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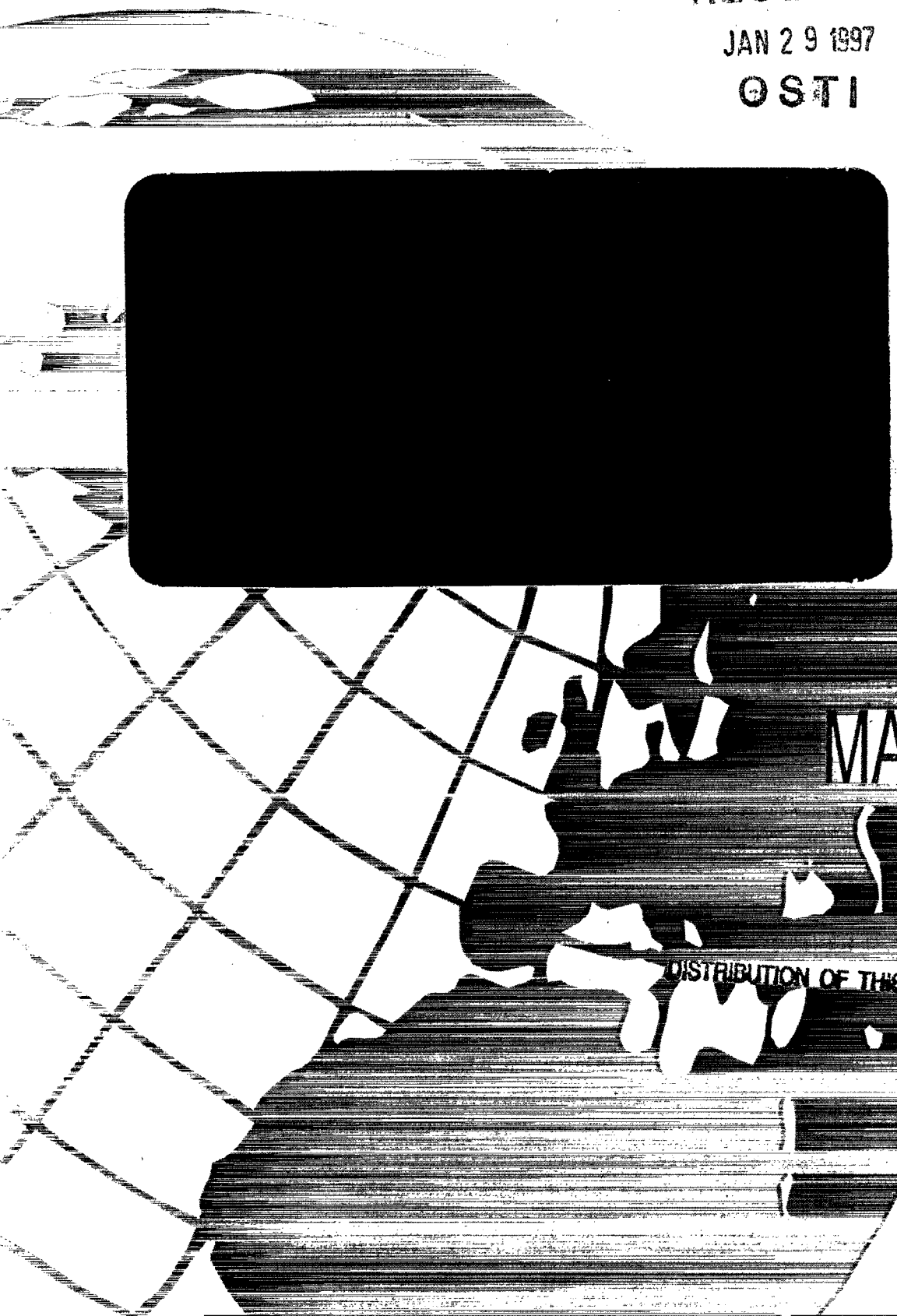



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# Exposure-Response Functions for Health Effects of Air Pollutants Based on Epidemiological Findings

by

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## Abstract

Quantitative knowledge about health damage due to air pollution is an important element in analyses of cost-effective abatement strategies, and it is also essential for setting Air Quality Standards. In this context epidemiological studies, in spite of the numerous problems and caveats connected to them, provide a sound basis for exposure-response functions, because they generally involve a random cross section of the population regarding sensitive subpopulations, age and gender, and also regarding personal exposure level relative to the average pollution level. The outdoor concentration levels, upon which epidemiological studies are often based, may be far from the actual exposure, but may probably in most cases serve as a reasonably good indicator of the relative pollution load. The exposure-response functions in this paper apply to the relation between air pollutant concentrations and relative effect frequencies, and involve the following health effect end-points: Reversible effects: *Acute* and *chronic respiratory symptoms* in *children* and *adults*; *asthma episodes* in *children* and *adults*; *eye irritations*; *headache*; and irreversible effects: *lung damage* in *children*; excess *mortality*; *lung cancer* incidence. The effects are attributed to one indicator component, which in many cases is *particles*, but for some effects $NO_2$, $SO_2$, $O_3$, or *CO*. A calculation procedure is suggested which makes it possible to estimate excess annual symptom-days for short-term effects using the annual average concentration.



*KEY WORDS*: Exposure-response functions; air pollution; health effects; excess symptom-days; epidemiology.

CONTENTS

## 1. INTRODUCTION

For centuries people have been aware of the association of air pollution and excess mortality and morbidity (see e.g. Brimblecombe, 1987). Much of the evidence has come from studies of associations between mortality rates and winter smog episodes, "the great stinking fogs" as it was called in London in the 17th century. Several scientists at that time were convinced that the polluted atmosphere took its toll of the lives of London citizens, and John Evelyn (1620-1706) drew attention not only to the increased death rates during pollution episodes, but also to the general decline in health that was brought about by the smoky atmosphere. As Brimblecombe notes in his book, Evelyn and his circle showed a particularly clear grasp of the risks air pollution posed for the well-being of the city, but, ironically, no use was made of their knowledge.

Since the mid-1960s a large relative and absolute decline in health status and life expectancy is seen in Eastern and Central Europe as compared to Western Europe. Lifestyle factors, as diet, abuse of tobacco and alcohol, are probably the main causes, but air pollution may also play an important role, up to ca. 10% (Faechem, 1994; World Bank, 1993).

Health risks due to exposure to air pollution comprise a continuum of effects, from harmless irritations to fatal effects. The specific symptoms in each individual are often determined by a combination of factors, e.g. genetic make-up, age, infant and childhood respiratory infections, general health status, tobacco smoke exposure, weather conditions, and occupational exposure (Euler et al., 1988)

Our efforts to reduce damage by air pollution are constrained by the economic resources, which, in turn, largely are based on economic activity giving rise to emissions from fossil fuel consumption. Thus, cleaner and more rational use of energy are important elements in risk reduction strategies. To enable decision-makers to develop cost-effective strategies, knowledge about the full marginal social costs of energy investment and utilisation is needed. Quantitative knowledge about health damage due to air pollution is an essential part of this (Seip et al., 1995; Aunan et al., 1995).

The objective of this paper is to provide exposure-response functions for health effects and air pollution, which can be used in analyses of the cost-effectiveness of different abatement measures. The functions apply to the relative collective risk associated with a change in concentration level, and make possible estimations of changes in average effect frequency in a population.

A rough, semi-quantitative, indication of the seriousness of the pollution situation as regards health effects can be obtained by estimating the number of people exposed to concentration levels above air quality guidelines (see e.g. Trønnes and Seip, 1988). Since these guidelines may vary considerably between countries depending on what criteria are used to define them, comparisons of such estimates should be interpreted with prudence. Whether the air quality guideline is based on a "no effect level" or a higher level, the prevalence of the effects will, however, increase in the population as the concentration rises above the guideline, and it is also shown that the exposure-response curves for some substances seem to continue below guideline levels as given e.g. by the World

Health Organization (1987) (see e.g. Schwartz et al., 1988; Sunyer et al., 1991; Schwartz, 1992; Brunekreef et al., 1995; Pope et al., 1995).

Urban air contains a mixture of components which contribute to a varying degree to the different effects. There are still large uncertainties as regards the relative and absolute contribution of the various components and which ones are appropriate indicator components for given effects. The multitude of variables that influence the prevalence of different health effects makes it very difficult to establish functions with a reasonable level of certainty. Besides, in many studies the statistical analysis focuses only on identifying statistically significant correlations between exposure and effects, instead of analyses that can be utilized in establishing exposure-response functions.

## 2. Some basic concerns within epidemiology, and the use of epidemiological findings in abatement planning

In this paper only exposure-response relations found in epidemiological studies are used, despite the large uncertainties these entail. In epidemiological studies some effects may be observed when the concentrations of individual components are considerably lower than levels observed to be associated with effects in clinical studies on humans. The reasons for this are not fully understood, but one reason is obviously that the more sensitive individuals do not participate in clinical studies. Synergism is probably also part of the explanation. Synergistic effects are shown to exist to various degrees between components as particles, $SO_2$, $NO_2$, $O_3$, CO, PAH and acid aerosols (SFT, 1992). Another part of the explanation may be that the personal exposure in epidemiological studies actually is higher than the ambient concentration levels indicate, as shown e.g. by Clayton et al. (1993). Thus, if functions from clinical studies are used to make estimates for a population, effects may generally be underestimated. Whether this is valid will, however, depend on the exposure assessment method used (see e.g. Vostal, 1994).

General concerns with epidemiological studies are misclassification of exposure, biases in the sample population, correlated variables (confounders) and omitted variables. When interpreting results from epidemiological studies it should be held in mind that the confidence limits only take into condsideration random variation in the data, not the systematic errors, the biases and confounders (see e.g. Taubes, 1995).

As regards the exposure assessment, outdoor concentrations are very often used as a measure of exposure or dose, giving an errors-in-variable problem. In addition to the fact that the dose is dependent on many other factors than outdoor concentrations, for instance activity level, the data on outdoor concentrations are often incomplete. Different measuring techniques pose a need for intercalibration, and because there are no standarized criteria for selection of monitoring sites, comparability of the absolute levels of measured pollutants is often questionable (Katsouyanni, 1995). Misclassification of exposure will result in a downward bias of the observed association between air pollution and health end-points (Roemer et al, 1993; Krupnick et al., 1990).

Even if a randomizing procedure is employed to choose the sample population, biases may arise if only parts of the sample are willing to participate. The people who do

participate could be different from those who don't, maybe in a health-related way (Taubes, 1995).

Correlation between variables occurs both for the different pollutants, and also between pollutants and other variables. For instance Buffler et al. (1980) point at the difficulty of statistically examining any independent contribution of air pollutants to lung cancer because socioeconomic status, and thereby smoking habits, diet and other lifestyle characteristics associated with lung cancer, are correlated with air pollution.

Omitted variables are generally only problematic if they are correlated with the pollution variables. Variables likely to be correlated are steps taken to avoid or mitigate health effects caused by pollution, like staying more indoors, avoiding heavy exercise and taking asthma medicine. Unobserved avoidance behaviour may cause the coefficients to be biased.

The great advantage of epidemiological versus experimental studies is the fact that effects are studied in a population with all degrees of susceptibility present, and even if the concentration levels measured may be far from the actual exposure, it may be a good indicator of the relative pollution load. Meta-analyses, analyses based on results from several studies by use of a formalized statistical technique, have become an important tool to establish exposure-response functions on a broader basis (Mann, 1990). It is a matter of course that the results are seen in the light of toxicological studies to ensure that assumed cause-effect relations are biologically plausible.

However, errors in the assumptions about causality do not necessarily imply that the functions are irrelevant when they are to be used in the context of ranking abatement measures. For instance Schwartz and Zeger (1990) showed a significant association between $NO_2$ and risk of eye irritation. As they stated, it seems more likely that this is due to the fact that $NO_2$ has a precursor role in the formation of PAN (peroxyacetyl nitrate), which is shown to be an eye irritant, rather than to a direct causality. In this case it does not matter which of the two components is the causal factor, actions should be taken to reduce emissions of $NO_x$.

In many cases there is a strong correlation between components, because they largely have the same sources. For instance in urban areas traffic is often a major source of pollution, but it may be very difficult to isolate the contributions of the different components (primary and secondary) to specific health effects that probably are induced by traffic pollution. However, even if a component chosen as indicator component for an effect is not a causal agent, this may not necessarily imply that estimated benefits from abatement measures are seriously wrong, unless the measures which are analysed are very specifically devised towards not causal components. (It may also lead to erroneous estimates if the indicator component and the causal agent are nonlinearly correlated).

These examples also underline one of the problems with transferring results from one study to a different location. For instance the composition of the car fleet in Western Europe and USA, where most of the epidemiological studies are performed, may differ substancially from that in other parts of the world. Extensive use of studded tyres in areas with cold winters is another factor which changes the traffic related pollution mixture. If the component in the exposure-response functions is not the causal agent, but

rather an indicator of the general traffic pollution, it may be less appropriate to use the function in another country. Other problems related to transferability are overall health status and age distribution in the population.

## 3. INDICATOR COMPONENTS FOR HEALTH EFFECTS

In the following the different effects are attributed to one component, primarily for pragmatic reasons. This implies that the chosen component is assumed to carry the full impact of an air pollution mixture.

There are strong indications that *particles* are a key agent for many effects, partly, but not solely, as a vector for other components. Particles constitute a polydisperse system and unlike most other air pollutants, such as $SO_2$, $NO_2$ and $O_3$, particles are not a specific compound, but a mixture of substances with significantly different health impacts. Both $SO_2$ and $NO_2$ participate in atmospheric reactions leading to formation of fine particles /aerosols and the association between health effects and these different components may therefore be difficult to disentangle.

A number of different particle mass measures are employed in different studies. This complicates an evaluation in terms of one single indicator component and is an obstacle for using any particle measure as indicator. Common measures are TSP (total suspended particles ), $PM_{10}$ (the thoracic fraction - the fraction most likely to pass the larynx and be deposited there - 50% collection efficiency cutoff at 10 μm aerodynamic diameter), $PM_{2.5}$ (the respirable fraction - the fraction most likely to reach the lung acinus and be deposited there - 50% collection efficiency cutoff at 2.5 μm aerodynamic diameter), black smoke (BS), and various measures of visual range and particle optical reflectance, e.g. Coefficient of Haze (CoH). While the coarser fractions (above 2.5 μm) most often have a basic pH and are derived from uncontrolled combustion and mechanical breakup of soil, asphalt etc., the fine fraction is often acidic and derived from fossil fuel combustion and biomass burning (Dockery and Pope, 1994). The fine fraction includes soot and acid-condensates and is about half carbon and half salts, mainly ammonium sulphates and ammonium nitrates. The carbon may have various organic chemicals, some of which may be mutagenic, adsorbed onto its surface (see e.g. Seaton et al. (1995) and references therein). Additionally, particles may contain heavy metals which may be involved in carcinogenic processes.

The different particle measures are usually highly correlated at the same location, but the correlation may have seasonal and meteorological variations. Particles in rural areas can have a substantially different size distribution compared to urban, because of more windborn dust with a larger share of coarser particles. To convert from TSP to $PM_{10}$ the factor suggested by EPA (1982) of 0.5-0.6 can be used in urban areas if no other data are given. The ratio BS/TSP is suggested to be from 0.55 (California Air Resources Board, 1982) to roughly one (given that the particle concentration is high) (EPA, 1984), but large variations with time and place make this relationship particularly uncertain. The $PM_{2.5}$ / $PM_{10}$ ratio is suggested to be 0.6, the CoH/$PM_{10}$ ratio is suggested to be 0.55 and the $SO_4^{2-}$/$PM_{10}$ ratio is suggested to be 0.25 (Dockery and Pope, 1994). It should be stressed that these ratios are based mainly on the situation in California and may differ from other areas.

Whereas the coarser fractions, up to as large as 100 μm, indeed are important for some upper airway effects, the finer fractions, below 10 μm, are assumed to be better indicators for airway effects in general and effects in the smaller airways and alveola in particular. However, often only TSP is measured and an exposure-response function for TSP is estimated, regardless of what kind of effect is looked at. TSP then acts as an indicator of $PM_{10}$ or some other particle related fraction, e.g. acid aerosols as discussed by Fairley (1990). According to a study by Özkaynak and Thurston (1987), particle measures related closely to the respirable fraction ($PM_{2.5}$) and/or the the toxic fraction (e.g. $SO_4^{2-}$) are even better predictors of health risks linked to mortality than both TSP and $PM_{10}$.

Particles, $SO_2$ and $NO_2$ are both chemically and biologically interrelated because the gases participate in the creation of particles, and because the components partly are associated with the same type of effects. $O_3$, on the other hand, is chemically more independent from reactions leading to particle formation and is partially associated with other types of effects, mainly in the lower respiratory system. In light of the consistent evidence for health impacts of $O_3$ independent from simultaneous exposure to particles, $O_3$ should be regarded as an indicator component in addition to particles. However, since $O_3$ formation depends on the concentration of $NO_2$, nitrate formation may be accelerated by $O_3$, and acidic components may potentiate the respiratory effects of $O_3$, this indicator is not fully independent of the particles/$SO_2$/$NO_2$ complex (see e.g. Lübkert-Alcamo and Krzyzanowski, in press).

The use of indicator components for cancer diseases is discussed in Section 5.8.

## 4. METHODOLOGIES USED IN EPIDEMIOLOGICAL STUDIES

Cross-sectional studies and cohort-studies are the two main epidemiological methods used in studies of air pollutants and health effects. In the first the relative increase in response is estimated from the prevalence of effects in e.g. cities and towns with significantly different concentration levels or in homes with or without gas stove. Most epidemiological evidence on effects of $NO_2$ comes from such indoor studies. These studies are best suited for studying medium- and long-term effects. Cohort-studies, which are generally more costly, have a time-series (longitudinal) design and the relative increase in response is estimated from how the prevalence of effects in a population varies during a time interval within which the concentration level varies. This method is particularly well suited for studying more acute effects. A third method, often applied in studies of cancer prevalence, is case-control, which involves investigating the exposure to pollution and other risk factors among a group with a particular type of disease compared to a control group.

Many epidemiological studies report the relative increase in the risk of experiencing an effect when going from one concentration level to a higher level, expressed as the relative risk, $RR = p_1/p_0$, or the odds ratio, $OR = p_1(1-p_0)/p_0(1-p_1)$, dependent on the regression model applied. $p_1$ and $p_0$ are the probabilities that a person has the effect, or

seen the other way, the average frequency (prevalence or incidence[1]) in a population, given a higher or lower concentration level, respectively. RR and OR are quite close if the risks concerned are small, as in most cases concerning air pollution effects due to ambient air pollution. As risks increase, OR will grow larger than RR.

Different mathematical models are used in the studies to approximate exposure-response relationships in a population. Many studies solely report the relative increase *within* the concentration range that is observed (or estimated), whereas in other studies a function assumed to be valid outside the range is adjusted to the data. Logistic regression models, which are discrete regression models well suited for 0-1 data (not effect - effect), are often applied in epidemiological studies of for instance respiratory effects (e.g. Schwartz et al., 1988; Dockerey et al., 1989; Schwartz and Zeger, 1990; Krupnick et al., 1990). A logistic function is given by:

$$f(x) = \frac{\exp(V)}{1+\exp(V)} \qquad \text{where} \qquad V(x) = \alpha+\beta x+\varepsilon$$

and $\alpha$ is the intercept of $V(x)$, $\beta$ is the regression coefficient, $x$ is the independent variable and $\varepsilon$ is the error component.

It is very difficult to demonstrate a specific no-effect level in a population by means of epidemiology. Clinical studies on humans may give indications of a threshold level, but the most sensitive individuals are, naturally, not represented in such studies. Air quality guidelines based on a no-effect level criterion may therefore merely give an indication of the level where, in simple statistical analysis, the role of air pollution is swamped by the background of much larger causal factors (see e.g. Waller and Swan, 1992). Concerning the exposure-response relation in a population the S-shaped curve is biologically more plausible than the "hockey stick" (threshold of zero response followed by a linear dose-response curve), because it reflects a normally distributed variation in susceptibility in a population (the logistic distribution is very close to the cumulative normal distribution). However, it is plausible that the response curve has a lower and upper cut-off.

Another feature of the logistic model, which makes it particularly attractive within epidemiology, is that the odds ratio is easily calculated:

$$OR_i = e^{\beta \Delta Ci} \tag{1a}$$

where $\beta$ is the regression coefficient and $\Delta C_i$ is the change in concentration. The same applies to Poisson regression, often used in studies of mortality rates and other low frequency events, where:

$$RR_i = e^{\beta \Delta Ci} \tag{1b}$$

[1] Prevalence is the percentage of the population which has the effect at any given point of time (point prevalence). Incidence is the percentage of the population for which a new episode of the effect occurs during a specific period. If a symptom has an average duration of 2 days, the average daily prevalence will be twice the average daily incidence.

Unlike the concept of *OR*, the *RR* function does not limit the probability of getting an effect (or the average frequency in a population) to a number between 0 and 1. This is, however, more of a theoretical than a practical problem, because the concentration levels in outdoor air are never so high that the predicted prevalence gets above 1.

Since $e^{\beta C} = 1 + \beta C + {}^1/_2 (\beta C)^2 .....$,

a *linear percent point increase in response* can easily be calculated to be

$1000\beta$ per 10 $\mu g/m^3$, if $\beta C << 1$.

When linearized functions are used there is a danger of biases by overestimating at lower concentrations and underestimating at higher. Within the concentration ranges usually observed in ambient air, however, nonlinearity in many exposure-response functions is often of little practical relevance.

Epidemiological studies focus on different end-points, that can be divided into two categories:

- *Biological end-points,* e.g. mortality or lost years of life, reduced lung function, prevalence of bronchitis, asthma attacks, and eye irritation. Biological end-points may be self reported or measured/reported by professionals.
- *Consequential end-points,* e.g. occupational and school absenteeism and hospital admissions (due to given health symptoms).

In connection with economic valuation of health damage due to air pollution, these categories have different advantages and drawbacks. Some of the biological parameters are assumed to be relatively reliable. This especially applies to measurements of changes in the lung function (CEC/US, 1993). The problem is that it is often difficult to predict the medical significance of these changes, e.g. in terms of affected physical capacity, respiratory morbidity and life quality (SFT, 1992). Consequential end-points, like emergency ward visits, are easier to assess in monetary units. On the other hand these parameters are highly dependent on social conditions, for instance access to and costs of these services. When results from one country are to be applied in another, these factors may imply great uncertainties. Studies reporting biological end-points are focused in the following. However, the relative response in the two categories of end-points should in many cases correlate.

## 5. EXPOSURE-RESPONSE FUNCTIONS FOR MAIN HEALTH END-POINTS

A number of different biological end-points are observed being associated with air pollutants. Classification of the different effects is a matter of balancing the need to define effect categories easily valuated in economic terms, and the need to render the information given in the studies as precisely as possible. (A summary of the exposure-response functions is given in Appendix.)

The following categories of health effects are focused here:

Reversible effects:
- Acute respiratory symptoms in children and in adults
- Chronic respiratory symptoms in children and in adults
- Asthma episodes in children and in adults
- Eye irritations
- Headache

Irreversible effects:
- Irreversible lung damage in children
- Excess mortality
- Cancer incidence

In addition to these effects an association between reduced pulmonary function and air pollutants is shown in many epidemiological studies (e.g. Moseler et al. 1994; Mohan Rao et al, 1992; Hoek and Brunekreef, 1994; Maeda et al. 1991/1992; Berry et al., 1991). Here reduced pulmonary function is not included as an effect category, because the medical consequences are unclear, as discussed above.

In some cases the studies do not provide exposure-response functions, but e.g. show a statistically significant variation in prevalence according to concentration levels. These are used to construct an OR function, assuming the data would fit a logistic curve. These functions are generally more uncertain than the others where coefficients are found by regression analysis, i.a. because possible co-variates and confounders are not considered.

### 5.1. Calculation procedures

The functions give relative increase in effect frequency, and not e.g. excess cases per population unit. This is because a relative estimate probably is more appropriate than an absolute when the function is to be employed in a new geographical context, where the frequency of the effects in question may be different for other reasons than air pollution. However, often one does not have data for background frequency of different symptoms and diseases. To make possible estimations of absolute changes in excess prevalence in such cases, an estimated *hypothetical zero-concentration prevalence,* denoted $p_0$, is estimated for each effect. These are calculated from the data for actual prevalence (or incidence rates multiplied with average duration) and concentration levels given in the studies, and are extrapolated down to zero concentration by use of the OR or RR functions. Data on prevalence may differ substantially depending on survey methodology, e.g. whether symptoms are self-reported or self-reported with subsequent clinical consultation (Norwegian Board of Health, 1991). This implies that prevalence figures should be employed with some discernment. The hypothetical zero-concentration prevalence is given by:

$$p_0 = \frac{p^{obs}(C_i)}{OR_i - OR_i \cdot p^{obs}(C_i) + p^{obs}(C_i)} \qquad (2a)$$

or

$$p_0 = \frac{p^{obs}(C_i)}{RR_i} \tag{2b}$$

where $OR_i$ and $RR_i$ are, respectively, the odds ratio and relative risk estimated (by use of the regression coefficient β) for an increase in the concentration level from zero to $C_i$, and $C_i$ is the concentration level at which the observed prevalence is $p^{obs}(C_i)$. The rationale for this procedure is that the observed prevalence to some extent is caused by air pollution.

For any concentration level, $C_i$, the prevalence, $p_i$, can be calculated:

$$p_i = \frac{OR_i \cdot p_0}{1 - p_0 + OR_i \cdot p_0} \tag{3a}$$

or

$$p_i = p_0 \cdot RR_i \tag{3b}$$

For *short-term health effects* the exposure-response functions given in the following are usually derived from the relation between daily mean concentrations, $C_i$, and the daily prevalence of the effects, $p(C_i)$. To estimate the annual number of symptom days ("person-days"), $S_{sum}$ , in a population $N$ one ideally should calculate the daily number of affected persons in the population and sum up over the year:

$$S_{sum} = \sum_{i=1}^{365} \left(p(C_i) \cdot N\right) = \sum_{i=1}^{365} \left( \frac{\exp(\beta \cdot C_i) \cdot p_0}{1 - p_0 + \exp(\beta \cdot C_i) \cdot p_0} \cdot N \right) \tag{4a}$$

or

$$S_{sum} = \sum_{i=1}^{365} \left(p(C_i) \cdot N\right) = \sum_{i=1}^{365} p_0 \cdot \exp(\beta \cdot C_i) \cdot N \tag{4b}$$

However, this procedure is time-consuming and in some cases one does not have data for daily means. An approximation of $S_{sum}$ can be obtained by using an estimated average prevalence as a function of the annual mean concentration, $\overline{C}_{ann}$. By doing this one assumes linearity in the response function around $\overline{C}_{ann}$ :

$$S_{averaged} = p(\overline{C}_{ann}) \cdot N \cdot 365 = \frac{\exp(\beta \cdot \overline{C}_{ann}) \cdot p_0}{1 - p_0 + \exp(\beta \cdot \overline{C}_{ann}) \cdot p_0} \cdot N \cdot 365 \tag{5a}$$

or

$$S_{averaged} = p(\overline{C}_{ann}) \cdot N \cdot 365 = p_0 \cdot \exp(\beta \cdot \overline{C}_{ann}) \cdot N \cdot 365 \quad (5b)$$

The difference between $S_{sum}$ and $S_{averaged}$ depends mainly on the linearity in the response function in the concentration range of concern and to some extent on the distribution of the daily concentration levels. The difference gets larger if large variations in daily $C_i$'s concur with a $\overline{C}_{ann}$ in a non-linear part of the curve. However, an approximate correction, which usually will be satisfactory, may be calculated if the standard deviations, *SD,* of the concentration levels are available or can be estimated. The correction factor, $C_f$, is given by:

$$C_f = \frac{p(\overline{C}_{ann} - SD) + p(\overline{C}_{ann} + SD)}{2p(\overline{C}_{ann})} \quad (6)$$

The adjusted number of symptom-days, $S_{adjust}$, is then given by:

$$S_{adjust} = S_{average} \cdot C_f \quad (7)$$

With the concentration levels and distributions usually found in ambient air, $S_{adjust}$ will be very close to $S_{sum}$, and considering other uncertainties connected to e.g. exposure assessment this procedure should provide a satisfactory approximation.

Finally, the number of excess symptom-days, $S_{excess}$, is calculated by subtracting the baseline number of symptom-days (calculated from $p_0$) from $S_{adjust}$.

**5.2 Acute and chronic respiratory symptoms**

Despite considerable research the last decades, the respiratory effects of long-term and short-term exposure to the prevalent pollutants still are only partially understood. Air pollution is in many cases not the most important cause of respiratory symptoms. Many symptoms are rather common, often have a viral etiology and may be associated with climatic conditions. On this background air pollution operates as a factor enhancing the susceptibility for infections and irritations, and prolonging and aggravating the symptoms.

A crucial question that yet has no generally agreed answer is what averaging times are appropriate for studying and predicting the effects. This may also vary among the different components and effects. Additionally, it may be that different exposures (component and concentration pattern) are associated with, respectively, *incidence rate* and *duration* of a symptom (Braun-Fahrländer et al., 1992; Schwartz, 1992). In the context of economic evaluation both are of interest. However, there is little consistent

evidence that justifies separating them[2], and often *prevalence* of effects is analysed instead.

One may distinguish between upper and lower respiratory symptoms (URS and LRS, respectively). The distinction is not quite clear, e.g. for cough, but generally symptoms as runny/stuffed nose, sneezing and sore throat is called URS, while e.g. wheeze, chest tightness, shortness of breath, and phlegm production are classified as LRS. In the following this distinction is not made.

*5.2.1 Acute respiratory symptoms in children:*

$SO_2$, $NO_2$, $O_3$, and particles have been shown to be associated with acute respiratory symptoms in children (e.g. cough, sore throat and runny nose) (SFT, 1992). Although the different components occurring together may intensify the total response, there seems to be some evidence that particles play a primary role. For instance, there are indications that associations between $NO_2$ and respiratory symptoms shown in some epidemiological studies may rather reflect confounding with particles (Braun-Fahrländer et al., 1992). In a study by Krupnick et al. (1990) particles (measured as CoH "coefficient of haze", a surrogate for fine particles) was the only air pollutant that remained significantly associated with respiratory symptoms in children (ozone, $NO_2$ and $SO_2$ were also measured). On the other hand, in a study by Charpin et al. (1988), $SO_2$, rather than particles, seemed to be related to symptoms in children. A study by Hoek and Brunekreef (1994) indicates weak associations between air pollutants and acute respiratory symptoms in children in an area with relatively low concentrations. The odds ratios for different symptom incidence rates estimated for a 50 $\mu g/m^3$ increase in $NO_2$ (lagged) were all larger than one, but the 95% CIs all contained OR<1.

In a study in Switzerland, Braun-Fahrländer et al. (1992), investigated the association between upper respiratory episodes (fever combined with sore throat and runny nose) in children (0-5 y of age) and different air pollutants. For an approximately 20 $\mu g/m^3$ increase in TSP (daily average) they found by logistic regression an OR of 1.10 (95% CI, 1.02-1.19) for upper respiratory symptom incidence rate. The daily TSP levels were in the range 20-100 $\mu g/m^3$. The study also gives account of how duration of symptoms is influenced by both TSP and $NO_2$. As an approximation it is here assumed that mean duration of upper respiratory illness and cough is 2 days.

Acute respiratory symptoms in children:

$OR=\exp(\beta \cdot C)$, where $\beta=0.00454$ (95% CI, 0.00113 - 0.00795) and C is given in $\mu g/m^3$ TSP (daily mean)

Hypothetical zero-concentration daily prevalence is 6.4% .

Another study from Switzerland (Rutishauser et al., 1990) indicates a significant increase in upper respiratory symptoms among children (0-5 y) exposed to higher outdoor $NO_2$ levels (6 weeks average). The number of symptoms per day and child increased with ca. 30% between those living in areas where $NO_2$ was lower than 30 $\mu g/m^3$ and those living

[2] An important reason why they are separated in some studies is that this serves as a method for avoiding the problem of serial correlation (the presence of an effect one day is a significant predictor of effect the next day) obscuring the relationship between the variables of interest (see eg. Schwartz et al., 1991).

where $NO_2$ was higher than 50 $\mu g/m^3$. The majority of the symptoms reported were less severe than in the above mentioned study. Particles were not measured. A lack of association between the indoor $NO_2$ level and respiratory symptoms, may indicate that the outdoor $NO_2$ association is confounded, or as suggested by the authors, that outdoor $NO_2$ rather is an indicator for the general pollution level. In the Braun-Fahrländer (1992) study a similar phenomenon is seen; outdoor $NO_2$ , and *not* indoor $NO_2$, is associated with respiratory symptom duration. Additionally, it showed that TSP (outdoor) was a more significant predictor of symptom duration.

In a study in five German cities Schwartz et al. (1991) showed, by Poisson regressions, an association between air pollution and daily counts of hospital/doctor visits due to *croup symptoms* in children. The study showed that a short-term increase in TSP and $NO_2$ levels from 10 $\mu g/m^3$ to 70 $\mu g/m^3$ was associated with a, respectively, 27% and 28% increase in cases of croup. Once again, however, a possible confounding between TSP and $NO_2$ was indicated. (Increased incidence rate of false croup has also been shown to be associated with $SO_2$, see SFT, 1992).

Taking into account that the relationship was strongest for TSP and assuming that croup symptoms generally imply that a doctor is contacted, and that the symptoms last for approximately two days, the following function for pseudo-croup prevalence is obtained:

Pseudo-croup in children:

RR=exp($\beta \cdot$ logC), where $\beta$=0.1244 (95% CI, 0.0638 - 0.1850) and C is given in $\mu g/m^3$ TSP (daily mean)

Hypothetical zero-concentration daily prevalence is $12.2 \cdot 10^{-6}$ of the total population.

The relationship is strongly non-linear in the concentration range normally seen, and a linear approximation should not be used.

*5.2.2 Acute respiratory symptoms in adults*

As for children, $SO_2$, $NO_2$, $O_3$, and particles are associated with different acute respiratory symptoms in adults (SFT, 1992). In studies reporting biological end-points the indications of particles being a primary component seem to be somewhat weaker than for acute symptoms in children. However, several studies reporting consequential end-points, e.g. school absenteeism, hospital admission, emergency room visits, asthma medication and restricted activity days, show that particles are significantly associated with these variables (e.g. Ransom and Pope, 1992; Pope, 1991; Sunyer et al., 1991; Ostro, 1987). A study by Ostro (1990) indicates that of the surrogate measures for particulate matter, sulphates appear to have the greatest association with acute respiratory morbidity.

A comprehensive study of acute respiratory symptoms in healthy young adults has been carried out in Los Angeles, an area with high ozone levels (Schwartz et al., 1988; Schwartz and Zeger, 1990; Schwartz, 1992), but unfortunately particles were not included in the study. Another study in the Los Angeles area (Krupnick et al., 1990) points at particles (measured as "coefficient of haze" CoH) and ozone as most

significantly related to presence of acute respiratory symptoms in adults[3]. This study also shows that among the four pollutants examined the highest correlation coefficients were found for $NO_2$ versus particles (0.84), thus indicating the possibilities for confounding between some particle related component and $NO_2$ in the studies by Schwartz and co-workers. This may also simply reflect the close interrelations within the particles/$NO_2$ /($SO_2$)-complex as discussed above.

To what extent $NO_2$ *per se* is an important causal agent or an indicator for traffic pollution is hard to tell based on the existing literature. In case it is just an indicator it is probably a good one, because of its close correlation to other components for which the experimental evidence for adverse effects may be stronger. The function given in Schwartz and Zeger (1990) for sore throat in healthy adults may therefore serve as a function for acute respiratory symptoms, even though it may underestimate the effects in the general adult population. Increase in risk of sore throat is 26% (95% CI, 18% - 35%) for an increase in $NO_2$ of 171 $\mu g/m^3$. The mean duration of the symptoms was 2 days.

Acute respiratory symptoms in adults:

OR=exp($\beta \cdot C$), where $\beta$=0.00136 (95% CI, 0.00098 - 0.00174) and C is given in $\mu g/m^3$ $NO_2$ (daily mean)

Hypothetical zero-concentration daily prevalence is 4.6%.

*5.2.3 Chronic respiratory symptoms in children*

It is more problematic to establish exposure-response function for chronic diseases than for acute effects, due to the fact that one ideally should distinguish between the possible influence of air pollution to development and thereby prevalence of the disease in itself, and to exacerbation of the symptoms. For instance asthmatics and others with hypersensitive airways are shown experimentally to be a vulnerable group as regards short-term elevated levels of some air pollutants, but there is sparse evidence as to whether air pollution contributes to the development of the disease. This could imply that asthmatics suffer more severely from their disease in highly polluted regions, even if the prevalence of the disease does not differ.

A complicating phenomenon sometimes seen in epidemiological studies is that asthmatics show less response than others to pollution episodes, probably due to preventative medication (Schwartz, 1992). In some studies medication is one of the investigated variables and is found to be significantly associated with air pollution (e.g. Pope et al., 1991 and Roemer et al., 1993).

Analyses of associations between symptom prevalence and long-term average concentration levels in cross-sectional studies are best suited for revealing a causal link between air pollution and chronic diseases. Longitudinal studies, though less apt to problems with confounding, must have a rather long time span to give this information (the US six-cities study is, however, an example of a long-term time-series cross-sectional study, see e.g. Ware et al. (1986), and Neas et al. (1990 and 1991).

[3] In this study "exposure-adjusted" concentration levels were used.

Chronic respiratory symptoms in children reported in epidemiological studies include illness frequency and symptom rates i.a. for bronchitis, asthma, chronic wheeze and cough, colds going to the chest and chest cough with phlegm, and are found to be associated with $NO_2$, particles and $SO_2$. (Possible long-term effects of ozone exposure are treated separately, and so is asthma, see below).

For prevalence of *bronchitis* the results given for $PM_{15}$ (50% collection efficiency cutoff at 15 μm aerodynamic diameter) in a cross-sectional study by Dockery et al. (1989) are used, in spite of the very broad 95% CI in the figures. By stratifying the data according to children with and without reported asthma or persistent wheeze, the authors show that approximately half of the response in the total sample is due to effects in the first group, although they make up only about 10% of the sample. The odds ratio for bronchitis is 2.5 (95% CI, 1.1 - 4.2) for a 39 $\mu g/m^3$ increase in the annual $PM_{15}$ concentration, which is the difference between the most polluted (59 $\mu g/m^3$) and least polluted (20 $\mu g/m^3$) city[4]. This corresponds to a logistic regression coefficient of 0.02368 (95% CI, 0.00246 - 0.04673). Assuming $TSP/PM_{15}$ and $TSP/PM_{10}$ ratios of 1/0.61 1/0.55 respectively (Özkaynak et al., 1985, Schwartz and Dockery, 1992a; see also Section 3) the following functions can be estimated:

Bronchitis in children:

$OR=\exp(\beta \cdot C)$, where $\beta=0.01445$ (95% CI, 0.00150 - 0.02851) and C is given in $\mu g/m^3$ TSP (annual mean)

or

$OR=\exp(\beta \cdot C)$, where $\beta=0.02629$ (95% CI 0.00273 - 0.05187) and C is given in $\mu g/m^3$ $PM_{10}$ (annual mean)

Estimated hypothetical zero-concentration prevalence is 3% of the children.

The relationship is strongly non-linear in the concentration level range commonly seen in urban air, and a linear approximation should not be used.

The OR for bronchitis in this study is close to the average OR for all chronic respiratory symptoms related to $PM_{15}$ with an OR >1. This function may therefore serve as an indicator of *chronic respiratory illness in children in general.* (Bronchitis, chronic cough, chest illness and persistent wheeze had an average OR=2.4 for a 39 $\mu g/m^3$ increase in $PM_{15}$, but only the bronchitis association was statistically significant).

As an alternative to the particle-associated relationship the results of a meta-analysis of several indoor air studies can be applied for estimating chronic respiratory illness in children (Hasselblad et al., 1992). If $NO_2$ concentrations are lower than TSP, as they often are in urban air, this function will give a lower effect estimate than the particle function given above. The analysis suggests an increase in the odds of respiratory illness in children of about 20% for a long-term increase in $NO_2$ of 30 $\mu g/m^3$, which is the presumed average increase in homes with unvented gas or kerosene appliances. The mean concentration may be 100 - 200 $\mu g/m^3$ in homes with such appliances, with the highest

[4] There are indications that the acidity of the aerosols would be more predictive of bronchitis in this study than just particles per se (Speizer, 1989).

short-term peaks occuring in the kitchen. The symptoms categorized as lower respiratory illness in the included studies varied, but in most cases had chronic features. They included colds going to the chest, chronic wheeze and cough, bronchitis, chest cough with phlegm and episodes of respiratory illness. If only the studies where $NO_2$ was actually measured were included, the increases in odds were 27% for an increase in $NO_2$ of 30 $\mu g/m^3$. However, here the relation as suggested by the authors (and the model-method giving the broadest 95% CI) is used to estimate a $\beta$, despite the indication that the odds ratio may be an underestimate:

Chronic respiratory symptoms in children:

OR=exp($\beta \cdot$ C), where $\beta$=0.0055 (95% CI, 0.0026 - 0.0088) and C is given in $\mu g/m^3$ $NO_2$ (annual mean)

*5.2.4 Chronic respiratory symptoms in adults*

A long-term effect which is important as a public health concern is the possibility that apparently reversible respiratory illness in childhood may lead to increased susceptibility for irreversible lung damage and prevalence of chronic respiratory diseases in adults (Gold et al., 1989; Glezen, 1989; Samet et al., 1983; Lebowitz and Burrows, 1977). However, this is difficult to take into account and epidemiological studies have not consistently demonstrated the risk of such effects due to long-term integrated exposure at levels seen in urbanized areas. Most studies of chronic effects are cross-sectional analyses of associations between prevalence of chronic symptoms, as for instance chronic cough, wheezing and phlegm, and e.g. annual average concentration levels. A study by Euler et al. (1988) indicates that TSP is more strongly associated with chronic obstructive pulmonary disease than ozone, $SO_2$ and $NO_2$, or it is the best *single surrogate* representing the mix of pollutants. (The study estimated relative risk of symptoms according to number of hours when various threshold levels were exceeded.)

A cross-sectional study among Japanese women by Maeda et al. (1991/1992) may be used to estimate exposure-response functions for chronic respiratory symptoms in adults. The reported average prevalence of chronic phlegm and chronic wheezing in three concentration zones, according to the distance from densely trafficked roads, is the basis for estimation of the odds ratio associated with certain increases in the concentration level. The symptom prevalence increased significantly with pollution level after controlling for age, smoking habits, type of heater etc. According to the previous discussions about particles as indicator component, the data for ambient concentration levels of TSP is used to indicate the exposure-response relation. Assuming a logistic function is appropriate, the following function is estimated:

Chronic respiratory symptoms in adults:

OR=exp($\beta \cdot$ C), where $\beta$=0.029 (estimated uncertainty interval, 0.015 - 0.054) and C is given in $\mu g/m^3$ TSP (annual mean)

Estimated hypothetical zero-concentration prevalence is 1.3% of the adult population.

Using the same calculation procedure for the $NO_2$-data (for which personal exposure was estimated), gives a $\beta$ of 0.024 (uncertainty interval, 0.018 - 0.029).

## 5.3 Asthma episodes

Concerning the frequency of acute asthma episodes, experimental and epidemiological studies have revealed that ambient air pollution contributes. Other important factors seem to be cold air, indoor air irritants and exposure to infections. A response to air pollution is seen both for extrinsic (atopic[5]) and intrinsic (non-atopic) asthma and there are indications of synergistic mechanisms between air pollution and antigens (e.g. pollen, house mites and organic compounds) (see e.g. Frøsig et al., 1993; SFT, 1992; and Berciano et al., 1989). There are indications that children are more affected by allergens and infections and adults are more sensitive to air pollutants (Bates et al., 1990 and Yoshida et al., 1976). A study by Berciano et al. (1989) among asthmatic children showed that while the slight form of asthma (type I) was more frequent in non-polluted areas, the severe forms (type II, III and IV) were more frequent in polluted areas.

Experimental studies have shown that asthmatics are a sensitive group as regards the respiratory effects of exposure to $SO_2$, particles and acid aerosols, and these associations are also confirmed by epidemiological studies. For $NO_2$ and $O_3$ the experimental evidence is somewhat less conclusive (see HMSO 1991 and 1993, and SFT 1992), even though there are some studies clearly indicating an increased sensitivity to $O_3$ in asthmatics, i.a. concerning acute inflammatory effects (Koenig, 1995). On the other hand, in some epidemiological studies strong associations between levels of $O_3$ as well as $NO_2$ and symptom rates for asthma are found. There are indications that the dose of allergen required for a given response in asthmatics (atopics) is reduced when there is a simultaneous exposure to $O_3$, maybe due to increased permeability (see McKee and Rodriguez, 1993 and references therein).

In Dockery et al. (1989) an increased annual level of $O_3$ of ca. 40 $\mu g/m^3$ were associated with an OR for asthma symptoms in children of 1.9 (95% CI 1.0 - 3.4). Pönkä (1991), showed by regression analysis that asthma problems (all ages) were most strongly correlated with NO and $O_3$, but also significantly with other components ($NO_2$, $SO_2$, CO and TSP). Whittemore and Korn (1980) also found a significant association between asthma attacks and $O_3$.

On the other hand, in the study by Roemer et al. (1993) $PM_{10}$ and $SO_2$, and not $NO_2$, was associated with asthmatic effects in a panel of children with chronic respiratory symptoms. Walters et al. (1994) show that particles, measured as BS, are a significant independent predictor of hospital admissions for asthma. However, $O_3$ and $NO_2$ were not included in the analysis.

### *5.3.1 Asthma symptoms in children*

A study of the relationship between prevalence of different chronic respiratory symptoms and air pollutants in Tokyo (see Kagawa, 1994) showed that asthmatic symptoms among children were significantly associated with $NO_2$ levels (the associations with $SO_2$ and TSP were less conclusive). Although no exposure-response function is given, the data may be used to estimate a function for *asthma symptoms in children*. By using the average prevalence for boys and girls (as surveyed by the Environmental Agency in Tokyo) in

[5] Specific allergens are identified.

relation to levels of $NO_2$ examined over 10 ppb intervals and assuming that a logistic function is appropriate, the following function is estimated:

Asthma symptoms in children:

OR=exp(β · C), where β=0.016 (uncertainty interval, 0.002-0.030) and C is given in μg/m$^3$ $NO_2$ (annual mean).

Estimated hypothetical zero-concentration prevalence of asthma symptoms among children is 2%[6].

The study by Pönkä (1991) does not provide an exposure-response function either, but using the same procedure as the above mentioned gave a somewhat lower coefficient for OR for the mean daily number of admissions with increasing $NO_2$ levels (β = 0.01). The indicated lower response in the total population as compared to the response in children seems reasonable.

*5.3.2 Asthma symptoms in asthmatic adults*

A function for asthma symptoms in asthmatic adults is estimated in a time-series study of Ostro et al. (1991). In this study the association between airborne acidity, measured i.a. as $H^+$, $SO_4^{2-}$, $SO_2$, $NO_3^-$, and $PM_{2.5}$, and daily asthma symptoms in a panel of asthmatics was investigated. Both a logistic regression model and an ordinary linear least square model (using the logarithm of the pollutant) were tested, the last one giving a slightly better fit. The analyses indicated that the hydrogen ion is the principal pollutant of concern. When the pollutants were investigated individually the only significant associations between an air pollutant and asthma symptoms were found for $H^+$ and $PM_{2.5}$. The results for the $PM_{2.5}$ relation did not change when exposure-adjusted measures were used, which is consistent with the fact that the penetration ratio of indoor to outdoor levels generally is high for the finer fractions of particles (Colome et al., 1992; Seaton, 1995).

The relationship between $PM_{2,5}$ and the incidence rate of asthmatics reporting a moderate or worse asthma day (i.e.daily prevalence, *p*) is given by:

$p = \beta \cdot \ln PM_{2,5}$ where β= 0.06 (95% CI, 0.001 - 0.119) and $PM_{2.5}$ is given in μg/m$^3$ (daily mean)

In light of the fact that this function applies to a group in the population where all are relatively sensitive compared to the general population, a logarithmic function seems plausible. Presupposing $PM_{2.5}$/TSP, $PM_{10}$/TSP, and BS/TSP ratios as indicated in Section 3 this function also corresponds well with two other studies using different particle measures as predictor of asthma episodes in asthmatics, namely Forsberg et al. (1993) and Whittemore and Korn (1980). The first is from an area with low levels (BS) and indicates a high regression coefficient and the other is from an area with high concentration levels (TSP) and indicates a much lower regression coefficient. When the odds ratios for a given range around the mean concentrations in the two studies are compared to the corresponding odds ratios estimated by using the logarithmic function,

[6] In Nordic countries the actual prevalence of asthma in children is probably in the range 3-6% (see Frøsig et al., 1993). Dockery et al. (1989) report a prevalence in the range 3-6% in six cities in USA.

they appear to be very close. The average daily incidence rates of asthma attack (or "severe shortness of breath") in the two studies are, respectively, approximately 20% and 27%. The corresponding figures, using the log function and the conversion ratios, would be 9% and 20%, thus indicating that the log function may slightly underestimate the response (of course the uncertainties in the conversion factors may also cause a discrepancy).

### 5.4 Eye irritations

Eye irritations are associated with photochemical air pollution, and are due to non-ozone components (SFT, 1992). In lack of dose-response functions for more plausible causal agents (e.g. PAN) and because monitoring data seldom are available for these, the function for $NO_2$ and eye irritation proposed by Scwartz and Zeger (1990) is chosen. The mean duration is 1 day:

Eye irritations:

OR=exp(β · C), where β=0.00085 (95% CI, 0.00058 - 0.00112) and C is given in $\mu g/m^3$ $NO_2$ (daily mean)

Estimated hypothetical zero-concentration daily prevalence is 3.2%.

### 5.5 Headache

Carbonmonoxide is found to be associated with headache (e.g. Schwartz et al., 1988 ; Schwartz and Zeger, 1990) and is also biologically a plausible agent, since hypoxia in general is associated with headache. Because automobiles are a main source of CO, some confounding with noise exposure is possible. It is also likely that there is a synergistic effect between the two.

In the study of student nurses by Schwartz and co-workers significant associations are shown and the function given in Schwartz and Zeger (1990) may be used. The mean duration is 1 day:

Headache:

OR=exp(β · C), where β=0.0109 (95% CI, 0.0066 - 0.0152) and C is given in $mg/m^3$ CO (daily mean)

Estimated hypothetical zero-concentration daily prevalence is 7.3%.

### 5.6 Chronic lung damage in children

Public health effect concerns for $O_3$ range from acute symptoms (e.g. cough), decreased lung function and impairment of immune defense, to permanent scarring of lung tissue (fibrotic changes), one factor in the development of chronic lung disease. There are large uncertainties about the extent to which lung tissue in children may be more sensitive to $O_3$ exposure than in adults. However, abnormal development of lung tissue in children would be particularly undesirable and could lead to a compromised respiratory condition later in life (McKee and Rodriguez, 1993 and SFT, 1992).

For numerous species the centriacinar region of the lung has been shown to be the location of maximum delivered $O_3$ dose and lung injury. There are indications that lesions and disease in this region may cause significant functional effects and may be a bellwether for later manifested lung disease for the general population (Sherwin, 1991).

A preliminary risk assessment based on expert judgments of prevalence of moderate lung lesion in children may be used to estimate a response function for chronic lung damage in children (McKee and Rodriguez, 1993). The expert judgements vary considerably, but as a rough average it seems reasonable to infer that the response rate for a seasonal concentration of about 100 $\mu g/m^3$ is in the range 15-40%. Assuming linearity from zero concentration, as an approximation, gives the following function for the prevalence (p) of moderate lung lesion, an appropriate indicator of potential chronic lung injury, and the long-term concentration of $O_3$:

$p = \beta \cdot O_3$ where $\beta = 0.0028$ (uncertainty interval 0.0015 - 0.0040) and $O_3$ is given in $\mu g/m^3$ (seasonal average)

**5.7 Excess mortality**

As noted in the introduction, increased mortality has for centuries been known to be connected to air pollution. Much of the evidence has come from studies of associations between mortality rates and winter smog episodes characterized by high particulate and $SO_2$ concentrations. However, publications also give account of associations between mortality rates and non-episode levels of pollutants and the basis for establishing exposure-response functions seems to be more firm for this effect than for numerous other air pollution health effects. Often the design of studies of air pollution and mortality is ecological, i.e. the basis is statistics on mortality and air pollution, and not detailed surveys of each individual case. This implies a limited possibility for control of confounders, e.g. smoking and indoor pollution, even though it sometimes is controlled for socioeconomic status.

Most studies suggest that particles and/or $SO_2$ are main agents (e.g. Wichmann et al., 1989; Derriennic et al., 1989; Katsyouyanni et al., 1990; Schwartz and Marcus, 1990; Krzyzanowski and Wojtyniak, 1991/1992; Schwartz and Dockery, 1992a and b; Schwartz, 1994) but $NO_2$, $O_3$ and CO have also been shown to be associated with mortality rates (see e.g. Saldiva et al., 1994; Kinney and Özkaynak, 1991; Hexter and Goldsmith, 1971).

Several studies suggest that the relationship between mortality and particles is more basic than mortality and $SO_2$ (e.g. Schwartz and Marcus, 1990; Schwartz and Dockery, 1992a and b; Dockery et al., 1992; Wichmann and Heinrich, 1995), and in search of an indicator component particles seem to be a good candidate. However, this may imply that mortality gets slightly underestimated if $SO_2$ concentrations are high compared to particles. In some areas one also may not have data for particles, only for $SO_2$. A separate, alternative function for $SO_2$ is therefore given below.

It has also been suggested that the acidity of the finer particle fractions is the main causal parameter, but this is being questioned by Brauer et al. (1995) in a study in former East Germany and the Czech Republic.

Many studies provide estimates for total excess mortality (deaths due to accidents and violence are excluded) and a variety of advanced disease states may predispose individuals to heightened susceptibility to premature death due to air pollution exposure. It is, however, obvious that the death rate increases much more among elderly as compared to the younger. It is also evident that death rates due to respiratory and cardiovascular failure increase relatively more than the total rate (Derriennic et al., 1989; Wichmann et al., 1989; Schwartz and Dockery, 1992a; Schwartz, 1994). Hitherto, the association between particles and cardiovascular deaths has not had any clear biological explanation. Seaton et al. (1995), however, suggest the hypothesis that ultra-fine particles (below about 100 nm in diameter), which are extremely abundant in urban air, are able to provoke alveolar inflammation and release of mediators capable of increasing blood coagulability, thus explaining cardiovascular deaths. Since cardiovascular failure is one of the most frequent causes of death, even a small increase in the rate has large implications.

A phenomenon seen in some studies of mortality, and which complicates an estimation of mortality by use of exposure-response functions, is the socalled "harvesting effect": In some cases one observes, even though a high pollution level prevails, a decrease in number of deaths after an increase associated with high pollution levels has been observed. This is assumed to be the result of the "pool of susceptibles" being depleted. The harvesting effect is assumed to be less pronounced in areas with lower concentration levels because the pool gets less depleted during pollution episodes (Wichmann and Heinrich, 1995). However, for instance in the study by Dockerey et al. (1992), where the $PM_{10}$ levels were rather low, this effect is seen for the association between death rate and the $PM_{10}$ concentration 4 days prior.

Quantitatively similar estimates for particles and mortality have been reported over a large range of concentrations, in a variety of communities, with varying mixtures of pollutants and different climatology. Most of the studies have a longitudinal design. The following functions are considered as a basis for the proposed functions:

Schwartz (1991):

$RR=\exp(\beta \cdot C)$, where $\beta=0.00055$ (95% CI, 0.00026 - 0.00083) and C is given in $\mu g/m^3$ TSP (daily mean)

Schwartz and Dockery (1992a):

$RR=\exp(\beta \cdot C)$, where $\beta=0.00066$ (95% CI, 0.00040 - 0.00092) and C is given in $\mu g/m^3$ TSP (daily mean)

For people > 65 year of age $\beta$ was 0.00091 (95% CI, 0.00059 - 0.00123), and for people <65 years of age $\beta$ was 0.00027 (95% CI, -0.00013 - 0.00068) in the TSP function.

New analyses of the Philadelphia data (Schwartz, 1994) confirm the relation between mortality and TSP, indicating a slightly higher $\beta$ of 0.00082 (95% CI, 0.00042 - 0.00121).

Schwartz and Dockery (1992b) (reported $PM_{10}$ /TSP= 0.51):

$RR=\exp(\beta \cdot C)$, where $\beta=0.00038$ (95% CI, 0.00022 - 0.00054) and C is given in $\mu g/m^3$ TSP (daily mean)

Dockery et al. (1992):

RR=exp(β ·C), where β=0.00150 (95% CI, 0.00015 - 0.00285) and C is given in μg/m$^3$ $PM_{10}$ (daily mean)

Pope et al. (1992):

RR=exp(β · C), where β=0.00147 (95% CI, 0.00086 - 0.00208) and C is given in μg/m$^3$ $PM_{10}$ (daily mean)

Considering both population sizes and t-values it is reasonable to give equal weight to these studies, and the following averaged function can be calculated (for those studies where the $PM_{10}$/TSP ratio is not reported it is assumed to be 0.55):

Total mortality:

RR=exp(β · C), where β=0.0007 (estimated 95% CI, 0.0003 - 0.0010) and C is given in μg/m$^3$ TSP (daily mean)

or:

RR=exp(β · C), where β=0.0012 (estimated 95% CI, 0.0006 - 0.0019) and C is given in μg/m$^3$ $PM_{10}$ (daily mean)

Using the relation between mortality risk for elder and younger found in Schwartz and Dockery (1992a) the following functions may be estimated:

Mortality (>65 y):

RR=exp(β · C), where β=0.0009 (estimated 95% CI, 0.0004 - 0.0014) and C is given in μg/m$^3$ TSP (daily mean)

or:

RR=exp(β · C), where β=0.0017 (estimated 95% CI, 0.0008 - 0.0026) and C is given in μg/m$^3$ $PM_{10}$ (daily mean)

Mortality (≤65 y):

RR=exp(β · C), where β=0.0003 (estimated 95% CI, 0.0001 - 0.0004) and C is given in μg/m$^3$ TSP (daily mean)

or:

RR=exp(β · C), where β=0.0005 (estimated 95% CI 0.0003 - 0.0008) and C is given in μg/m$^3$ $PM_{10}$ (daily mean)

The mortality rate in a population will of course depend very much on the age distribution. An indication about typical levels (in US cities) may be estimated from the larger of these studies. Estimated hypothetical zero-concentration daily mortality rate is estimated to be 25.1 per million. For the group≤65 y the number is 9.1 per million (total population) and for the group >65 y the corresponding number is 16.0 per million (total population).

A cross-sectional and longitudinal study by Dockery et al. (1993) indicates a much higher β than those given above. β can be derived from mortality-rate ratio to be 0.0085 (95% CI, 0.0027 - 0.0136) when C is given in μg/m$^3$ $PM_{10}$ (daily mean).

In a study in Cracow (Krzyzanowski and Wojtyniak, 1991/1992), where both particulate ($PM_{20}$) and $SO_2$ levels were rather high, a correlation between both $SO_2$ and particles

versus mortality was shown. When both components were included in the regression analysis only $SO_2$ remained significant. An increase of $SO_2$ concentration of 100 $\mu g/m^3$ was associated with a 9% increase in total mortality. In the study by Scwartz and Dockery (1992a), where the average $SO_2$ level was considerably lower than in Cracow, an increase of $SO_2$ concentration of 100 $\mu g/m^3$ was associated with a 5% increase in total mortality. Several other studies also indicate that $SO_2$ acting alone or as a surrogate for other sulphur-related species, is associated with increased risk of mortality, but most of the available studies do not provide exposure-response functions (US/ECE, 1992).

When data for particles are not available, or the $SO_2$ concentration is considerably higher than the particle concentration, the following function, based on Krzyzanowski and Wojtyniak (1991/1992), may be used to estimate excess total mortality:

Total mortality:

$RR=\exp(\beta \cdot C)$, where $\beta=0.0009$ (95% CI, 0.0006 - 0.0012) and C is given in $\mu g/m^3$ $SO_2$ (daily mean)

There are rather few studies on exposure-response relations for *infant mortality*. However, Bobak and Leon (1992) in a study in the Czech Republic use logistic regression to indicate the increase in risk ratio associated with certain intervals of the annual concentration of $PM_{10}$, $SO_2$ and $NO_2$. The association between postneonatal mortality (age 1month -1y), when adjusted for socioeconomic characteristics (on a district level), and an air pollutant component was stronger for $PM_{10}$ than for $SO_2$ and $NO_2$. The strongest association was found for postneonatal *respiratory* mortality and $PM_{10}$. The effect on neonatal (0-1 months) mortality was somewhat weaker, probably due to the fact that mortality in the first month is dominated by causes other than respiratory disease. Assuming that the weak association found for neonatal mortality is artificial and using the model where $PM_{10}$ carries the full impact of the pollution mixture, an exposure-response function for infant mortality (age 0-1 y) can be estimated from the data:

Infant mortality (0-1 y):

$OR=\exp(\beta \cdot C)$, where $\beta=0.014$ (estimated 95% CI, -0.001 - 0.029) and C is given in $\mu g/m^3$ $PM_{10}$ (annual mean)

Baseline infant mortality is highly dependent on several factors and a general applicable number can not be indicated. Using the data from the study, the estimated hypothetical zero-concentration infant mortality rate in this region is 4.7 pr. 1000 live births.

The study gives no basis for a corresponding function for $SO_2$ and total infant mortality. However, it is possible to estimate a function for infant respiratory mortality. The following function applies to situations where the annual $SO_2$-concentration is above ca. 35 $\mu g/m^3$ (below this level a positive association was not found):

Infant respiratory mortality (0-1 y):

$OR=\exp(\beta \cdot C)$, where $\beta=0.024$ (estimated 95% CI, 0.001 - 0.044) and C is given in $\mu g/m^3$ $SO_2$ (annual)

Using the data from the study the estimated hypothetical zero-concentration infant respiratory mortality rate in this region is 0.22 per 1000 live births.

### 5.8 Lung cancer incidence rate

Despite the fact that epidemiological studies provide evidence on presence and magnitude of cancer risks in humans, the approach has serious limitations. Development of cancer is a multistage event for which the effects pertain to exposure during years or decades. E.g. for lung cancer the latency time is of the order of 30 years, thus it may not be possible to resolve exposure-response relationships conclusively by epidemiology. Nevertheless, the strongest epidemiological evidence for an effect of air pollution on cancer is seen for lung cancer, which will be focused in the following.

Comparisons of urban and rural dwellers indicate that the risk for lung cancer (adjusted for smoking) is higher by a factor around 1.5-2 in urban areas in the western Europe and USA, and generally higher in men than in women (Godish, 1991; Hemminki and Pershagen, 1994). This implies that at least one third of the cases among urban dwellers are attributable to being an urban dweller (the attributable risk is 33.3%). The extent to which air pollution contributes to this excess is unknown, but it is far less than for smoking. A study by Buffler et al. (1980) indicates that air pollution, measured as TSP, accounted for 3% of the total variation in intraurban lung cancer mortality among men in Texas, being responsible for an excess of 1.9 deaths per 100.000 when the long-term concentration increases from 63 $\mu g/m^3$ to 79 $\mu g/m^3$. Their model included a number of sociodemographic factors in addition to age and smoking indexes, and overall explained 21% of the total variations in lung cancer mortality.

Many studies indicate a multiplicative rather than an additive interaction between smoking and air pollution (see the survey of cohort and case-control studies by Hemminki and Pershagen, 1994). This may partly be explained by stimulatory effects of particularly $NO_x$, but also $SO_2$, on the conversion of various carcinogens to their reactive intermediates (Constantin et al., 1994) due to inflammatory processes. Additionally, $NO_2$ is involved in processes in the atmosphere where the mutagenicity of incompletely combusted hydrocarbons may be increased by conversion to e.g. nitrated PAH-compounds (see Nishioka and Lewtas (1992) and references therein). These mechanisms strongly indicate synergistic interactions between urban air carcinogens and $NO_x$ (and to some extent $SO_2$), in terms of atmospheric chemistry as well as in a biological sense.

Ozone has also been suggested to be a potential carcinogen. However, the scanty information currently available does not suggest that exposure to ambient levels represents a significant hazard in this respect (HMSO, 1991).

Generally, most of the mutagenicity in urban air originates from incomplete combustion, with road traffic and residential home heating as major sources, and important components are i.a. polycyclic aromatic compounds, ethene, propene, butadiene and other alkenes, benzene, formaldehyde and acetaldehyde (see e.g. Törnquist and Ehrenberg, 1992). Since air quality data for these substances in most cases are rare, indicator substances may be useful in cancer risk estimations. Boström et al. (1994) discussed the use of $NO_x$ as a tracer and estimated the relationship between $NO_x$ and several genotoxic substances in Sweden. Since polyaromatic substances adsorbed onto particles emitted from incomplete combustion probably make a major contribution to

human cancer risk (Lewtas et al., 1992), particles (preferably the finer fractions) could possibly also serve as an indicator component. The mutagenic activity of particles may, however, vary considerably depending on the sources (see e.g. Maeda et al., 1991/1992).

In western countries, the effects of air pollution on lung cancer risk have been difficult to identify and disentangle from the effects of smoking and occupational exposure. However, in countries as for instance Poland and China, where very high levels of air pollution provide a wider range of exposure over which to evaluate exposure-response trends, estimates may be given. In China a distinct geographical gradient of lung cancer mortality is found, associated with i.a. industrial activity and atmospheric pollution levels (Xu et al., 1989).

A case-control study by Jedrychowski et al. (1990) in Cracow, an area with very high pollution levels, gives estimates of how air pollution, measured by particles and $SO_2$ (which were strongly correlated), may increase the relative risk of lung cancer death. It also indicates that air pollution acts multiplicatively together with the much larger risk factors smoking and industrial exposure. It was estimated that 4.3% of the lung cancers in men and 10.5% in women were attributable to air pollution. By use of a multiple logistic model the OR for the "high" pollution level (TSP >150 $\mu g/m^3$ *and* $SO_2$ >104 $\mu g/m^3$) compared to the "low" pollution level (TSP <150 $\mu g/m^3$ *and* $SO_2$ <104 $\mu g/m^3$) was estimated to be 1.46 (95% CI, 1.06 - 1.99) for men. For women an OR of 1.17 (95% CI, 0.71 - 1.96) was estimated for the "medium" (TSP >150 $\mu g/m^3$ *or* $SO_2$ > 104 $\mu g/m^3$) and "high" pollution level together, as compared to "low". The reason for the lower OR for women is, in addition to the somewhat smaller concentration difference between the compared groups, probably less smoking and occupational exposure (hence the multiplicative effect is less pronounced). Assuming that TSP may serve as an indicator component, and that lung cancer cases are proportional with lung cancer deaths, the following functions may be obtained. The estimated 95% CIs are uncertain, due to the fact that the real average concentration level ranges are uncertain. It is assumed that the difference in average TSP concentration associated with the above given odds ratios for men and women are 50 $\mu g/m^3$ and 45 $\mu g/m^3$, respectively. The function only provides a very rough estimate of relative risk:

Lung cancer incidence rate (men):

$\exp(\beta \cdot C)$, where $\beta$=0.0076 (estimated 95% CI, 0.0012 - 0.0138) and C is given in $\mu g/m^3$ TSP (long-term)

Lung cancer incidence rate (women):

$\exp(\beta \cdot C)$, where $\beta$=0.0035 (estimated 95% CI, -0.0079 - 0.0150) and C is given in $\mu g/m^3$ TSP (long-term)

Averaging the functions could give an indication of a function for a general population where multiplicative interaction with smoking and occupational exposure takes place for parts of the population:

Lung cancer incidence rate:

$\exp(\beta \cdot C)$, where $\beta$=0.006 (estimated 95% CI, -0.003 - 0.014) and C is given in $\mu g/m^3$ TSP (long-term)

The data do not allow any estimation of hypothetical zero-concentration lung cancer incidence rate. Background incidence rate in western populations is estimated to be 300 lung cancer (male and female) /year/$10^6$ (see Hemminki and Pershagen, 1994).

## 6. Conclusions

The atmosphere is a dynamic system, and the concentrations of different air pollutants may vary considerably over the day, month and year, depending on source variability and climatic conditions. The extent to which people inhale the air pollutants also varies considerably, depending on where they stay and their level of activity. In the context of making decisions about abatement measures, the potential for reductions in public health effects on an averaged level is an important element. Epidemiology provides a sound basis for such estimates because these studies generally study a random cross section of the population regarding sensitive subpopulations, age and gender, and also regarding personal exposure level during the studied time period. The outdoor concentration levels, upon which epidemiological studies are often based, may be far from the actual exposure, but probably serve as a reasonably good indicator of the relative pollution load, unless there are important widespread indoor or occupational pollution sources.

Because the different air pollutants often contribute to the same type of effects, and there often are uncertainties about their relative contribution, it may be wise to choose indicator components. These are single surrogates for a mixture of components. In an exposure-response function they are, as an approximation, assumed to carry the full impact on the health effects of this mixture. Concerning a number of health end-points, particles probably may serve as an indicator. However, since particles are such a diverse air pollution component, it becomes particularly important to use reliable and comparable methods for sampling and analyses. In modeling of particle pollution health effects and measures to reduce particle concentrations in ambient air it is important to consider source information and thereby particle distribution and composition of the particles.

Even though estimates of health effects based on exposure-response functions inherently will be uncertain, there is no doubt that these effects play a significant role in cost-benefit analyses of abatement measures.

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Appendix. Summary table of exposure-response functions for health effects.
OR or RR = $e^{\beta \cdot C}$, β: regression coefficient, C: concentration level.

| Health end-point | Relative risk model | β (95% CI) | C unit (averaging time) | $p_0$[1] |
|---|---|---|---|---|
| *Acute resp. symptoms:* | | | | |
| Acute URS, children | OR | 0.0045 (0.0011 - 0.0080) | $\mu g/m^3$ TSP (daily) | 0.064 |
| Pseudocroup, children | RR | 0.1244 (0.0638 - 0.1850) | log $\mu g/m^3$ TSP (daily) | 0.0000122 |
| Acute URS, adults | OR | 0.0014 (0.0010 - 0.0017) | $\mu g/m^3$ $NO_2$ (daily) | 0.046 |
| *Chronic resp. symptoms:* | | | | |
| Chronic RS, children | OR | 0.0145 (0.0015 - 0.0285) | $\mu g/m^3$ TSP (annual) | 0.03 |
| *or* | OR | 0.0055 (0.0026 - 0.0088) | $\mu g/m^3$ $NO_2$ (annual) | |
| Chronic RS, adults | OR | 0.029 (0.015 - 0.054)[2] | $\mu g/m^3$ TSP (annual) | 0.013 |
| *Asthma:* | | | | |
| Symptoms, children | OR | 0.016 (0.002 - 0.030)[2] | $\mu g/m^3$ $NO_2$ (annual) | 0.02 |
| Symptom incidence, asthmatic adults | Absolute[3] | 0.06 (0.001 - 0.119) | $\mu g/m^3$ $PM_{2.5}$ (daily) | |
| *Chronic lung damage:* | | | | |
| Children | Absolute[4] | 0.0028 (0.0015 - 0.0040)[2] | $\mu g/m^3$ $O_3$ (seasonal) | |
| *Other effects:* | | | | |
| Eye irritations, adults | OR | 0.0009 (0.0006 - 0.0011) | $\mu g/m^3$ $NO_2$ (daily) | 0.032 |
| Headache, adults | OR | 0.0109 (0.0066 - 0.0152) | $mg/m^3$ CO (daily) | 0.073 |
| *Mortality:* | | | | |
| Total mortality | RR | 0.0007 (0.0003 - 0.0010)[2] | $\mu g/m^3$ TSP (daily) | 0.0000251 |
| *or* | | 0.0009 (0.0006 - 0.0012 | $\mu g/m^3$ $SO_2$ (daily) | 0.0000218 |
| >65 y | RR | 0.0009 (0.0004 - 0.0014)[2] | $\mu g/m^3$ TSP (daily) | 0.0000160 |
| <65 y | RR | 0.0003 (0.0001 - 0.0004)[2] | $\mu g/m^3$ TSP (daily) | 0.0000091 |
| Infant mortality (0-1 y) | OR | 0.014 (-0.001 - 0.029)[2] | $\mu g/m^3$ $PM_{10}$ (annual) | see text |
| *or* | | | | |
| Infant resp. mortality | OR | 0.024 (0.001 - 0.044) | $\mu g/m^3$ $SO_2$ (annual) | see text |
| *Lung cancer* incidence | OR | 0.006 (-0.003 - 0.014) | $\mu g/m^3$ TSP (long-term) | 0.0003 per y |

[1] Hypothetical zero-concentration prevalence, see Section 5.1.
[2] Estimated uncertainty interval
[3] Daily incidence = β•lnC
[4] Prevalence = β•C

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