of the APHEA data (Air Pollution and Health: a European Approach) showed that an increase in the maximum 1 hour daily ozone levels of 100 $\mu g/m^3$ was associated with responses of 1% (Rotterdam), 3% (Paris), 7% (Amsterdam) and 19% (London) increase for respiratory emergency admissions for the elderly (<65 years). Only the London results were significant at the 95% level (Touloumi, 1996).

If the exposure-response relationships are not linear functions, being steeper at higher levels, the proposed estimates are likely to overestimate effects at lower levels and underestimate at higher levels. The ozone effects on hospital admissions tend to be independent of the effects of other pollutants.

Mortality

Various studies have been reported from North America and these have been reviewed by Schwartz (1994). In addition data are available from a number of European studies in the APHEA series (Dab et al., 1996; Katsouyanni et al., 1996; Ponce de Leon et al., 1996; Touloumi et al., 1996; Verhoeff et al., 1996; Wietlisbach et al., 1996). The proposed estimate here is an increase in daily mortality of 1 to 4% per 100 $\mu g/m^3$ increase in daily maximum 1 hour value of ozone. The lower level comes from the American studies, the higher from the European investigations. Analysis of the APHEA data indicates increase in daily total number of deaths of 5% (Athens and Barcelona), 8% (Lyon) and 18% (London) for increases of 100 $\mu g/m^3$ of maximum daily 1 hour levels. The only non-significant relationships (at the 95% level) were for the results from Lyon. The increases for respiratory deaths in Lyon, Paris, London and Barcelona were 2, 4, 24 and 7% respectively. However, only the London data was significant at the 95% level (Touloumi, 1996).

7. Discussion and conclusions

Exposure to O_3 or photochemical oxidant air pollution of which O_3 is a principal component for the induction of health effects may potentially result in an array of health effects some of which with a definite adverse character. The exposure conditions at which acute health have been observed in field studies, do frequently occur during the summer season in industrialised countries. To estimate the health risk in quantitative terms of a population exposed to summer smog, it is imperative to have insight in factors governing the individual response and of the distribution of these factors over the whole population.

The response of an individual to O_3 exposure appears to be largely determined by the inhaled dose and the intrinsic O_3 sensitivity. The inhaled dose is a function of O_3 concentration, level of exercise and exposure time. In this function, the O_3 concentration has more influence than level of exercise and exposure time respectively. The time period during which a certain dose is inhaled, the dose rate, also is an important determinant of dose. Several factors modifying or influencing the sensitivity to O_3 exposure have been identified as mentioned earlier. These factors are important determinants for deriving exposure-response relations for O_3. Quantitative health risk assessment is seriously hampered by our lack of knowledge of exposure-response relationships as well as population exposure. Some of these caveats are touched upon hereafter.

O_3 is a strong oxidant and is for that matter known to react with macromolecules from membranes, proteins, etc. The expression of the eventual resulting oxidant induced injury in terms of health effects is however poorly understood. Furthermore, it is still not possible to extrapolate with confidence the findings from experimental toxicological research to humans in a quantitative manner. Toxicological research does indicate however, that episodic O_3 exposure elicits effects that differ from and are judged to be more adverse than the alterations provoked by a single exposure and that chronic exposure to O_3 may result in irreversible structural alterations of the lung.

The question remains whether the effects of exposure to summer smog can be explained completely by the exposure to O_3 alone and to what extent and under which circumstances other confounding factors influence the observed health outcome. For example, O_3 does not cause eye irritation but summer smog does, probably by organic nitrates and other eye irritants like aldehydes. Sometimes the association of exposure and a health effect is equally strong with particles as with O_3. In a Norwegian study of short-term exposure with personal exposure measurements and effects in a densely populated, industrial area a weak association was found with O_3 and self reported health effects and a stronger association was observed with nitrate (NILU/NIPH, 1991).

Mechanistically, a combination effect of fine particles and ozone is not unlikely (oxygen radical formation, predisposing tissue damage). These "problems" underline the strengths and weaknesses of epidemiological investigations at the same time: the real-life exposure situation to several pollutants at the same time (with one or more indicator compounds) and the difficulty to single out the dominant agent with respect to effects (COST 613, 1994). Extrapolating exposure-response relations from human controlled situation studies may therefore underestimate the responses as they arise from the exposure to the photochemical oxidant air pollution mixture. These caveats in our knowledge restrict our possibilities to construct accurate exposure-response relations for all health endpoints known from toxicological research with animals. It is important to realise our limitations in this matter. Research aimed at developing credible probabilistic exposure-response relations, not only for some of the health endpoints as they occur after a single exposure but also for episodic and seasonal exposures, should have a high priority at our research agendas. The more so since environmental health risk management is increasingly based on quantitative risk assessment and a lack of this type of information is sometimes used by some to deny or minimise the health risk caused by exposure to air pollution and summer smog in particular.

Part of this research should be devoted to methods development like extrapolation modelling, the shape of exposure-response curves especially for low level exposures, threshold vs. non-threshold performing meta-analyses etc. At this moment in time, our knowledge on the actual exposure of the population to air pollution is mostly such that it is limitative for the outcome of our risk assessments. Potential population exposure is the hitherto mostly used. This is the concentration of ambient air pollution to which the population is exposed if they were outside 24h per day. We are now in a transformation phase towards actual

exposure. The exposure proxy may be constructed by knowledge of the activity pattern of subpopulations (in which micro-environment, for what period of time and how physically active) and the concentration in those various micro-environments. Information on actual exposure which enables "head count" risk assessment, is a prerequisite for quantitative O_3 summer smog risk assessment.

In conclusion, exposure-response relationships for O_3 have been derived from human controlled studies and from epidemiological studies for single exposures and for a limited number of health endpoints. Inhaled dose appears to be a useful measure for FEV_1 decrements and symptoms in exposure-response relation based on controlled studies. Daily maximum 1 or 8 h O_3 concentrations are surrogates for exposure in exposure-response relations for FEV_1 decrements and hospital admission based on epidemiological studies. Factors modifying response and subpopulations at increased risk have been identified. Data on actual population exposure appears to be the critical factor when quantitative risk assessments are to be performed at this moment.

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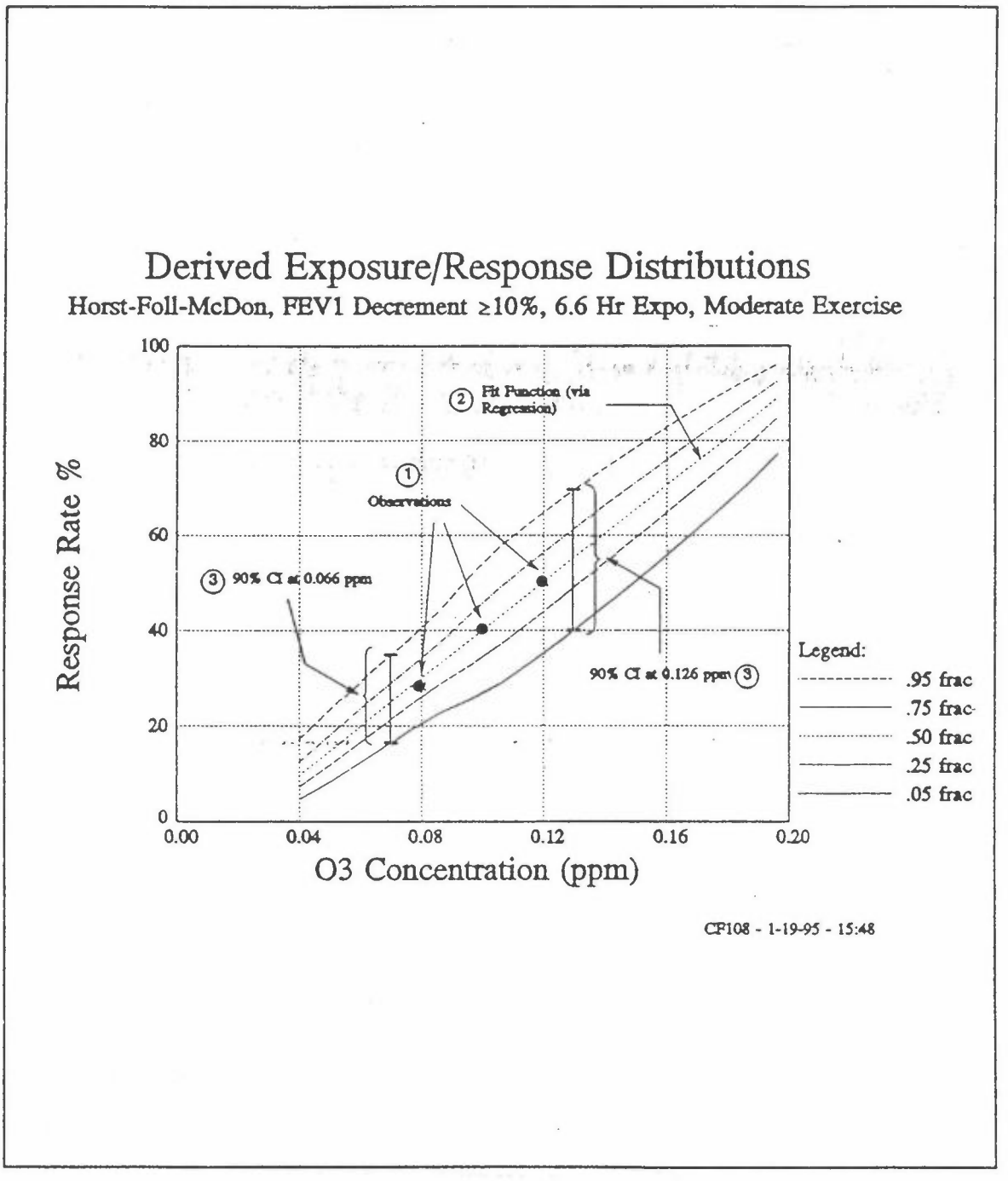

Figure 1: Steps used to develop probabilistic exposure - response relationships. (EPAb, 1995).

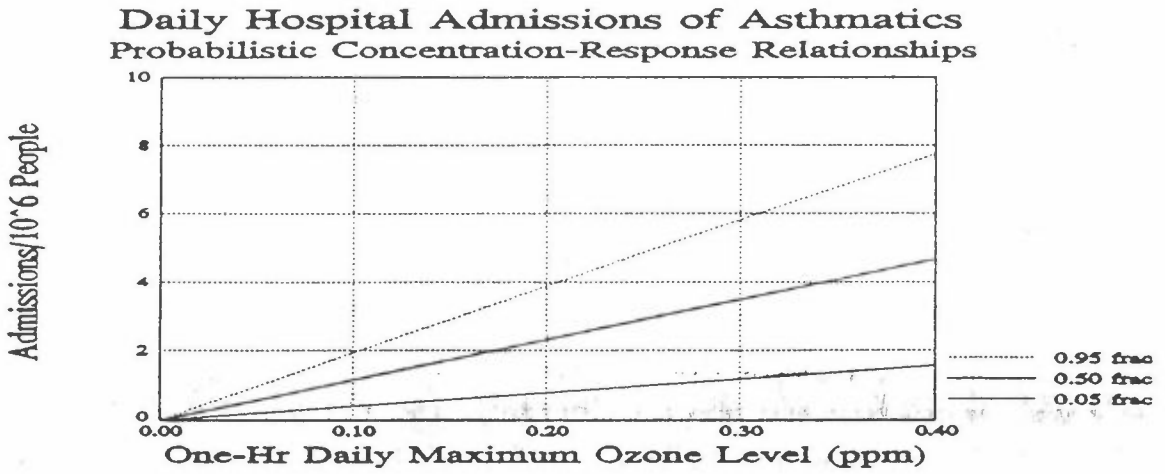

Figure 2: Concentration-response relationship for daily hospital admissions of asthmatics in New York city area. (Based on Thurston et al., 1992).

Table 1 *Logistic and exponential exposure response models of FEV_1 decrements after a single ozone exposure of young adult healthy subjects. Coefficients are converted to facilitate the use of total inhaled dose D in the exponential functions. Dimensions: C (mg/m^3), T (hour), and V_E (m3/h). The response is expressed as the fractional change in FEV_1, 1-r, where r equals the ratio $FEV_{1,a}/FEV_{1,b}$ (a = after and b = before exposure).*

Reference	Type of model	Algebraic of the fractional change in FEV_1 and the statistic R^2	Remarks
McDonnell et al., 1983	Logistic	$1-r = 0.015 + \frac{0.16}{1+e^{4.72-2.53\times D}}$ $R^2 = 0.50$	C = 0.24 to 0.80 mg/m^3 T = 2.1 hour V_E (mean) = 2.2 m^3/h $FEV_{1,b}$ = 4.42 l
McDonnell et al., 1993	Logistic	$1-r = \frac{0.17}{1+e^{3.62-2.32\times D}}$ $R^2 = 0.34$	C = 0.24 to 0.80 mg/m^3 T = 2 hour V_E (mean) = 2.2 m^3/h $FEV_{1,b}$ = 4.53 l
McDonnell and Smith, 1994	Logistic with and without dose-rate $C\times V_E$	$1-r = \frac{0.17}{1+e^{4.37-2.98\times D}}$ or: $1-r = \frac{0.21(1-e^{-0.98\times CVe})}{1+e^{4.03-3.32\times D}}$ $R^2 = 0.93$ $R^2 = 0.89$	C = 0.24 to 0.80 mg/m^3 T = 1 to 2 hour V_E (mean) = 2.2 m^3/h $FEV_{1,b}$ = 4.49 l
McDonnell and Smith, 1994	Logistic with and without dose-rate $C\times V_E$	$1-r = \frac{0.12}{1+e^{3.47-2.24\times D}}$ or: $1-r = \frac{0.12(1-e^{-9.10\times CVe})}{1+e^{3.67-2.52\times D}}$ $R^2 = 0.96$ $R^2 = 0.96$	C = 0.16 to 0.24 mg/m^3 T = 1 to 6.6 hour V_E (mean) = 2.1 m^3/h $FEV_{1,b}$ = 4.44 l
Higfill and Costa, 1995 from Horstman et al., 1990	Exponential	$1-r = 1-e^{-0.032\times D}$ $R^2 = 0.80$	C = 0.16 to 0.24 mg/m^3 V_E (mean) = 2.1 m^3/h T = 1 to 6.6 hour $FEV_{1,b}$ = 4.40 l

Nitrogen dioxide

Evaluation of Nitrogen dioxide at the Nordic Expert Meeting

Quantifiable relationships

An overall evaluation indicates that the epidemiological evidence of effects following short-term or long-term exposure to outdoor NO_2 is not consistent enough for quantitative risk assessment. Associations between ambient levels of NO_2 and different types of adverse effects (respiratory symptoms and diseases, pulmonary function), have been observed in several studies, but generally without support from other similar investigations. Furthermore, the specific impacts of NO_2 are difficult to elucidate in complex ambient air exposure situations. The results of studies concerned with NO_2 indoors are not considered suitable for the assessment of health risk of outdoor air pollution due to differences in the exposure pattern.

Measurable effects that are as yet non quantifiable

Short term effects

The epidemiological evidence under evaluation for short-term exposure to NO_2 is based on studies focusing on annoyance and symptoms reported in diaries, on hospitalization for respiratory diseases or on pulmonary function. Both children and adults have been included, often subjects believed to be particularly sensitive to air pollution, such as asthmatics. As a rule, daily health effect measures were compared with estimated or measured NO_2 levels which were mostly used as an indicator of ambient air pollution mix. The average NO_2-concentrations in the different studies were in the order of 10-50 $\mu g/m^3$ with maximum hourly concentrations ranging up to several hundred micrograms per cubic meter. A few of the studies provided some evidence of association between NO_2 exposure and health effects after control for outdoor temperature, which is generally a strong risk factor. The reporting of results in these studies was often based on regression or correlation coefficients, which makes it difficult to determine threshold or lowest effect levels.

Controlled human studies suggest that a 5-10% decrease in pulmonary function may be observed in asthmatics following exposure to 560 $\mu g/m^3$ during 0.5-3 h of exercise. An effect on airway responsiveness probably occurs at even lower levels. It is not clear if the most sensitive subjects have been included in the chamber studies.

Long-term (chronic) exposure

Most studies on effects of long-term exposure to NO_2 have focused on the indoor environment, where gas appliances constitute a major source. More than a dozen studies are available on symptoms and diseases of the lower respiratory tract in children in relation to gas appliances in residences. The average NO_2 concentrations measured in such residences (excluding kitchens) range from about 40 to 80 $\mu g/m^3$ in the different studies, but short-term peaks in kitchens can

exceed 1000 μg/m³. Long-term average NO_2 concentrations outdoors were generally lower than in the homes with gas appliances. A meta-analysis of the studies shows a statistically significant increase in risk of about 20% for lower respiratory tract illness in association with gas appliances, which contributed an average of about 30 μg/m³ to the indoor NO_2 levels (Hasselblad et al., 1992).

The few studies on respiratory diseases in children and outdoor NO_2 exposure are more difficult to interpret because of the complex exposure environments (Braun-Fahrländer et al., 1992; Goren and Hellmann, 1988; Kagamimori et al., 1986; Love et al., 1982; Mostardi et al., 1981; Pershagen et al., 1995). One study on children living near a trinitrotoluene plant and exposed to average outdoor NO_2 levels of about 40-90 μg/m³ (Love et al., 1982) and two studies in urban areas with average concentrations of about 30 and 50 μg/m³ indicate increased respiratory disease rates or duration of symptoms. Studies on long-term exposure to NO_2 and pulmonary function in children provide inconsistent results. One study on asthmatic children showed a 12 per cent decrease in peak expiratory flow rates associated with a 20 μg/m³ increase in weekly outdoor NO_2 level (Quackenboss et al., 1991).

The studies on long-term exposure to NO_2 and symptoms or diseases of the respiratory tract in adults mostly concerned areas where motor vehicles constituted a major contributor to outdoor levels. Increased prevalence rates were observed in nonsmokers in four studies with average NO_2 concentrations in the "exposed" areas ranging from about 30 to 100 μg/m³,but no corresponding effects were seen in two other studies of populations exposed to similar concentrations. In two studies the prevalence of lower respiratory tract symptoms was related to gas-cooking or measured personal NO_2 exposure but not in a third study. Two studies on pulmonary function showed no effect in relation to long-term average NO_2 levels in urban air of about 100 μg/m³, while, in a third study, a small decrease was apparent among nonsmokers and smokers. Three studies on nonsmokers indicated a decreased pulmonary function in relation to the use of gas for cooking or measured indoor NO_2 levels, but another study showed no such effect.

Among the issues which make the quantitative interpretation of the present information difficult are the assessment of personal exposure to NO_2 as well as the accounting for confounding, including that caused by ambient air pollutants (mainly PM) generated in the same processes as NO_2. While the bias in the exposure misclassification may dilute the effect of NO_2, the confounding may cause both under- or over-estimation of the true impact. Further, the role of short-term peaks and long-term low-level exposure in producing health effects remains unclear.

Nitrogen dioxide

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1. Introduction

Toxic effects of NO_2 have been investigated extensively using animal experiments, controlled human studies and epidemiologic methodology. The primary aim of this review is to obtain quantitative estimates of exposure-response relationships of adverse health effects following exposure to nitrogen dioxide in ambient air. Consequently, the review focuses on human evidence. Epidemiologic data are of primary interest, but for some effects, such as reversible lung function disturbances, information from human experiments is also available. Several health risk evaluations of nitrogen dioxide have recently been performed (Berglund et al., 1993; USEPA, 1993; WHO, 1995).

The epidemiologic evidence on NO_2 exposure covers a wide range of health effects, from acute annoyance reactions and lung function disturbances to chronic pulmonary diseases, such as asthma and chronic bronchitis. This review mainly focuses on studies relevant to the risk assessment of low-level exposure in the general environment (i.e., on effects in sensitive parts of the population, such as diseases of the lower respiratory tract in children). The possible role of NO_2 exposure for the excess risk of allergic sensitization in urban areas is discussed only briefly because of the lack of specific exposure data, and is not used in the risk evaluation.

Much of the evidence relates to NO_2 exposure in ambient air, where NO_2 is only one of several components whose exposure may be correlated, and it is thus difficult to define etiologic relationships. Only studies providing data on actual NO_2 concentrations based on measurements or model calculations have been included in this review. Gas appliances are an important source of indoor NO_2 exposure, which can be a main contributor to total NO_2 exposure for people spending most of their time indoors. Epidemiologic studies on NO_2 exposure from gas appliances has received particular attention, as concomitant exposure to other agents may be less important than in the outdoor environment; this situation facilitates the assessment of causal relationships.

Acute effects of short-term exposure are discussed first. Symptoms and diseases of the respiratory tract in children and adults are then considered. They were generally reported in relation to long-term exposure, but it cannot be excluded that short-term peaks were of importance. Pulmonary function disturbances are treated separately and include effects of both short-term and long-term exposures. Finally an attempt is made to estimate exposure-response relationships in relation to NO_2.

2. Acute effects

Several studies have investigated the relation between NO_2 levels in ambient air, often measured as hourly or daily averages, and acute health effects. These effects primarily include annoyance reactions and subjective symptoms reported in diaries and hospital admissions. Studies on lung function which may represent both acute and chronic effects are reviewed separately.

A total of 128 elementary school-age children from a region in Pennsylvania with coal-fired power plants participated in an eight-month diary study on respiratory symptoms (Vedal et al., 1987). The children were selected from an earlier cross-sectional study and divided into the following three groups: persistent wheeze, cough or phlegm, and no respiratory symptoms. The daily mean of maximum 1 h NO_2 concentrations in the region ranged from 12 to 79 $\mu g/m^3$ with an average of 40.5. No differences in NO_2 concentrations were observed between days with high and low incidence rates of respiratory symptoms or illnesses. Respiratory illness on the preceding day was the most important predictor of current illness.

Weekly changes in air pollutant levels were compared with respiratory infections in children and adults diagnosed at municipal health centers and with absenteeism from day-care centers during one year in Helsinki, Finland (Pönkä, 1990). The annual average NO_2 concentration measured at one station was 47 $\mu g/m^3$. After standardization for temperature, no correlation was seen between the NO_2 levels and respiratory infections or absenteeism from day-care centers.

Approximately 200 student nurses in Los Angeles were included in a diary study extending over three years (Schwartz and Zeger, 1990). Daily maximum 1 h NO_2 concentrations measured at a station near the school averaged 244 $\mu g/m^3$ (0.13 ppm) with a 75th percentile of 320 $\mu g/m^3$ (0.17 ppm). In a logistic regression analysis controlling for temperature and serial correlation between days, an increase in 171 $\mu g/m^3$ (0.091 ppm) corresponded to excess risks of phlegm [relative risk (RR) 1.08, $P<0.01$], sore throat (RR 1.26, $P<0.001$) and eye irritation (RR 1.16, $P< 0.001$). The associations persisted also after adjustment for smoking and allergies.

A diary study of 162 children and adults in Oslo registered annoyance and symptoms on an hour-by-hour basis during two weeks (Clench-Aas et al., 1991). The estimated mean NO_2 exposure levels based on time activity patterns ranged from 10 to 53 $\mu g/m^3$ for the different individuals, with maximum hourly concentrations of up to 188 $\mu g/m^3$ for children and teenagers, and up to 163 $\mu g/m^3$ for elderly persons. Fatigue, sneezing, sore/irritated throat, tight chest, annoying smell, and annoying noise were significantly associated with estimated NO_2 exposures, showing relative risks ranging from 1.17 to 2.45 comparing a concentration of 100 with 10 $\mu g/m^3$. The relative risks comparing different exposures were calculated from the regression coefficients in multiple regression analyses including a number of variables, such as symptoms the preceding hour, outdoor temperature, relative humidity and smoking.

Another Norwegian study was performed in Grenland, an industrially polluted area where three groups of subjects were followed on an hour-by-hour basis for four months (Clench-Aas and Bjerknes Haugen, 1991). The three groups included a population sample of adults (N = 312), as well as adults (N = 67) and children (N = 18) with pulmonary disease. Estimated NO_2 exposures based on time activity patterns and indoor and outdoor measurements showed median levels of 14 and 13 µg/m³ for the population sample and subjects with pulmonary disease, respectively, with maximum hourly concentrations up to 334 and 214 µg/m³, respectively. The results showed a rather incoherent picture comparing NO_2 exposures with subjective symptoms in multiple regression analyses including outdoor temperature, relative humidity, and some air pollution components. Estimated NO_2 exposures seemed to correlate with symptoms from the upper respiratory tract and fatigue or stress in the population sample. NO_2 concentrations giving rise to a 50% increase in relative risk compared with an assumed background of 5 µg/m³ were estimated to be 42 and 229 µg/m³ respectively, for these two types of symptoms. The results for subjects with pulmonary disease were less consistent.

Daily counts of children's visits to physicians for croup symptoms and obstructive bronchitis in five German cities were compared with air pollution data for more than two years (Schwartz et al., 1991). Altogether 6630 cases of croup and 4755 cases of obstructive bronchitis were recorded. The median NO_2 levels in the five cities ranged from 14 to 55 µg/m³. Physicians' visits for croup were correlated to daily concentrations of both NO_2 and suspended particulates. No significant effect of temperature or humidity on disease rates were observed after control for seasonal and other cyclical patterns. An increase in NO_2 concentration from 10 to 70 µg/m³ was estimated to result in a relative risk of 1.28. No corresponding association was seen for obstructive bronchitis.

A diary study during five weeks included 449 subjects believed to be sensitive to air pollution from answers to a questionnaire on asthma symptoms and medication, other respiratory symptoms, and annoyance (Forsberg et al., 1992). The subjects lived in 43 Swedish towns with average NO_2 concentrations ranging between about 10 and 40 µg/m³ during the observation period. Annoyance and symptoms from the respiratory tract were related to daily NO_2 concentrations ($P<0.001$) but not to sulphur dioxide, soot, temperature, or humidity. The daily symptom rate increased from 13.5 to 27.4% for days with NO_2 at less than 10 µg/m³ to days with NO_2 at more than 50 µg/m³ The associations became stronger when only days preceded by a symptom-free day were included in the analysis.

A panel of 31 asthmatic patients in a town in northern Sweden recorded respiratory symptoms during two winter months (Forsberg et al., 1993). The daily concentrations of NO_2 ranged from 7.4 to 55.8 µg/m³ (mean 20.0 µg/m³). Daily variations in severe symptoms of shortness of breath were related to black smoke levels but not to other air pollutants or meteorologic variables. Cough and phlegm did not show significant relationships to any environmental condition.

Hospital admissions for exacerbations of chronic bronchitis and emphysema were analysed in relation to air pollution levels during 1987 to 1989 in Helsinki, Finland (Pönkä and Virtanen, 1994). The average of 24 h concentrations was 39 µg/m3 (range 4-170). Daily admissions were correlated with NO_2 levels after a 6-day lag but was significant only among those over 64 years of age (RR 1.31, 95% CI 1.03-1.66). A correlation was seen also for SO_2 but only among those under 65 years of age. Neither temperature nor the concentration of TSP or O_3 had any significant effect on the admissions.

Short term variations in mortality have been analysed in relation to air pollution levels in a large number of investigations (Brunekreef et al., 1995). In general, the most consistent associations are seen for respirable particulate, and the evidence for NO_2 is inconclusive. It is often difficult to interpret the studies because of high correlations between different pollutants.

3. Symptoms and diseases of the respiratory tract in children

Symptoms and diseases of the respiratory tract are very common in children. A subdivision is often made into conditions affecting the lower and upper respiratory tract. Studies on lower respiratory tract symptoms include questions on persistent cough, wheezing, and colds going to the chest. The predominant illnesses among children affecting the lower respiratory tract are bronchitis, asthma, and pneumonia. Symptoms of the upper respiratory tract used in epidemiologic investigations include runny nose, cold, sore throat, earache, stuffiness of the head, and the like. Most studies on non-infectious environmental causes of respiratory diseases in children have focused on symptoms and diseases of the lower respiratory tract that may represent critical effects for some types of exposures, such as environmental tobacco smoke.

The design and results of the epidemiologic studies on NO_2 exposure and respiratory symptoms or diseases in children are summarized in table 1. Most of the studies were based on comparisons between children from homes with and without gas appliances. The design was often cross-sectional in which exposures and health effects were measured at the same time, for example via questionnaires to parents. However, a few longitudinal studies exist, both of cohort and case-control design. As is evident from the table, several of the studies included NO_2 measurements based on indoor, outdoor or personal monitoring. In a few studies time activity patterns were also considered in the estimates of NO_2 exposure. The assessment of the respiratory diseases of the children was generally based on parental reports in questionnaires without any attempts for validation. Information on potential confounding factors, such as parental smoking habits and socioeconomic status, was also obtained from the questionnaires.

The studies on gas appliances and respiratory diseases in children give somewhat inconsistent results. Figure 1 shows relative risks (odds ratios) for respiratory diseases or symptoms associated with gas stoves or measured NO_2 exposure in 13 studies. The relative risks and 95% confidence intervals were sometimes estimated from the data given in the original publications (Hasselblad et al., 1992). A few of the investigations provide statistically significant excess risks (Melia et al.; 1977, Melia et al., 1979; Melia et al., 1980; Neas et al., 1991) while

the others fail to do so. However, the confidence intervals were wide in many of the "negative" studies, often having point estimates of relative risks (odds ratios) exceeding 1, which means that the studies do not provide strong evidence against an effect. Only one study showed a clear exposure-response relationship (Neas et al., 1991), however, most of the investigations did not attempt such analyses.

A meta-analysis has been performed of the studies on NO_2 exposure, mostly originating from domestic gas appliances, and lower respiratory tract illnesses in children (Hasselblad et al., 1992). In order to combine the results, the relative risk associated with long-term exposure to a 30 $\mu g/m^3$ increase in the NO_2 level was calculated (comparable to the increase resulting from exposure to a gas stove). If no measurement data were given in the original studies, the exposure was estimated from information on the use of gas stoves. The relative risks for lower respiratory tract illnesses in the 11 included studies ranged from 0.63 to 1.53, with an overall estimate of 1.18 and a 95% confidence interval of about 1.1-1.3 (depending on the method of analysis). In other words, the overall evidence is consistent with an excess risk of about 20% for lower respiratory tract illness in children in association with long-term exposure to an NO_2 increase of 30 $\mu g/m^3$. Subsequent evaluations of the data indicate that the effect is mostly seen in children around 5 to 12 years of age (USEPA, 1993; WHO, 1995).

A few studies focused on outdoor exposure to NO_2 or NO_x (Braun-Fahrländer et al., 1992; Goren and Hellman, 1988; Kagamimori et al,. 1986; Love et al., 1982; Mostardi et al., 1981; Pershagen et al., 1995). The design and results of these studies are also summarized in Table 1. In general, increased risks of respiratory diseases and symptoms were observed in children related to comparatively low outdoor NO_2 concentrations. Three of the studies were performed near fossil fuelled power plants or in industrial areas with a complex exposure environment (Goren and Hellman, 1988; Kagamimori et al., 1986; Mostardi et al., 1981), and therefore it is difficult to assess the etiologic role of NO_2.

One study included communities near a trinitrotoluene plant, where NO_2 exposures dominated, although total suspended particulate concentrations were comparatively high in one of the areas (Love et al., 1982). These communities had been investigated earlier, when the exposure levels were higher, and an excess bronchitis morbidity in children had been indicated (Pearlman et al., 1971). In the later study the respiratory disease rates in pre-school children were increased in the designated high-exposure area during a period characterized primarily by high peak concentrations of NO_2 (1-h 99th percentile 692 $\mu g/m^3$). Similar but less pronounced effects were seen in schoolchildren.

Two studies concerned areas where motor vehicles constituted the primary source of environmental NO_2. A significant association was found between measured NO_2 levels outdoors and duration of respiratory symptoms among pre-school children from Basel and Zürich in Switzerland (Braun-Fahrländer et al., 1992). The duration increased by 13% (95% CI:1%-27%) per 20 $\mu g/m^3$ increase in outdoor NO_2 concentration. Annual average NO_2 levels in the two cities were 47 and 51 $\mu g/m^3$. Another study was performed in Stockholm, Sweden, and showed a statistically significant excess risk of wheezy bronchitis in girls having

an estimated mean time-weighted outdoor NO_2 level exceeding 70 µg/m³ as the 99th percentile of 1-h values (Pershagen et al., 1995). This level corresponds to a winter half-year mean of 27 µg/m³. No comparable relation was seen for the boys. An excess risk in homes with gas stoves was also observed for the girls only. This finding is supported by the results of some other investigations (Melia et al., 1977, Neas et al., 1991). However, most of the studies on NO_2 exposure and respiratory disease in children did not look at boys and girls separately.

4. Allergic sensitization in children

A few studies indicate that sensitization to aeroallergens, such as pollen and animal dander, is more common among children living in urban areas (Bråbäck and Kälvesten, 1991; Linna, 1983) or near roads with heavy traffic (Ishizaki et al., 1987). This has also been confirmed in adults (Gergen et al., 1987; Popp et al., 1989). It is possible that outdoor air pollution may have contributed to these findings; however, other differences between urban and rural areas should also be considered in the interpretation, such as personal habits and the indoor environment. NO_2 levels were reported only in one study (Bråbäck and Kälvesten, 1991), where the hourly average concentration of 190 µg/m³ was exceeded on 20 and 27 occasions during the two years of study at one station in the investigated town. No measurement data were available for the rural area used as comparison.

5. Symptoms and diseases of the respiratory tract in adults

A number of studies have investigated symptoms and diseases of the respiratory tract in adults in relation to NO_2 exposure. The design has been cross-sectional, with particular emphasis on symptoms or diseases of the lower respiratory tract. Most of the studies focused on outdoor air pollution, NO_2 being used as the indicator of pollution mainly originating from motor vehicles. Tobacco smoking is the primary determinant of some important symptoms and diseases of the lower respiratory tract, such as persistent cough, phlegm production and chronic bronchitis, and, to avoid confounding, only nonsmokers were included in some of the studies. A disadvantage with such a design is that interactions between NO_2 exposure and smoking cannot be assessed.

Respiratory symptoms were studied via questionnaires to 3873 nonsmokers in two communities in California with mean hourly NO_2 concentrations of 96 and 43 µg/m³ (0.051 and 0.023 ppm) during 1963-1967 (Cohen et al., 1972). No difference in the prevalence of cough (with and without phlegm) was seen between the two areas.

The prevalence of chronic respiratory disease assessed via questionnaire tended to be higher among both nonsmokers and current smokers working as traffic officers in a study of 268 policemen from Boston, Massachusetts (Speizer and Ferris, 1973). The mean NO_2 concentration during the year of study was 103 µg/m³ (0.055 ppm) with maximum hourly levels of up to 564 µg/m³ (0.33 ppm)

Questionnaires were distributed to more than 5000 individuals living in two Californian communities exposed to different levels of photochemical oxidants, including NO_2 (Detels et al., 1981). The annual means of daily maximum hourly concentrations of NO_2 were 60 and 211 $\mu g/m^3$ in the two areas. The prevalence of cough, sputum production, and wheezing was increased in the high pollution area among the nonsmokers, while for smokers the excess was primarily seen for wheezing.

No increase in respiratory symptoms or disease rates was found for adults from homes with cooking gas in the study by Keller et al. (1979), discussed in the section on lower respiratory tract illness in children.

Respiratory symptoms were recorded for 708 non-smoking adults in Maryland and related to exposure to environmental tobacco smoke and gas cooking (Helsing et al., 1982). Symptom rates were significantly increased for chronic cough (with and without phlegm) in subjects from households using gas cooking after adjustment for socioeconomic status. An earlier study, based on the same group but also including smokers, indicated that the effects were less pronounced among smokers (Comstock et al., 1981).

More than 100 housewives living at different distances from a major traffic artery in Tokyo answered a questionnaire on respiratory symptoms, smoking habits, and the use of kerosene heaters (Yokoyama et al., 1985). NO_2 concentrations measured in ambient air during 7 d ranged from 68 to 129 $\mu g/m^3$ within 20 m from the roadside and from 45 to 80 $\mu g/m^3$ up to 150 m from the road. Personal samplers indicated that the use of kerosene heaters was the main determinant of NO_2 exposure. Increased prevalence rates of persistent cough and phlegm were determined for women living closest to the road, particularly for the nonsmokers and those not using kerosene heaters. The effects were less clear in relation to kerosene heater use.

A total of 7445 Seventh-day Adventists who were non-smokers from California were included in a study on chronic obstructive disease symptoms in relation to exposure to photochemical oxidants (Euler et al., 1988). About 20% of the population was estimated to be exposed to NO_2 at 94 $\mu g/m^3$ (0.05 ppm) or higher during 4900 h a year. No association between estimated NO_2 exposure and respiratory symptoms was seen in a multiple regression analysis including gender, age, race, education, passive smoking, and the like. On the other hand, symptom rates were significantly associated with exposure to total oxidants, sulphur dioxide, and, most strongly, total suspended particulate.

Respiratory symptom rates were compared with NO_2 exposure measured by personal samplers during two weeks among 319 women from Hong Kong (Koo et al., 1990). The mean NO_2 level of 36 $\mu g/m^3$ was influenced by occupational exposure, cooking fuels (liquid petroleum gas and kerosene), ventilation, and incense burning in the home. Among the 312 nonsmokers the symptom rates were associated with NO_2 exposure for allergic rhinitis and chronic cough. A significant trend ($P<0.01$) was also seen between the number of respiratory symptoms and the NO_2 levels.

A questionnaire on annoyance and respiratory symptoms was answered by more than 6000 subjects living in towns near 55 measurement stations for air pollution in Sweden (Forsberg et al., 1991). Winter half-year average NO_2 levels ranged between about 10 and 30 µg/m³ in the different towns. Statistically significant correlations ($P<0.01$) were seen between NO_2 levels and annoyance due to bad smell, irritation, and dust or soot pollution of the air. Similar effects were observed in nonsmokers, ex-smokers, and smokers. With regard to respiratory symptoms, the highest correlation appeared for throat irritation and irritating or inproductive cough during the last three months ($P<0.01$). Weaker correlations were generally found between symptom rates and concentrations of sulphur dioxide and soot.

A panel of 164 non smoking asthmatics recorded the occurrence of respiratory symptoms in a daily diary during three winter months (Ostro et al., 1994). Use of a gas stove was related to several lower respiratory treat symptoms including cough (OR 1.48, 95% CI 1.00-2.17) and shortness of breath (OR 1.60, 95% CI 1.05-2.44). Similar effects were also suggested for exposure to environmental tobacco smoke.

6. Pulmonary function

Human chamber studies generally involving exposure during 0.5 to several hours show that NO_2 can cause bronchoconstriction in normal subjects at concentrations of several thousand µg/m³ and an increased airway responsiveness at about 2,000 µg/m³ (Berglund et al., 1993; USEPA, 1993; WHO, 1995). In asthmatics some studies indicate statistically significant changes of about 5-10% in expiratory flow rates and airway resistance at 560 µg/m³ (0.3 ppm) during exercise, but the evidence is not consistent. A metaanlysis suggests that an increased airway responsiveness in asthmatics can occur at NO_2 concentrations above 190 µg/m³ (Follinsbee, 1992). Recent studies point to an interaction between NO_2 and other agents, such as ozone, sulphur dioxide and house dust mite allergen (Devalia et al., 1994; Hazucha et al., 1994; Tunnicliffe et al., 1994). The interpretation of the controlled human studies is difficult, because it is not clear if the most sensitive individuals have been investigated, even in the studies based on asthmatics.

Epidemiologic studies on pulmonary function in relation to NO_2 have been performed on children and adults after both short-term and long-term exposures. Although most of the studies were cross-sectional, some also included longitudinal follow-up of lung function. Unfortunately, very few investigations focused on asthmatics or other subjects who may be particularly sensitive to airway irritants. Two studies looked at acute effects on pulmonary function in children in relation to NO_2 levels in ambient air (Kagawa and Toyama, 1975; Vedal et al., 1987). In the first study there was a correlation between daily NO_2 levels and PEF, while the second failed to show such an association. The hourly average NO_2 concentrations in the first study ranged between about 10 and 400 µg/m³ and the daily means of the hourly maximum concentrations were between 12 and 79 µg/m³ in the second study.

Thirty children with current diagnosed asthma were followed during two week periods with lung function measurements (peak expiratory flow rate) up to four times a day (Quackenboss et al., 1991). Exposure to NO_2 was estimated from indoor and outdoor measurements as well as via personal samplers. The estimated average exposure for the children was 19.4 µg/m³. A 12% decrease in the flow rate was associated with a 20 µg/m³ increase in the weekly average outdoor NO_2 level. No effects were seen in nonasthmatic children. Lung function was measured twice over a 6 month period in 423 school children of 4 towns in Austria (Frischer et al., 1993). NO_2 concentrations ranged from 14.9 to 21.6 µg/m³ during the first survey and between 9.8 and 16.1 µg/m³ during the second survey. There was an increase in forced vital capacity between the two surveys corresponding to 3.1 ml per µg/m³ in 12-hr mean NO_2 level.

An early study on children living near a trinitrotoluene plant indicated a small decrease in pulmonary function ($FEV_{1.0}$) in comparison with control children (Shy et al., 1970). Winter half-year mean NO_2 concentrations at different stations in the high exposure area ranged from 117 to 205 µg/m³ (0.062-0.109 ppm) and corresponding TSP levels (total suspended particulates) were also increased (63-96 µg/m³). Later studies showed slight decreases in pulmonary function measures associated with gas cooking or estimated NO_2 exposure in some groups (Dijkstra et al., 1990; Hoek and Brunekreef, 1994; Schwartz, 1989; Speizer et al., 1980; Ware et al., 1984;) but not in others (Hasselblad et al., 1981; Lebowitz et al., 1985; Neas et al., 1991). One study indicated that children with asthmatic symptoms may be particularly susceptible to lung function effects by NO_2 at concentrations exceeding 40 µg/m³ (Moseler et al., 1994). Lung function growth measured over a 2-year period was not associated with NO_2 exposure in one investigation (Dijkstra et al., 1990). It should be noted that the effects were small in the studies showing statistically significant results (i.e., only a few percent decrease in the flow rates or less)

One study found an increased prevalence of bronchial hyperreactivity among schoolchildren in an urban area of Switzerland, primarily in those children without asthma or other allergic diseases (Gschwend-Eigenmann et al., 1989). Average NO_2 levels during a 10-month period in the urban and rural comparison areas were 36 and 26 µg/m³, respectively.

Acute effects on pulmonary function in adults from NO_2 exposure was assessed in four studies. A preliminary investigation of eight asthmatics and six nonasthmatics from Toronto, Canada, compared daily pulmonary function measurements and NO_2 exposure based on personal sampling (Silverman et al., 1982). The average NO_2 level during the 40 d study period was 37 µg/m³, and the corresponding particulate concentration 106 µg/m³. The daily decrease in pulmonary function was associated with NO_2 exposure, but statistically significant only for the asthmatics. A small study on asthmatics suggested a drop in FVC and PEF at indoor NO_2 levels above 564 µg/m³ (0.3 ppm) in association with meal preparation on a gas stove (Goldstein et al., 1988). No corresponding effects were seen for non-asthmatics. In the studies by Clench-Aas and Bjerknes Haugen

(1991) and Clench-Aas et al. (1991), described above, no consistent associations between hourly air pollution measurements and PEF values were observed.

Long-term exposure to NO_2 and effects on pulmonary function in adults have been investigated in a few studies. Two studies discussed previously also included data on pulmonary function in relation to domestic gas appliances, one showing no effect (Keller et al., 1979), and the other, with nonsmokers only, indicating a reduced $FEV_{1.0}$ (Helsing et al., 1982). Use of gas for cooking showed a suggestive association with low $FEV_{1.0}$ (RR 1.82, P = 0.08) in a case-control study on 213 non-smoking women from Michigan (Jones et al., 1983). The NO_2 levels measured during one week in the homes of 97 non-smoking Dutch women were negatively associated with several pulmonary function parameters, including $FEV_{1.0}$ and FVC (Fischer et al., 1985). However, no significant association was found between NO_2 exposure and pulmonary function decline during 17 years. The estimated personal exposure on a weekly average basis ranged from 11 to 125 $\mu g/m^3$.

No effects on pulmonary function were seen in the studies by Cohen et al. (1972) and Speizer and Ferris (1973) from California and Massachusetts, respectively, in relation to outdoor NO_2 levels. The study by Detels et al. (1981), also described earlier, on two communities in California, showed no consistent differences between the areas in pulmonary function tests associated with small airways. However, the prevalence of subjects with a poor $FEV_{1.0}$ or FVC was increased ($P<0.01$) in the high pollution area, both among nonsmokers and smokers. In a follow-up of the nonsmokers after five to six years a greater deterioration in pulmonary function was observed in the high-exposure area, particularly for tests associated with small airways (Detels et al., 1991).

7. Conclusions and risk estimation

NO_2-induced health effects can result from both short- and long-term exposures. The health effects related to the two types of exposure are often different in character, acute conditions being associated with short-term exposures and more chronic diseases being related to long-term exposures. Furthermore, the methodology is generally quite different for the study of acute reversible conditions and chronic health effects. Thus it is pertinent to separate effects occurring after short-term and long-term exposure in the evaluation. However, it should be realized that it is sometimes difficult to determine whether observed health effects result from short-term or long-term exposure, such as in cross-sectional studies on respiratory symptoms or pulmonary function.

Short-term exposure

The epidemiologic evidence under evaluation for short-term exposure to NO_2 is based on studies focusing on annoyance and symptoms reported in diaries, on hospitalization for respiratory diseases or on pulmonary function. Both children and adults have been included, often subjects believed to be particularly sensitive to air pollution, such as asthmatics. As a rule, daily health effect measures were compared with estimated or measured NO_2 levels, which were mostly used as an indicator of ambient air pollution. The average NO_2 concentrations in the different

studies were in the order of 10-50 μg/m³ with maximum hourly concentrations ranging up to several hundred micrograms per cubic meter. A few of the studies provided some evidence of association between NO_2 exposure and health effects after control for outdoor temperature, which is generally a strong risk factor. The reporting of results in these studies was often based on regression or correlation coefficients, which makes it difficult to determine threshold or lowest effect levels.

An overall evaluation indicates that the epidemiologic evidence of effects following short-term exposure to NO_2 is inconclusive and thus not suitable for quantitative risk assessment. Associations between NO_2 and different types of adverse effects have been observed in some studies, but generally without support from other similar investigations. Furthermore, possible etiologic relations specifically involving NO_2 are difficult to elucidate in complex ambient air exposure situations. Controlled human studies suggest that a 5 to 10% decrease in pulmonary function may be observed in asthmatics following exposure to 560 μg/m³ during 0.5 to 3 h of exercise. An effect on airway responsiveness probably occurs at even lower levels. It is not clear if the most sensitive subjects have been included in the chamber studies.

Long-term exposure

Most studies on effects of long-term exposure to NO_2 have focused on the indoor environment, where gas appliances constitute a major source. More than a dozen studies are available on symptoms and diseases of the lower respiratory tract in children in relation to gas appliances in residences. The average NO_2 concentrations measured in such residences (excluding kitchens) range from about 40 to 80 μg/m³ in the different studies, but short-term peaks in kitchens can exceed 1000 μg/m³. Long-term average NO_2 concentrations outdoors were generally lower than in the homes with gas appliances. A meta-analysis of the studies shows a statistically significant increase in risk of about 20% for lower respiratory tract illness in association with gas appliances, which contributed an average of about 30 μg/m³ to the indoor NO_2 levels.

The few studies on respiratory diseases in children and outdoor NO_2 exposure are more difficult to interpret because of the complex exposure environments. One study on children living near a trinitrotoluene plant and exposed to average outdoor NO_2 levels of about 40-90 μg/m³ and two studies in urban areas with average concentrations of about 30 and 50 μg/m³ indicate increased respiratory disease rates or duration of symptoms. One-hour peak exposures of up to 700 μg/m³ were encountered near the trinitrotoluene plant.

Studies on long-term exposure to NO_2 and pulmonary function in children provide inconsistent results. An early study of children living near a trinitrotoluene plant and exposed to outdoor NO_2 levels of between 100 and 200 μg/m³ indicated a small decrease in pulmonary function. Later investigations on children exposed via domestic gas appliances and/or outdoor sources showed statistically significant effects in some but not in other studies.
The studies on long-term exposure to NO_2 and symptoms or diseases of the respiratory tract in adults mostly concerned areas where motor vehicles

constituted a major contributor to outdoor levels. Increased prevalence rates were observed in nonsmokers in four studies with average NO_2 concentrations in the "exposed" areas ranging from about 30 to 100 µg/m³ but no corresponding effects were seen in two studies of populations exposed to similar concentrations. In two studies the prevalence of lower respiratory tract symptoms was related to gas-cooking or measured personal NO_2 exposure (36 µg/m³) but not in a third study.

Two studies on pulmonary function showed no effect in relation to long-term average NO_2 levels in urban air of about 100 µg/m³, while, in a third study, a small decrease was apparent among nonsmokers and smokers. Three studies on nonsmokers indicated a decreased pulmonary function in relation to the use of gas for cooking or measured indoor NO_2 levels, but another study showed no such effect.

In the interpretation of the epidemiologic evidence on long-term exposure to NO_2, it is necessary to consider the possible influence of various types of bias. Primarily two types of bias are of interest, misclassification and confounding. The methods used in the different studies to estimate NO_2 exposure result in some misclassification. Personal monitors were rarely used, and, if so, only during short measurement periods. The role of short-term peaks and long-term low-level exposure remains unclear. To the extent that the misclassification is unrelated to the outcome under study, it will generally tend to dilute any association. Nondifferential misclassification of health effects, resulting, for example, from poor quality in the questionnaire information or pulmonary function measurements with regard to specificity, will have the same consequences.

Uncontrolled confounding must also be considered in the interpretation of the findings. The meta-analysis on domestic gas appliances and low respiratory tract illnesses in children showed a relative risk of only 1.2. Important risk factors for lower respiratory tract illnesses, such as parental smoking and socioeconomic status, were often controlled in the studies. However, it cannot be ruled out that residual confounding from these factors and other risk factors which were not controlled contribute to explaining the observed association. Confounding by other environmental factors is of particular concern in the studies on outdoor exposure to NO_2.

In conclusion, an overall assessment of the epidemiologic evidence on long-term exposure suggests that gas appliances in the home are associated with an increased risk of lower respiratory tract illness in children. The increase in risk is around 20 per cent and the gas appliances contributed an average of about 30 µg/m³ to the indoor NO_2 levels. Some studies on pulmonary function in children and lower respiratory tract symptoms and pulmonary function in adults show associations to NO_2 exposure, but the evidence is not conclusive.

The epidemiologic findings on outdoor NO_2 exposure are difficult to interpret because of the complex exposure environments. Inconsistent evidence of health effects is available at long-term average outdoor concentrations ranging from about 30 to 100 µg/m³. In a comparison of exposure-response relationships with the studies focusing on indoor measurements, it is necessary to consider time

activity patterns, which indicate that personal exposures are more influenced by indoor levels in most populations under study. Another complexity is the role of high short-term exposures for the reported health effects, which is currently unclear.

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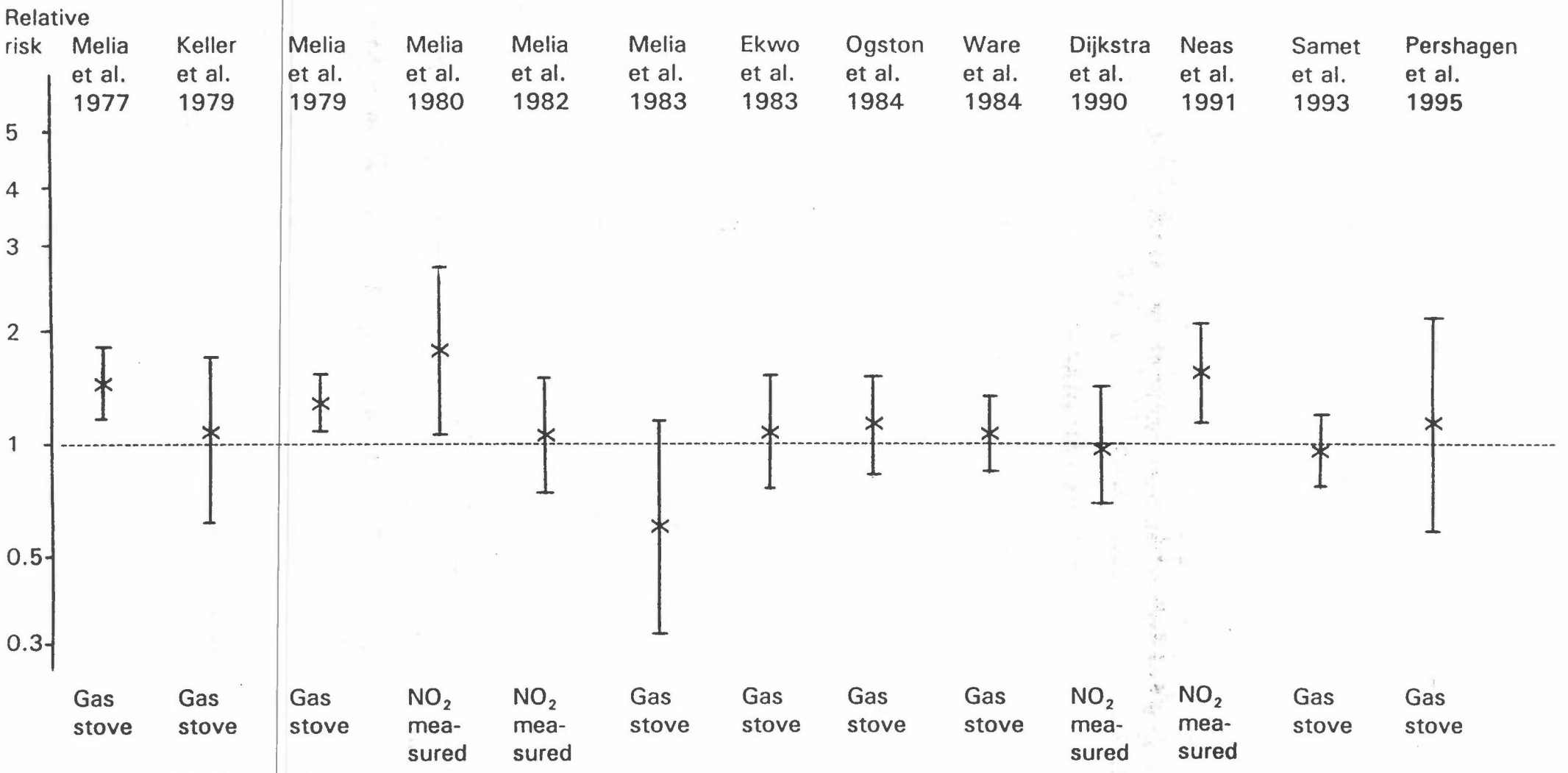

Figure 1: Relative risk for lower respiratory tract illness among children in relation to domestic gas appliances or measured indoor NO_2 concentrations (bars indicate 95% confidence intervals).

Table 1: Summary of design, exposure and results in epidemiologic studies on NO_2 and respiratory illness in children

COUNTRY	NUMBER/AGE	EXPOSURE	RESULTS	COMMENTS	REFERENCES
England & Scotland	5758 children 6-11 years	Gas cooking	RI* and LRS+ (one or more symptoms): OR**=1.31 children< age 8. Girls p<0.05, boys p=0.30	Not adjusted for parental smoking	Melia et al. (1977)
England & Scotland	4827 children 5-10 years	Gas cooking	RI and LRS (one or more symptoms): OR=1.25 Boys (p<0.05), 1.19 girls (p=0.07)	Adj for parental smoking	Melia et al. (1979)
England	808 children 6-7 years	Gas cooking, one week NO_2-measurement: 34 (11-353) µg/m^3 in kitchen with electric cookers. 210 (10-596) µg/m^3 in kitchen with gas cookers. 26 (6-70) µg/m^3 in bedroom without gas 57 (8-318) µg/m^3 in bedroom with gas	RI and LRS (one ore more symptoms) associated with NO_2 level in bedroom (p<0.1). Later estimated by Hasselblad et al. (1992) that 30 µg/m^3 increase in bedroom corresponds to RR++= 1.53(1.04-2.24)	Adj for smoking, social class	Melia et al. (1980)
England	337 children 5-6 years	Gas cooking, weekly average NO_2 concentrations 17-549 µg/m^3 in living rooms and 9-302 µg/m^3 in bedrooms	RI or LRS (one or more symptoms) was not associated with NO_2 level in living room or bedroom. Later estimated by Hasselblad et al. (1992) that 30 µg/m^3 increase in bedroom corresponds to RR= 1.11 (0.83-1.49)	Positive association was found for relative humidity(P<0.05). Adj for parental smoking.	Melia et al. (1982)
Scotland	1565 infants <1 year	Gas cooking	At least one episode of RI: RR=1.14 (0.86 - 1.50)	Adjusted for parental smoking and type of heating	Ogston et al. (1985)
USA Ohio	176 children <12 years	Gas cooking 38 µg/m^3 not exposed, 94 µg/m^3 exposed (annual mean)	LRS (one or more symptoms): OR=1.10 (0.74-1.54)	No adj for parental smoking	Keller et al. (1979)

Table 1 (cont.)

COUNTRY	NUMBER/AGE	EXPOSURE	RESULTS	COMMENTS	REFERENCES
USA "six cities"	8120 children 6-10 years	Outdoor air pollution, gas stove. Geometric mean NO_2 level (24-hour) indoor ranging from 3.6 (electric) and 14.7 (gas) $\mu g/m^3$ to 41.4(electric) and 54.3(gas) $\mu g/m^3$ in different cities. Short-term peaks of 1100 occurred in kitchens. Geometric mean outdoor levels ranged from 5.9 to 41 $\mu g/m^3$ in the six cities	Doctor diagnosed RI before age 2: OR=1.12 (1.00-1.26) for homes with gas stove compared to homes with electric stove	Adj for parental smoking and social class	Speizer et al. (1980)
(six cities)	10106 children 6-10 years	Gas stove	Doctor diagnosed respiratory disease before age 2: OR= 1.11 (0.99-1.28) History of bronchitis: OR= 0.86 (0.74-1.00)	Adjusted for smoking and parental education	Ware et al. (1984)
(six cities)	1567 children 7-11 years	Weekly measurements of indoor NO_2 during 1983-1988 (annual mean) ranged from 16 $\mu g/m^3$ to 43 $\mu g/m^3$ (with nitrogen dioxide source in household)	Cumulative incidence of LRS (one or more symptoms) with 30 $\mu g/m^3$ difference in NO_2: OR=1.4 (1.1-1.7) total OR=1.7 (1.3-2.2) girls OR=1.2 (0.4-1.5) boys	Adj for parental history of LRI education, single parent family status, measured levels of respiratory particles	Neas et al. (1991)
USA Ohio	Approximately 300 children 9-11 years	Industrial area Scholar mean NO_2 levels 54 and 37 $\mu g/m^3$ in high and low exposure areas	RR= 2.25 (p= 0.04) for wheezing dyspnea comparing high and low exposure areas	School year mean levels of SO_2 and TSP 77 and 55 $\mu g/m^3$ in high exposure area and 21 and 52 $\mu g/m^3$, respectively, in low exposure area	Mostardi et al. (1981)

Table 1 (cont.)

COUNTRY	NUMBER/AGE	EXPOSURE	RESULTS	COMMENTS	REFERENCES
USA Tennessee	pre-school children	Trinitrotoluene-plant Low exposure/high exposure area (NO_2 in $\mu g/m^3$): 24-hour 43/37-91 (mean) 75/120-333 (99-th percentile) 1-hour 43/27-94 (mean) 113/188-692 (99-th percentile)	Higher rate of acute respiratory disease in area of high exposure compared to low exposure area (RR ≈ 1.4, p=0.0004)	Adj for education, crowding, smoking by parents, paternal bronchitis. Mean TSP concentration exceeded 75 $\mu g/m^3$ in low exposure area.	Love et al. (1982)
USA Iowa	1355 children 6-12 years	Gas cooking	Hospitalisation for RI before age 2: RR=2.4 (p=0.001)	RR=9.25 (p<0.0006) gas+parental smoking.	Ekwo et al. (1983)
USA Pennsylvania	4071 children 5-14 years	Coal fired power plant Gas cooking stove. No NO_2 concentrations reported	No association between gas cooking stove and RI, RS or serious respiratory illness before 2 years of age.	Younger age, male sex, low socioeconomic status are independent risk factors for most RS and RI: significant trend for RI with number of current parental smokers	Schenker et. al (1983)
USA New Mexico	1205 infants followed until 18 months of age	Year round two week indoor NO_2 measurements Mean bedroom concentrations during winter were 40 $\mu g/m^3$ and 13 $\mu g/m^3$ in homes with gas and electric stoves, respectively	No association between indoor NO_2 concentrations and LRS. OR 0.91 (0.81-1.04) for LRS in homes with gas stove	Adjustment for season, age, sex, ethnicity, birth order, day care, income, maternal education, breast feeding, parental atopy and asthma and maternal symptom reporting	Samet et al. (1993)

Table 1 (cont.)

COUNTRY	NUMBER/AGE	EXPOSURE	RESULTS	COMMENTS	REFERENCES
Netherlands	128 children suffering from bronchitis, asthma frequent coughs and allergy, 103 controls aged 6 years	NO_2 levels in kitchen 144, living room 80, bedroom 50 and ambient air 45 µg/m^3	No clear associations between measured NO_2-exposure and RI, however, suggested excess OR:s for some symptoms such as persistent cough and asthma in relation to measured NO_2 levels in living rooms and bedrooms.	Adjusted for parental respiratory symptoms, indoor humidity, parental education, bedroom heating and maternal smoking	Hoek et al. (1984)
Netherlands	775 children 6-12 years	Weekly average NO_2 concentrations were about 20, 40 and 60 µg/m^3 in homes without kitchen geyser, with kitchen geyser and flue, and with kitchen geyser but no flue, respectively	LRS compared with 0-20 µg/m^3: 20-40 µg/m^3: RR= 0.84 (0.48 - 1.47) 41-60 " : RR= 0.83 (0.36 - 1.93) >60 " : RR= 0.96 (0.40 - 2.31)	Adjusted for home dampness, ETS exposure and parental education. Association with environmental tobacco smoke (ETS) RR=2.06 (1.6-3.66) and dampness RR=2.07 (0.94-4.55)	Dijkstra et al. (1990)
Japan	About 1500 schoolchildren 6-14 years	Outdoor air pollution Annual mean NO_2-concentrations 20 - 60 µg/m^3 in different study areas	Correlation between annual mean NO_2 concentration and wheezing in children with positive skin reaction to house dust extract ($p<0.01$), but not in children with negative skin reactions. Correlation for "subacute phlegm" in both skin reaction groups ($p<0.05$)	Air pollution from oil fired power station also included SO_2 and particulates	Kagamimori et al. (1986)
Israel	3374 second and fifth grade schoolchildren	NOx concentrations in ambient air. Hadera:6-10 ppb (monthly average) 37-128 ppb (max conc 30 minutes) Ashdod:8-33 ppb (monthly average) 38-528 ppb (max conc 30 minutes)	Ashdod compared with Hadera: RR=2.66 for asthma ($p=0.04$) RR=2.30 for bronchitis ($p=0.01$)	Adj for socioeconomic status, parental smoking and respiratory disease. Ashdod is an industrial polluted area and no distinction was made in the effect of different components (SO_2, NOx TSP etc.)	Goren and Hellmann (1988)

Table 1 (cont.)

COUNTRY	NUMBER/AGE	EXPOSURE	RESULTS	COMMENTS	REFERENCES
Switzerland	625 children 0-5 years	Annual average NO_2 levels were 47 and 51 $\mu g/m^3$ (outdoor) and 22 and 31 $\mu g/m^3$ (indoor) in the two cities under study	The duration of any respiratory episode was increased by 13% (95% CI 1-27%) per 20 $\mu g/m^3$ increase in outdoor NO_2 level. For indoor NO_2 the increase was 5 % (-5 - 16). Corresponding data for upper respiratory symptom incidence were 19% (-1 - 42%) (outdoor) and 3% (-11 - 18%) (indoor)	Total suspended particulate was a predictor of both respiratory symptom incidence and duration	Braun-Fahrländer et al. (1992)
Hong-Kong	362 primary schoolchildren 7-13 years	Personal sampling during two weeks: Mean concentration: 34.5 $\mu g/m^3$ boys. 35.7 $\mu g/m^3$ girls.	No association between NO_2-concentrations and LRS		Koo et al. (1990)
Sweden	199 children with hospital treated wheezing bronchitis or asthma and 351 population controls 4 month - 4 years	Outdoor air pollution, gas stove. Estimated time-weighted 99-percentile outdoor NO_2-level: 20 - 205 $\mu g/m^3$ in different study subjects (mean 55 $\mu g/m^3$)	LRI associated with estimated outdoor NO_2 exposure in girls (p=0.02), but not in boys. Gas stove in homes: RR=1.9 (0.7 - 5.0) in girls, 1.1 (0.5 -2.2) in boys.	Adjusted for asthma heredity and maternal smoking	Pershagen et al. (1995)

* LRI = Lower respiratory illness (bronchitis, asthma, pneumonia, chest illness)
\+ LRS = Lower respiratory tract symptoms (colds going to the chest, persistent cough, wheezing, breathlessness)
** OR = Odds ratio
\++ RR = Relative risk (range in parenthesis indicates 95% confidence interval)

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ABSTRACT
Estimates of exposure–response relationships are needed to assess the health impact of environmental factors. Based on available research evidence, the relationships for the common air pollutants – particulate matter, sulphur dioxide (SO_2), ozone and nitrogen dioxide (NO_2) – were reviewed by the Nordic Expert Meeting. The Meeting concluded by quantifying exposure–response relationships for particulate matter, SO_2 and ozone; the relationship for NO_2 was not quantified. The Meeting also identified other exposure–response relationships that were felt to be substantiated, but for which the available data did not provide sufficient background to quantify the risk. The reported concentration–response associations relate to short-term changes in risk due to changes in levels of pollutants. For chronic effects of prolonged exposures the data were judged to be insufficient for quantification.

NORWEGIAN TITLE

KEYWORDS		
Short-term health effects	Air pollution	Chronic health effects

ABSTRACT (in Norwegian)

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