EFFECTS OF AIR POLLUTION ON CHILDREN'S HEALTH AND DEVELOPMENT

WORLD HEALTH ORGANIZATION
EUROPE

A REVIEW OF THE EVIDENCE

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WORLD HEALTH ORGANIZATION

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ABSTRACT

Concerns about the adverse effects of air pollution on children's health and development are important determinants of environmental and public health policies. To be effective, they must be based on the best available evidence and research. This book presents an assessment of research data gathered over the last decade, and provides conclusions concerning the risks posed by ambient air pollutants to various aspects of children's health. The authors of this evaluation, constituting a WHO Working Group, comprise leading scientists active in epidemiology, toxicology and public health. They summarize research into the effects of air pollution common in contemporary European cities on infant health, the development of lung function, childhood infections, the development and severity of allergic diseases (including asthma), childhood cancer and neurobehavioural development. On all of these health issues, the Working Group formulates conclusions regarding the likelihood of a causal link with air pollution

FOREWORD

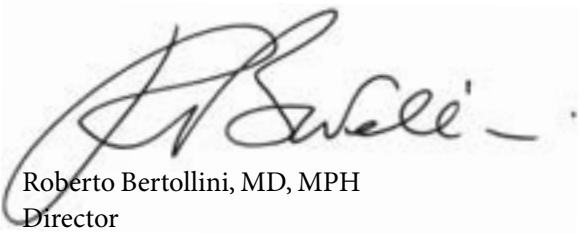
Few things are as precious as our children's health. Protecting children's health and environment is an essential objective for the health policies of any modern society, and is also crucial to sustainable development. European Member States of WHO made clear their commitment to this issue at the Fourth Ministerial Conference on Environment and Health, held in Budapest in June 2004, when they adopted the Budapest Declaration and the Children's Environment and Health Action Plan for Europe. Reducing the adverse effects of air pollution on children's health is one of the four priority goals on which Member States have pledged to take action.

This presents policy-makers and researchers with an extraordinary challenge. To be effective, measures must be based on accumulated evidence from research and must focus on the factors that affect children's health. However, the complexity of exposure patterns, changes in the vulnerability of children at various stages of prenatal and postnatal development, and practical limitations to research mean that understanding of the impacts of air pollution on children's health is still incomplete. Research to reduce this gap in knowledge is conducted by various scientific disciplines in various countries, and is not often readily accessible to policy-makers.

One of WHO's role is to evaluate the accumulated scientific evidence and prepare a synthesis on which Member States can base their policies. This monograph is one of the products of the WHO project entitled "Systematic assessment of health aspects of air pollution in Europe", which underpins the development of the Clean Air for Europe programme of the European Commission.[1] The evaluation of the effects of air pollution on children's health and development was prepared by a group of leading scientists active in epidemiology, toxicology and public health in Europe and North America. We are grateful for their contributions and their involvement in this process which allowed clear conclusions to emerge from the complex evidence spread across hundreds of studies and research reports produced worldwide each year. Although the evaluation indicates that numerous issues require further research, it also points to the sound evidence that already exists indicating a causal link between air pollution and children's health. Air pollution affects children as early as the prenatal period, affecting lung development and increasing the risk of infant death. Air pollutants at concentrations common

[1] The "Systematic Review of Health Aspects of Air Pollution in Europe" project was partially supported by European Community grant agreement 2001/321294.

in European cities can aggravate respiratory infections, which are a primary cause of morbidity and death in young children. Moreover, traffic-related air pollution affects lung growth rates. These conclusions provide strong arguments for policy-makers, legislators, administrators and all citizens to reduce air pollution and prevent its harmful influence on children's health and development.



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EXECUTIVE SUMMARY

The accumulated evidence indicates that children's health is adversely affected by air pollution levels currently experienced in Europe. This report reviews and summarizes the results of the most recent research and presents an assessment and evaluation of the strength of evidence for different health outcomes.

This review has been conducted within the scope of the project "Systematic review of health aspects of air pollution in Europe", implemented by the WHO Regional Office for Europe in support of air pollution policy development in Europe, and in particular of the European Commission's Clean Air for Europe (CAFE) programme. Based on the epidemiological and toxicological literature, mainly that published during the last decade, experts invited by WHO prepared synthesis papers. These were externally reviewed and subsequently discussed at a Working Group meeting. The meeting provided a consensus assessment of the strength of the evidence concerning the links between various health outcomes and air pollution. The review considered factors affecting children's susceptibility to air pollution, effects on pregnancy outcomes, infant and childhood mortality, lung function development, asthma and allergies, neurobehavioral development and childhood cancer. The authors were asked to provide conclusions as to the likely causality of observed associations with air pollution, according to a multilevel scale: (*a*) evidence sufficient to infer causality; (*b*) evidence suggestive of causality; (*c*) evidence insufficient to infer causality; and (*d*) evidence showing no association.

The special vulnerability of children to exposure to air pollution is related to several differences between children and adults. The ongoing process of lung growth and development, incomplete metabolic systems, immature host defences, high rates of infection by respiratory pathogens and activity patterns specific to children can lead to higher exposure to air pollution and higher doses of pollutants reaching the lungs. The efficiency of detoxification systems exhibit a time-dependent pattern during prenatal and postnatal lung development that in part accounts for the increased susceptibility of young children to pollutants at critical points in time.

The review highlights concern about the longer-term implications of lung injury during childhood. Exposure of the developing lung to air pollution reduces the maximal functional capacity achieved as the child enters adulthood, and thus reduces the functional reserve. This could lead to enhanced susceptibility during adulthood to the effects of ageing and infection as well as to other pollutants, such as tobacco smoke and occupational exposures.

Some children are more susceptible than others. Individuals with underlying chronic lung disease, particularly asthma, are potentially at greater risk than those not having such conditions. Polymorphic variation in genes involved in protecting against tissue injury or regulating tissue repair may explain some of the variation in individual susceptibility to the adverse effects of pollutants on health. Furthermore, patterns of exposure to indoor pollutants vary among children; those receiving higher exposures indoors, for example from tobacco smoke, are at greater risk of being affected by outdoor pollutants.

There is now substantial evidence concerning adverse effects of air pollution on different pregnancy outcomes and infant health. The evidence is sufficient to infer a causal relationship between particulate air pollution and respiratory deaths in the post-neonatal period. The evidence is suggestive of causality for the association of birth weight with air pollution, although further studies are needed. For preterm births and intrauterine growth retardation, the current evidence is insufficient to infer a causal relationship. Molecular epidemiological studies suggest possible biological mechanisms for the effect on birth weight, premature birth and intrauterine growth retardation, and support the view that the relationship between pollution and these pregnancy outcomes is genuine. For birth defects, the evidence so far is insufficient to draw firm conclusions. In terms of exposure to specific pollutants, evidence is strongest for the relationships between particulates with infant deaths. Otherwise, the existing evidence does not allow precise identification of the specific pollutants and the timing of exposure that can result in adverse pregnancy outcomes.

Evidence is sufficient to infer a causal relationship between exposure to ambient air pollutants and adverse effects on lung function development. Both reversible deficits of lung function and chronically reduced lung growth rates and lower lung function levels are associated with exposure to air pollution, with clearer relationships for particulates and traffic-related air pollution (indicated by nitrogen dioxide). Findings of various population-based studies are supported by animal exposure studies, indicating that intrauterine as well as postnatal exposures to pollutants can lead to impaired lung growth.

The available evidence is also sufficient to assume a causal relationship between exposure to air pollution and aggravation of asthma (mainly due to exposure to particulate matter and ozone) as well as a causal link between increased prevalence and incidence of cough and bronchitis due to particulate exposure. There is little evidence for a causal association between asthma prevalence/incidence and air pollution in general, though the evidence is suggestive of a causal association between the prevalence/incidence of asthma symptoms and living in close proximity to traffic.

A significant body of evidence supports the explanation that much of the morbidity and mortality related to air pollution in children occurs via interactions with respiratory infections, which are very frequent among children. Evidence

suggests a causal relationship between exposure to ambient air pollution and increased incidence of upper and lower respiratory symptoms (many of which are likely to be symptoms of infections).

Recent studies suggest that pollutants can enhance allergic sensitization in those genetically at risk, lending plausibility to the role of potentially injurious effects of ambient air pollutants in the causation of paediatric lung disease, including asthma. The possible mechanisms of these effects need further research.

There is evidence of adverse effects of environmental contaminants, such as certain heavy metals and persistent organic pollutants, on the development of the nervous system and behaviour in children. There is sufficient evidence of a causal relationship between exposure to lead, indicated by blood lead levels of 100 μg/l and lower, and neurobehavioral deficits in children. There is evidence suggestive of a causal link between adverse health effects and exposure to mercury and to polychlorinated biphenyls/dioxins at current background levels in industrialized European countries. Concerning the effects of manganese, more studies are needed before any firm conclusions can be reached. Although inhalation is typically not the main route of exposure to these contaminants, their emission to the air and their atmospheric transport constitutes an important source.

Accumulated epidemiological evidence is insufficient to infer a causal link between childhood cancer and the levels of outdoor air pollution typically found in Europe. However, the number of available studies is limited and their results are not fully consistent. Future studies, considering exposure during different periods from conception to disease diagnosis, may help to support a clearer conclusion about the role of childhood exposures to air pollution in causing cancers in both childhood and adulthood.

There are, as yet, relatively few studies evaluating the effects of reduced air pollution on children's health. Nevertheless, those that exist show that reduced exposure to air pollutants can lead to a decrease in hospital admissions for respiratory complaints, a lower prevalence of bronchitis and respiratory infections, and improvements in impaired lung function growth rates. The results provide some direct evidence that reducing exposures to air pollution will improve children's health.

Relative risk estimates for the health outcomes reviewed are generally small. Nevertheless, owing to the widespread nature of the exposure and the relatively high incidence of many of the relevant outcomes, the population attributable risks are high, i.e. the amount of ill-health attributable to air pollution among European children is high. More research is needed to clarify the role of specific air pollutants on children's health, as well as their interactions with other environmental insults such as respiratory virus infection or allergen exposure, with specific genetic factors affecting susceptibility and with diet. Such studies will require a careful monitoring of the environment to allow more precise exposure assessment, as well as a better understanding and consideration of host susceptibility.

While recognizing the need for further research, current knowledge on the health effects of air pollution is sufficient for it to be strongly recommended that children's current exposure to air pollutants be reduced, particularly in regard to traffic-related pollutants. The experts who conducted this review consider that such reductions in air pollution levels will lead to considerable health benefits in children.

INTRODUCTION

Michal Krzyzanowski, Birgit Kuna-Dibbert

BACKGROUND

Concerns about children's health and the factors that affect it are important determinants of health policies. In particular, policies that aim to prevent the adverse effects of environmental factors on health consider children as the population group that deserves the highest level of protection. High-level international policy documents, such as the declarations of the Ministerial Conferences on Environment and Health convened in London in 1999 and Budapest in 2004, highlight this concern *(1,2)*. The Budapest Conference also adopted the Children's Environment and Health Action Plan for Europe, which formulates actions aiming to prevent and reduce the burden of environment-related diseases in children in the WHO European Member States *(3)*. Reduction of the adverse effects of air pollution on children's health, and in particular on the occurrence of respiratory disease, is one of the four regional priority goals of the Action Plan.

The most effective policy actions are those based on well-established evidence of the links between children's health and environmental exposures, ensuring that the prevention of exposure leads to improved health. As a result of studies conducted around the world in recent decades, knowledge and understanding of the risks of air pollution to children is growing. Nevertheless, the available studies are not always consistent in terms of the health outcomes and exposures assessed, and employ a wide range of analyses and reporting methods. Recent studies have tended to be more sophisticated and to consider in more detail the complexity of children's exposure to environmental factors, changes in the physiology of the developing organism, and morbidity characteristic for the age of the child. The synthesis of accumulated evidence thus requires it to be thoroughly and systematically analysed, looking for logical links between studies that point to causal associations between exposures and health effects. Such synthesis furnishes the most solid policy basis and allows one to focus on the relevant exposures and to effectively reduce the burden of disease due to these exposures.

The *Air quality guidelines for Europe*, first published by WHO in 1987 and updated at the end of the 1990s, provide a comprehensive assessment of the hazards of air pollution to all population groups, including children *(4)*. Several new studies carried out over the last few years, however, potentially provide new insight into the evidence, employ new study methods, and address exposure to pollution mixes and levels now characteristic of European cities. To identify the relation-

ships between children's health and development and air quality for which there is conclusive combined toxicological and epidemiological evidence, the WHO Regional Office for Europe (European Centre for Environment and Health, Bonn Office) began work on this monograph in mid-2003. An important objective was to support the development of European policies, in particular the Clean Air for Europe (CAFE) programme of the European Commission.

PROCESS OF PREPARING THE MONOGRAPH

The work was conducted within the framework of the project "Systematic review of health aspects of air pollution in Europe", implemented by the Regional Office and co-sponsored by the European Commission's DG Environment under grant agreement 2001/321294 *(5)*. The WHO secretariat prepared the outline of the review for the acceptance by the project's Scientific Advisory Committee, which also recommended the authors of each chapter of this monograph. In conducting the review, the authors were asked to follow the WHO guidelines on "Evaluation and use of epidemiological evidence for environmental health risk assessment" *(6)*. The materials prepared for former steps of the systematic review were used whenever appropriate, in particular the results of the meta-analysis of short-term studies (including panel studies) *(7)*. The first drafts of the chapters, prepared by the chapter authors, were distributed to a group of invited reviewers, to the members of the Scientific Advisory Committee, and to the authors of other chapters. The list of contributors to the text and its review is presented in Annex 1. The reviewers were asked to judge the validity and clarity of the contributions and, in particular, to assess whether recent research been correctly interpreted, whether any influential papers had been overlooked, and whether (and if so what) alternative interpretations of the evidence would have been more appropriate.

The drafts of the chapters, together with the comments of the reviewers, were discussed by the WHO Working Group meeting in Bonn on 26–27 April 2004, chaired by Jonathan Samet. The meeting participants also agreed on conclusions concerning the likely causality of observed associations with air pollution. The discussion used a multilevel scale: (*a*) evidence sufficient to infer causality; (*b*) evidence suggestive of causality; (*c*) evidence insufficient to infer causality; and (*d*) evidence showing no association. The Working Group members also agreed on the text of the Executive Summary, published soon after the meeting and made available before the Ministerial Conference in Budapest. Furthermore, the Working Group provided editorial recommendations concerning the chapters. Based on those comments, the authors revised their contributions to the monograph, and the changes were then integrated and edited by WHO staff.

SCOPE OF THE REVIEW

The review considers the effects of air pollution on the health and development of the child in the prenatal period, on the development of the respiratory system

and lung function, on respiratory morbidity and on the incidence of child cancer, together with its neurodevelopmental and behavioural effects. An attempt was also made to use indirect indices of children's ill-health, such as school absenteeism, in describing the health effects of air pollution. The review is introduced by a brief discussion of the vulnerability and susceptibility of children to air pollution. Owing to the scope of the systematic review project, the focus of this monograph is on the most common outdoor air pollutants. Nevertheless, where available, supporting evidence based on studies of indoor exposures is also used. The evaluation of evidence was limited to the assessment of the hazards of the pollution, without attempting to estimate quantitatively the contribution of air pollution to the burden of disease in children. Such quantification has recently been demonstrated *(8,9)*. The evidence summarized in this monograph, and the conclusions of the review, add to credibility of such impact assessment and allow its broader application in support of policies and actions.

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SUSCEPTIBILITY OF CHILDREN TO AIR POLLUTION

Jonathan Samet, Robert Maynard

The susceptibility of children, or other special groups, to air pollution is relevant to regulatory processes that seek to protect all persons exposed to environmental agents, regardless of their susceptibility. While it is often accepted that protecting the most susceptible members of a susceptible group may not be feasible, the need to protect the great majority in such a group has been accepted, for example by WHO in preparing the second edition of the Air Quality Guidelines for Europe *(1)* and by the 1970 Clean Air Act in the United States, which explicitly recognized the challenge of susceptibility and the intention to protect even the most susceptible citizens.

Scientists carrying out research need to provide evidence to guide the protection of susceptible populations. In fact, susceptible populations have often been the focus of research and some methods, such as time-series techniques, inevitably reflect effects on such groups. Many epidemiological studies have addressed the health effects of air pollution on children, partly because they can be readily studied at school age by collecting data from schools. Also, there are a number of biological reasons for being concerned about the susceptibility of children to air pollution.

This chapter provides a brief introduction to the potential susceptibility of children to air pollution and the determinants of its susceptibility. This is an extensive topic, and for greater detail we direct readers to a recent comprehensive review of the susceptibility of children to environmental agents published in the journal *Pediatrics* in April 2004 (*2*). Within this review, all aspects of the susceptibility of children to environmental agents are covered. We highlight here those topics that are of particular relevance to considering children as a susceptible population for air pollution. In addition, we refer readers to the statement of the American Thoracic Society *(3)*, which gives consideration to the topic of susceptibility, and to the 2004 report of the US National Research Council's Committee on Research Priorities for Airborne Particulate Matter *(4)*, which covers the most recent information on to this particularly prominent air pollutant.

Table 1 provides a listing of factors that might heighten the susceptibility of children to air pollution. The listing begins with preconception exposures and extends through to the adolescent years. Broadly, potential determinants of susceptibility include the continuing process of lung growth and development, incomplete metabolic systems, immature host defences, high rates of infection with

Table 1. Categories of factors determining susceptibility of children to inhaled pollutants

Related to lung growth and development	• Vulnerability of developing and growing airways and alveoli • Immature host defence mechanisms
Related to time-activity patterns	• Time spent outdoors • Increased ventilation with play and exercise
Related to chronic disease	• High prevalence of asthma • Rising prevalence of cystic fibrosis
Related to acute disease	• High rates of acute respiratory infection

respiratory pathogens, and activity patterns that heighten exposure to air pollution and to lung doses of pollutants.

In addition, children may have varying degrees of susceptibility and the large proportion with underlying chronic lung disease (particularly asthma) may be at greater risk than children without such conditions. There is also an increasing population of older children with cystic fibrosis, as survival has improved and most children live into adulthood. Within susceptible categories, there may also be a range of severity of disease with a corresponding range of susceptibility. Childhood asthma is heterogeneous, with some children having far more serious disease than others, and some evidence suggests that responsiveness to environmental agents may also vary among children with asthma. Also, patterns of exposure to indoor pollutants vary among children and those receiving higher exposures indoors, for example to cigarette smoke, may be at greater risk of being affected by outdoor pollutants.

An additional basis for concern about the susceptibility of children is the longer-term implications of lung injury during childhood. Damage to the developing lung may reduce the maximal functional capacity achieved, reducing the functional reserve as the child enters adulthood and thereby enhancing susceptibility during the adult years to cigarette smoking, occupational exposures and other factors. For example, active and passive smoking during childhood reduce the rate of lung growth and the maximum level of function achieved *(5)*.

There is substantial literature on the health effects of air pollution on children in general and on children within certain subgroups of susceptibility, particularly those with asthma. These studies provide a picture of how air pollution affects health in this population. There have not been studies – nor are they needed – specifically contrasting the susceptibility of children and adults. The evidence is clear in showing that children have been adversely affected by air pollution, and that their susceptibility needs to be considered when air pollution regulations are developed to protect public health.

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INTRAUTERINE GROWTH RETARDATION, LOW BIRTH WEIGHT, PREMATURITY AND INFANT MORTALITY

Radim J. Šrám, Blanka Binková, Jan Dejmek, Martin Bobak

INTRODUCTION

This chapter reviews the evidence on adverse effects of ambient air pollution on several types of pregnancy outcome: childhood mortality, birth weight, premature birth, intrauterine growth retardation (IUGR) and birth defects. Virtually all of the studies reviewed were population-based. Information on different types of air pollutant was derived largely from routine monitoring sources. Overall, there is evidence implicating air pollution in adverse effects on pregnancy outcomes.

It is increasingly apparent that there is a critical period of development when the timing of exposure, and the rate at which a dose is absorbed, can be even more important for the biological effects than the overall dose *(1)*. The fetus in particular is considered to be highly susceptible to a variety of toxicants because of its exposure pattern and physiological immaturity *(2,3)*. The developing organ systems of the fetus can be more vulnerable to environmental toxicants during critical periods owing to higher rates of cell proliferation or changing metabolic capabilities *(4)*. Prenatal exposure to environmental pollution can thus result in some adverse pregnancy outcomes.

The study of pregnancy outcomes is an important emerging field within environmental epidemiology. Pregnancy outcomes are important in their own right, because they are indicators of the health of neonates and infants. In addition, low birth weight, intrauterine growth retardation and impaired growth in the first years of life are known to influence subsequent health status, including increased mortality and morbidity in childhood and an elevated risk of hypertension, coronary heart disease and non-insulin-dependent diabetes in adulthood *(5,6)*.

To examine the evidence linking adverse pregnancy outcomes with ambient air pollution, we divided the pregnancy outcomes into five groups: (*a*) fetal and infant mortality; (*b*) low birth weight; (*c*) premature (preterm) birth; (*d*) intrauterine growth retardation; and (*e*) birth defects. We review the evidence on each of these separately. Finally, we try to draw some conclusions about the currently available evidence on air pollution and pregnancy outcomes.

AIR POLLUTION AND CHILDHOOD MORTALITY

The possible impact of air pollution on children's health was first connected to early child mortality. One of the earliest reports was based on an ecological study of counties in England and Wales in 1958–1964, with air pollution estimated

from indices of domestic and industrial pollution *(7)*. The study found significant correlations between air pollution and infant mortality, particularly infant respiratory mortality. The Nashville Air Pollution Study conducted in the 1950s *(8)* indicated that dustfall, a measure of air pollution estimated for each census tract, was related to neonatal deaths with signs of prematurity, but the results were inconclusive. Another early signal that air pollution may be associated with deaths in infancy came from the extensive analyses of air pollution and mortality in 117 American metropolitan areas in the 1960s *(9)*. Particulates and, to a lesser degree sulfate concentrations, were positively associated with infant mortality; a 10% increase in pollution was associated with a 1% increase in infant mortality.

It took almost two decades before a new generation of studies addressed this question in more detail. These newer studies confirmed, in principle, the early results. A small ecological study in Rio de Janeiro metropolitan area reported a positive association between annual levels of particulates and infant mortality from pneumonia *(10)*.

Bobak & Leon *(11)* studied infant mortality in an ecological study in the Czech Republic. They found an association between sulfur dioxide and total suspended particles (TSP) on the one hand and infant mortality on the other, after controlling for a number of potentially confounding variables (at the ecological level). The effects were specific to respiratory mortality in the post-neonatal period. These results were later confirmed in a nationwide case-control study based on the Czech national death and birth registers *(12)*; this design allowed one to control for social and biological covariates at the individual level. The study found a strong effect of sulfur dioxide and TSP on post-neonatal mortality from respiratory causes: the relative risks, per 50 $\mu g/m^3$ increase in pollutant concentration, were 1.95 (95% CI 1.09–3.50) for sulfur dioxide and 1.74 (95% CI 1.01–2.98) for TSP.

Woodruff et al. *(13)* analysed the association between early post-neonatal mortality and levels of PM_{10} (particulate matter <10 μm) in about 4 million babies born between 1989 and 1991 in the United States. Infants were categorized as having high, medium or low exposure based on tertiles of PM_{10}. After adjustment for other covariates, the relative risk of total post-neonatal mortality in the high-exposure vs the low-exposure group was 1.10 (CI 1.04–1.16). In normal-birthweight infants, high PM_{10} exposure was associated with respiratory death (relative risk 1.40, 95% CI 1.05–1.85) and sudden infant death syndrome (relative risk 1.26, 95% CI 1.14–1.39).

Pereira et al. *(14)* investigated the associations between daily counts of intrauterine mortality in the city of Sao Paulo, Brazil in 1991–1992 and several pollutants: nitrogen dioxide, sulfur dioxide, carbon monoxide, ozone and PM_{10}. The association was strongest for nitrogen dioxide (P <0.01). A significant association was also observed with exposure combining nitrogen dioxide, sulfur dioxide and carbon monoxide together (P <0.01).

Loomis et al. *(15)* conducted a time-series study of infant mortality in the south-western part of Mexico City in 1993–1995. Exposure included nitrogen dioxide, sulfur dioxide, ozone and particulate matter with particle size <2.5 μm ($PM_{2.5}$). A 10 μg/m^3 increase in the mean level of fine particles during the previous three days was associated with a 6.9% (95% CI 2.5–11.3%) excess increase in infant deaths.

Dolk et al. *(16)* examined infant mortality in populations residing near 22 coke works in Great Britain. Data on specific pollutants were not provided; exposure was based on proximity to the pollution source. The study found no evidence of an increased risk of stillbirth (ratio of observed to expected cases (O/E) 0.94), infant mortality (O/E 0.95), neonatal mortality (O/E 0.86), post-neonatal mortality (O/E 1.10), respiratory post-neonatal mortality (O/E 0.79) or post-neonatal sudden infant death syndrome (O/E 1.07) associated with proximity to the coke works. The study, however, had limited statistical power owing to its relatively small size.

AIR POLLUTION AND BIRTH WEIGHT

The potential effects of air pollutants on fetal growth were first observed by Alderman et al. *(17)*, who observed a relationship between the ambient levels of carbon monoxide in a pregnant woman's neighbourhood during the third trimester and low birth weight. However, the effect of carbon monoxide on risk of low birth weight was not statistically significant after adjustment for the mother's race and education.

Wang et al. *(18)* examined the effects of sulfur dioxide and TSP on birth weight in a time-series study in four relatively highly polluted residential areas of Beijing, China. A spectrum of potentially confounding factors was adjusted for in multivariate analysis. A graded dose–effect relationship was found between maternal exposure to sulfur dioxide and TSP during the third trimester and birth weight. Mean birth weight was reduced by 7.3 g and 6.9 g, respectively, for each 100 μg/m^3 increase in sulfur dioxide and TSP. The relative risks of low birth weight associated with a 100-μg/m^3 increase in sulfur dioxide and TSP were 1.11 (95% CI 1.06–1.16) and 1.10 (95% CI 1.05–1.14), respectively. The authors speculated that sulfur dioxide and particles, or some complex mixtures associated with these pollutants, during late gestation contributed to the low birth weight risk in the studied population.

Bobak & Leon *(19)* conducted an ecological study of low birth weight and levels of nitrogen oxides, sulfur dioxide and TSP in 45 districts of the Czech Republic in 1986–1988. After controlling for socioeconomic factors, the relative risks of low birth weight associated with an increase of 50 μg/m^3 in the annual mean concentrations were 1.04 (95% CI 0.96–1.12) for TSP, 1.10 (95% CI 1.02–1.17) for sulfur dioxide and 1.07 (95% CI 0.98–1.16) for nitrogen oxides. When all pollutants were included in one model, only sulfur dioxide remained related to low birth weight (OR 1.10, 95% CI 1.01–1.20).

In a subsequent study, Bobak *(20)* analysed individual-level data on all single live births in the Czech Republic that occurred in 1991 in the 67 districts where at least one pollutant (nitrogen oxides, sulfur dioxide or TSP) was monitored. The risk of low birth weight was analysed separately for each trimester of pregnancy. The association between low birth weight and pollution was strongest for pollutant levels during the first trimester. The relative risks of low birth weight per 50-μg/m^3 increase in the mean concentration of sulfur dioxide and TSP during the first trimester were 1.20 (95% CI 1.11–1.30) and 1.15 (95% CI 1.07–1.24), respectively.

In a population-based study in Southern California, Ritz & Yu *(21)* examined the influence of pollution levels during the third trimester on risk of low birth weight in a cohort of 126 000 term births. Exposure to ozone, nitrogen dioxide and PM_{10} in the last trimester was estimated from the monitoring station closest to the mother's residence. After adjustment for potential confounders, the risk of low birth weight was associated with maternal exposure to >5.5 ppm carbon monoxide during the third trimester (relative risk 1.22, 95% CI 1.03–1.44). The association between risk of low birth weight and pollution exposure during earlier gestational stages was not significant.

A population-based case-control study in Georgia, United States by Rogers et al. *(22)* analysed the combined effect on very low birth weight (<1500 g) of sulfur dioxide and total suspended particle levels, using annual exposure estimates. The risk of very low birth weight was increased in babies of mothers who were exposed to concentrations of the combined pollutants above the 95th percentile of the exposure distribution (56.8 μg/m^3); the relative risk was 2.88 (95% CI 1.16–7.13).

Maisonet et al. *(23)* examined the association between low birth weight at term and ambient levels of sulfur dioxide PM_{10} and carbon monoxide in six large cities in the north-eastern United States. Their results suggested that the effects of ambient carbon monoxide and sulfur dioxide on the risk of low birth weight at term may differ by ethnic group. In Caucasians (n ~ 36 000), the risk of low birth weight associated with a 10-ppm increase in sulfur dioxide was 1.18 (95% CI 1.12–1.23) in the first, 1.18 (95% CI 1.02–1.35) in the second and 1.20 (95% CI 1.06–1.36) in the third trimester. By contrast, in African Americans (n ~ 47 000), low birth weight was associated with carbon monoxide: a 1-ppm increase in carbon monoxide concentration was associated with a relative risk of 1.43 (95% CI 1.18–1.74) in the first and of 1.75 (95% CI 1.50–2.04) in the third trimester. No effects were seen in Hispanics (n ~ 13 000), although this may have been due to the lower statistical power of the study in this group.

Lin et al. *(24)* compared the rates of adverse pregnancy outcome in an area polluted by the petrochemical industry and in a control area in Taiwan, China. The exposed and control areas differed substantially in the levels of air pollution; for example, the difference in the mean concentration of PM_{10} was 26.7 μg/m^3. The

relative risk of low birth weight at term, when comparing the affected with the control area, was 1.77 (95% CI 1.00–3.12).

Ha et al. *(25)* examined full-term births between 1996 and 1997 in Seoul, Republic of Korea, to determine the association between low birth weight and exposure to carbon monoxide, sulfur dioxide, nitrogen dioxide, TSP and ozone in the first and third trimesters. They found that ambient carbon monoxide, sulfur dioxide, nitrogen dioxide and TSP concentrations during the first trimester of pregnancy were associated with low birth weight; the relative risks were 1.08 (95% CI 1.04–1.12) for carbon monoxide, 1.06 (95% CI 1.02–1.10) for sulfur dioxide, 1.07 (95% CI 1.03–1.11) for nitrogen dioxide and 1.04 (95% CI 1.00–1.08) for TSP.

Vassilev et al. *(26)* used the USEPA Cumulative Exposure Project data to investigate the association between outdoor airborne polycyclic organic matter and adverse reproductive outcomes in New Jersey for newborn infants born in 1991–1992. The relative risk of low birth weight in term babies, comparing the highest and the lowest exposure groups, was 1.31 (95% CI 1.21–1.43).

Bobak et al. *(27)* investigated the hypothesis that low birth weight is related to air pollution in data from the British 1946 cohort. They found a strong association between birth weight and air pollution index based on coal consumption. After controlling for a number of potential confounding variables, babies born in the most polluted areas were on average 82 g lighter (95% CI 24–140) than those born in the areas with the cleanest air.

Chen et al. *(28)* examined the association between birth weight and PM_{10}, carbon monoxide and ozone levels in northern Nevada from 1991 to 1999. The results suggested that a 10-$\mu g/m^3$ increase in mean PM_{10} concentration during the third trimester of pregnancy was associated a reduction in birth weight of 11 g (95% CI 2.3–19.8).

Wilhelm & Ritz *(29)* studied the effect on low birth weight of residential proximity to heavy traffic in Los Angeles County in 1994–1996. The risk of low birth weight at term increased by 19% for each 1 ppm increase in the mean annual concentration of background carbon monoxide. In addition, an elevated risk was observed for women whose third trimester fell during the autumn and winter months (relative risk 1.39, 95% CI 1.16–1.67); this is probably due to the more stagnant air conditions during the winter period. Overall, the study reported an approximately 10–20% increase in the risk of low birth weight at term in infants born to women exposed to high levels of traffic-related air pollution.

A time-series study in Sao Paulo, Brazil *(30)* found that birth weight was inversely related to carbon monoxide levels in the first trimester; after controlling for potential confounders, a 1 ppm increase in the mean carbon monoxide concentration in the first trimester was associated with a 23-g reduction in birth weight (95% CI 5–41).

The results of studies of outdoor exposures are complemented by studies of indoor and personal exposures. Boy et al. *(31)* studied the association between

birth weight and the type of fuel (open fire with wood smoke, chimney stove and electricity/gas) used by women in rural Guatemala during pregnancy. The use of an open fire produced average 24-hour PM_{10} levels of about 1000 μg/m^3. Babies born to women using wood fuel and open fires were on average 63 g lighter (95% CI 0.4–126) than those born to women using electricity or gas.

Perera et al. *(32)* evaluated the effects of prenatal exposure to airborne carcinogenic polycyclic aromatic hydrocarbons (PAHs) monitored during pregnancy by personal air sampling in 263 non-smoking African American and Dominican women in New York. The mean total exposure to PAHs was 3.7 ng/m^3 (range 0.4–36.5 ng/m^3). Among African Americans, high prenatal exposure to PAHs was associated with lower birth weight ($P = 0.003$) and smaller head circumference ($P = 0.01$). No such effects were observed among Dominican women.

AIR POLLUTION AND PREMATURE BIRTHS

Perhaps the first study that suggested a possible association between air pollution and preterm births was the Nashville Air Pollution Study. The results suggested that dustfall (a measure of particulate pollution) was associated with neonatal deaths among infants born prematurely *(8)*. However, the study did not address the question of preterm births specifically, and there were concerns about confounding by socioeconomic variables.

The first "modern" investigation of the possible influence of air pollution on premature birth was a time-series study in Beijing conducted by Xu et al. *(33)*. The study found an inverse relationship between gestational age and concentration of sulfur dioxide and TSP; the relative risks of premature birth associated with a 100-μg/m^3 increase in the mean sulfur dioxide and TSP concentrations during pregnancy, after controlling for potential confounders, were 1.21 (95% CI 1.01–1.45) and 1.10 (95% CI 1.01–1.20), respectively. Trimester-specific effects were not studied.

Bobak *(20)* examined the relationship between premature birth and ambient levels of nitrogen oxides, sulfur dioxide and TSP during each trimester of pregnancy. The association was strongest for sulfur dioxide, weaker for TSP and only marginal for nitrogen oxides. For exposure during the first trimester, the relative risks of prematurity associated with a 50-μg/m^3 increase in pollutant concentrations were 1.27 (95% CI 1.16–1.39) and 1.18 (95% CI 1.05–1.31) for sulfur dioxide and TSP, respectively. The effects of pollutants on premature birth in the later two trimesters were weak.

The possible effect of carbon monoxide, nitrogen dioxide, ozone and PM_{10} on premature birth was studied by Ritz et al. *(34)* in Southern California. After adjustment for a number of biological, social and ethnic covariates, premature births were associated with carbon monoxide and PM_{10} levels in the first month of gestation and during late pregnancy. The relative risk of premature birth per 50-μg/m^3 increase in ambient PM_{10} level averaged over the first gestational month

was 1.16 (95% CI 1.06–1.26); exposure in the last six weeks of gestation was associated with a relative risk of 1.20 (95% CI 1.09–1.33) per 50 μg/m^3. The association of premature birth with carbon monoxide level is not consistent throughout the study area.

The study by Lin et al. in a petrochemically polluted area in Taiwan, China *(35)* found a relative risk of preterm birth in the polluted area, compared to the clean area, of 1.41 (95% CI 1.08–1.82), after controlling for potential confounders.

AIR POLLUTION AND INTRAUTERINE GROWTH RETARDATION

IUGR is defined as birth weight below the 10th percentile of the birth weight for a given gestational age and sex. Most of the available evidence so far has come from the Teplice Study in the Czech Republic.

Dejmek et al. *(36)* examined the impact of PM_{10} and $PM_{2.5}$ on IUGR in a highly polluted area of Northern Bohemia (Teplice District). The mean concentrations of pollutants in each month of gestation for each mother were estimated from continuous air quality monitoring data. A significantly increased risk of giving birth to a child with IUGR was established for mothers who were exposed to PM_{10} levels >40 μg/m^3 or $PM_{2.5}$ levels >27 μg/m^3 during the first month of gestation. The relative risk associated with 20-μg/m^3 increase in mean PM_{10} was 1.50 (95% CI 1.15–1.96); a similar, though weaker, association was seen for $PM_{2.5}$. There was no association between IUGR and particulate levels in later gestational months or with sulfur dioxide, nitrogen oxides or ozone.

Analysis of a four-year dataset *(37)* shows that the risk of IUGR was 1.44 higher (95% CI 1.03–2.02) in the group exposed to mean PM_{10} from 40 to <50 μg/m^3 and 2.14 higher (95% CI 1.42–3.23) in those exposed to mean PM_{10} >50 μg/m^3 compared to those exposed to mean PM_{10} <40 μg/m^3 during the first month of gestation. Using a continuous exposure indicator, the relative risk of IUGR was 1.19 (CI 1.06–1.33) per 10 μg/m^3 increase of PM_{10} in the first month of gestation.

In further analyses of this cohort, Dejmek et al. *(37)* investigated the association between carcinogenic PAHs and IUGR in two Czech districts: Teplice and Prachatice. In the Teplice data, there was a highly significant increase of IUGR with exposure to carcinogenic PAHs (carc-PAHs) (benz[*a*]anthracene, benzo[*b*]fluoranthene, benzo[*k*]fluoranthene, benzo[*g,h,i*]perylene, benzo[*a*]pyrene, chrysene, dibenz[*a,h*]anthracene and indeno[*1,2,3-c,d*]pyrene) above 15 ng/m^3. Again, the effect was specific for the first month of gestation. The adjusted relative risks were 1.59 (95% CI 1.06–2.39) for medium levels of carc-PAHs and 2.15 (95% CI 1.27–3.63) for high exposure levels. Using a continuous measure of exposure, a 10-ng/m^3 increase in the level of carc-PAHs was associated with relative risk of 1.22 (95% CI 1.07–1.39). While there was no effect of PM_{10} on IUGR found in Prachatice, the association between carc-PAHs and IUGR was close to that found in Teplice. Again, the only consistent association between carc-PAHs and IUGR was observed in the first month of gestation: compared to the lowest category of

exposure to carc-PAHs, the relative risk of IUGR was 1.63 (95% CI 0.87–3.06) in the medium category and 2.39 (95% CI 1.01–5.65) in the highest category.

In contrast to the Teplice/Prachatice study, analysis of the Czech national birth register linked with air pollution data did not reveal any significant association between IUGR and ambient levels of nitrogen oxides, sulfur dioxide and TSP *(20)*. The reasons for the discrepancy between the studies are not entirely clear.

Vassilev et al. *(38)* examined the association of polycyclic organic matter in outdoor air with "small for gestational age" births (definition identical to that of IUGR). Information from birth certificates in New Jersey from 1991 to 1992 was combined with data on air toxicity derived from the USEPA Cumulative Exposure Project, using the annual mean concentrations of polycyclic organic matter estimated for each census tract. The relative risk for low birth weight at term, adjusted for a number of covariates, was 1.09 (95% CI 1.03–1.21) and 1.31 (95% CI 1.21–1.43), respectively, for the medium- and high-exposure tertiles, suggesting that residential exposure to airborne polycyclic organic matter is associated with an increased prevalence of IUGR.

AIR POLLUTION AND BIRTH DEFECTS

At present, evidence on the relationship between outdoor air pollution and birth defects is limited to only one report. Ritz et al. *(39)* evaluated the effect of carbon monoxide, nitrogen dioxide, ozone and PM_{10} on the occurrence of birth defects in Southern California for the period 1987–1993. The average monthly exposure for each pollutant throughout pregnancy was calculated. Dose–response patterns were observed for (*a*) exposure to carbon monoxide in the second month of gestation and ventricular septal defects (relative risk for the highest vs lowest quartile of exposure 2.95, 95% CI 1.44–6.05) and for (*b*) exposure to ozone in the second month and aortic artery and valve defects (relative risk 2.68, 95% CI 1.19–6.05), pulmonary artery and valve anomalies (relative risk 1.99, 95% CI 0.77–5.13) and conotruncal defects (relative risk 2.50, 95% CI 0.82–7.66).

DISCUSSION

The studies reviewed above indicate that ambient air pollution is inversely associated with a number of birth outcomes. This is a relatively new area of environmental epidemiology, with most reports stemming from the last 10 years. A critical assessment of the evidence is therefore timely. In interpreting the evidence, we will consider the following questions: publication bias; methodological issues such as bias and confounding; consistency of the studies; and the biological plausibility of the effects.

Publication bias

Negative studies are less likely to be published, and studies published in non-English journals are less likely to be included in reviews. We included all studies

we were able to identify. Although we cannot exclude the possibility that some negative studies, especially the early ones, remain unpublished, it is unlikely that they would substantially change the balance of the evidence.

Methodological issues

Three issues may affect the validity of an epidemiological study: random error (chance), selection or measurement bias, and confounding. All studies reviewed used standard statistical techniques to assess the role of chance. In several studies, there is a potential problem of multiple comparisons. The more comparisons made, the higher the probability that some of them will be "statistically significant". In some instances, a more stringent use of statistical testing would be helpful. Overall, however, this was not a major problem in the majority of the studies. Selection bias, in general, was not an issue, since most of the studies reviewed were population-based and included either total populations or population samples in defined areas. Measurement bias is potentially more important, since most studies relied on routine monitoring of air pollution in large areas, and extrapolation from city- or area-wide measurements to individual exposures can be difficult.

Confounding factors may also distort the observed relationship between air pollution and birth outcomes. In particular, the socioeconomic characteristics of people living in more polluted areas can be less favourable than those of people living in less polluted areas, and this can lead to higher rates of adverse outcomes in polluted areas. However, confounding is unlikely to explain the results of the reviewed studies for at least three reasons. First, all recent studies controlled for socioeconomic factors and other potential confounders. In most instances, the differences between the crude and adjusted effect estimates were minimal. This does not suggest a presence of residual confounding. Second, a large proportion of the studies reviewed were time-series studies. It is very unlikely that the social composition of the studied populations would change substantially over the relatively short periods covered by these studies. In our view, the time-series design practically precludes the presence of social confounding. Third, the studies were conducted in very different populations, ranging from China to the United States and from Brazil to the Czech Republic; it is highly unlikely that the distribution of socioeconomic disadvantage with respect to air pollution would be similar in all these different countries to produce the same pattern of results.

Consistency of the studies

The studies reviewed differed substantially in design and measurements, and it is likely that this affected the consistency of the results. The results were most consistent for post-neonatal respiratory mortality: the three largest studies produced very similar estimates of relative risk *(11–13)*.

Studies of birth weight, preterm birth and IUGR mostly suggest an association with air pollution, but the results are inconsistent with respect to which pollut-

ants have the largest effect and the critical timing of the exposure. The extent of the inconsistencies was such that the studies were not "combinable" into a formal meta-analysis to produce pooled effect estimates. It is possible that the mix of pollutants differs between different settings, and that this underlies the discrepancies in results. Nevertheless, the inconsistency of the findings is of concern, and it needs to be clarified by future research.

In the case of birth defects, there has been only one study of the potential role of air pollution *(39)*. The results suggest that the exposure to increased levels of ambient carbon monoxide and ozone during pregnancy may contribute to the occurrence of ventricular septal defects. The associations of ozone with other defects were not statistically significant. Further studies are required to support these results.

Biological plausibility

Molecular epidemiological studies are particularly valuable for the interpretation of the epidemiological data. The molecular epidemiological studies suggest biological mechanisms for the effect of air pollution on maternal markers and birth outcomes. The molecular epidemiological studies used biomarkers of exposure, mainly as DNA adducts measured by ^{32}P-postlabelling and PAH-DNA adducts assessed by ELISA *(40)*. Overall, these studies suggest that DNA adduct levels in maternal blood and placentas are higher in areas with higher pollution levels *(41–43)*. In addition, significant district and seasonal differences in DNA adducts were found in genetic subgroups (e.g. defined by the GSTM1 null genotype *(44,45)*. The increase in the levels of DNA adducts related to pollution is similar to, but smaller in magnitude than, differences between smoking and non-smoking mothers. All this indicates that ambient air pollution levels do translate to higher individual exposures, even for unborn babies.

Levels of DNA adducts are positively related to risk of IUGR *(37,42)*, birth weight and head circumference *(2,46)* and hypoxanthine-guanine phosphoribosyl transferase locus (HPRT) mutation frequency in infants *(47)*.

PAHs and/or their metabolites may bind to the aromatic hydrocarbon receptor and accumulate in the nucleus of cells, resulting in increased rates of mutagenesis. Binding of PAHs to the aromatic hydrocarbon receptor may result in anti-estrogenic activity through increased metabolism and the depletion of endogenous estrogens *(48)*. Bui et al. *(49)* have also hypothesized that exposure to benzo[*a*]pyrene may interfere with uterine growth during pregnancy because of its anti-estrogenic effects, thereby disrupting the endocrine system. The finding of higher DNA adduct levels in the infant compared to the mother suggests an increased susceptibility of the developing fetus to DNA damage *(11)*. With respect to IUGR, it appears that the increased risk is principally due to exposure to carc-PAHs. This finding is consistent with the idea of a primary role for carc-PAHs in fetal growth modulation *(50–53)*.

In addition, there appears to be an interaction between PAH exposure and genotype to produce DNA adducts *(54)*. While the specific steps of these pathways need to be further clarified, it seems that the effects of air pollution on birth outcomes are biologically plausible.

SUMMARY AND CONCLUSIONS

Overall, there is evidence implicating air pollution in adverse effects on birth outcomes, but the strength of the evidence differs between outcomes. The evidence is solid for infant mortality: this effect is primarily due to respiratory deaths in the post-neonatal period and it appears to be mainly due to particulate air pollution. Studies on birth weight, preterm births and IUGR also suggest a link with air pollution, but there were important inconsistencies in the results that were probably due to differences in design and measurement of exposure(s). Molecular epidemiological studies suggest biological mechanisms for the effect on birth weight and IUGR, and thus suggest that the link between pollution and these birth outcomes is genuine. There are too few data on birth defects to draw firm conclusions. While the overall evidence is persuasive, the available data do not allow precise identification of specific pollutants and timing of exposure that can result in low birth weight, preterm births, IUGR and birth defects.

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EFFECTS OF AIR POLLUTION ON THE CHILD'S RESPIRATORY SYSTEM

The child's respiratory system is a primary target for air pollutants. They cause a wide range of acute and chronic effects, either as a single risk factor or, more often, in combination with other external agents and/or the child's susceptibility characteristics. This chapter reviews in detail the role of exposure to air pollution in acute respiratory infections, in the development and manifestation of asthma and allergies, and in the de velopment of lung function. The introductory section provides an overview of mechanisms of injury caused by air pollution on the child's respiratory system, addressing the possible links between the pollution, acute infections and chronic respiratory diseases.

Besides the objectively or subjectively recognized symptoms, or objective measures of effects of pollution on lung function, some studies have addressed indirect indicators of ill-health in children such as absenteeism from school. Since respiratory symptoms are the most plausible health reason for such absenteeism, a short summary of these studies is provided at the end of this chapter. These studies contribute to the overall evidence on the short-term effects of air pollution on children's health and activities.

MECHANISMS BY WHICH AIR POLLUTION INJURES THE CHILD'S RESPIRATORY SYSTEM

Stephen Holgate

BACKGROUND

The interaction of air pollutants with the lung represents a good example of interplay between genes and environment in a complex system. An important aspect of this is variation in the genes that protect from or generate a response to air pollutants to create variable susceptibility. The receptors and metabolic pathways involved mature at different rates during lung development and throughout childhood, giving rise to the concept of a critical window when vulnerability to the adverse effects(s) of a pollutant may be especially pronounced.

Although from epidemiological studies there is increasing evidence for short-term effects of outdoor air pollutants on children's health and lung growth, very few studies have addressed the question of whether exposure to pollutants can initiate asthma, as has been shown for passive smoking. There is, however, mounting evidence from animal and in vitro studies to support the view that high levels of ambient air pollution increase the risk of children developing lung disease.

The lung is a highly complex heterogeneous structure with the principal function of delivering oxygen to and removing carbon dioxide from the body. On account of the enormous volume of air that passes into the lung during ventilation, it is well equipped to neutralize or break down chemical and biological substances present in inhaled air. The epithelium that overlies the conducting airways and lines the alveoli has an enormous capacity to protect the underlying cells and tissue from inhaled toxicants *(1)*. In the case of outdoor air pollution, it is the oxidant pathways that are especially important, since the majority of the tissue-damaging effects of ozone, nitrogen oxides and particulates result from their direct or indirect actions as oxidants *(2,3)*. There is important cell–cell communication within lung compartments fundamental to understanding how pollutants lead to damage and repair *(4,5)*. More than 40 cell phenotypes have been found in the lungs and all have the capacity to respond to toxic stress, even when only one subpopulation is exposed, such as columnar epithelial cells *(1)*.

Age at the time of exposure to inhaled pollutants plays a major role in the pattern of injury and repair. This is especially true for the very young in the early postnatal period, when the respiratory system is completing its growth and maturation *(6–8)*. Infants are more susceptible to injury by lung toxicants than are adults of the same species, even at doses below the no-effect level (NOEL) for adults *(9,10)*. This appears to be closely governed by the differentiation of target cell populations and

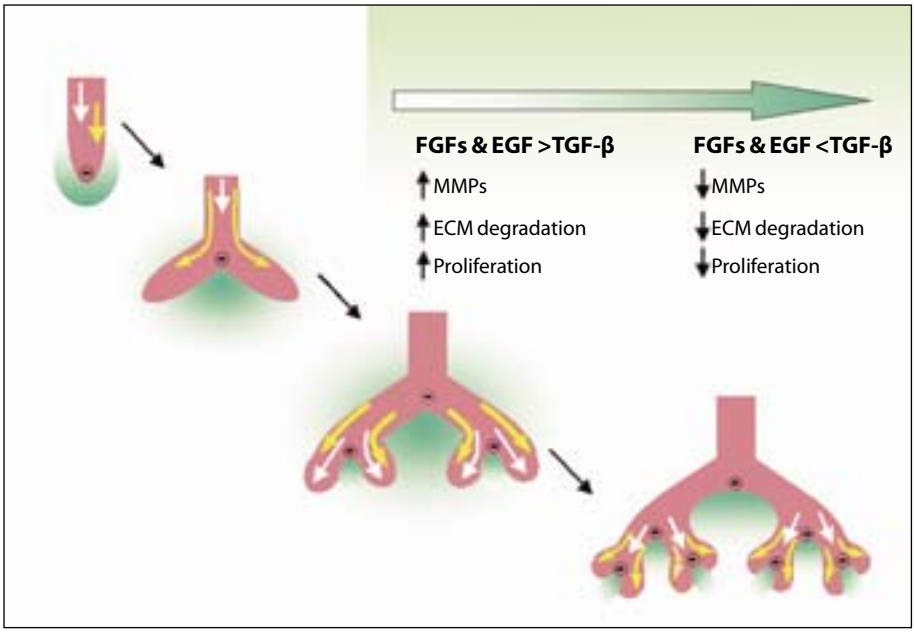
the induction and maturation of their relevant enzyme systems *(11)*. Differential expression of detoxification systems also shows a time-dependent pattern during postnatal lung development, and could suggest mismatches between activation and detoxification potential that could account for the increased susceptibility of infants *(12)*. There appear to be critical points during prenatal and postnatal lung development when this susceptibility is higher than at other times. Another impact of age as it relates to the postnatal development of infant lungs is the failure of acute epithelial injury in the lung to repair properly *(1,10)*.

HOW THE LUNG DEVELOPS

The human lung begins to develop as an outgrowth from the foregut and undergoes a complex series of linear growth and branching that is internally programmed within the primitive epithelial and mesenchymal cells that comprise the lung bud. The development of the human respiratory system begins approximately 24 days after fertilization *(13)*. Branching of the airway system down to the terminal bronchioles is complete by 17 weeks *in utero*, but further growth and cellular differentiation continues at various distinct periods until early adulthood *(14)*. Alveolar development starts at 28 weeks of gestation, but by term between one third and one half (150 million) of the ultimate number of alveoli (300–600 million) are present *(15,16)*, the remainder developing rapidly after birth such that the final number is achieved by about 18 months of age *(17)*.

Reciprocal signalling between the overlying epithelium and underlying mesenchymal stem cells, which occurs in a phasic manner during lung development, results in alternating linear growth and branching *(18,19)*. At different stages during branching morphogenesis and alveolar maturation, a series of growth factors and their receptors are engaged in the epithelium and underlying mesenchymal cells to produce a pre-programmed pattern of growth and branching (Fig.1). Linear growth of the airways is promoted by fibroblast growth factors, especially fibroblast growth factor 2 (FGF-2) *(20)*. FGF-2 is intimately involved in the development of the subepithelial basement membrane, whose function is to integrate communication between the epithelium and the underlying mesenchyme *(21)*. FGF-2 *(22)*, as well as other FGFs (FGF-9 and FGF-10) *(23–25)* and the cell adhesion molecule laminin-α5 *(26)*, are encrypted within the subepithelial basement membrane, enabling their biological functions to be finely controlled. At the level of the mesenchymal stem cells, proliferation and differentiation is regulated by *Sonic hedgehog* (*Shh*) protein *(24)* and its target receptor *Patched (Ptc)*. *Shh* increases the expression of *Ptc*, as well as a set of epithelial- and mesenchymal-cell-differentiating factors related to transforming growth factor-β (TGF-β) (TGF-β itself, bone morphogenetic protein-4 (BMP-4) and *Noggin*) *(27)*. Other molecules that contribute to lung development through their interaction with mesenchymal stem cells include proteoglycans *(25)* and metalloproteases (MMP3 *(28)* and MMP9 *(29)*) that mediate remodelling responses within the tissues.

Fig. 1. Development of the fetal lung



In the fetus the lung develops as an outgrowth of the foregut. By differentially regulating the release and actions of growth factors secreted by the epithelium and underlying mesenchymal cells, the airway undergoes branching morphogenesis in which some factors promote linear growth and others branching. Linear growth is driven by epidermal- and fibroblast-growth factors that induce the synthesis and release of metalloprotease enzymes (MMPs) and degradation of extracellular matrix. Growth arrest and branching is promoted by members of the TGF-β family that inhibits epithelial mesenchymal cell proliferation and reduces MMP-induced matrix degradation.

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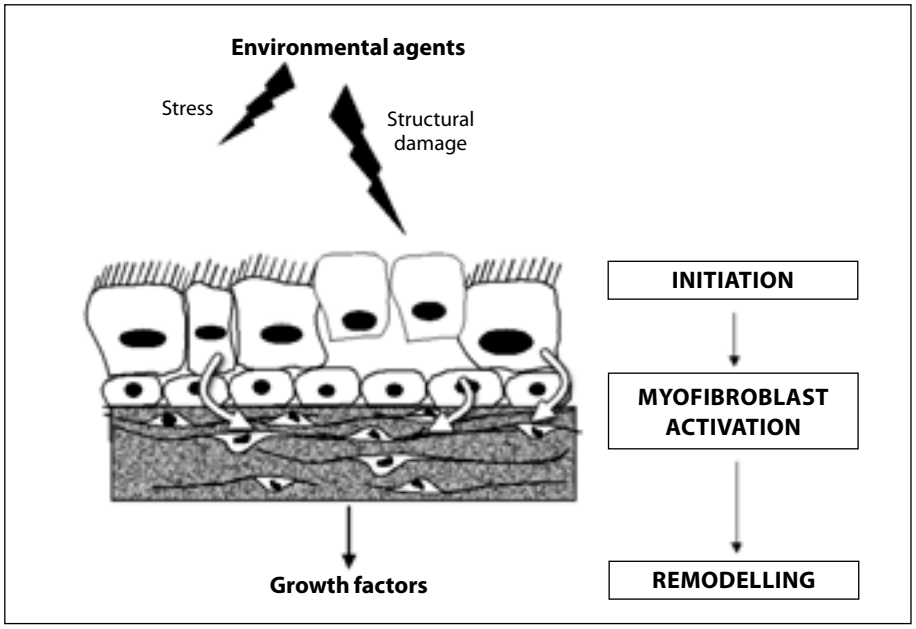
Together, the opposing layers of epithelial and mesenchymal cells in the developing lung comprise the epithelial mesenchymal trophic unit *(30–32)*. The area between the two layers of cells, the basement membrane zone, contains extracellular matrix and a network of nerve fibres. Recognition of the attenuated fibroblast sheath as a distinct layer of resident fibroblasts is not only key to understanding branching morphogenesis in the developing fetal lung but also provides a basis for alterations in structure and function that follow lung injury, either in the fetus through placental transfer of toxicants or during the first few years of infant life by environmental factors that impinge upon the epithelium *(30)* (Fig. 2). It is likely that there is direct communication between the primitive fibroblasts via gap junctions, as described between pericrypt fibroblasts present in the gastrointestinal tract *(31)*. Creation of adhesion plaques and gap junctions provides a means of communication, since the fibroblast sheath is an anatomical unit that is continuous throughout the interstitial space, including the alveoli. The concept of the epithelial mesenchymal trophic unit in establishing the trajectory and pat-

Fig. 2. Effects of environmental agents on airway epithelium



In conditions such as asthma and transplant rejection, damage to the airway epithelium and reduced capacity to efficiently repair leads to the production of pro-fibrogenic growth factors, with the capacity to "remodel" the airways and cause thickening. It this way, the aberrant epithelial–mesenchymal communication in response to injury recapitulates some of the events in lung morphogenesis shown in Fig. 1.

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tern of lung development *in utero* and during the first few years of postnatal life is fundamental to understanding how maternal diet and exposure to environmental chemicals might influence lung development and maturation *(33,34)*. This includes alveolar development in the first three to five years of life *(35–37)* and the response of the airways and alveoli to environmental insults associated with chronic diseases such as asthma *(38–42)*.

INFLUENCE OF POLLUTANTS ON LUNG DEVELOPMENT

As in the differentiation and maturation of any organ, toxic substances that cross the placenta may influence development. It has long been known that tobacco smoking by the mother is one of the strongest environmental risk factors for developing asthma, through its effects on lung morphogenesis linked to altered mesenchymal function and abnormal airway alveolar attachment points *(35–37)*. Maternal smoking also alters cytokine production, thus predisposing infants to allergy.

At present it is not known whether maternal exposure to high ambient air pollutant levels influences intrauterine lung development, although profound effects

have been observed both in ferrets and in non-human primates over the postnatal period. Rasmussen & McClure have described effects of NO_2 (0.5 ppm and 10 ppm) on postnatal lung development in ferrets *(38)*. Over an exposure period of 14 weeks, these concentrations of NO_2 resulted in thickening of the alveolar walls, increased cellularity and collagen deposition indicative of oxidant damage. It remains possible that both the developing fetal lung and the postnatal lung during alveolar growth and maturation are especially sensitive periods, when air pollutant exposure impairs responses as revealed in epidemiological studies.

Ozone is a more powerful oxidant than NO_2, with a clearly defined effect in causing acute exacerbations of asthma, impairing lung growth and resulting in a greater decline in lung function over time, especially in children of low birth weight *(39)*. Acute inhalation of ozone damages both proximal and distal airway epithelium, initiating a cascade of inflammatory and functional responses that subside as the airway epithelium undergoes repair *(40)*. In adult rhesus monkeys, episodic exposure to ozone at high ambient concentrations, as experienced during photochemical pollution episodes, causes an altered response to ozone-induced epithelial damage resulting in a diminution of inflammation and reduced epithelial cell proliferation. This diminished response to ozone-induced injury is associated with progressive airway remodelling, characterized by epithelial cell hypertrophy, hyperplasia and interstitial fibrosis *(41)*. The possibility that ozone may alter the normal postnatal development of the lung is indicated by the identification of growth factors important in lung repair following injury, many of which are also involved in fetal lung morphogenesis. Thus, remodelling of the lung by environmental agents in many ways recapitulates the cellular and molecular pathways of lung development *(42)*. As a result, infants repeatedly exposed to ozone would be expected to demonstrate alterations in the regional distribution and relative amounts of individual growth factors within the lung, which might compromise morphogenesis and lung maturation.

Environmental factors frequently interact. In the rhesus monkey, episodic exposure to ozone and house dust mite antigen deplete the basement membrane zone of the proteoglycan perlican and cause atypical development of this subepithelial zone *(43,44)*. When studied in more detail, this dual insult resulted in altered regulation of fibroblast growth factors (e.g. FGF-2) in the airway epithelial mesenchymal trophic unit. The authors suggested that alterations in FGF-2 regulation are associated with atypical development of the lung observed in rhesus monkeys after exposure to ozone. In infant monkeys sensitized to house dust mites, a combination of allergen and ozone exposure resulted in a greater inflammatory and mediator response as well as evidence of substantially greater airway wall remodelling than with either of these stimuli given alone *(44,45)*.

If translated to humans, this would suggest that atopic children exposed to cyclical high ambient ozone concentrations, as reported in cities such as Mexico City *(39)*, might be at greater risk of developing asthma or disease of greater severity

than would those exposed to clean air. Whether a similar effect could occur with other pollutants such as nitrogen dioxide or particulates, alone or in combination, requires further study. Preliminary evidence with diesel particulates in non-human primates suggests that similar responses to ozone occur, although the mechanisms have yet to be defined *(46)*. The dramatic effect of high ambient ozone concentrations on the epithelial mesenchymal trophic unit in the developing primate lung, in disorganizing the basement membrane and altering its interaction with growth factors and cytokines, has clear implications for the epidemiological studies that report adverse effects of air pollutants on lung growth *(47,48)*.

ENHANCEMENT OF ALLERGIC INFLAMMATION

Asthma and rhinitis are characterized by polarization of the immune response to a subset of T helper lymphocytes, designated Th2, with release of a range of pro-allergic cytokines encoded in a cluster on chromosome 5q31-34. There is subsequent recruitment of mast cells, eosinophils and basophils. Further, B lymphocytes tend to release IgE, the allergic antibody, instead of IgG or IgM *(49)*. Recently, there has been an increased focus on the role of vehicle-related air pollutants, specifically diesel exhaust particles (DEPs), in exacerbating allergic airways inflammation *(50)*. In rodents, DEPs have been shown to exert a mucosal adjuvant effect to enhance existing allergic inflammation, including IgE production *(51)*, the hallmark of atopy. Simultaneous exposure of DEPs with allergen in the human upper respiratory tract markedly increases IgE levels specific to the allergen while deviating the cytokine repertoire towards a Th2-like pattern *(52)*. DEPs have been shown to interact with ragweed allergen in the nasal mucosa, to drive in vivo isotype switching to IgE and to induce sensitization to a new allergen in people who otherwise would not become sensitized *(53)*. DEPs have also been shown to directly activate both mast cells *(54)* and basophils *(55)* for inflammatory mediator independent of IgE signalling. Taken together, these studies provide a basis whereby exposure to one form of particulate pollution may induce allergic sensitization. It is not known whether exposure to ambient air pollutants can enhance allergic sensitization in children, although there is evidence in non-human primates of a positive interaction between ozone and house dust mite exposures in enhancing both the immunological and inflammatory airway responses in sensitized animals in parallel with airway remodelling *(44,56)*. In vitro, interleukin-4 and interleukin-13, two important Th2 cytokines produced in allergic inflammatory responses, are able to interact with the epithelial mesenchymal trophic unit to enhance TGF-β and related growth factor production, thereby providing a mechanism for further driving airway remodelling *(57)*.

INTERACTIONS BETWEEN AIR POLLUTANTS AND INFECTIONS

There is an emerging literature indicating that innate immunity plays a key role in setting the direction of immune responses early in life *(58)*. Antigen-presenting

cells such as dendritic cells in the lung, as well as the epithelium itself, express a range of pattern recognition or toll-like receptors (TLR) that can be activated by a large range of biological pollutants in the environment. Examples of such interaction include double-strand viral RNA with TLR3, bacterial endotoxin (lipopolysaccharide) with TLR4 and unmethylated bacterial DNA (CpG) with TLR9 *(59)*. Activation of these receptors serves as a "danger signal" and redirects the behaviour of an antigen-presenting cell if stimulated at the same time as contact with allergen occurs. Since chemical air pollutants are often encountered in the same environment as infectious agents or components of them, it is highly likely that at least some interaction occurs. One example of this is the influence of endotoxin exposure in reducing allergen sensitization in children and associated rhinitis and asthma *(60,61)*. This, in part, might explain why children raised in urban environments have in general a higher incidence of allergy than those raised in the countryside and on livestock farms *(62)*. Since diesel particulates have been shown to augment the pro-inflammatory activity of microbial components acting through toll receptors *(63,64)*, it is possible that this will have consequences if a child comes into contact with an infectious agent at the same time. Clearly, this is an important area for future research.

GENETIC SUSCEPTIBILITY TO AIR POLLUTANT-INDUCED LUNG INJURY AND REPAIR

It is now becoming clear that gene–environment interactions are pivotal in determining the susceptibility of individuals to the injurious effects of air pollutants and their long-term effects *(1,33)*. The first line of antioxidant defence resides in the fluids lining the airways and alveoli, which are rich in a range of enzymatic and low-molecular-weight non-enzymatic antioxidants such as vitamins C and E *(3,34)*. Epithelial cells in the airways and alveoli are protected against oxidative stress by a wide range of defences, including members of the glutathione *S*-transferase (GST) superfamily (GSTM1, GSTT1 and GSTP1). The GST enzymes use a wide variety of products of oxidative stress as substrates and have an important role in neutralizing reactive oxygen species. Common genetic variants of the GST genes exist, and some of these are associated with severe inflammatory disorders, including asthma. For example, Gilliland et al. *(65)* have reported that GSTM1-null children exposed to tobacco smoke *in utero* have an increased prevalence of early-onset asthma and a range of other respiratory conditions, and that the GSTP1 genotype increases both the risk and severity of respiratory infection in school-age children. Further studies by the same group have shown that the GSTM1-null or GSTP1 Ile105 genotypes exhibit enhanced nasal allergic responses to diesel exhaust particles *(66)*. The GSTM1-null children showed a larger increase in IgE and histamine in nasal lavage fluid after exposure with DEPs or allergen than children with a functional GSTM1 allele. Because DEPs comprise approximately 40% of the PM_{10} in major cities, these findings have implications

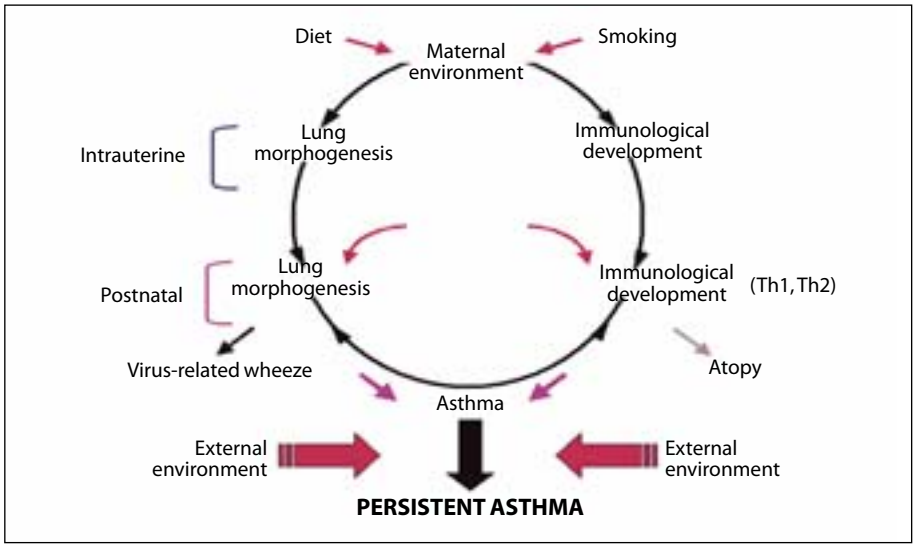
for the health consequences of ambient air pollution. The ability of DEPs to enhance allergic responses is highly repeatable within individuals *(52)* and supports the view that genetic factors are important in determining individual sensitivity to air pollution. At an epidemiological level, a further study has shown that asthmatic children in Mexico City with a genetic deficiency of GSTM1 may be more susceptible to the deleterious effects of ozone on their small airways *(67)*. Supplementation of the diet with vitamin C (250 mg/day) and vitamin E (50 mg/day) compensates for this genetic susceptibility. It remains possible that the association between the antioxidant status of the diet and the clinical manifestations of asthma are mediated through this mechanism.

More recent epidemiological and chamber studies have also demonstrated that the –308-promoter polymorphism of TNFα increases the sensitivity of the airways to the bronchoconstrictor response to inhaled sulfur dioxide *(68)* and ozone *(69)*.

CONCLUSIONS

The intrauterine, perinatal and early childhood periods, during which the lung is developing and maturing, constitute a particularly vulnerable time during which

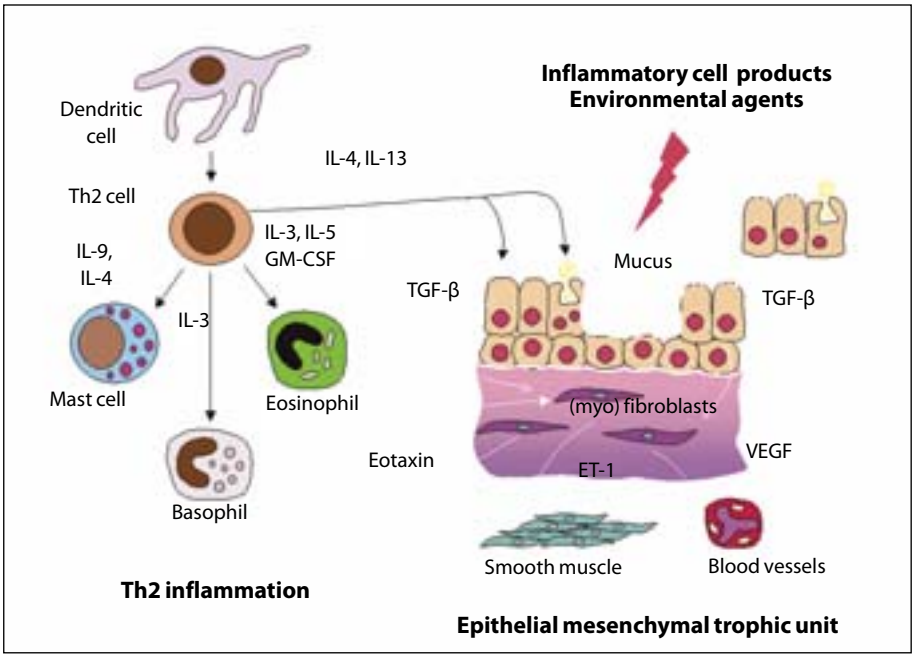
Fig. 3. Early life interactions in the development of asthma



Important genetic and intrauterine environmental interactions are implicated in determining lung development, such as tobacco smoking and diet that influence both lung growth and maturation, as well as development of a competent immune response. In the case of allergic disease in the offspring, reduced Th1-type and increased Th2-type immune responses extend into early childhood to increase the risk of allergy developing. For this to manifest itself in a specific organ such as the lungs, morphogenetic genes are involved that also have complex interactions with environmental factors. When these two components come together, clinical atopic disease emerges on further exposure to environmental insults.

air pollutants may exert deleterious effects. With the knowledge that air pollutants can also enhance pro-allergic pathways in those genetically at risk, additional plausibility is provided for the potentially injurious effects of ambient air pollutants in the causation of paediatric lung disease, including asthma. The interaction between Th2-mediated inflammation and the epithelial mesenchymal trophic unit provides a basis for the origins of asthma, one set of environmental and genetic factors being responsible for predisposing to atopy and the other towards structural changes of tissue remodelling (Fig. 3). One intriguing possibility is that the structural changes in the airways characteristic of asthma occur very early in life (e.g. before or shortly after birth) and are necessary to provide the microenvironment for Th2-mediated inflammation associated with atopy to take up long-term residence in the airways, a characteristic feature of chronic asthma. Thus, what has previously been termed "remodelling" sequential to inflammation may need to be renamed "premodelling" when applied to the onset of asthma. The genetic basis of lung growth and asthma (as opposed to atopy) may reside within

Fig. 4. The interaction between airway inflammation and tissue remodelling in the pathogenesis of asthma



A disease such as chronic asthma necessitates both Th2-type inflammation and an abnormal tissue response, with important interactions between the two. The interactive nature of the epithelium and associated mesenchyme has led to the term "epithelial mesenchymal trophic unit" to capture the concept that these cells are also involved in lung development and will be susceptible to environmental insults, including air pollutants.

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the structural elements as well as involve immune or inflammatory cells *(70)*. The importance of air pollutants alone or in concert with other environmental insults such as respiratory virus infections *(71,72)*, allergen exposure *(44,73,74)* and diet in driving the epithelial mesenchymal trophic unit towards a chronic asthma phenotype (Fig. 4) will only be recognized once careful monitoring of the environment and genetic susceptibility of the host are taken into account in relation to lung development over time.

SUMMARY

- The developing fetal lung, as well as the infant lung, is more susceptible to injury by lung toxicants that include air pollutants at doses below the no-effect level for adults.
- Detoxification systems exhibit a time-dependent pattern during pre- and postnatal lung development that in part accounts for the increased susceptibility of young children to pollutants, with critical points when susceptibility is higher than at other times.
- Animal studies indicate that intrauterine as well as postnatal exposure to pollutants can lead to impaired lung growth, a feature that has also been described in population-based longitudinal birth cohorts.
- Exposure to diesel particulates, both in vitro and in vivo in animals and humans, enhances the generation of the allergic antibody IgE and sensitization to aeroallergens.
- Polymorphic variation in susceptibility genes involved in protecting against or driving tissue injury and repair explains some of the variation in individual susceptibility to the adverse health effects of pollutants.
- Based on current knowledge, air pollutants interact with other environmental exposures, such as allergens, viruses and diet, that influence the overall impact of air pollutants on children's health.

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ACUTE RESPIRATORY INFECTIONS

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INTRODUCTION

A major burden of respiratory illness in children and adults is due to the morbidity and mortality associated with acute respiratory infections (ARIs) *(1)*. A reported four million deaths globally were attributed to respiratory infections between 1997 and 1999 *(2)*. In Europe in 2001, ARIs were responsible for a quarter of all deaths in children under five. Many socioeconomic factors contribute to the risk of ARIs in children, including poor sanitation, low birth weight and poverty, but indoor and outdoor air pollution is a growing problem. A relationship between indoor pollution and respiratory infections (especially in developing countries) has been recognized for at least two decades and has recently been reviewed elsewhere *(3–5)*. This review focuses on the relationship between outdoor air pollution at levels encountered in Europe and the risk and severity of acute respiratory infections in children.

IDENTIFICATION OF EVIDENCE

Our search strategy and selection criteria included the key words "air pollution" and "infection" (both alone and in combination). This produced from Medline over 15 000 references for air pollution, over 40 000 for infection and 609 for the two combined. The present review is therefore of necessity our selection of some of the major and important studies pertaining to the outdoor pollutants encountered in Europe, including studies conducted elsewhere in areas with pollutant levels appropriate for Europe. We have also included studies relevant to the biological and mechanistic considerations. The review is based on a systematic Medline search up to late 2004 and on over 10 years of research in the field.

BIOLOGICAL CONSIDERATIONS

Mechanisms of interaction between infection and air pollution

The lung's defence against inhaled particles and gaseous pollutants include innate mechanisms such as aerodynamic filtration, mucociliary clearance, particle transport and detoxification by alveolar macrophages, as well as local and systemic innate and acquired antiviral immunity. In particular, alveolar macrophages provide an innate defence mechanism against bacteria and viruses. Virus particles are ingested by phagocytosis and macrophages, in common with epithelial and other virus-infected cells, produce interferons that potently inhibit

viral replication. Macrophages will also contribute to the neutralization of viral infections by removing the debris of the destroyed, virus-containing cells and by presenting viral antigens to T lymphocytes. In addition to the resulting humoral immune response, cell-mediated responses such as the development of cytotoxic T lymphocytes (capable of destroying cells infected with virus), play an important role in the control of many viral infections of the respiratory tract. Many of these functions can be modulated by exposure to PM_{10}, nitrogen dioxide and other pollutants in experimental models.

Infectivity models and impaired local immunity

The effects of pollutants on pulmonary antibacterial activity following exposure and disease leading to death have been studied in animals. The majority have been performed using rodents, using different acute exposures to determine the concentrations of pollutants at which antibacterial defences are overwhelmed. A detailed discussion is beyond the scope of this review, but impairment of pulmonary bactericidal capacity and an increased risk of reinfection following exposure have been described *(4)*.

Collective evidence from both animal and human models provides some evidence of alterations in local bronchial immunity. Acute exposure to oxidant pollutants results in ciliostasis in both the upper *(6)* and lower airways *(7)*, which may prevent the nasal and bronchial mucosa from filtering inhaled particles such as aero-allergens, bacteria and viruses delivered to the airway. In studies from the United Kingdom (performed in the absence of antioxidant protection), exposure of cultured human bronchial epithelial cells to nitrogen dioxide concentrations of >1000 $\mu g/m^3$ reduced ciliary beat frequency and caused ciliary dyskinesis. These observations have been confirmed in a study of 24 healthy subjects in vivo *(8)*. Studies investigating single exposures to nitrogen dioxide and other oxidant pollutants have found increases in mast cells, lymphocytes and natural killer cells in BAL fluid *(9)*. Studies of repeated exposure to 7520 $\mu g/m^3$ nitrogen dioxide have shown evidence of impaired local bronchial immunity by demonstrating reductions in one or more of the following: total macrophages, B cells, natural killer lymphocytes and peripheral blood lymphocytes; and also by a reduction in the T-helper-inducer/T-cytotoxic-suppressor ratio in alveolar lavage *(10)*.

Alveolar macrophage interactions

Recent work has suggested that pollutant particles are able to penetrate the lower airway in children ranging in age from 3 months to 16 years. This has been confirmed by the detection of heterogeneous particles in alveolar macrophages (AM) recovered by broncho-alveolar lavage *(11)*. Furthermore, the percentages of particles containing alveolar macrophages were increased in children who lived on a main road compared with those living on a quiet residential road (median 10% vs 3%). Taken together with evidence from epidemiological and controlled animal

and human studies, it is likely that alterations in alveolar macrophage function are important in the increased probability of infection. Activated macrophages provide protection against bacterial and viral infections by a variety of mechanisms including oxygen dependent pathways involving superoxide radical-anion mechanisms (e.g. myeloperoxidase) and cytokine production.

Exposure of human alveolar macrophages to concentrations of nitrogen dioxide ranging from 188 to 940 μg/m^3 for short durations resulted in a functional impairment of the macrophages without significant alterations in cytotoxicity *(12)*. More recent work investigated exposure to particulates of three size ranges between PM_{10} and $PM_{0.1}$ and the effect on antigen-presenting cells by evaluating the expression of four surface receptors involved in T cell interaction on both human alveolar macrophages and blood-derived monocytes. Monocytes increased the expression of all four receptors in response to each of the particle fractions, whereas expression was unaffected in alveolar macrophages. When monocytes and alveolar macrophages were separately exposed to the three PM size fractions and assessed for T helper lymphocyte chemoattraction (by production of IL-16), alveolar macrophages alone (and not monocytes) produced IL-16, and this chemoattractant was released only in response to $PM_{2.5}$–PM_{10}. This suggests that a wide size range of pollution particles contain materials that may promote antigen presentation by monocytes, while the ability to specifically recruit T helper lymphocytes is contained in alveolar macrophages stimulated with the "coarse" PM fraction *(13)*. When the experiments were extended to different particle sizes and compositions, the response of alveolar macrophages were highly variable, leading the authors to conclude that composition rather than size was responsible for the oxidant response and that oxidant activation by various sources of particulate matter is cell-specific *(14)*.

In considering interaction with viral infection, it is known that alveolar macrophages from humans, mice and guinea-pigs allow acute respiratory syncytial virus (RSV) infection, production of pro-inflammatory cytokines and reduction in phagocytic capability. In a recent study *(15)*, the sequential effect of RSV infection and PM_{10} exposure on phagocytosis and production of pro-inflammatory cytokines in guinea-pig alveolar macrophages was investigated. The yield of infectious virus was markedly depressed in PM_{10}-exposed alveolar macrophages, regardless of sequence of exposure. Both RSV and PM_{10} exposure increased production of alveolar macrophage TNF-α. Furthermore, exposure of alveolar macrophages to PM_{10} significantly reduced RSV-induced production of IL-6 and IL-8, suggesting an interaction with both virus replication and cytokine production independent of exposure sequence. These observations confirm earlier findings that, in the presence of PM_{10}, the response of alveolar macrophages to RSV is blunted and leads to reduced levels of pro-inflammatory cytokines MCP-1 (macrophage chemoattractant protein-1), MIP-1 (macrophage inhibitory protein-1) and IL-8, and to a 50% reduced uptake of viral antigen. This suggests that alveolar

macrophage-regulated inflammatory responses to viral infection are altered by exposure to PM_{10} *(16)*.

A recent series of studies *(17)* investigated the effect of up to 1000 μg/m^3 diesel particulates (levels likely to be encountered in European outdoor air) in a rodent model. Increases in RSV gene expression (indicating viral replication), lung inflammation, lung morphology and markers of airway epithelial function, and reductions in levels of immunomodulatory proteins and impaired host defence mechanisms were all observed after prior exposure to diesel particulates. The likely interaction with bacterial endotoxins and the mechanism involving activation of the transcription factor NF-κB has recently been described *(18)*. Diesel exhaust particles synergistically enhanced neutrophilic lung injury related to endotoxin from gram-negative bacteria. In the presence of endotoxin, particulates further activated the nuclear translocation of the p65 subunit of NF-κB in the lung and increased the lung expression of ICAM-1 (intercellular adhesion molecule-1), MCP-1, MIP-1 and Toll-like receptors.

The effect of ozone on susceptibility to virus infection has also been investigated. No significant effects were observed with exposure to 2000 μg/m^3 ozone for two hours on the susceptibility of alveolar macrophages to RSV infection or production of pro-inflammatory cytokines *(19)*.

This confirms that at least rodent lungs are susceptible to lung disease in response to RSV infection and bacterial endotoxin with concurrent particulate air pollution *(17)*. These observations suggest that the ability of different pollutants and particle fractions to cause variable defects in bronchial immunity may also determine the risk of symptoms following pollutant exposure and infection.

Epithelial function

Viral infections can cause severe pathological abnormalities in both the upper and lower respiratory tract, although the extent of epithelial damage may vary between viruses. Experimental studies of oxidant pollutant exposure show that the lower airway epithelium (particularly the transitional zone between bronchial epithelium and proximal alveolar regions) is particularly susceptible. In contrast, nasal, laryngeal and tracheal regions are not readily damaged by oxidant pollutants because they have a thicker, extracellular antioxidant hypophase *(20)*. It is possible that the penetration of allergen into the epithelium would be facilitated both by epithelial shedding and by reduced ciliary clearance, resulting in easier access of allergen to antigen-presenting cells and therefore increased inflammation. The epithelium is also an important source of regulatory proteins or mediators with protective roles, such as nitric oxide or bronchodilator prostaglandins E_2 and I_2, which may play a role in maintaining bronchial potency.

The epithelium may also interact directly with viral infections and air pollutants. Recent reports *(21)* describe the infection of primary human (nasal) epithelial cells and the BEAS-2B bronchial epithelial cell line with human rhinovirus

type 16 (RV16) and exposure to 3880 μg/m^3 nitrogen dioxide or 400 μg/m^3 ozone for three hours. Infection with rhinovirus, nitrogen dioxide and ozone independently increased the release of IL-8 through oxidant-dependent mechanisms. The combined effect of RV16 and oxidant ranged from 42% to 250% greater than the additive effect for nitrogen dioxide, the corresponding range for ozone being 41–67%. Both individual and combined effects were inhibited by antioxidant treatment. Perhaps the most interesting observation is that the surface expression of ICAM-1 underwent additive enhancement in response to combined stimulation. These data indicate that oxidant pollutants can amplify the generation of pro-inflammatory cytokines by RV16-infected cells and suggest that virus-induced inflammation in upper and lower airways may be exacerbated by nitrogen dioxide and ozone. Given that ICAM-1 is also the receptor for the major group of rhinoviruses, a potential mechanism for the way in which oxidant pollutants might increase susceptibility to rhinovirus infection is also suggested. Another study *(22)* investigated RSV replication and virus-induced IL-6 and IL-8 production in BEAS-2B cells following exposure to approximately 1000, 2000 and 2500 μg/m^3 nitrogen dioxide. Internalization, release of infectious virus and virus-induced cytokine production were all significantly reduced at the highest level of exposure. This led the authors to conclude that increases in viral clinical symptoms associated with nitrogen dioxide may not be caused by increased susceptibility of the epithelial cells to infection alone, but may result from additional effects of nitrogen dioxide on other aspects of antiviral host defences.

The mechanisms underlying the relationship between infection and the development of lower airway symptoms after air pollution exposure are not fully understood. Oxidant pollutant exposures have the potential to exacerbate the inflammatory effects of virus infections in the lower airway, especially in individuals with pre-existing lung disease. Fig. 1 and 2 summarize some of the mechanisms that may be involved in the synergistic interaction.

EVIDENCE REVIEW

Controlled exposure studies

Largely owing to methodological difficulties and ethical constraints, only a limited number of studies have been conducted on the effects of controlled pollutant exposure and infection in humans, and none in infants and children. There is some evidence from controlled exposure of a link between "acid summer haze" and increased symptoms in 9–12-year-old children with allergies and asthma *(23)*. A few studies in young adults suggesting an interaction with infection are discussed briefly here.

Three studies have investigated alveolar macrophage function after exposure to oxidant pollutant exposure in vivo and infection in vitro. In one study, nine volunteers were exposed to >1000 μg/m^3 nitrogen dioxide continuously, or interspersed with three 15-minute peak levels of >3500 μg/m^3 nitrogen dioxide, and

Fig. 1. The biological mechanisms of interaction between air pollutants and viral infections

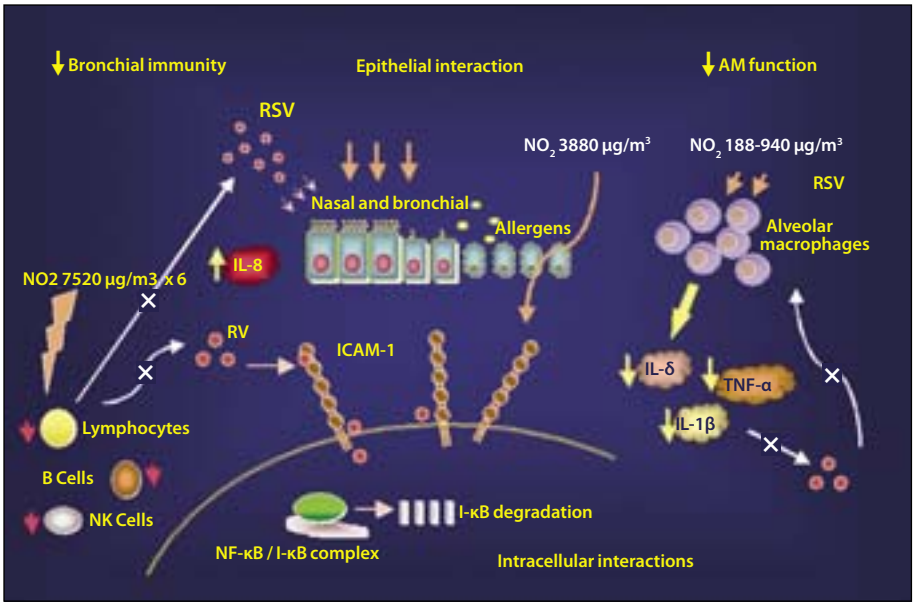

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Fig. 2. The synergistic pathological and immunological interactions between air pollutants and viral infections

Effect	Pollutant	Infection
Bronchoconstriction	+	+++
Bronchial hyperresponsiveness	+	+++
Inflammatory mediator release	++	+++
Ciliary dyskinesis	++	+++
Inflammatory cell activation	++	+++
Epithelial damage	++	++/±
T lymphocyte function	++	+++
Alveolar macrophage function	+++	++
Interaction with allergens	++	+++
↑ Epithelial-derived cytokines	++	+++
↓ Macrophage-derived cytokines	++	+

'mild' +
'moderate' ++
'severe' +++

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alveolar macrophages were obtained by lavage and incubated with influenza virus *(24)*. Alveolar macrophages from four of the nine people showed depressed inactivation of the virus, whereas five showed no difference. There were no differences from the intermittent peak exposure group. This indicates that differences in susceptibility to infection after oxidant pollutant exposure could occur in a larger population. Another study investigated the effects of exposure to high nitrogen dioxide levels (9400, 18 800 or 28 200 μg/m^3) in vitro on alveolar macrophages obtained from 15 people *(25)*. After stimulation with influenza virus, cells exposed to both air and nitrogen dioxide released increased amounts of IL-1 (indicating macrophage activation) but there was no significant difference between groups. The results suggest that human alveolar macrophages are resistant to injury by nitrogen dioxide in vitro and that those toxicity effects of nitrogen dioxide may require local factors in the lung. In another 10 people exposed to >3500 μg/m^3 nitrogen dioxide, alveolar macrophages obtained by lavage showed a 42% reduction in ability to phagocytose *C. albicans* and a 72% decrease in superoxide production (superoxide production being important in phagocytosis) *(26)*.

A study using 152 young volunteers reported exposure to 1880 or 3760 μg/m^3 nitrogen dioxide, two hours a day for three days, and challenge with influenza A virus immediately after exposure *(27)*. Although only one of the volunteers developing any symptoms, 91% of those exposed to nitrogen dioxide became infected (as determined by virus recovery and/or antibody titres) compared with 71% of air-exposed controls. This difference was not, however, statistically significant. As most of the infected subjects did not become ill, the study could address the effect of nitrogen dioxide exposure on infection but not on severity of illness. A smaller study of 24 healthy volunteers investigated upper airway inflammation following inoculation with type 39 rhinovirus and ozone exposure at 600 μg/m^3 for six hours per day over five days. There were no differences in rhinovirus titres in nasal secretions, recruitment of neutrophils into nasal secretions or levels of interferon in nasal lavage fluid *(28)*.

These limited studies suggest, though they do not prove, that oxidant pollutants may play a role in increasing susceptibility to respiratory viral infections. The levels of pollutants used, however, have been far in excess of those encountered in most European cities, and experimental infection may not mimic naturally occurring upper respiratory infections.

Epidemiology: outdoor and indoor air pollution and symptoms

The combustion of fuels in European countries produces a variety of outdoor pollutants, principally nitrogen dioxide, ozone, sulfur dioxide and PM_{10}, the most consistently studied being PM_{10} and nitrogen dioxide. Both are produced in indoor and outdoor air from sources such as gas stoves, fires, fossil fuels and motor traffic. There is increasing evidence to suggest that exposure to these pollutants is linked to respiratory disease in children and adults in the developed world.

In a similar fashion to those of other pollutants, many of the epidemiological studies of outdoor nitrogen dioxide and PM_{10} exposure have found associations between exposure to the pollutant and health effects, often at levels well below current WHO guidelines. For nitrogen dioxide, for example, these health effects have included visits to accident and emergency departments *(29,30)*, hospital admissions *(31,32)*, mortality *(33,34)*, increased symptoms *(35,36)*, school absenteeism due to respiratory illness *(37)* and reduced lung function *(38,39)*.

There are many methodological issues that complicate the interpretation of outdoor pollutant studies, such as exposure misclassification, confounding, colinearity and insensitive measures of health effects. Consideration of the effects of any air pollutant will require a balanced risk estimate based on both indoor and outdoor exposures and the effect of personal exposure. A detailed discussion of factors determining indoor and outdoor exposure to other pollutants is beyond the scope of this review, but the risks based on outdoor exposure should not be taken in isolation of information already available from indoor exposure studies. In this review, studies showing associations between respiratory symptoms attributed to infections from point sources of pollution have not been included *(40–42)*.

Defining infections

Respiratory infections are common and of variable severity, yet difficulties remain in defining clinically significant respiratory infections. ARIs include clinical conditions of different etiology and severity and are divided into two main groups: upper respiratory tract infections (URTIs) and lower respiratory tract infections (LRTIs). The risk of severe ARIs is greatest in very young children and in the elderly. While there are clinical and epidemiological criteria for separating URTIs from LRTIs, there are no uniformly accepted criteria and the definitions in use are not consistent between studies.

For epidemiological research in less developed countries, WHO defines URTIs as a combination of symptoms including one or more of the following: cough with or without fever, blocked or runny nose, sore throat and ear discharge *(43)*. URTIs are usually viral in origin and include the common cold viruses such as rhinoviruses and coronaviruses, which can usually be managed successfully with supportive care at home without antibiotics. In contrast, LRTIs can range in severity from mild to severe ARIs involving lung infection with cough and dyspnoea, bronchitis and pneumonia being the most serious forms. Clinically significant infections are commonly caused either by bacteria or viruses, and the severity of infection does not always allow confirmation of the infective etiology of such episodes. Clinical signs of severe LRTIs in children include rapid respiration, chest in-drawing and/or stridor. Such effects cannot readily be estimated in epidemiological studies, but severity can be assumed if the infection leads to hospital admission compared to the primary care treatment of less severe infections.

Furthermore, URTIs and LRTIs are not mutually exclusive. These clinical conditions frequently coexist during the same episode of respiratory infection. Bacteria and viruses cause infection in both the upper and lower respiratory tracts, and upper respiratory infection is often followed or accompanied by lower respiratory infection. This is particularly important in those children with pre-existing respiratory disease such as asthma and cystic fibrosis, where URTIs are more frequently accompanied by lower respiratory symptoms or infection. For example, it has been confirmed that viral URTIs are the major precipitants of acute exacerbations of asthma in children *(44)* and that episodes of viral infection are strongly associated in time with increases in hospital admissions for asthma *(45,46)*. In the former study, human rhinoviruses alone accounted for 50% of exacerbations. If adequate virus detection methods are used, viruses are detected in the vast majority of children (>80%) and infants (up to 100%) admitted to hospital with acute URTIs and LRTIs. These data demonstrate that acute episodes of upper and lower respiratory illness in predisposed children, both in the community and in those admitted to hospital, are related to virus infections. Most of the epidemiological indoor pollution studies have alluded to the presence of respiratory infection, although until recently very few (including those from the developing world) have attempted to confirm the presence of infection microbiologically.

In brief, studies of indoor and outdoor pollutants and ARIs in children (and adults) suggest a relationship but few have confirmed infection microbiologically, instead relying on clinical criteria based on symptoms. Consequently, little is known of the spectrum of infectious agents or whether these pollutants increase susceptibility to infection generally or to individual infectious agents, or whether they exacerbate pre-existing morbidity following infection. This review will focus on studies on outdoor air pollution in which the nature of the respiratory illness has been attributed to infection by diagnosis or case definition according to the symptoms outlined above. Those studies, using clinical descriptions of disease such as "colds", "croup" and "bronchitis", have been grouped according to whether they relate to the upper or lower respiratory tract.

The irritant effects of air pollutants such as sulfur dioxide on the upper and lower respiratory tracts are known, and studies related to nonspecific symptoms and not attributed to infection have not been included in this review. Epidemiological studies include time series, cross-sectional, case-control, cohort and longitudinal analyses. Owing to the multi-component nature of outdoor air pollutants and the difficulties in separating out the effects of single pollutants in individual studies, pollutants have been considered together. It is likely that clinical infections requiring admission to hospital represent a more severe spectrum of disease than those occurring in the community; these have therefore been considered separately. The following examines the relationship between outdoor pollutants at levels likely to be relevant to European exposures and symptoms likely to be related to infections.

URTIs in the community

There has been a series of studies investigating the link between URTIs and air pollution (particularly by nitrogen dioxide). Two studies investigated the incidence of croup (laryngo-tracheo-bronchitis, commonly due to parainfluenza viruses) and air pollution. The effects of nitrogen dioxide, total suspended particulates (TSP) and sulfur dioxide exposure were investigated in more than 6000 paediatrician-reported cases of croup and more than 4500 cases of "obstructive bronchitis" in five German cities over three years *(47)*. Increases in TSP and nitrogen dioxide levels of 10 and 70 $\mu g/m^3$, respectively, were associated with 27% and 28% increases in cases of croup. In illustration of the point made earlier, the close relationship between TSP and nitrogen dioxide levels did not allow their causal effects to be separated. In three other German cities *(48)*, levels of sulfur dioxide, nitrogen dioxide, carbon monoxide, ozone and dust were analysed in relation to 875 cases of croup over a 24-month period. There were significant associations between croup frequency and the daily mean levels of nitrogen dioxide for the period between September and March (the peak virus season) and with daily nitrogen dioxide and carbon monoxide levels over the whole year.

Several studies have compared the incidence of URTIs between historically high and low outdoor pollutant areas. The findings from studies comparing health effects between areas with different air pollutant levels have varied in the quality of study design. Many co-factors determine the risk of ARI in children. For example, poor socioeconomic status, living in crowded areas and family size may be correlated, and potential biases from confounding and effect modification are important issues in interpreting the epidemiological evidence. The following include studies that have made some allowance for such factors.

Three cities in Finland with pollution levels ranging between "high" and "low" were studied over a 12-month period, the studies including 679 cases of parent-reported URTIs and 759 controls *(49)*. The annual mean concentration of nitrogen dioxide in the more polluted city was 15 $\mu g/m^3$ higher than in the other two. The odds ratios for one or more URTIs in children in the polluted city versus those in the less polluted cities were 2.0 in the younger age group and 1.6 in the older age group. The authors did not separate the effects of the individual pollutants in the analyses. The pollutant concentrations were within WHO guidelines, even in the most polluted city. Another study from Finland compared weekly changes in sulfur dioxide and nitrogen dioxide levels and temperature with respiratory infection in children (and adults) and absenteeism from day-care centres and schools during a one-year period. The annual average level of sulfur dioxide was 21$\mu g/m^3$ and that of nitrogen dioxide 47 $\mu g/m^3$. Higher levels of sulfur dioxide were associated with the numbers of URTIs, and a 15% increase in URTIs was observed when the sulfur dioxide level was above the mean *(50)*. The sulfur dioxide levels and temperature were significantly correlated.

Further similar studies have (to date) been published in the respective national languages only. In a comparison of a highly polluted with a less polluted area of the former German Democratic Republic from 1978 to 1988, the incidence of URTIs was higher in infants and children in an area with higher urban air pollution, with a significant relationship with sulfur dioxide in colder areas and with school absenteeism due to URTIs *(51)*. In a study in the Czech Republic, 452 children were followed for the first three years of life. Those born in Teplice (higher pollution, mainly sulfur dioxide) showed a significantly higher rate of ear and gastrointestinal symptoms, URTIs and pneumonia, but did not differ in their risk for bronchitis *(52)*.

A recent study has investigated traffic-related pollutants and the risk of a spectrum of respiratory diseases, including infections. This study, in the Netherlands, investigated a birth cohort of 4000 children at two years of age and related symptoms including URTIs, with validated models of traffic-generated pollutants outside the home of each child. Positive associations were observed but few were statistically significant *(53)*. A cohort study in the United Kingdom *(54)* investigated the effects of winter outdoor nitrogen dioxide, sulfur dioxide, sulfate and PM_{10} levels on daily peak expiratory flow (PEF) and the daily presence or absence of URTIs assessed by diary over two months. There were no clear effects of any pollutant on daily mean PEF, but when reductions in PEF were analysed as a dichotomous variable (<20% or >20% decrement from median PEF), consistent associations with five-day lag nitrogen dioxide (odds ratio 1.043), sulfate (odds ratio 1.090) and PM_{10} (odds ratio 1.037) were observed. The effects of PM_{10} were stronger in wheezy children (odds ratio 1.114). The odds ratios corresponded to a 10–48% increase in odds of a large decrement in PEF for a 20-$\mu g/m^3$ increase in pollutant. There were no consistent associations between large decrements and ozone or sulfur dioxide levels.

Two community panel studies measured personal, fixed-site and outdoor monitoring of nitrogen dioxide exposures in children in relation to heterogeneous upper respiratory symptoms related to infection. In a study in Finland on 172 children aged 3–6 years, there were more days of reported "stuffy nose" (26% vs 20%) and cough (18% vs 15%) in a central polluted area than in a less polluted suburban area *(36)*. In a study in Australia, 388 children aged 6–11 years were followed longitudinally with 1- and 6-hourly nitrogen dioxide monitoring over 2–9 weeks in 41 classrooms and outdoors. There were significant dose–response relationships for sore throat, cough, colds and absences from school for 1-hourly levels ≥150 $\mu g/m^3$ compared to background levels of 40 $\mu g/m^3$ *(55)*.

It is possible that more severe URTIs lead to health care use, such as visits to primary care practitioners, than the URTIs of heterogeneous severity observed in panel, cross-sectional or cohort analyses. Several studies have recently investigated the effect of outdoor air pollution on visits to primary care or general practitioners, allowing for confounding factors such as season, weather and pollen con-

centration. A total of 36 112 consultations, of which 31 303 were for URTIs, were studied in the Hong Kong Special Administrative Region of China *(56)*. The mean daily PM_{10} concentration was 49.6 μg/m^3, and each 10-μg/m^3 increase in PM_{10} was associated with a very small but significant risk of URTI (1.0301) and all respiratory illness (1.0328). A study in the United Kingdom investigated general practitioner consultations for upper respiratory tract diseases, excluding allergic rhinitis (and therefore likely to be URTIs), with outdoor pollutants. In children aged 0–14 years, a 3.5% increase in such consultations was observed with an increase in sulfur dioxide levels between the 10th and 90th centiles (13–31 μg/m^3) *(57)*. Significant and stronger associations were observed for consultations by adults. Another large study in Taiwan, China evaluated daily pollutant levels and primary care clinic visits for lower respiratory tract infections. There was an average of 2.5 visits per 1000 children aged 0–14 years, and same-, one- and two-day pollutant lags were considered. Increases in consultations ranging from 0.3% to 1.3% were seen for a 10% increase in levels of nitrogen dioxide, sulfur dioxide and PM_{10} *(58)*.

LRTIs in the community

A cross-sectional study *(59)* examined 4470 children aged 6–15 years living in 10 different areas in Switzerland. Reported rates of chronic cough and bronchitis were investigated in relation to PM_{10}, nitrogen dioxide and sulfur dioxide levels. The average levels of outdoor pollution were moderate, the nitrogen dioxide level varying between 12 and 50 μg/m^3 and that of PM_{10} between 10 and 33 μg/m^3. The risk of bronchitis between the most and least polluted areas was significant, with an odds ratio of 1.35 for nitrogen dioxide and 2.17 for PM_{10}. There was no association with asthma or allergic symptoms. This study was one of a series from Switzerland, the others being performed in adults. They show an effect at levels well below concentrations seen in many European countries.

One of the largest comparative studies in Europe investigated the prevalence of infectious airways diseases and levels of outdoor sulfur dioxide and TSP *(60)*. The outcomes, including pneumonia, tonsillitis and number of colds relating to infection, as well as other allergic symptoms, were studied cross-sectionally in 19 090 children. Four areas in eastern Germany and two in western Germany were studied every year from 1991 to 1995, over which period outdoor sulfur dioxide and TSP levels showed a sharp decline. Most airways diseases were more frequent in eastern than in western Germany in 1991 and were associated with sulfur dioxide or TSP. The decrease in these pollutants from 1991 to 1995 in eastern Germany was mirrored by similar reductions in the prevalence of infectious symptoms. Allergies and related symptoms showed no differences in time trends or any association with sulfur dioxide or TSP in eastern Germany.

A recent study from the United Kingdom investigated the association between lower respiratory conditions and primary care consultations in London *(61)*. For a 10–90th percentile increase in pollutant levels in winter, increases

in consultations for respiratory illnesses in children were observed for nitrogen dioxide (7.2%), carbon monoxide (6.2%) and sulfur dioxide (5.8%). In adults, the only consistent association was with PM_{10}. A cross-sectional study from Australia *(62)* reported the prevalence of asthma symptoms that also included "chest colds" in 3023 primary-school children aged 8–10 years from industrial and non-industrial areas. There was no significant association with sulfur dioxide but there was an increased risk of chest colds (odds ratio 1.43) per 10 μg/m^3 increase in PM_{10}.

A study in the Russian Federation *(63)* investigated the influence of both indoor and outdoor factors on the prevalence of bronchitis between highly and less polluted areas, based on sulfur dioxide concentrations of 150–350 μg/m^3. Significant differences in the prevalence of asthma (2.1 vs 3.0%), acute bronchitis (10.6 vs 45.1%) and acute obstructive bronchitis (2.4 vs 15.0%) were observed between the less and the highly polluted areas. Furthermore, passive smoking and stove heating were significantly more frequent in children with respiratory complaints compared to those without such complaints. A study in Thailand *(64)* investigated daily upper and lower respiratory symptoms in three panels consisting of children, adults and nurses in relation to daily outdoor $PM_{2.5}$ and PM_{10} concentrations over three months. A 45-μg/m^3 (approximately interquartile range) change in PM_{10} was associated with risk of 1.10 and 1.13, respectively, for upper and lower respiratory illnesses in children.

There have been several reports from the database of the "Six Cities Study", a long-term prospective study on the health effects of exposure to outdoor pollution in children (seen annually) and adults aged 25–74 years (seen every three years) randomly selected from six cities in the eastern United States. Some of these reports present an analysis of an association between rates of "bronchitis" in children and air pollution. In one early report focusing on indoor exposure, cross-sectional analyses of 8120 children aged 6–10 years showed an increased risk for physician-diagnosed respiratory infection before the age of two years in children from homes with gas stoves *(65)*. Further analysis of 1567 children aged 7–11 years showed an association between the incidence of lower respiratory symptoms and a 30-μg/m^3 difference in measured nitrogen dioxide level *(66)*.

Further studies have been made on outdoor exposures; one study enrolled 10 106 children over three years, 8380 of whom were followed up a year after recruitment. Measurements were made of TSP, the sulfate fraction of TSP and sulfur dioxide. Frequency of cough was associated with 24-hour mean concentrations of all three pollutants across all six cities, and the rates of bronchitis and lower respiratory illness were associated with TSP concentrations *(67)*. In a second cross-sectional assessment of 5422 children aged 10–12 years, reported rates of chronic cough, bronchitis and chest illness were associated with all measures of particulate pollution used in the study (including TSP, PM_{15} and $PM_{2.5}$). There were no associations with asthma, persistent wheeze, hay fever or non-respira-

tory illness *(68)*. In keeping with the results of the studies from Switzerland, there were associations with "bronchitis" but not with asthma.

There have been several studies of outdoor PM_{10} exposures and risk of upper and lower respiratory infections and illnesses in children. Two time series analyses from the Utah Valley in the United States measured outdoor pollutants and daily mean PM_{10} exposures. One study reported a 3.7% and 5.1% increase in upper and lower respiratory symptoms, respectively, per 10-$\mu g/m^3$ increase in PM10 *(69)*; the other evaluated both symptomatic and asymptomatic children, revealing non-significant increases in upper and lower respiratory symptoms in both groups *(70)*. Similarly, a study in the Netherlands on over 1000 children aged over three months showed no association between any outdoor pollutant and incidence or prevalence of upper or lower respiratory symptoms *(71)*. A further longitudinal study in the Netherlands on 112 children during an acute pollution episode reported non-significant increases in upper and lower respiratory illnesses following PM_{10} exposure *(72)*.

Several community studies have addressed the risk of respiratory infection in infants and children exposed to nitrogen dioxide, and that have also included some data on exposure to nitrogen dioxide indoors. A large birth cohort study of 1205 infants measured nitrogen dioxide levels in each infant's home and the risk of daily respiratory illness. There was a lack of association between measured indoor nitrogen dioxide level and lower respiratory illness *(73)*. Other smaller studies have also used individual measurement of static indoor nitrogen dioxide levels among infants: neither a cross-sectional study in the United Kingdom *(74)* nor a case-control study in Norway *(75)* found any association with respiratory symptoms among infants.

Further studies of measured outdoor nitrogen dioxide exposure have shown an effect with respiratory health outcomes (probably infections). Birth cohort studies from Germany and the Netherlands showed an association between a variety of upper respiratory infections and physician-diagnosed severe colds *(53)* and respiratory symptoms *(76)* and outdoor nitrogen dioxide and $PM_{2.5}$ levels. Further studies in older children in Japan *(77)* and the Netherlands *(78)* showed similar associations between exposure to traffic pollution and nitrogen dioxide levels and various symptoms, including those in asthmatic children. In a further study from Switzerland, as part of the SAPALDIA (Study on Air Pollution and Lung Diseases in Adults) project, the duration of lower respiratory symptoms in children under 5 years of age was related to outdoor (though not indoor) nitrogen dioxide level and also, more consistently, with TSP level *(35)*. These data suggest that the health effects may be related to pollutants that have the same environmental source characteristics and dynamics as nitrogen dioxide; a less likely possibility is that these different pollutants have additive effects.

ARIs and hospital admissions

In a case-control study on outdoor nitrogen dioxide in Stockholm, Sweden, 197 children admitted to hospital with wheezing bronchitis (reasonably assumed to be of infective etiology) were compared with 350 controls ranging in age from 4 months to 4 years *(79)*. Time-weighted personal nitrogen dioxide exposures were estimated based on outdoor levels. The risk of wheezing bronchitis was significantly related to outdoor nitrogen dioxide exposure in girls ($P = 0.02$) but not in boys, and the presence of a gas stove in the home appeared to be a risk factor only for girls.

In a study in Rome, Italy, daily mean levels of TSP, sulfur dioxide, nitrogen dioxide, carbon monoxide and ozone were compared with daily emergency hospital admissions for respiratory disease from 1995 to 1997. Nitrogen dioxide and carbon monoxide together on the same day were associated with increased total admissions (2.5% and 2.8% change per interquartile range, respectively) and previous-day ozone was associated with admissions in children (5.5% increase per interquartile range). The effect of same day nitrogen dioxide was stronger on acute respiratory infections (4.0% increase per interquartile range) and previous day nitrogen dioxide on asthma among children (10.7% increase per interquartile range). Similarly, consistent relationships were observed in multi-pollutant models with nitrogen dioxide, carbon monoxide and ozone, indicating a possible role of traffic-generated pollutants in hospital admissions *(80)*.

A recent study in Canada evaluated the effects of ozone on hospital admissions for respiratory disease in infants aged under two years over a 15-year period. During the period between May and August, a 5-day moving average of hourly peak ozone concentration was associated with a significant risk estimate of a 35% increase in admissions (95% CI 19–52) and was present even when controlled for other pollutants and weather. No such relationship was observed during the peak viral season of September–April. An overall 85-$\mu g/m^3$ increase in ozone was associated with an increase in admissions of 45.3% for croup, 45.7% for acute bronchitis and 23.3% for pneumonia *(81)*. A series of recent studies also suggest an association between particulate concentration and post-neonatal infant mortality, and the likely mechanism of toxicity may relate to susceptibility to infection *(82)*. A more detailed discussion is presented in Chapter 2.

One of the most common infections in children before the age of three years, otitis media, was recently reviewed in epidemiological studies in respect to air pollution levels. Although firm conclusions could not be drawn, evidence of an increased risk of contracting otitis media after exposure to environmental tobacco smoke and ambient air pollution levels in some studies led to a recommendation for future research in this area *(83)*.

Air pollution in children with concurrent infection

It is possible that air pollution may modify symptoms in individuals who are already infected. Short-term effects of sulfur dioxide and particulate matter (but

with low acidity) were studied for 7 months in 89 children with asthma. Exposure to elevated levels of air pollution was associated with reduced PEF, increased respiratory symptoms, increased school absenteeism and fever and increased medication use. Furthermore, there was evidence that exposure to air pollution might have enhanced respiratory symptoms while children were experiencing respiratory infections *(84)*.

Another study specifically examined short-term nitrogen dioxide exposures at school, outdoors and in the home in 388 children aged 6–11 years. Exposure to nitrogen dioxide at hourly peak levels of the order of <160 μg/m^3, compared with background levels of 40 μg/m^3, was associated with a significant increase in sore throat, colds and absences from school, although infection was not confirmed *(85)*. Also, significant dose–response relationships were demonstrated for these four indicators of respiratory effects with increasing levels of nitrogen dioxide exposure.

One recent study related upper respiratory virus infections confirmed microbiologically, personal nitrogen dioxide exposure and the severity of asthma exacerbation in children. A cohort of 114 asthmatic children aged 8–11 years prospectively recorded daily URTI and LRTI symptoms, PEF and personal nitrogen dioxide exposures every week for up to 13 months. Outdoor concentrations of nitrogen dioxide were also available from a central monitoring station. Nasal aspirates were taken during reported URTI episodes and tested for infection with common respiratory viruses and atypical bacteria by RT-PCR assay. The severity of associated exacerbation of asthma was analysed in relation to high versus low nitrogen dioxide exposure in the week prior to the viral infection. There were significant increases in the severity of asthma symptoms with high nitrogen dioxide exposure: 60% for all virus infections and >200% for respiratory syncytial virus infection. The highest category of nitrogen dioxide exposure was also associated with falls in PEF of up to 75% during virus infection compared to the lowest category of exposure. These effects were observed at levels within current air quality standards *(86)*. Mean personal nitrogen dioxide exposures were low at 1–496 μg/m^3 (mean 17 μg/m^3) and daily outdoor concentrations of nitrogen dioxide were in the range 4.3–29.8 μg/m^3 (mean 12.3 μg/m^3). There was no evidence of seasonal variation in outdoor concentrations, or any significant effect of outdoor nitrogen dioxide on variations in personal exposure when averaged over a week *(87)*.

Exacerbations of pre-existing diseases such as asthma can frequently be attributed to foregoing viral or bacterial infections, and therefore the effects of additional lower airway symptoms such as bronchitis in such children could be important in relation to outdoor air pollution. Three studies suggest that bronchitis symptoms may be exacerbated in such circumstances. A panel of 7–11-year-old children with and without bronchitic symptoms (presumed asthma by definition) living in areas of high traffic density in the Netherlands were followed over two winters. Associations with PM_{10} and black smoke were observed in children with-

out symptoms, but the effect estimates were much smaller than in children with symptoms. In those children using regular medication, and therefore presumably more severe bronchitics, a 100-μg/m^3 increase in five-day mean PM_{10} was associated with a 50% increase in lower respiratory symptoms, an 8% increase in reductions in PEF and a two-fold increase in use of bronchodilators. This suggests that those with prior respiratory disease are susceptible to exacerbation of their bronchitis by PM_{10} *(88)*. Another cross-sectional survey of 3676 children suggests that those children with an established history of asthma are more likely to develop lower respiratory tract symptoms, the strongest associations being observed with nitrogen dioxide (increase in risk for chronic phlegm of 2.7 per 50-μg/m^3 change in pollutant concentration) *(89)*. These relationships were confirmed in further observations in a cohort of asthmatic children from Southern California *(90)*.

These studies thus suggest a link between air pollution and severity of illness associated with respiratory infection, and that individuals with pre-existing lung disease may be at greater risk. The majority of the studies of air pollution and infection have been conducted in children, although until recently studies had not clarified the exact nature of the respiratory illness and infection. There is now good evidence of such a link in children with pre-existing asthma.

Could improving outdoor air quality reduce morbidity from infections?

A significant body of evidence now supports the possibility that much of the morbidity and mortality related to air pollution can occur via interactions with respiratory infection. Nevertheless, a discussion of the role of air pollutants and infection is not complete without considering whether improving air quality can reduce the burden of respiratory disease, and possibly infections. The success of the clean air and similar legislation that eradicated severe smog from London, Europe and the United States in the last century provides proof that improved air quality can reduce adverse health effects. Findings of improvements in respiratory health following control of indoor pollutants in developing countries also support the evidence.

Early evidence of a beneficial effect of the control of outdoor pollutants on respiratory infections in children came from Sheffield in the United Kingdom in the 1960s. Concentrations of sulfur dioxide and particulates were high in different parts of the city (annual mean black smoke 97–301 μg/m^3 and sulfur dioxide 123–275 μg/m^3) and respiratory infections were more common in the more polluted areas *(91)*. In a follow-up study four years later when pollution levels were lower following clean air legislation (annual mean black smoke 48–169 μg/m^3 and sulfur dioxide 94–25 μg/m^3), such differences in respiratory illness were no longer evident *(92)*. Further evidence of the effects of reducing outdoor sulfur dioxide and TSP had been presented earlier from the area corresponding to the former German Democratic Republic, where infectious airway diseases were more frequent than in western Germany in 1991 and were associated with outdoor sulfur

dioxide and TSP. The decrease in levels of these pollutants from 1991 to 1995 was associated with a parallel reduction in the prevalence of infectious respiratory illnesses *(60)*.

A further demonstration of the beneficial effects of pollutant reduction was observed in the Utah Valley following the closure of a steel mill for 14 months in 1987 due to a labour strike. Outdoor particulate concentrations and respiratory hospital admissions in both children and adults fell dramatically during the period when the mill was closed, but returned to the pre-closure levels when the mill reopened *(42)*. This related to a twofold reduction in admissions for "bronchitis and asthma" and a threefold reduction in admissions for "pneumonia and pleurisy" in children aged 0–17 years. A cross-sectional study from eastern Germany took advantage of the change in outdoor pollutant levels in the unified Germany to investigate whether this related to a reduction in childhood morbidity. Over 5000 schoolchildren aged 5–14 years were studied between 1992/1993 and 1995/1996 in three different areas. The annual mean particulate levels decreased from 65, 48 and 44 $\mu g/m^3$ in 1993 to 43, 39 and 36 $\mu g/m^3$ in 1995. During the period between surveys, there were significant reductions in the prevalence of bronchitis (odds ratio 0.55), otitis media (odds ratio 0.8), frequent colds (odds ratio 0.74) and febrile infections (odds ratio 0.76) *(93)*. In Finland, a cohort study (that also included adults) examined the reduction in sulfur emissions from a pulp factory *(94)*. In the most polluted community, a reduction of sulfur pollutants from 11 to 6 $\mu g/m^3$ led to a significant decrease in ARIs by 0.53 episodes per person per year. A more moderately polluted community also showed a significant though smaller reduction in ARIs by 0.36 episodes per person per year. The incidence of nasal symptoms and cough were also reduced. Further data on the beneficial effects of reducing air pollution have been described from Dublin (Ireland), Hong Kong (China) and Atlanta (United States) and included adults. These studies are not discussed here.

EVIDENCE SYNTHESIS

A variety of cross-sectional and longitudinal epidemiological approaches have investigated acute upper and lower respiratory symptoms in children in relation to outdoor air pollutants. The majority of studies have described various conditions including bronchitis, pneumonia, wheeze, persistent cough, infectious cough, "stuffy nose", colds, sore throats and breathlessness, and also physician-diagnosed infections such as croup and laryngo-tracheo-bronchitis. Few studies have confirmed infection, but there is now evidence from community studies that most URTI and LRTI symptoms in children are likely to be related to infections of mixed but largely viral etiology. The severity of infection has been difficult to ascertain from the epidemiological data, although the health effects have ranged from mild URTI symptoms in longitudinal cohorts of children, to more severe infective exacerbations of pre-existing disease (mainly asthma), to more severe

LRTIs requiring admission to hospital. There are relatively few circumstances in which URTIs alone have led to hospital admission.

Levels of pollutants encountered at historical levels have suggested a causal role, together with respiratory infections, and the majority of studies of contemporary levels of pollutants also suggest a causal role. Associations at contemporary pollutant levels have, however, not been entirely consistent owing to problems inherent in epidemiological studies, including exposure classification, confounding and co-linearity of pollutants. The traditional pollutants, sulfur dioxide and TSP, have been associated with respiratory infections, even though levels of these pollutants are now lower in many European areas. A causal role is also suggested for other pollutants, principally nitrogen dioxide, but it is not known whether this pollutant is a marker of general traffic pollution in outdoor air. The data on nitrogen dioxide for indoor studies has also been less consistent. Studies of PM_{10} and $PM_{2.5}$ and the association with respiratory infection at contemporary levels are also inconsistent, but the majority of data suggests a small though significant increased risk of respiratory disease.

CONCLUSIONS

These analyses of outdoor air pollution, including PM_{10}, $PM_{2.5}$, nitrogen dioxide, sulfur dioxide and ozone, provide evidence that air pollution is associated with increased upper and lower respiratory symptoms in children (much of which are likely to be related to infections), provide evidence for possible mechanisms of interaction with infection, and confirm that reducing pollutants could improve the health of children. These effect estimates are mainly small, but the population attributable risks are high. Further studies are required on the mechanisms of interaction and on whether the risk varies according to the infectious agent.

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THE IMPACT OF AIR POLLUTION ON ASTHMA AND ALLERGIES IN CHILDREN

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INTRODUCTION

Asthma is a chronic disease of the respiratory system characterized by inflammation of the airways and variable airflow obstruction *(1,2)*. The underlying mechanisms are not fully understood. There is a strong atopic component, i.e. tests often show positive skin prick tests for specific allergens, the presence of allergen-specific IgE and increased levels of total IgE in asthmatic children. Nevertheless, systematic reviews have suggested that a substantial proportion of asthma is not related to "atopy" *(3)*. The term "asthma" probably encompasses several disparate groups of disorders that produce similar clinical effects *(3)*. Clinical symptoms include wheezing, shortness of breath, cough and chest tightness. Lung function measurements generally find reduced levels of air-flow parameters (FEV_1, PEFR, MEF_{50}, etc.) as well as increased bronchial responsiveness. A substantial proportion of the affected children suffer from other atopic diseases also, such as allergic rhinitis or atopic eczema *(4)*. Asthma and allergies can have a major impact on the quality of life of the affected children and their families. A severe asthma crisis is a medical emergency.

IDENTIFICATION OF EVIDENCE

We conducted a systematic review of the effects of air pollution on asthma and allergies in children, focusing on particulate matter, nitrogen dioxide, ozone and, more generally, motor vehicle exhaust emissions. The review is divided in two main sections: (*a*) the effects of air pollution on the prevalence and incidence of asthma and allergies (long-term effects); and (*b*) the effects of air pollution on aggravation of asthma (short-term effects). Methodological recommendations published by WHO *(5)* were followed. We did not conduct a formal quantitative meta-analysis. As disease entities, we focused on asthma, allergic rhinitis and atopic eczema. In the case of particulate matter, we considered studies describing the effects of total suspended particles (TSP), PM_{10}, $PM_{2.5}$, black smoke (BS), coarse particles ($PM_{10-2.5}$) and ultrafine particles. There was no a priori restriction of the area of the study.

The Medline database was searched using several different search strings in order to be as inclusive as possible. Additional searches using the same search strings were conducted in Biosis and Toxnet. The full reference and abstract for each of the citations were identified. The abstracts of all studies were reviewed; studies on

adults and those not reporting findings of studies on long- or short-term effects of air pollution on asthma and allergies in children were excluded. Copies of the remaining studies were obtained, reviewed and if relevant assigned to either (*a*) or (*b*) as described above. At a final stage, reviews, studies of low quality or using poor statistical methods, and studies that did not provide numerical estimates for the effects of air pollution were excluded.

For each study, relevant elements were recorded and reported in tables, which were part of the material reviewed by the experts before the WHO consultation that reached agreement about the interpretation of the accumulated evidence. Whenever possible, we included numerical estimates of the observed associations, using the units reported by the original investigators. If studies reported more than one result for the relation of one exposure to one outcome, we decided to present the one having the largest (positive or negative) effect or the one that was statistically significant.

STUDIES ON THE PREVALENCE AND INCIDENCE OF ASTHMA AND ALLERGIES (LONG-TERM EFFECTS)

Questionnaire-based reports of asthma symptoms (mostly wheezing) and physician diagnoses of asthma remain the cornerstone of the assessment of asthma in epidemiological studies of prevalence and incidence *(6,7)*. Additional measurements of physiological parameters, such as measurement of lung function, bronchial responsiveness and levels of total or allergen-specific immunoglobulin E (IgE) should be interpreted as measures in their own right and complementary to the questionnaire-based information. The assessment of allergic rhinitis (mostly hay fever) and atopic eczema basically follows the same principle.

Many studies on the health effects of air pollution in children were cross-sectional. It is important to keep in mind that this type of study allows one to measure only the prevalence of disease, which is a reflection of both incidence and duration. Thus, if a higher prevalence of asthma and allergies are observed in cross-sectional studies, it is not possible to attribute these to either a higher incidence (i.e. of the occurrence of new cases) or to a longer duration, or to greater severity of clinical manifestations (i.e. more symptoms) in children with already existing diseases. Consequently, the association of asthma incidence with air pollution can only be investigated by prospective cohort studies.

There are several reports of studies that investigated the association between air pollution and health, comparing two or up to five study areas. For example, comparisons of morbidity among children in Munich (western Germany) and Leipzig/Halle (eastern Germany) found higher rates of bronchitis and cough in the east while the prevalence of asthma, hay fever, bronchial hyperresponsiveness (BHR) and atopic sensitization was higher in the west *(8–10)*. It is, however, difficult to attribute these differences merely to the differences in air pollution (sulfur dioxide and TSP higher in the east, nitrogen dioxide higher in the west)

since many other factors differed between the study areas. Nevertheless, others had similar findings and also observed reductions in the prevalence of bronchitis with decreasing levels of TSP *(11)*. For the purpose of this review, however, we focused on studies with at least six study areas in an attempt to reduce the potential for spurious findings.

Studies making comparisons between study areas

Cross-sectional studies

North America

The American "Six Cities Study" investigated the effects of air pollution on the respiratory health of pre-adolescent children living in communities with different levels of air pollution *(12)*. Between 1974 and 1977 a total of 10 106 children were studied using parental questionnaires and spirometric examinations. Of these, 8380 were examined again the following year. Air pollution was monitored in each community around the time of the first examination. TSP, the sulfate fraction of TSP (TSO_4) and sulfur dioxide concentrations were measured at study-affiliated outdoor stations and other public and private monitoring sites and the data were combined. The frequency of cough and bronchitis was significantly associated with the average of 24-hour mean concentrations of TSP, TSO_4 and sulfur dioxide during the year preceding the health examination. There was no association between these air pollutants and the prevalence of asthma symptoms.

A subsequent report from this study presents an analysis of the respiratory health data from 5422 children who were 10–12 years old when they participated in a follow-up visit in 1980–1981 *(13)*. There was no association between levels of particulate matter and the prevalence of asthma symptoms or diagnoses. Exposure to nitrogen dioxide was negatively correlated, while levels of ozone showed a significant positive association. Again there was a positive association between exposure to particulate matter and the prevalence of bronchitis (significant with $PM_{2.5}$) and cough (significant with PM_{15}). This relationship was particularly strong in asthmatics. At the time, the strength of the Six Cities Study was that it included six rather than just two study areas in the comparisons and that it was able to adjust for individual risk factors. Nevertheless, the number of study locations was still low and the number of associations investigated was high; the observed association should therefore be interpreted with caution.

In a subsequent investigation, the research group included 13 369 children aged 8–12 years from 24 different communities, focusing on the effects on health of acid aerosols *(14,15)*. The prevalence of wheeze and asthma was not related to any of the measures of particle exposure. Levels of gaseous acids did show a significant association with the prevalence of asthma, but the relationship was driven mainly by one centre. Diagnoses and/or symptoms of bronchitis were related to particle and sulfur dioxide exposure. No susceptible subgroup could be identified. The results of lung function measurements in these children showed signifi-

cant reductions in FVC (3.5%, 95% CI 2.0–4.) and FEV_1 (3.1%, 95% CI 1.6–4.6) in relation to increases in annual mean particle strong acidity of 52 nmol/m^3.

Children in Southern California were studied to assess chronic respiratory effects due to long-term exposure to four pollutants: ozone, particulate matter, acids and nitrogen dioxide *(16)*. Outdoor levels of ozone, PM_{10} and nitrogen dioxide in this region have historically been among the highest in the United States and often exceeded state clean air guidelines, at least for ozone and PM_{10}. The study selected 12 demographically similar communities on the basis of historical monitoring information to represent extremes of exposure to one or more pollutants. About 300 students from three grades (4, 7 and 10) were enrolled in each community through their classrooms. Information about the children's lifetime residential histories, past and current health status, residential characteristics and physical activity were obtained by questionnaire. A total of 3676 students participated in the baseline survey. The prevalence rates of wheeze were positively associated with levels of acids (OR 1.3, 95% CI 1.1–1.6). However, the effect was seen mainly in boys, among whom wheeze was also associated with nitrogen dioxide level (OR 1.5, 95% CI 1.1–2.2). Further analyses showed that children with asthma were particularly sensitive to the effects of air pollution *(17)*. In these children, the prevalence of bronchitis and phlegm was positively associated with levels of PM_{10}, $PM_{2.5}$, acid vapour and nitrogen dioxide, but not ozone.

Europe

A Swiss group investigated the impact of long-term exposure to air pollution on respiratory and allergic symptoms and diseases in 4470 children aged 6–15 years living in 10 different communities *(18)*. Air pollution (PM_{10}, nitrogen dioxide, sulfur dioxide and ozone) data were collected in each community. The prevalence of wheeze, as well as of diagnosed asthma or hay fever, was not associated with any of the measured pollutants. Conjunctivitis symptoms were more prevalent in communities with higher levels of PM_{10}, nitrogen dioxide and sulfur dioxide. The reported rates of chronic cough, nocturnal dry cough and bronchitis were, in turn, positively associated with levels of PM_{10}, nitrogen dioxide and sulfur dioxide, even after adjustment for individual risk factors. With the exception of ozone, concentrations of the air pollutants were highly correlated and it was difficult to discern individual effects. Associations with ozone were not found for annual means. All associations were adjusted for individual risk factors and exposures. This study is important in that it provides evidence that rates of respiratory illnesses and symptoms among children increase with rising levels of air pollution, even in countries with moderate levels of air pollution.

Researchers in Austria investigated whether outdoor nitrogen dioxide was associated with the prevalence of asthma and respiratory symptoms *(19)*. They selected eight non-urban communities with differences in exposure and studied a total 843 children who had lived there for at least two years. There were central

monitors for nitrogen dioxide and the three-year mean exposure was calculated. The communities were grouped according to their nitrogen dioxide levels into four categories: very low (reference), 6–7 ppb; low, 8–9 ppb; regular, 12–13 ppb; and high, 15–17 ppb. Positive associations were found with the prevalence of diagnosed asthma. There was also a positive (albeit not statistically significant) relationship with "wheeze" and "cough apart from colds" in the last year. Nitrogen dioxide was considered to be primarily an indicator of traffic-related air pollution. A strength of this study is the adjustment of associations for individual risk factors, while limitations include the cross-sectional design and relatively low sample size.

Investigators in France looked at the relationship between long-term exposure to the main gaseous air pollutants and prevalence rates of asthma and allergic rhinitis *(20)*. A total of 2445 randomly selected children aged 13–14 years of age, who had lived in their area for at least three years, were studied by written and video questionnaires from the International Study of Asthma and Allergy in Childhood (ISAAC). The communities had been chosen to have a large contrast in ozone exposure, five being in a high-exposure region and two in a low-exposure region for comparison. In all communities, air quality measurements were performed routinely. For the analyses the investigators chose to use the measurements taken during the period of data collection (i.e. January and February 1993). In the bivariate analyses, levels of ozone were found to be positively ($P<0.05$) associated with the prevalence of current wheeze, current nocturnal dry cough and asthma. However, these associations did not remain significant after adjustment for individual risk factors. This study has limitations in that the analysed exposure measurements may not adequately reflect differences in long-term exposure, and that the observed bivariate associations may be confounded, since they did not remain after adjustment. A study of 2073 children aged 10–11 years in the same communities measured the prevalence of atopic sensitization by skin prick *(21)*. There was very little difference in prevalence between the communities with differing levels of sulfur dioxide, nitrogen dioxide, and ozone. Bivariate and multivariate analyses did not show any statistically significant associations (numerical values not provided).

Another French group reanalysed data from the *Pollution Atmosphérique et Affections Respiratoires Chroniques* (PAARC) survey, which were collected in 24 areas of 7 French towns during 1974–1976 *(22)*. Measured air pollutants included sulfur dioxide, TSP, BS, nitrogen dioxide and nitric oxide. Prevalence data on asthma symptoms and diagnoses were available for 3193 children; these were not related to any of the air pollutants.

Asia

In Taiwan, China, a nationwide survey investigated the relationship between the prevalence of respiratory illness and symptoms in 13–15-year-old children *(23)*.

Parental written questionnaires and the ISAAC video questionnaire were used. The study population was reduced to those children (n = 331 686) who were non-smokers and who attended schools located within 2 km of 55 air monitoring stations. Factor analyses identified two types of air pollution: (*a*) "traffic-related" air pollutants, i.e. carbon monoxide, nitrogen dioxide (positively correlated) and ozone (negatively correlated); and (*b*) "fossil-fuel-combustion-related" air pollutants, mainly sulfur dioxide and PM_{10}. After adjustment for age, history of atopic eczema and parental education, asthma prevalence was associated with traffic-related air pollution, especially carbon monoxide and nitrogen oxides. Non-traffic-related air pollution was not related to asthma prevalence. Despite the large sample size, the study suffers from the usual limitations of prevalence studies. Nevertheless, the nationwide approach and the high number of monitoring stations make major bias less likely. The group also analysed the effects of air pollution on the prevalence of diagnosed allergic rhinitis, assessed by parental responses to written questions on doctors' diagnoses and typical symptoms *(24)*. Again, there was a positive correlation, adjusted for several potential confounding and climatic factors, between the prevalence of rhinitis and traffic-related air pollutants.

Cohort studies

A cohort of 1150 children was followed for 3 years to assess long-term effects of outdoor ozone exposure *(25)*. Nine study areas were selected on the basis of air quality data to represent a broad range of ozone exposure. Lung function was measured twice a year, before and after the summer season, in 1994, 1995 and 1996. Multivariate regression analysis allowed the study area, sex, atopy, environmental tobacco smoke, baseline lung function and increases in height to be considered as potential confounding factors. Ozone levels were significantly associated with reductions in lung function parameters (FEV_1 and FVC) in 1994 and 1995. No consistent effects on lung function were found for nitrogen dioxide, sulfur dioxide and PM_{10}. The strength of this study is the prospective design and the ability to control for potential confounders. However, it is noteworthy that the paper does not give information about potential differences in the incidence of clinical manifestations of asthma. In the original cross-sectional comparisons between study sites, however, there was a negative association between ozone levels and the prevalence of asthma in the previous 12 months. A later cross-sectional analysis of urinary eosinophil protein X as a marker of eosinophil activation (based on 877 children from the cohort) showed a positive correlation with ambient ozone levels *(26)*. Reanalysis of the lung function data in relation to an extended assessment of air pollutant exposure (mainly PM_{10}) confirmed the association between long-term seasonal mean concentrations of ozone and deficits in lung parameters *(27)*. The analysis also revealed a negative relationship between outdoor levels of PM_{10} and deficits in the development of large (FEV_1) and small (MEF_{25-75}) airways.

The effect of ozone exposure on lung function growth over a follow-up period of 3½ years was also investigated *(28)*. For this analysis, 2153 schoolchildren from 15 study sites in Austria and Germany were measured twice a year and differences between consecutive measurements divided by days were considered as a measure of lung growth. Exposure was analysed separately for winter and summer, and regression methods for repeated measurements were used. For a semi-annual mean ozone exposure in summer of between 46 and 54 ppb, the authors report a significantly lower FVC increase (estimated at –19.2 ml/100 days) compared to exposures of between 22 and 30 ppb. In winter, however, the estimated difference in FVC was 16.4 ml/100 days between semi-annual ozone classes 28–36 ppb and 4–12 ppb. Similar effects were seen for FEV_1. Linear regression analyses showed no association between growth rates and mean summer ozone levels for FVC and FEV_1 over a 3½-year period. The authors conclude that medium-term effects on the lung growth of children are possibly present, but that longer-term effects were not detectable over a 3½-year period.

Follow-up of the children in Southern California after a period of four years (1993 to 1997) showed significant deficits in growth of lung function associated with exposure to $PM_{2.5}$, PM_{10}, nitrogen dioxide and inorganic acid vapour *(29)*. These associations were statistically significant in the fourth-grade cohort and generally larger among children spending more time outdoors. The findings were generally confirmed by the results of the second cohort study that followed 1678 Southern California children from their enrolment in the fourth grade in 1996 until 1999 *(30)*. Significant deficits in lung function growth rate were associated with exposure to acid vapour, nitrogen dioxide, $PM_{2.5}$ and elemental carbon. The strongest and most consistent effects were seen for acid vapour. Estimated deficits in lung function growth rate were again larger in children who reported spending more time outdoors.

The Californian group also studied changes in lung function of participants (n = 110) who had moved to other communities *(31)*. They found reductions in annual lung function growth rates (FEV_1, MMEF and PEF) among children in areas with more pollution and, interestingly, improvements among children who had moved to less polluted areas. There was no evidence of systematic differences between children who stayed or moved out of their communities.

Further discussion of the impacts of air pollution on lung function is presented in Chapter 3.4.

The impact of air pollution on the incidence of bronchitic symptoms, assessed yearly by questionnaire from 1996 to 1999, in children with asthma was also examined in 12 Southern California communities *(32)*. There was a positive association with the annual variation of $PM_{2.5}$ (OR 1.1 μg/m^3, 95% CI 1.0–1.2), organic carbon (OR 1.4 μg/m^3, 95% CI 1.1–1.8), nitrogen dioxide (OR 1.1 ppb, 95% CI 1.0–1.1) and ozone (OR 1.1 ppb, 95% CI 1.0–1.1). Interestingly, associations were stronger with annual within-community variability in air pollution than with be-

tween-community four-year average concentrations. The effects of annual variation in organic carbon and nitrogen dioxide were only modestly reduced by adjusting for other pollutants.

McConnell et al. *(33)* looked at the effect of exercise (assessed by the number of team sports played by the children studied at the beginning of the study) on the incidence of asthma over a period of four years, in relation to the level of outdoor air pollution in the community. They found a significant positive association in communities with high ozone exposure, which was not seen in areas with low levels of ozone. The strength of this study is the prospective design and the good quality of air pollution measurements. This finding also has some plausibility, since exercise may increase the ventilation rate substantially and thus increase pulmonary transport of ozone to more distal and vulnerable sites in the lungs.

A Japanese group *(34)* investigated the effects of outdoor and indoor nitrogen dioxide levels on the prevalence and incidence of respiratory symptoms among children. A cohort study was conducted over a period of 3 years on 842 schoolchildren living in 7 different communities. Indoor nitrogen dioxide concentrations over 24 hours were measured in winter and summer in the participants' homes, and a 3-year average of outdoor nitrogen dioxide concentration was calculated. While cross-sectionally there was no relationship between the prevalence of asthma or wheeze and outdoor levels of nitrogen dioxide, the incidence of asthma and wheeze was positively associated with outdoor nitrogen dioxide levels. The number of incident cases, however, was low (e.g. 18 new asthma cases).

Summary of the reviewed evidence

Particulate matter

The reviewed studies reveal no association between long-term concentrations of particulate matter measured at the community level and the prevalence and/or incidence of asthma. However, the majority of the reviewed studies showed statistically significant associations between long-term concentrations of particulate matter and the prevalence of cough and bronchitis. Several studies found that these associations were more pronounced in asthmatics. The available evidence does not allow one to attribute the health effects to particles of specific sizes. Three out of six studies also found significant adverse effects on lung function.

Nitrogen dioxide

The reviewed studies show little evidence for an effect of long-term exposure to nitrogen dioxide on prevalence and/or incidence of asthma, allergic rhinitis or atopic eczema. For asthma diagnoses and symptoms, an equal number of studies show positive and negative associations. Three out of four studies showed an association with bronchitis and cough, while two out of three showed significant reductions in lung function.

Ozone

There is no clear evidence from the reviewed studies for an adverse effect of long-term exposure to ozone on the prevalence and incidence of asthma. Only three out of five studies found a positive association with diagnosed asthma; three out of six found a positive association with wheeze, but only one was statistically significant. Also, no consistent effects were found for bronchitis and cough. Most of the studies (five out of six), however, found statistically significant deficits in lung function parameters. One large cohort study found an increase in asthma incidence among highly active children living in areas with high ozone concentrations.

Other pollutants

One large study found significant adverse effects of traffic-related air pollutants on the prevalence and/or incidence of asthma and hay fever. Apart from this study, however, the reviewed studies provide no evidence for an adverse effect of outdoor air pollution on the prevalence and incidence of allergic rhinitis, atopic eczema or atopic sensitization.

Studies making comparisons within study areas

Cross-sectional studies

Studies on the effects of outdoor air pollution that compare areas with different levels of air pollution generally assume that the relevant exposure can be captured by measurements from one single station, which are then generalized to all children living in that area. More recent studies, however, have shown that there may well be relevant differences in exposure to outdoor air within a larger area *(35–37)*. As a result, attempts have been made to incorporate more accurate estimates of individual and small-area variations in exposure, which are nowadays largely determined by motor traffic *(38,39)*.

An early study in Japan *(40)* on children and adults found that the prevalence of Japanese cedar pollinosis was particularly high among families living close to busy streets in urban areas where cedars were also prevalent, suggesting a potential interaction between exposure to air pollutants and specific allergens. However, the publication does not give information on several aspects that are important for a proper assessment of epidemiological validity.

A later study in Germany *(41)* used data from a large prevalence study conducted in 9–11-year-olds (n = 6537) in Munich. The instruments included parental questionnaires and measurements of lung function. Exposure to traffic was assessed by census data on car traffic in the school district (range 7000–125 000 cars per 24-hour period). Exposure to car traffic was positively related to the prevalence of coughing, recurrent wheeze and recurrent dyspnoea. Lung function measurements (PEFR, MEF_{25}, MEF_{50}, MEF_{75}) were reduced among children who were more exposed to traffic.

Other studies assessed exposure to traffic by inquiring about the density of truck traffic in the street of residence *(42–44)*. A high frequency of truck traffic was associated with a significantly increased risk of wheeze and allergic rhinitis *(43,45)*. The Italian study *(44)* also found an increased risk of recurrent bronchitis, bronchiolitis and pneumonia. In the metropolitan areas (Turin, Milan and Rome) there was also an association with current respiratory symptoms, such as asthma, attacks of wheeze, speech-limiting wheeze, persistent cough and persistent phlegm. After extensive evaluation, the authors felt that reporting bias seemed unlikely. The validity of enquiring about traffic density on the street of residence was also assessed by a German group, using traffic counts and outdoor measurements of nitrogen dioxide *(46)*. Traffic density and nitrogen dioxide level were closely correlated; there was no evidence of preferential reporting by those affected by asthma. Nevertheless, studies relying only on self-reported traffic exposure should be interpreted with caution, because of concerns regarding potential preferential reporting of exposure.

An important contribution to addressing concerns about potential selection bias was made by a Dutch group *(47)*. They compared the prevalence of respiratory disorders in 106 children aged 0–15 years living in streets with a high traffic density in the city of Haarlem with a control sample of 185 children from the same neighbourhoods but living in quiet streets. After adjustment for potential confounders, children living in busy streets were found to have a higher prevalence of respiratory symptoms (mainly wheeze) than children living in quiet streets. In the full sample, adjusted odds ratios were statistically significant ($P<0.05$) only for respiratory medication use. Odds ratios were higher for girls than for boys, with significant adjusted odds ratios of between 2.9 and 15.8 for girls. In adults, those living in busy streets reported only "occasional dyspnoea" more often. While the use of neighbourhood controls is interesting, this study has a rather low sample size of children. It is noteworthy that the observed effects were much larger in children than in adults, suggesting that children may be more susceptible to the harmful effects of exposure to pollutants from traffic.

A different and probably more objective approach to exposure assessment was used in another Dutch study *(48)*. These authors investigated the prevalence of respiratory and allergic disorders among children aged 7–12 years who went to schools located less than 1 km from a major highway. Respiratory symptoms, including cough, wheeze, asthma attacks and a stuffy and runny nose, were more prevalent among children attending schools located close (<100 m) to a highway, particularly if the highway had a high density of truck traffic. Associations were stronger and statistically significant in girls. Lung function measurements of children attending schools located close (<300 m) to highways were inversely related to truck traffic and concentrations of BS *(49)*.

The impact of urban air pollution on the manifestation of respiratory and atopic diseases in 5421 children (two age groups: 5–7 and 9–11 years) was studied cross-

sectionally in Dresden, Germany *(50)*. The study instruments included parental questionnaires, skin-prick testing, measurements of serum IgE and lung function, and tests of bronchial responsiveness (using hypertonic saline). Exposure was assessed individually by relating mean annual air pollution levels (sulfur dioxide, nitrogen dioxide, carbon monoxide, benzene and ozone), which had been measured for one year on a 1-km^2 grid, to the home and school addresses of study participants using the geographical information system (GIS). After adjustment for potential confounders, positive and statistically significant associations between air pollutants and prevalence were observed for cough and bronchitis (several pollutants), asthma (only benzene), reduced lung function ($MEF_{25–75}$ <70%; only benzene) and BHR (only ozone). The prevalence of BHR was negatively associated with levels of nitrogen dioxide and carbon monoxide. The prevalence of atopic sensitization was not related to any of these pollutants. The observed associations were stronger in non-atopic children. A further analysis, addressing the association between exposure to road traffic and specific sensitization to latex in children, found no relationship *(51)*. However, the situation in Dresden is special in that the study was conducted during a period of rapid transition after German reunification, for example the levels of TSP and sulfur dioxide dropped drastically while those of nitrogen dioxide increased during the same period *(42)*.

The value of more precise exposure measurements was nicely demonstrated by an English group who had conducted large prevalence surveys among primary (n = 22 968) and secondary (n = 27 826) schoolchildren, followed by nested case-control studies to adjust for personal risk factors *(52,53)*. When traffic exposure was assessed in the locality of the schools, no association was observed with prevalence of wheezing *(52)*. However, when the proximity of the family home to the nearest main road (estimated by GIS software) was considered in the analysis, there was a positive and significant association with the prevalence of current wheeze in both age groups *(53)*. Most of the increased risk occurred within 90 metres of the roadside. Among primary-school children, the effects were more pronounced in girls than in boys.

German investigators looked at the association between traffic-related air pollution and parameters of atopy in 317 nine-year-old children living near major roads in one suburban and two urban areas of a city in western Germany *(54)*. Atopic sensitization was measured by skin-prick tests and analyses of allergen-specific serum IgE. Personal nitrogen dioxide exposure and nitrogen dioxide concentrations in front of the children's homes were measured. Outdoor nitrogen dioxide level was correlated with traffic exposure but not with personal nitrogen dioxide exposure. In the urban areas, outdoor levels of nitrogen dioxide (though not personal nitrogen dioxide levels) were associated with symptoms and diagnoses of hay fever, wheezing and allergen-specific sensitization (association for pollen sensitization only slightly stronger than for "house dust mite/cat" or "milk/egg"). The strength of this study is the detailed exposure measurement; limita-

tions are the low participation rate (38%) and number of participants (n = 182 in the urban areas). Nevertheless, results from a questionnaire-based inquiry of non-respondents suggested no selection bias.

A large representative population survey in Germany investigated the effect of traffic on the prevalence of asthma and atopy *(55)*. Random samples of schoolchildren (n = 7509, grades 1 and 4) were studied using parental questionnaires, skin-prick tests and measurements of serum IgE and lung function. This study laid great weight on the measurement of exposure. Traffic exposure was assessed using GIS to relate the home address to traffic counts in the area and to an emission model that predicted soot, benzene and nitrogen dioxide *(39)*. The prevalence of current asthma, wheeze and cough was increased in the category with the highest density of traffic. In children also exposed to environmental tobacco smoke, these associations were stronger and traffic was also associated with a positive skin-prick test to pollen. Cough was associated with soot, benzene and nitrogen dioxide, current asthma with soot and benzene, and current wheeze with benzene and nitrogen dioxide. Allergic sensitization was related to none of the specific pollutants.

An important study from the Netherlands was designed specifically to distinguish the effects of car traffic from those of truck traffic (i.e. exposure to diesel emissions) in relation to respiratory health in children *(56)*. It involved 2071children attending 24 schools located within 400 metres of busy motorways carrying 5190–22 326 trucks and 30 399–155 656 cars per day. Locations were chosen for their low correlation between truck and car traffic counts. Air pollution was measured at the schools for one year. The prevalence of respiratory disorders was determined by parental questionnaire, measurements of allergen-specific serum IgE and skin-prick test reactivity, and tests of bronchial responsiveness (hypertonic saline challenge). Chronic respiratory symptoms were positively correlated with a high level of truck traffic (though not car traffic) and with air pollutants related to truck traffic. Lung function and bronchial responsiveness were not affected by traffic exposure. Sensitization to pollen and levels of total serum IgE increased in relation to the level of truck traffic. The observed associations between respiratory symptoms and traffic exposure were seen mainly in children with BHR or atopic sensitization.

Cohort studies

Prevalence studies have well-known limitations with regard to etiological research, the most important being an inability to establish a temporal relationship between exposure and outcome. It will therefore be very interesting and important to evaluate the results of cohort studies that investigate the impact of outdoor air pollution on asthma and allergies in children. The results of a few studies have already been published.

Investigators in the Netherlands examined the relationship between traffic-related air pollution and the incidence of asthmatic and allergic symptoms up to the age of two years in a birth cohort *(57)*. For each cohort member (n = 3730 at two years of age) a validated model was applied to assign outdoor concentrations of traffic-related air pollutants (nitrogen dioxide, $PM_{2.5}$, soot) at home. After adjustment for potential confounders, wheezing and physician-diagnosed asthma were positively associated with exposure to the three pollutants, but the associations reached only borderline statistical significance. The observed correlations with bronchitis and cough were less pronounced, and atopic eczema was not associated. A limitation of this study is that the children were still quite young and the observations need to be confirmed at older ages.

A birth cohort study in Germany looked at the health effects associated with long-term exposure to $PM_{2.5}$, $PM_{2.5}$ absorbance, and nitrogen dioxide levels in the city of Munich *(58)*. A GIS-based exposure model was used to estimate traffic-related air pollutants at the birth addresses of 1756 infants. After adjustment for potential confounders, significant associations were observed between the three pollutants and the incidence of "cough without infection" and "cough at night" in the first year of life. In the second year of life, these effects were less pronounced. Wheeze, asthmatic bronchitis and symptoms of allergic rhinitis were not associated with traffic exposure. Again, it is noteworthy that the study population was again quite young and it may be too early to draw firm conclusions about long-term effects.

A recent Japanese study in older children (n = 2506, 6–9 years of age at beginning of follow-up) investigated the effects of traffic-related air pollution on respiratory symptoms in eight different communities *(59)*. The incidence of asthma during the follow-up period of four years was significantly higher among boys living <50 metres from roads than among those living in rural areas. Among girls, the incidence of asthma was also higher, albeit not statistically significantly. These findings are consistent with a role of traffic-related air pollution in the development of asthma. Nevertheless, the number of incident cases was low and the prevalence in boys was not significantly related to traffic exposure.

Summary of the reviewed evidence

The studies making comparisons within areas, mostly looking at variation in traffic exposure, provide a slightly different picture than studies making comparisons between areas. Many of the reviewed studies show an association with the measured health outcomes. In line with the studies comparing areas, there is again an association with the prevalence and/or incidence of bronchitis and, more pronouncedly, cough.

Of the 13 studies, however, 12 also show a positive association with wheeze, and in 6 this association is statistically significant. There is also a suggestion of a positive correlation with asthma. Nine out of 10 studies show an increase in the

prevalence and/or incidence of asthma (3 statistically significant). Three studies found deficits in lung function (2 statistically significant). Relationships with BHR were investigated by 3 studies, but none found a statistically significant positive association.

While there is little evidence for an effect on atopic eczema, 6 out of 7 studies reported a positive association for hay fever (4 statistically significant). This relationship is partly supported by studies that measured allergic sensitization, although their number was lower: 3 out of 4 studies found a positive association (2 statistically significant).

STUDIES ON AGGRAVATION OF CHILDHOOD ASTHMA (SHORT-TERM EFFECTS)

In asthmatics, episodes of airflow obstruction and aggravation of symptoms are often precipitated by viral infections. The symptoms of asthma can be triggered by exposure to allergens, cold air, irritants, strong emotions and exercise. In addition, exposure to high levels of air pollutants has been shown to aggravate symptoms in children with asthma. Among the various air toxicants, particulate matter, nitrogen dioxide and ozone are of concern because of the results of the epidemiological studies conducted in the last decades *(60)*. Several reviews have evaluated the short-term effects of particulate matter on asthma hospital admissions and asthma exacerbations *(60–65)*. A systematic review of panel studies in children regarding the effect of particulate matter has recently been published *(66)*. Reviews are also available for nitrogen dioxide and ozone *(67)*.

Two types of epidemiological study are reviewed here: (*a*) time-series studies that examine at population level the daily number of children requiring urgent medical attention because of asthma in a given community in relation to the daily level of air pollutants, generally measured at a fixed site; and (*b*) panel studies that monitor at the individual level the variation in symptoms and other clinical signs in relation to air pollutants.

Population-level, time-series studies on hospital admissions, emergency department visits for asthma and doctors' home visits for asthma

European time-series analyses, conducted mostly within the APHEA-1 study (the European initiative on short-term health effects of air pollution) *(68)* have suggested that gaseous air pollutants and particulate mass are important determinants of acute hospitalization for respiratory conditions. Three quantitative summaries of the APHEA city-specific results have evaluated the relationship between various pollutants – particles (measured as either BS or TSP), sulfur dioxide, nitrogen dioxide and ozone – and total respiratory hospital admissions in five cities *(69)*, admissions for chronic obstructive pulmonary disease in six cities *(70)* and emergency admissions for asthma in four cities *(71)*. The study by Sunyer *(71)* considered three cities (Helsinki, London and Paris) with available data for

children aged 0–14 years during the period 1987–1992 (the largest contributions came from London and Paris, since the number of asthma admissions in Helsinki was limited. The strongest and statistically significant effect was found for nitrogen dioxide, with an estimated 3.7% increase (range 0.4–6.7%) per 50 m^3 at a cumulative lag of three days. Black smoke was also associated with asthma admissions (4.6% per 50 m^3) but the estimate was not statistically significant. No effect was found for ozone (0.6% per 50 m^3). Sulfur dioxide was also related to children's hospital admissions for asthma in this study.

Before the publication of the APHEA-1 results, Buchdahl et al. *(72)* had published an analysis of visits to emergency departments for acute wheezing (age 0–16 years) at a large London hospital in 1992–1993. Nitrogen dioxide, ozone and sulfur dioxide were evaluated in this study but particle measurements were not available. After adjusting for seasonal trends and temperature, ozone was the only pollutant that increased the risk of visits to an emergency department. There was a U-shaped relationship with ozone in this study, but the interpretation of the findings was limited because the series was short and restricted to one hospital.

Medina et al. *(73)* analysed doctors' house calls for asthma in Paris for the period 1991–1995. Both PM_{13} and BS were used as a measure of particulate matter. The study also evaluated nitrogen dioxide, sulfur dioxide and ozone. House calls for asthma were divided into three age groups: all ages, 0–14 years and 15–64 years. Associations were reported for the full age group of 0–64 years, but especially for children below age the age of 14. The effect estimate for children, based on a four-day moving average of BS, was several times higher than that of the older population. Statistically significant associations were found for PM_{13} and nitrogen dioxide

More recent investigations, after the APHEA-1 results, have underlined the importance of the effect of air pollutants on hospital admissions or emergency visits for asthma, particularly in children. The series of observations in London are of great importance. The 1987–1992 London data set has been analysed by Anderson et al. *(74)* while considering the possibility of confounding/interacting effects of aeroallergens. In a single pollutant model, only nitrogen dioxide and sulfur dioxide were significantly related to children's hospital admissions; associations with BS and ozone were lower and not statistically significant. When the analysis for ozone was stratified by season, a statistically significant negative effect was found during the warm season, whereas a paradoxical protective effect was found during the cool season. Atkinson et al. *(75)* analysed hospital admissions for asthma during 1992–1994 in London, considering PM_{10} together with other pollutants for the first time in a European study. All pollutants except ozone were positively associated with asthma admissions, although none of the associations was statistically significant. The analysis of the association between outdoor pollutants and visits to emergency departments for respiratory complaints in London during 1992–1994 *(76)* revealed a strong relationship between nitrogen

dioxide levels and asthma visits in children, especially during the warm season. PM_{10} and BS also had an effect, but ozone showed a non-significant protective effect. A parallel analysis of daily doctors' visits for asthma and other lower respiratory conditions in London showed strong effects for nitrogen dioxide in children, again particularly during the summer, but no effect in adults *(77)*. The same study revealed an effect of PM_{10} and BS, though lower than that found for nitrogen dioxide. As in other London studies, ozone was protective and this time the estimate was statistically significant. The authors noted that the analysis for ozone during the warm season did not show results different than those for the whole year.

The results found in the time-series analysis of respiratory admissions in Rome during 1995–1997 were very similar to what has been suggested by the London studies with regard to children's asthma admissions: nitrogen dioxide was strongly related to total respiratory admissions, and in particular to acute respiratory infections and asthma among children *(78)*. Although ozone was strongly associated with total respiratory admissions in children, no effect was detected for asthma admissions.

A cautionary note on the evaluation of time-series studies on ozone is needed, especially when the studies are on children. Ozone has a strong seasonal variation, with higher values during the summer than during the winter, and control for season is therefore very important. On the other hand, in many cities ozone tends to be strongly inversely correlated with fine particles from traffic sources during the winter, whereas such a correlation is not found during warm weather. The protective effect for ozone observed in some European studies may be due to the strong confounding effect of fine particles. A way to avoid such confounding is to restrict the evaluation to the summer period. There may, however, be a problem in controlling for the fact that many children move out of the city during the warmest period when ozone peaks occur.

The results of APHEA-2, evaluating the association between particulate matter and hospital admissions for respiratory symptoms in eight cities, were published in 2001 *(79)*. The paper considered PM_{10} and BS to be the main factors of interest, while gaseous pollutants were considered only in order to evaluate their potential confounding role. The summary estimates for each 10 m^3 were a 1.2% increase for PM_{10} and a 1.3% increase for BS. In multipollutant models, ozone and sulfur dioxide did not substantially alter the effect estimates for PM_{10} and BS, but the inclusion of nitrogen dioxide in the models dramatically reduced the effect. Such confounding from nitrogen dioxide has been interpreted as indicating that the particles' effects may be due to particles derived from traffic-related sources and strongly correlated with nitrogen dioxide. A recent revision of the estimates *(80)*, while using updated methods, gave very similar results with an estimated effect of 1.5% (95% CI 0.1–2.8) per 10 m^3 in PM_{10}. Again, using the APHEA-2 data set of seven European cities, Sunyer et al. *(81)* found daily values of sulfur dioxide to be associated with increases in the number of daily emergency admissions for asth-

ma in children. Given the high correlation of sulfur dioxide with other pollutants, the study cannot determine whether these associations were due to sulfur dioxide itself or to other pollutants emitted from the fuel combustion processes.

Anderson et al. *(82)* evaluated a range of air pollutant measures in relation to hospital admissions in the West Midlands conurbation in the United Kingdom during the period 1994–1996. Separate measures for fine ($PM_{2.5}$) and coarse ($PM_{10-2.5}$) particles were available in this study, together with PM_{10}, BS and gases. A strong and statistically significant effect for PM_{10} and BS (and sulfur dioxide) was found, but neither $PM_{2.5}$ nor $PM_{10-2.5}$ were better predictors of hospital admissions for asthma than PM_{10}. The nitrogen dioxide effect was borderline significant, whereas ozone showed a statistically significant protective effect.

The study in Belfast *(83)* ends the European series. The authors considered three years of visits to the emergency department at the main Belfast hospital. PM_{10} and other traffic-related pollutants were evaluated. Statistically significant associations were found for PM_{10}, nitrogen dioxide, nitrogen oxides, nitric oxide and benzene. A non-significant protective effect was found for ozone.

Several studies have been conducted outside Europe since the early 1990s. Seminal papers from North America by Bates, Baker-Anderson & Sizto *(84)* in Vancouver, Pope *(85)* in the Utah Valley, Schwartz et al. *(86)* in Seattle and Burnett et al. *(87)* in Ontario indicated a specific role for particulate matter and ozone in the number of emergency department visits or hospital admissions for asthma in all age groups. Three studies on children's emergency department visits published in the mid 1990s, conducted respectively in Atlanta *(88)*, Mexico City *(89)* and New Brunswick, Canada *(90)* found a strong and statistically significant effect of ozone. White et al. *(88)* observed that the effects of ozone on children's emergency department visits for asthma in Atlanta occurred when ozone concentrations exceeded 110 pbb; no effect was found for values below 110 pbb.

Emergency department visits in Seattle for childhood asthma during 15 months in 1995–1996 were evaluated in relation to particulate matter, nitrogen dioxide and other pollutants *(91)*. The study found a small but statistically significant effect of PM_{10} and fine particles. Daily maximum one-hour mean nitrogen dioxide and eight-hour mean ozone also had an effect, albeit not significant.

Tolbert et al. *(92)* examined the effects of air pollution on paediatric emergency department visits for asthma during the summers of 1993–1995 in Atlanta. Several different statistical models were used to explore the sensitivity of the results to the model selection. PM_{10} concentrations were highly correlated with 1-hour maximum ozone ($r = 0.75$). Associations between daily visits, PM_{10} and ozone were reported, with consistent results across all models.

In São Paulo, Brazil, Gouveia & Fletcher *(93)* studied admissions to hospital for respiratory symptoms among children under five years of age. Asthma admissions were specifically evaluated; non-statistically significant associations were found for PM_{10}, nitrogen dioxide and ozone.

A report from Sydney, Australia, indicated 1-hour maximum nitrogen dioxide as the single pollutant related to childhood asthma admissions *(94)*. Daily hospital admissions during 1990–1994 were considered in this study. Nitrogen dioxide, ozone and particulates, measured with a nephelometer, were the air pollutants examined. While the effect of nitrogen dioxide was large and robust in sensitivity analyses, both ozone and particulates had a (non-significant) protective effect. In an analysis of hospital admission data in Brisbane during 1987–1994 *(95)*, the only pollutant associated with asthma admissions in the 0–14-year group was ozone. Particulates (measured with a nephelometer) and nitrogen dioxide had a non-significant protective effect.

Only one report is available from Asia. Lee *(96)* analysed hospital admissions for acute asthma in Seoul, Korea, over a two-year period. PM_{10}, nitrogen dioxide and ozone were all related to asthma admissions, the strongest and most robust effects being for nitrogen dioxide and ozone.

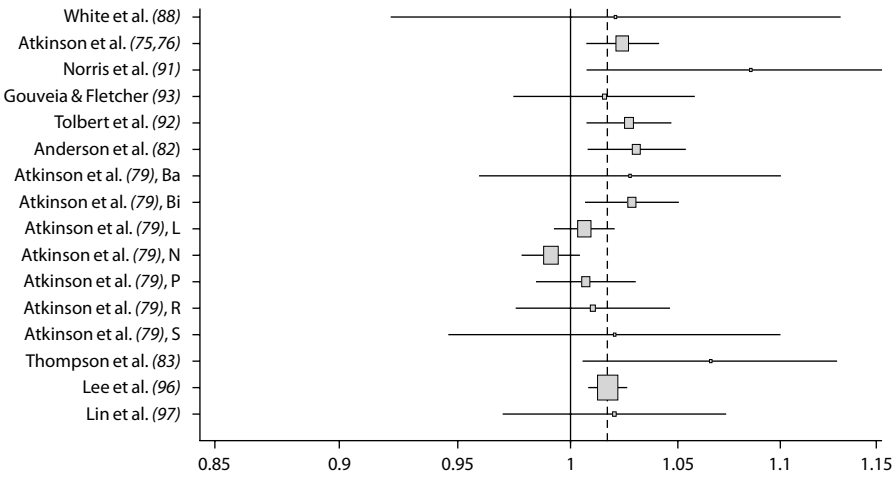
Finally, a comprehensive study was conducted in Canada, with a specific evaluation of the role of fine and coarse particles and gaseous pollutants. Lin et al *(97)* applied a time-series and a case-crossover analysis to study hospital admissions for asthma in 6–12-year-old children living in Toronto between 1981 and 1993. $PM_{2.5}$ and $PM_{10-2.5}$ values were measured every sixth day for 272 days, while estimates of daily values for the entire series were obtained using daily concentrations of sulfates, TSP and coefficient of haze. Coarse particles ($PM_{10-2.5}$) in this study were strongly related to hospital admissions, with a long lag of about six days. The effect of coarse particles was robust to the control of gases in multipollutant models. No effect of fine particles was found in this study, whereas the estimates for PM_{10} were lower than for coarse particles. In a subsequent paper *(98)*, the same authors reported analysis for the effect of gases. This time, a statistically significant effect for nitrogen dioxide was found that was robust to adjustment for coarse particulate matter. On the other hand, no effect of ozone was found.

Of the few published studies that have looked at the health effects of air pollution in the primary care setting, the association of daily consultations with general practitioners for allergic rhinitis has only been studied in London *(99)*. This study suggests that air pollution worsens allergic rhinitis symptoms, leading to a substantial increase in consultations. The daily numbers of children consulting for allergic rhinitis in 1992–1994 increased with the averaged ozone level (lag 0–3). A 23-ppb increase in ozone was associated with a 37.6% rise (95% CI 23.3–53.5). An effect was also found for sulfur dioxide.

A summary of the results of time-series studies on hospital admissions or emergency department visits is given in Fig. 1.

A consistent association between air pollution and hospital admissions, emergency department visits and calls to doctors for asthma in children was found in the epidemiological studies published in the period 1990–2003. The evidence concerning individual pollutants can be summarized as follows.

Fig. 1. Results of time-series studies on hospital admissions or emergency department visits



Note: Ba = Barcelona; Bi = Birmingham; L = London; N = Netherlands; P = Paris; R = Rome; S = Stockholm.

Particulate matter. All the studies that considered BS were conducted in Europe, while several studies considering PM_{10} (or TSP) were conducted in Europe or elsewhere. Most of the studies indicated a negative effect of particulate matter, with at least eight studies showing a statistically significant effect. The APHEA results indicate an increase of 1.5% in asthma admissions per 10 m3 for PM_{10}. There are only two studies evaluating the effect of coarse particles ($PM_{10-2.5}$) and both suggest a positive association. Results concerning fine particles ($PM_{2.5}$), mostly conducted outside Europe, are more controversial. Understanding of the specific influence of particles of different sizes on health can thus be said to be limited.

Nitrogen dioxide. Most of the studies conducted in Europe suggest that nitrogen dioxide is strongly related to hospital admissions or emergency department visits for asthma. Indications of an effect also come from studies conducted outside Europe.

Ozone. Almost 20 studies have evaluated the effect of ozone. Some studies in Europe paradoxically found a protective effect of this pollutant. On the other hand, studies conducted outside Europe tend to show an increase in hospital admissions for asthma. When the analysis was restricted to the warm period of the year, larger effect estimates were found.

In summary, the overall results of the time-series studies suggest an effect from traffic-related pollutants. Nitrogen dioxide seems to be an important pollution marker, with the effects of PM_{10} generally less strong than those of nitrogen dioxide. No conclusions can be drawn, however, on the size of particulates relevant to health. The results for ozone are more controversial, owing to issues concerning the design of time-series studies of this pollutant; final conclusions cannot therefore be drawn, although there is evidence supporting an effect. Finally, it is noteworthy that in many of the studies reviewed where hospital admissions for asthma in adults were also analysed, children showed stronger effects. This may suggest a difference between children and adults in their susceptibility to components of the ambient pollutant mix.

Individual-level, time-series studies on asthma exacerbation in children

Panel studies among asthmatics and children with chronic respiratory symptoms were evaluated. Such studies combine individuals with different levels of asthma severity and medication use, or combine asthmatics and non-asthmatics. The study subjects record daily health outcomes over several months. Air pollution is measured concurrently along with potential confounders that also change on a daily basis, such as weather or days of the week. Various symptoms are considered as outcomes, including cough (unspecified cough, cough in combination with wheeze and tight chest, nocturnal cough), wheeze, shortness of breath with wheeze, and asthma attacks (summary tables are available under the following internet address: http://www.euro.who.int/document/aiq/child3_3annex.pdf). We considered lower respiratory symptoms when there was no information about wheezing or cough *(100)*. Some studies reported both the incidence and prevalence of symptoms, but only incidence estimates were considered. For studies on medication use (summary tables are available under the internet address given above), the use of bronchodilator or ß-agonist was considered. In the same panel studies, lung function changes (PEF, FEV and FVC) were also evaluated, requiring subjects to perform unsupervised daily PEF manoeuvres in the morning or evening or to attend repeated supervised spirometric tests.

Panel studies of asthmatic children have been conducted in Europe countries. In the Netherlands, Roemer, Hoek & Brunekreef *(101)* conducted a comprehensive study on 73 symptomatic children followed for three months during the winter. Measurements of PM_{10}, BS and sulfur dioxide were available, and a health assessment was completed for symptoms, medication use and morning and evening PEF measurements. They observed a consistent positive association between the three pollutants and prevalence of wheeze and all the other outcomes investigated. The same protocol was used by Gielen et al. *(102)* to evaluate the effect of summer air pollution in Amsterdam among 61 children with asthma. Non-significant positive associations were found between PM_{10}, BS and ozone and prevalence of cough and other symptoms. However, medication use was

strongly associated with PM_{10} and BS. Morning PEF were mostly affected by BS and ozone. Children in urban and rural areas of the Netherlands were studied by Boezen et al. *(100)* and categorized according to their BHR and serum IgE. Based on data from three winters, there was a strong association between the occurrence of lower respiratory tract symptoms, including wheeze, and both PM_{10} and nitrogen dioxide among subjects with increased BHR and high IgE levels. No associations were found among children who did not have both of these factors. Evening PEF was also negatively influenced by PM_{10} and nitrogen dioxide. Van der Zee et al. *(103)* examined PEF and respiratory symptoms among children in urban and rural areas with and without asthma, chronic cough or wheeze (classified as symptomatic). In the urban areas, associations were found between PM_{10} and lower respiratory symptoms, medication use and a decrease in PEF among the symptomatic children. The effects of nitrogen dioxide were limited to an increased frequency of bronchodilator use. However, only minimal effects were observed in the non-urban areas. No associations were found among the non-symptomatic children. Finally, the European study PEACE, coordinated by researchers in the Netherlands and conducted in 14 centres, evaluated 2010 symptomatic children with a follow-up of two months. There was no clear association of PM_{10}, BS or nitrogen dioxide with various outcomes, including symptoms, medication use and PEF measurements. Only previous-day PM_{10} was negatively associated with evening PM_{10}. This study was conducted during the winter of 1993–1994, when there was a particularly severe influenza epidemic *(104)*.

Peters et al *(105)* examined asthmatic children from three centres in eastern Europe (Erfurt, Weimar and Sokolov) with relatively high levels of sulfur dioxide and particulates (range of daily means 87–112/m^3) over a period of four weeks. Sulfur dioxide was the pollutant most strongly related with symptoms and PEF, but particulates also showed an effect ($P>0.05$ for symptoms, $P<0.05$ for PEF). A subsequent analysis of children in Sokolov *(106)* confirmed the negative effects of PM_{10} on respiratory symptoms.

A number of studies have been conducted in Finland. In 1997, Timonen & Pekkanen *(107)* published the results of the PEACE study conducted in Kuopio concerning PM_{10}, BS and nitrogen dioxide. For the period of the study, measurements of ultrafine particles were available and were more strongly associated with variations in PEF than PM_{10} or BS. However, after exclusion of the days with the most extreme air pollution values, all associations disappeared. Tiittanen et al. *(108)* examined the association between PM and PEF and cough over a period of six weeks among 49 children with chronic respiratory symptoms living in Kuopio. Several different measures of PM were available, including PM_{10}, $PM_{2.5}$, $PM_{10-2.5}$ and ultrafine particles. Associations were reported between morning PEF and all of the sizes of particulates. Incidence of cough was also associated with all particulate sizes. For cough, however, the strongest association was with a four-day cumulative average of both $PM_{2.5}$ and ultrafine particles. Finally, Timonen

et al. *(109)* examined the results of repeated lung function tests (maximum five) performed at schools with 33 children who participated in the PEACE study in Kuopio. Increased levels of PM_{10}, BS, ultrafine particles and nitrogen dioxide were associated with impairment of lung function.

In two studies conducted in Paris, Segala et al. *(110)* studied children with mild (n = 43) and moderate (n = 41) asthma during a period of six months. Nocturnal cough was the symptom most strongly associated with air pollution in mild asthmatics, particularly PM_{13}, BS and nitrogen dioxide. No association between pollutants and PEF was found in the overall group, but when the analysis was restricted to 21 children taking no corticosteroids and no regularly scheduled ß-agonist, borderline statistically significant effects for PM_{13} and nitrogen dioxide were observed. A later study *(111)* examined symptoms, medication use and PEF among 82 children followed for three months. Again, nocturnal cough was associated with BS and nitrogen dioxide whereas no association was found for ozone. The authors reported that the effect of ozone on asthma attacks became statistically significant when interaction with pollens was considered. In addition, ozone was strongly related to ß-agonist use on days when no steroids were taken. An effect of ozone on PEF variability was reported by the authors but complete data are not available in the original paper.

Several studies on asthma aggravation have been conducted outside Europe, mostly in the United States. One pilot study on 30 asthmatic children conducted by Quackenboss et al. *(112)* in Tucson, suggested an association of PM_{10} and nitrogen dioxide with PEF using both central monitors and personal measurements for two weeks. Pope & Dockery *(113)* studied two cohorts of fifth- and sixth-grade students in Utah Valley. One group had symptoms of asthma or had been diagnosed with asthma by a physician, but were not currently on medication. The other group had no history or symptoms of asthma. Associations were found for both groups between PM_{10} and both PEF and lower respiratory symptoms, especially cough. The symptomatic group demonstrated a greater effect from exposure to PM_{10}. Regarding changes in lung function, Hoek et al. *(114)* reanalysed data on PEF from four other studies conducted in Utah Valley, the Netherlands, Uniontown and State College. Symptomatic children made the panel in Utah Valley. Significant decrements in PEF were found in this group, defined as a daily change greater than 10% below a person's mean, associated with changes in PM_{10}.

Thurston et al. *(115)* examined children with asthma at a summer camp in Connecticut. Associations were reported between both sulfates and ozone (which were highly correlated) and asthma symptoms, PEF and bronchodilator use. Data on PM_{10} were not available.

Delfino et al. *(116)* examined a panel of asthmatics living in a semi-rural area of Southern California with high levels of summer smog. The panel of 24 asthmatics, aged 9–17 years, were followed from August to October 1995. Asthma symptoms were associated with both PM_{10} and ozone, with a greater relative effect from PM_{10}.

The largest effects of PM_{10} were on those children not taking anti-inflammatory medication at the time. In a later study conducted in the same location, Delfino et al. *(117)* confirmed the association of PM_{10} and ozone with asthma symptoms and found nitrogen dioxide to be a relevant pollutant also. Adjustment for pollens was carried out in this study; the effects were stronger in children with respiratory infections and in children who were not taking anti-inflammatory medication. The latest report from the same group *(118)* evaluates asthma symptoms among Hispanic children living in an area of Los Angeles County that has major freeways and trucking routes. A total of 22 asthmatics were followed, and provided with a diary to monitor symptoms. Significant associations were found for PM_{10} and nitrogen dioxide. Ozone also had an effect but was not statistically significant. In addition, elementary carbon and organic carbon were measured in this study and both had an effect on symptoms. The effects of PM_{10}, however, were insensitive to the inclusion of elementary and organic carbon in multipollutant models. No associations were found with PEF measurements.

An early study in the Seattle area was reported by Koenig et al. in 1993 *(119)*. A group of 30 asthmatics were followed for six days and given repeated spirometry tests. Particulates were monitored with a nephelometer. A strong and significant negative effect on FVC and FEV_1 was found. In a later study, Yu et al. *(120)* followed 133 asthmatics aged 5–13 years living in Seattle. A strong association was reported between asthma symptoms and both nephelometry data (approximately equal to $PM_{1.0}$) and PM_{10}. Effects increased with the level of carbon monoxide, which the authors assumed served as a marker for vehicle exhaust. The latest report on this panel *(121)* gives positive associations of symptoms and medication use with $PM_{2.5}$.

Ostro et al. *(122)* examined the effect of PM_{10} and $PM_{2.5}$ on 138 African American children with current physician-diagnosed asthma living in Los Angeles from 10 August to October 1993. Daily reports of cough, shortness of breath and wheeze, and asthma episodes (i.e. the start of several consecutive days with symptoms) were associated with PM_{10} and $PM_{2.5}$ but not with ozone, which showed a protective effect. The PM_{10} effects were slightly stronger than those for $PM_{2.5}$.

The results of the National Cooperative Inner-City Asthma Study (an investigation conducted in eight urban areas in the United States) were reported by Mortimer et al. *(123)*. A total of 846 children were followed for two weeks during the summer by means of a diary and PEF measurements. All the pollutants investigated (PM_{10}, nitrogen dioxide, ozone and sulfur dioxide) were related to increases in morning symptoms. Only ozone was related to a decline in morning PEF.

The publication of the latest report from the United States *(124)* has gained the attention of the scientific literature *(125)*. The study investigated the relationship between outdoor air quality and severity of symptoms in children with asthma in

southern New England over a 183-day period. Symptoms and medication use in 271 asthmatic children were recorded daily. $PM_{2.5}$ and ozone data were available. Higher ozone levels significantly increased the incidence of respiratory symptoms in children using maintenance medications. Furthermore, the use of medications used to relieve symptoms in this group increased significantly as ozone levels increased. The effects of higher ozone levels were not seen in children who were not using maintenance medications. $PM_{2.5}$ was relatively low during the study period and was not associated with symptoms or medication use in either group.

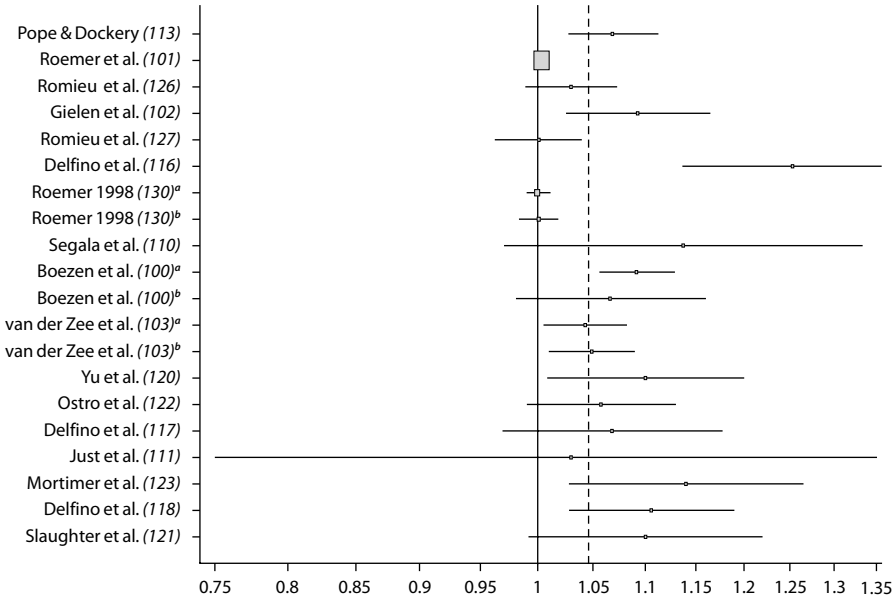
Outside of the United States, few studies are available. Two investigations by Romieu et al. *(126,127)* reported associations between PM_{10}, $PM_{2.5}$, ozone and symptom exacerbation and PEF decline among two panels of children living in Mexico City followed for at least two months. Vedel et al. *(128)* examined 75 physician-diagnosed asthmatic children aged 6–13 years living in Port Alberni, British Columbia. Several other groups of non-asthmatics were also studied. For the entire group (n = 206), particulates were associated with increases in both cough and phlegm and a reduced PEF. Stratified analysis indicated effects among asthmatic children only; no consistent effects were found in the other groups of children. Finally, Jalaludin et al. *(129)* conducted a study on 125 children in Australia. A strong association was found between PEF and ozone, especially in children with increased bronchial responsiveness.

Finally, the recently published systematic review on particulate air pollution and panel studies in children provides an interesting overview *(66)*. The authors considered 22 panel studies conducted on children (with or without asthma or respiratory symptoms at the baseline) so there is only a partial overlap with our review. Summary estimates of the effects for cough, lower respiratory symptoms including wheeze, and lung function changes (PEF) were reported. Pooling the results for PM_{10} indicated no overall effect for cough but a statistically significant effect for lower respiratory symptoms. Pooled results from studies conducted in conditions of relatively high levels of ozone suggest a greater impact of PM_{10} on both cough and lower respiratory symptoms than for studies as a whole. The overall results for lung function changes indicated that PEF is negatively affected by both PM_{10} and $PM_{2.5}$, but the largest effect was detected for $PM_{2.5}$. It has been underlined that the results show considerable heterogeneity and there is evidence of possible publication bias. Therefore, the summary estimates of effect should be interpreted with caution.

A summary of the results of panel studies on exacerbation of asthma in children is given in Fig. 2.

Heterogeneity in the results of panel studies is somehow expected, given possible differences in selection criteria, duration of follow up and outcomes under investigation. The emerging overall picture is nevertheless rather clear: among children with asthma, air pollutants are associated with an increase in the frequency of respiratory symptoms, an increase in medication use, and transient deficits in

Fig. 2. Results of panel studies on exacerbation of asthma in children, indicated by wheeze and PM_{10}



[a] Urban areas.
[b] Rural areas.

lung function. The evidence concerning the effects of individual pollutants can be summarized as follows.

Particulate matter. The results of the panel studies regarding particulate matter consistently show an association with respiratory symptoms. All seven studies considering BS (all in Europe) did find an effect, albeit not always statistically significant. A total of 21 studies are available for PM_{10}, 10 in Europe and 11 elsewhere, and the majority found an association (with the important exception of the large PEACE study, which did not find a clear effect for particulates. Six studies have been conducted with $PM_{2.5}$ and all showed a statistically significant effect. There are too few studies available for $PM_{10-2.5}$ and for ultrafine particles to allow an evaluation. The number of studies reporting results on medication use is more limited, but the overall picture is very similar to that reported on aggravation of symptoms. Most of the studies on BS or particulates showed statistically significant findings. Only two studies evaluated $PM_{2.5}$ and both showed an association.

The results of studies on particulates and lung function changes are rather heterogeneous with regard to the magnitude of the effect. Eight panel studies evaluated the association between BS and lung function and 17 considered PM_{10}. With the exception of the large PEACE study, all the studies showed some effects of

particulates on respiratory function. All three studies evaluating $PM_{2.5}$ showed statistically significant negative effects. Only one study is available on coarse particles and two studies on ultrafine particles: all showed some effect but none gave significant results.

Nitrogen dioxide. When compared with the number of studies evaluating particulates, the investigations on nitrogen dioxide are less numerous. Nine studies are available on nitrogen dioxide and the majority reported a negative effect on symptoms. The three studies evaluating nitrogen dioxide and medication use showed an effect, but only one achieved formal significance. The results for nitrogen dioxide and lung function changes (six studies) are controversial, as both negative and positive associations were found.

Ozone. Of a total of 12 studies on ozone and respiratory symptoms, the vast majority indicated the ability of ozone to increase the frequency of respiratory symptoms. These results are supported by the findings of the five studies on ozone and medication use. The majority of the seven studies on lung function changes found a statistically significant effect.

EVIDENCE SYNTHESIS

Most studies investigating long-term exposure to outdoor air pollutants at the community level found an increased prevalence and/or incidence of bronchitis and cough and reduced lung function. These effects seemed to be stronger in asthmatics. Only a few studies of this type suggested an association with an increased incidence or prevalence of asthma and allergic rhinitis. The studies making comparisons within areas, mostly looking at variation in traffic exposure, provided a slightly different picture. Many of the reviewed studies showed associations with the measured health outcomes, mostly symptoms and/or diagnoses of asthma and hay fever. In line with the studies comparing areas, there was again an association with the prevalence and/or incidence of bronchitis and, more pronouncedly, cough. It is noteworthy that two out of four studies found a statistically significant association with traffic exposure and, interestingly, in all three positive studies this was more pronounced or restricted to outdoor, but not indoor, allergens. A similar association of sensitization to pollen, but not to indoor allergens, with exposure to traffic-related air pollution was also observed in adults *(131)*.

It is not possible to attribute the observed effects to specific components of traffic exposure. Several studies have pointed towards a particular role of diesel fuel. The observed associations with sensitization to outdoor allergens are very interesting in this context, since experimental studies suggest that diesel particles may enhance immunological responses to allergens and inflammatory reactions in the airways *(132–137)*. However, a potential interaction with the effects of allergen exposure has also been suggested for other air pollutants *(138)* and studies

that did not discriminate between truck and motor vehicle exhaust also found effects on respiratory heath and atopic disorders in children.

The study of air pollution and aggravation of asthma is difficult, since the disease and its triggers are complex and multidimensional. Overall, the effects of air pollutants on asthma exacerbation are not always consistent, owing to the complexity of the disease itself and the subsequent difficulties in estimating the impact of air pollution. Nevertheless, several well-conducted prospective cohort studies, often involving hundreds of children with asthma, have found associations of air pollutants with a range of asthma symptoms, medication use or lung function deficits. Panel studies tend to suggest a specific role of particulate matter, as the results of time-series studies on emergency admissions indicate. Fine particles show a clear negative effect in panel studies, but there are too few studies on coarse and ultrafine particles to clearly define the respective role of different particulate sizes. The results for nitrogen dioxide in panel studies are more controversial than those for time-series analyses. Most of the studies on symptoms indicate strong adverse effects of this pollutant but the results of lung function measurements are more equivocal. Finally, although investigations on hospital admissions and emergency department visits gave inconsistent results for ozone, most of the panel studies (especially those conducted in United States) are clearly positive.

When the overall evidence of time-series studies and panel studies is considered, the conclusion is that there is evidence sufficient to infer causality: air pollution contributes to asthma aggravation, leading to an increase in symptoms, greater use of relief medication and a transient decline in lung function. Such worsening of the disease leads to an increased demand for medical care. More research is needed to better determine the role of the various air pollutants and their interaction with individual susceptibility.

CONCLUSIONS AND IMPLICATIONS

The evidence for a link between increased prevalence and incidence of cough and bronchitis and air pollution, particularly from particulates, was "sufficient to infer causality". There is also sufficient evidence for a causal link between deficits in lung function and exposure to air pollution.

There was little evidence for a causal association between the prevalence/incidence of asthma and air pollution in general, though the evidence is suggestive for a causal association between the prevalence/incidence of asthma symptoms and living in close proximity to traffic. The evidence for an association between the prevalence/incidence of hay fever and exposure to traffic was "suggestive of causality".

The evidence for an association between air pollution exposure and the frequency of hospital admissions or emergency department visits for asthma was "sufficient to infer causality". These effects were seen for different traffic-related pollutants, including particulate matter and nitrogen dioxide.

The evidence for an association between air pollution exposure and exacerbations of respiratory symptoms (wheeze and cough) or increased medication use among children with asthma was "sufficient to infer causality". These effects were seen for different pollutants, including particulate matter, nitrogen dioxide and ozone.

The evidence for an association between air pollution exposure and transient changes in lung function among children with asthma was "sufficient to infer causality". These effects were seen for different pollutants, including particulate matter, nitrogen dioxide and ozone.

More research is needed to better understand the role of the various air pollutants and their interaction with individual susceptibility. Nevertheless, the already available data provide strong evidence that the respiratory health of children, particularly those with increased susceptibility such as children with asthma, will benefit substantially from reduction in air pollution, especially that from motor vehicle exhausts.

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[1] References 139 and 140 appear only in the appendixes to Chapter 3.3, available through the link given on page 89.

DEVELOPMENT OF LUNG FUNCTION

Douglas W. Dockery, Patrick J. Skerrett, Dafydd Walters, Frank Gilliland

INTRODUCTION

The development of the respiratory system is a complex process that begins approximately 24 days after fertilization *(1)*. Branching of the airway system down to the terminal bronchioles is complete by 17 weeks *in utero*, but further growth and cellular differentiation continue through various distinct periods until early adulthood *(2)*. Alveolar development starts at 28 weeks of gestation, and by term between a third and half (150 million) of the ultimate number of alveoli (300–600 million) are present *(3,4)*. The remainder develop rapidly after birth such that the final number is almost achieved by 18 months of age *(5)*. Males generally possess more alveoli than females at all ages over 1 year, independent of weight *(6)*. Age-related growth levels off for females by the late teens and for males by the early twenties *(7)*. As in many other areas of human development, "the child is father to the man". In a variety of studies, lung function at maturity has been shown to be a strong predictor of both future lung function *(8,9)* and all-cause mortality *(10–18)*.

Many factors influence lung function and its growth during fetal and neonatal development, infancy, childhood and adolescence. These include genes, nutrition and a host of environmental factors, potentially including air quality. The average young person takes approximately 200 million breaths by his or her 20th birthday. Each inspiration draws in air and other natural substances and may also include a complex mixture of man-made substances, some of which have the ability to impair respiratory function or inhibit the growth and development of lung function.

To date, numerous cross-sectional studies and several recent prospective studies suggest that air pollution in general, and several toxicants in particular, affect lung function and lung function growth in children and young adults (Table 1). Numerous studies have shown that short-term exposure to air pollution episodes is associated with acute but apparently reversible reduced lung function in children. Less well established is whether repeated acute exposures lead to irreversible depression of lung function, and whether chronic exposure leads to chronically depressed lung function.

CHILDREN AS A SPECIFIC RISK GROUP

Air pollution poses a major environment-related threat to health. According to the United Nations Environment Programme, an estimated 1.1 billion people breathe unhealthy air, and mortality related to air pollution is an estimated three

Table 1. Acute and possible chronic effects of ambient air pollution on children's respiratory health

Acute effects	Chronic effects (putative)
Increased respiratory symptoms	Impaired functional lung growth
Increased respiratory illness	Earlier onset and increased rate of decline in lung function with age
Exacerbation of asthma	Increased lifetime risk for chronic respiratory diseases including chronic obstructive pulmonary disease, asthma and lung cancer
Increased health care utilization	Altered lung structure, including metaplasia of the respiratory epithelium in respiratory bronchioles, mononuclear peribronchiolar inflammation, localized deposition and alteration in collagen, and remodelling of the peribronchiolar airspace
Excess cardiorespiratory mortality	
Respiratory tract inflammation	
Increased airway reactivity	
Altered host defences, including oxidant defences, mucociliary clearance, macrophage function and immune response	

Source: American Thoracic Society *(19)*.

million lives a year *(20)*. Much of this global burden falls on the populations of developing nations.

Children are particularly sensitive to the effects of air pollution. Their smaller-diameter airways are more likely to be affected by inflammation produced by air pollution. Children breathe more air per unit of body weight than adults, and thus receive proportionately higher doses of pollutants. They generally spend more time outdoors than adults, often during midday when air pollution levels tend to be higher. They are also more active than adults when outdoors, and so have significantly higher oxygen demand and respiration rates *(21)*. Indeed, children represent the largest subgroup of the population susceptible to the effects of air pollution *(22)*. See Chapter 1 for a more complete discussion of this topic.

NORMAL GROWTH OF LUNG FUNCTION

Normal lung development and growth are necessary for optimal gas exchange. Alterations in lung structure during the life course can adversely affect lung function and result in an increased occurrence of respiratory-related morbidity and mortality.

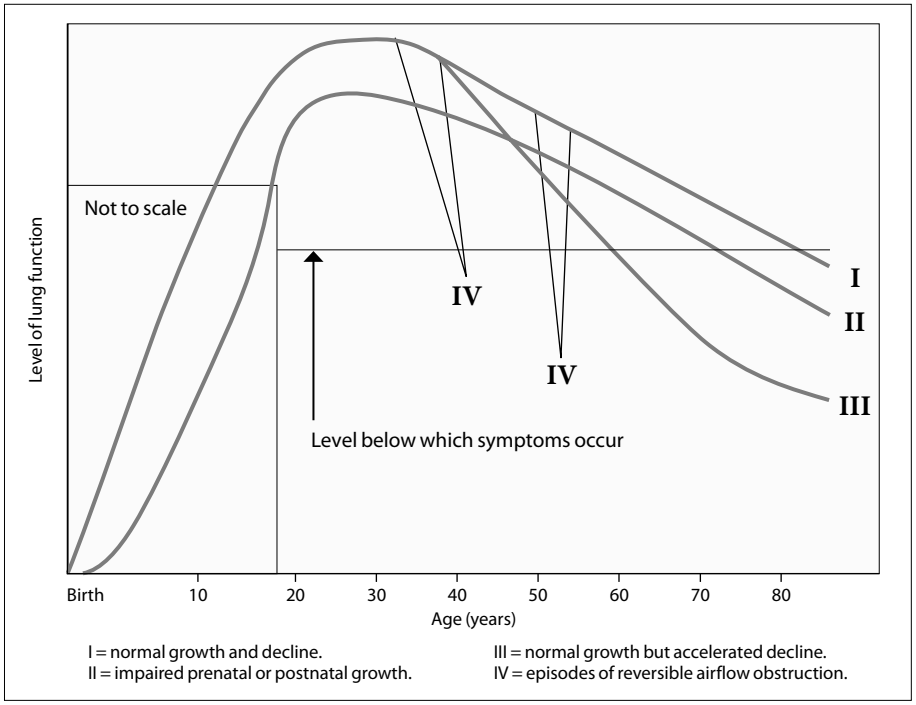
Lung function can be assessed using a broad array of tests that measure lung volume, airflow and gas diffusion. The most convenient spirometry tests measure how well the respiratory system functions in exhaling air. Maximal forced expiratory volume manoeuvres and spirometers are used to assess forced vital capacity (FVC), forced expiratory volume in one second (FEV_1) and maximum mid-expiratory flow (MMEF). Peak expiratory flow rate (PEF) may be determined from spirometry or a simple peak flow meter. The information gathered using spirometry is useful in assessing airway obstruction and functional lung capacity. Poor cooperation limits the use of these tests in children under five.

Fig. 1 shows the change in lung function over the life course, using FEV_1 as an example. Curve I shows the optimal growth and decline of FEV_1. Rapid lung growth begins *in utero* and continues until the late teens and early twenties, where lung function reaches a maximum by age 18–20 years in females and 22–25 years in males *(23)*. Some males may show a small amount of lung function growth into their mid-20s. FEV_1 plateaus among non-smokers without respiratory symptoms for up to 10 years for males and less for females before beginning a slow decline *(23)*. Although pulmonary function growth rate varies with a child's stage of growth, pulmonary function in children follows a relatively consistent track over time *(24–27)*.

While the rate of decline in lung function in adults clearly influences lung function level at any given age, the differences in the rate of decline are fairly modest. A non-smoker loses about 1% of lung function per year, while a smoker loses 1.5% per year *(28)*. The big differences in lung function among adults are due to attained lung function at maturity, which can differ by a factor of two for individuals of the same age, sex, height, weight and race. Thus, factors that affect growth of lung function in children are important in determining level of lung function in adulthood.

A number of insults can disrupt lung development and growth, leading to reduced lung function. These include intrauterine growth retardation, viral infec-

Fig. 1. Schematic representation of the life course of FEV_1



tions, premature birth, inflammatory conditions, genetic mutations and environmental toxicants. Airborne environmental toxicants pose a unique threat to the development and maintenance of maximum attained lung function. Exposures to tobacco smoke and combustion-derived ambient air pollutants are common. Large volumes of air are inhaled daily, and in polluted environments substantial inhaled and deposited doses to airways and air exchange regions occur. If lung defences are breached, normal developmental and homeostatic process can be disrupted, leading to disturbances in development and acute damage that can, in turn, lead to a chronic reduction in lung function.

Impaired prenatal or postnatal growth may result from exposure to environmental toxicants such as tobacco smoke and ambient air pollutants. The temporal patterns of exposures and lung function growth and development may be important in understanding the long-term adverse effects of exposures. Active and passive tobacco smoke exposure has been extensively investigated, and recent studies show that even *in utero* effects of maternal smoking are important *(29,30)*. Reduced prenatal or postnatal growth rates prevent lungs from reaching their developmental potential. This diminished capacity may result in symptoms at an earlier age with normal age-related decline in function or acute respiratory conditions. The effects of toxicants on postnatal growth may be permanent. However, it is not known whether "catch-up" or prolonged growth occurs during late adolescence, resulting in normal attained lung function levels.

Normal or reduced lung function growth rates may also be followed by a shorter plateau phase and/or a period of accelerated decline that produces early onset of chronic respiratory diseases. Superimposed on these lifetime patterns are acute episodes of reversible airflow obstruction. For a given amount of obstruction, symptoms may be more severe depending on baseline function.

Lung function in a child at any age is the result of cumulative lung growth up to that age, and children with the highest lung function are thought to have had the highest lung growth rates. The evidence from studies of environmental tobacco smoke (ETS) suggests that environmental influences can handicap a child prenatally. Thus, it is important to consider the evidence that exposure to air pollution during the prenatal period may affect birth weight and other indices of health. This may be especially important in that the lungs are the last organ to develop and are not fully developed at birth.

EFFECTS OF ENVIRONMENTAL TOXICANTS ON LUNG FUNCTION GROWTH AND DECLINE

Based on studies of occupational groups and model systems, a large number of toxicants have the potential to adversely affect lung function growth and decline. In order to understand the effects of environmental toxicants on lung function growth and decline, the timing of exposure must be considered. Critical windows of susceptibility occur during the fetal and childhood periods of growth and

development. Exposure during these periods may have larger long-term consequences than exposure at the same level during the phase of decline in adulthood. The fetal period appears to be a critical window for the effects of toxicants on lung function. Recent studies showing that current levels of ambient air pollution increase the risk for low birth weight and preterm birth suggest that lung function could be adversely affected by air pollution exposure during the fetal period *(31,32)*. However, the effects of ambient air pollutant exposure *in utero* on lung function at birth or during childhood have yet to be established. Premature birth can result in severe damage to lungs in the neonatal period, but a measured deleterious effect of air pollution on long-term lung function through this effect remains to be established. Studies of air pollution during specific periods and lung function levels in neonates, as well as of lung function growth in children, will be required in order to address this important issue.

Periods of exposure during later life are often correlated with exposure in earlier periods. For example, active smoking, exposure to ETS and *in utero* exposure to maternal smoking are highly correlated. If the temporal correlation of *in utero* and ETS exposure during childhood is not accounted for, the effects of *in utero* exposure could be incorrectly ascribed to ETS exposure during childhood *(29,30)*. Lastly, toxicants can induce disease states that affect later exposure or recall of previous exposure history, suggesting that prospective studies may be necessary to clarify the temporal relationships between exposures and adverse respiratory outcomes.

TOBACCO SMOKE AND GROWTH IN LUNG FUNCTION DURING CHILDHOOD

Tobacco smoke is a prototype toxicant because its effects on lung function have been most extensively studied over the life course *(33–35)*. *In utero* exposure to maternal smoking is associated with decreased lung function at birth *(30)*, which persists into adolescence and adulthood *(36,37)*. The effects of *in utero* exposure are largest in children who also develop childhood asthma *(38)*. Because *in utero* exposure also increases the risk for asthma, *in utero* exposure affects lung function directly during this period of growth and development and indirectly through increased occurrence of childhood asthma. A large number of studies have investigated the role of ETS exposure on lung function in children *(1,39–44)*. Although they demonstrate that ETS exposure is prospectively associated with growth in lung function, most studies did not assess the effects of the highly correlated exposure of maternal smoking during pregnancy. Tobacco smoke exposure is associated with a shorter plateau and an accelerated rate of decline in lung function in susceptible smokers that may lead to an early onset of disability and death from chronic lung diseases. Smoking cessation results in a rate of decline in lung function similar to that in those who have never smoked, even after the onset of disability *(27)*.

CROSS-SECTIONAL STUDIES

Studies examining lung function at specific points in time from Europe *(45–55)*, Asia *(56–59)* and North America *(60–64)* have assessed the impact of air pollution on lung function and/or lung function growth in children. Data from the Second National Health and Nutrition Examination Survey (NHANES II) in the United States showed significant negative correlations between annual concentrations of total suspended particulates (TSP), nitrogen dioxide and ozone and FVC and FEV_1 among individuals aged 6–24 years *(63)*. The 24 cities study *(61)* showed a strong association of annual mean PM_{10}, ozone and particle strong acidity with the lung function of elementary-school children. A difference of 17.3 μg/m^3 in annual mean PM_{10} was associated with a 2.4% (95% CI 0.5± 4.3) decrement in adjusted FVC and a 2.1% (95% CI 0.1± 4.0) decrement in adjusted FEV_1. The results are not, however, entirely consistent. In the Six Cities Study, for example, chronic effects on lung function were not observed among more than 5000 children *(64)*. Overall, however, results from these studies indicate that poor air quality is associated with deficits in attained lung function or lung function growth, as measured by a variety of indices.

It is difficult to relate the results of cross-sectional studies examining the association between level of lung function and ambient air pollution to longer-term consequences of growth or decline in lung function. A key underlying assumption in such studies is that level of lung function reflects cumulative effects of air pollution over a lifetime. Presumably, children with the highest level of lung function at any given age must have been growing faster. This is the "horse racing effect" described by Fletcher & Peto *(65)*. This assumes that all children start at the same point in their lung function development. Yet, as noted earlier, factors such as genetics, nutrition, ETS and even air pollution may have effects on lung function prenatally, and thus influence lung function and development from birth onwards. Finally, because cross-sectional surveys assess both exposure and disease at a single point in time, they cannot demonstrate causality *(66)*.

POST-MORTEM STUDIES

An autopsy study was performed on 107 young accident victims aged between 14 and 25 years, most of them lifelong residents of Southern California where air quality is generally poor (67) The results revealed widespread evidence of early signs of chronic lung disease, including low-level bronchitis, chronic interstitial pneumonia and an unprecedented rate of severe chronic inflammation of the respiratory bronchioles, even though few of the victims had had breathing disorders when they were alive. Eighty percent showed some degree of subclinical centriacinar region disease; 27% had severe and extensive centriacinar region disease. These results are suggestive of an association between air pollution and impaired lung function in children and young adults, but they are not definitive since the

subjects were not screened for the use of tobacco or other factors that could damage lung function and there was no control group for comparison.

LONGITUDINAL STUDIES

Longitudinal cohort studies offer a number of advantages for examining the association between air pollution and lung function and growth. Repeated assessments can establish the temporal sequence between exposure and disease. Repeated measurement of children's lung function over several weeks or months (panel studies) provides information on the acute, potentially reversible effects of short air pollution episodes. Repeated lung function measurements over many years (prospective cohort studies) provide information on the effect of air pollution on lung growth and development. Such studies also allow investigators to examine multiple effects of a single exposure *(66)*.

Panel studies

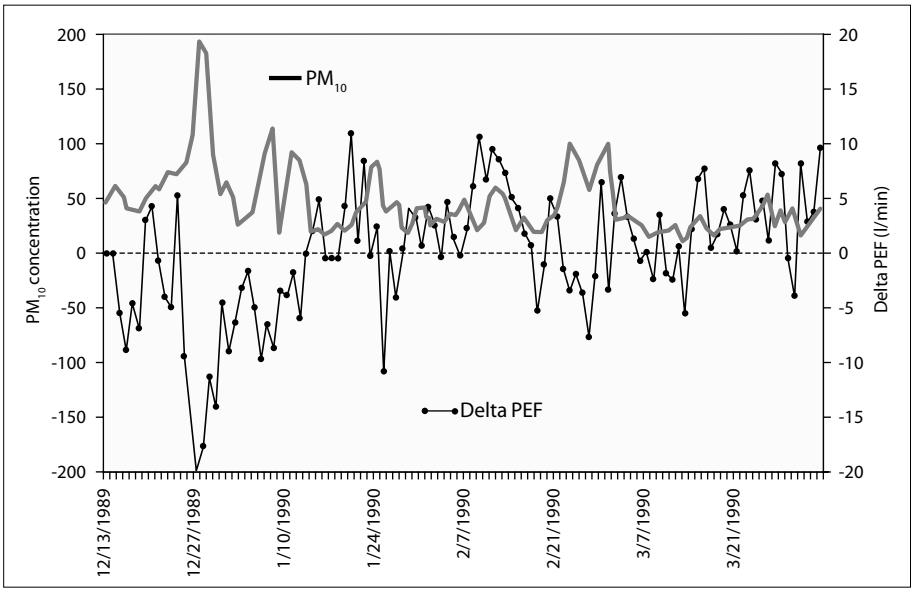
In one of the first panel studies, lung function of children was measured weekly before, during and after air pollution episodes in Steubenville, Ohio *(68)*. Spirometric measures of lung function decreased in the week after episodes of very high TSP and sulfur dioxide air pollution, but returned to pre-episode levels within a few weeks. Similar acute changes in lung function measured by spirometry were found in schoolchildren exposed to high particulate and sulfur pollution in the Netherlands *(69)*.

This design was applied in a series of studies of supervised daily peak expiratory flow measured in children attending outdoor summer camps over one- to two-week periods *(70–76)*. These studies showed a consistent reduction in peak flow associated with daily ambient ozone concentrations.

These methods were also applied in a panel study that included schoolchildren in Utah Valley, who measured their own peak flow daily for four months before going to bed *(77)*. There was a strong negative correlation between decreased peak flow (compared to the child's mean) and daily ambient PM_{10} concentrations (Fig. 2). This design has since been applied in multiple studies in Europe *(78–84)*, North America *(85–91)* and other continents *(92,93)*.

Meta-analyses of these panel studies have found acute, apparently reversible decreases in lung function associated with short-term air pollution exposures *(94–97)*. The results of these panel studies in asthmatic children are summarized in Chapter 3.3. In a recent meta-analysis of 14 panels of children, the effects of particulate air pollution were less for asthmatic than for non-asthmatic children *(96)*. Asthmatic children might be expected to be more sensitive to the effects of air pollution. However, with appropriate medical management, asthmatic children will respond with bronchodilators and other rescue treatments in response to indications of an asthma attack, such as a drop in peak flow. Thus, in studies of asthmatics in the community, the effect of air pollution will be blunted so that

Fig. 2. Mean deviation in PEF by day versus ambient PM_{10} concentration for children participating in panel study in Utah Valley



Source: Pope et al. *(77)*.

asthmatics appear to be less responsive than non-asthmatics to air pollution episodes *(98)*.

Prospective cohort studies

While there is extensive literature showing acute effects of air pollution on lung function, this does not necessarily mean that irreversible changes are associated with repeated or chronic exposure to air pollution. To date, only a handful of prospective studies have examined the impact of air quality on lung function growth in children.

In Poland, Jedrychowski and colleagues assessed lung function growth in 1001 preadolescent children living in two areas of Krakow with different levels of ambient air pollutants. In the city centre, the area with the highest concentrations, the mean annual level of suspended particulates was 53 μg/m^3 and that of sulfur dioxide 44 μg/m^3, while in the outlying control area the levels were 33 μg/m^3 and 32 μg/m^3, respectively *(51)*. Mean lung function growth rate adjusted to height velocity and lung function level at study entry was significantly lower among children living in the city centre than among those living in the control area, while the proportion of children with slower lung function growth was higher in the city centre.

In Austria, Frischer and colleagues investigated the long-term effects of ambient air pollution in a cohort of 1150 children from nine study areas selected to represent a broad range of ozone exposure sites *(45)*. Over a three-year period

(1994–1996) the investigators recorded lung function twice a year – before and after summertime. After adjusting for sex, atopy, passive smoking, baseline lung function and increase in height, significant deficits in FVC, FEV_1 and MMEF were associated with ozone levels. There was also some evidence that sulfur dioxide and nitrogen dioxide were associated with deficits in MMEF growth.

After an additional year of follow-up of 975 schoolchildren from eight of these communities in Lower Austria, these investigators reported a slower increase in FEV_1 and MMEF with age in children exposed to higher summer PM_{10} *(46)*. After adjusting for potential confounders, an increase of summer PM_{10} by 10 $\mu g/m^3$ was associated with a decrease in FEV_1 growth of 84 ml/year, suggesting impaired development of large airways, and a decrease in MMEF of 329 ml/s/year, suggesting a decline in the development of small airways.

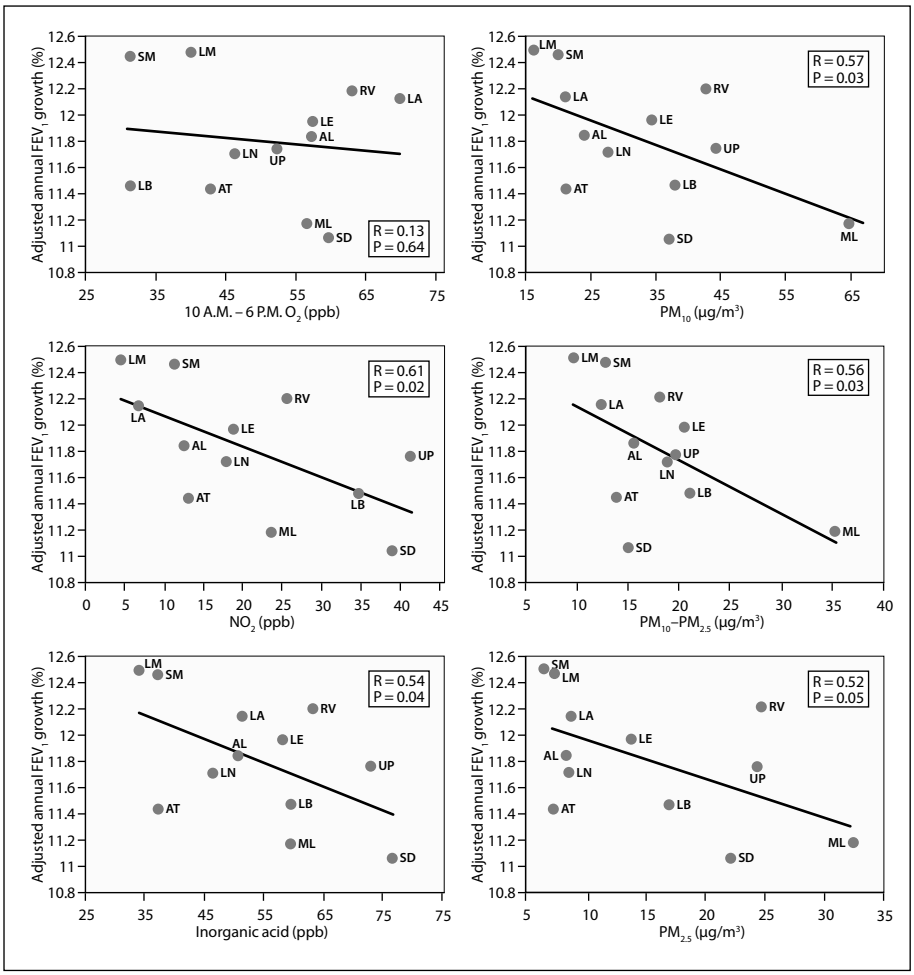
The largest and, to date, longest prospective cohort study was conducted in 12 communities within a 200-mile radius of Los Angeles, California *(99)*. Known as the Children's Health Study, it followed more than 3000 children who were in grades 4, 7 and 10 in 1993 for a four-year period. Spirometric evaluations performed annually yielded measures of FVC, FEV_1 and MMEF. Air pollution data were collected from stations established in each of the 12 communities to monitor hourly concentrations of ozone, nitrogen dioxide and PM_{10}. Integrated samplers were used to determine $PM_{2.5}$ and acid vapour.

Average growth of lung function was modelled as a function of average exposure to ambient air pollutants after appropriate adjustment for personal and household characteristics. In the fourth-grade cohort, deficits in growth of lung function, as measured by changes in FEV_1 (Fig. 3), FVC and MMEF were significantly associated with exposure to PM_{10}, $PM_{2.5}$, PM_{10}–$PM_{2.5}$, nitrogen dioxide and inorganic acid vapour. No significant associations were observed with ozone. Because the concentrations were so highly correlated across communities, the investigators could not identify the independent effects of each pollutant. These similarities indicate that exposures associated with mobile sources (nitrogen oxides and particulates) are important.

Compared to children living in the least polluted community, those living in the most polluted community had a cumulative reduction of 3.4% in FEV_1 and 5.0% in MMEF over the four-year study period. The estimated deficits were generally larger for children spending more time outdoors. Although similar trends were observed in the seventh- and tenth-grade cohorts, none achieved statistical significance owing to smaller sample sizes. The estimated deficit in annual FEV_1 growth rate of 0.9% per year across the range of PM_{10} exposure exceeds that associated with passive smoke exposure in children *(44)*.

A second cohort of more than 1600 fourth-grade children from the same communities followed from 1996 to 2000 also exhibited an association between ambient levels of air pollutants in southern California and impaired lung function growth *(100)*. Reduced FEV_1 and MMEF growth was most strongly associ-

Fig. 3. Adjusted average annual FEV_1 growth rates for the fourth-grade cohort in 12 communities vs mean pollutant levels over the study period, 1993–1997



Source: Gauderman et al. *(99)*.

ated with levels of vapour acids, nitrogen dioxide, $PM_{2.5}$ and elemental carbon (a marker for diesel exhaust).

Results from the second cohort provide important confirmation of the results of the first *(99)*. This replication, along with the observation of a greater impact among children who spent more time out of doors, supports a causal association between air pollution and lung function growth deficits. Results from the second cohort suggest that long-term pollution exposure may affect the development of small airways in the lung. This conclusion is based on larger observed pollutant–effect estimates for MMEF than for other measures of pulmonary function and on significant associations between pollution and the volume-corrected measure, MMEF/FVC.

Across the two cohorts, significant associations were observed between both particulate and gaseous pollutants and measurements of lung function. Although the correlations among pollutants were high, fine particles ($PM_{2.5}$) and the elemental carbon portion of particulates showed stronger associations with lung function growth than PM_{10} or the organic carbon portion.

The latest report from the Children's Health Study substantially extends the follow-up to eight years. After adjustment for several potential confounders and effect modifiers, deficits in the growth of FEV_1 were associated with exposure to a variety of air pollutants, including nitrogen dioxide, acid vapour, $PM_{2.5}$ and elemental carbon among 1759 children followed from 10 to 18 years of age *(101)*. Associations were also observed for FVC and MMEF. These results are consistent with those of previous epidemiological studies that have implicated fine particulate matter and associated combustion-related air pollutants as being largely responsible for the observed health effects of air pollution. The fact that such associations were observed in boys and girls, in children with and without asthma, and in smokers and non-smokers suggests that most children are susceptible to the chronic respiratory effects of air pollution. The investigators also note that the effect of these pollution-related deficits in lung function may occur later in life, with reduced lung function acting as a risk factor for complications and death during adulthood.

Collectively, these prospective studies strengthen earlier evidence from cross-sectional studies that long-term exposure to elevated levels of air pollution during childhood can produce deficits in lung function growth. Whether the deficits in growth result in reduced maximum attained lung function in adulthood is an active area of research.

POSSIBLE REVERSIBILITY OF AIR-POLLUTION-RELATED DEFICITS

One important question is whether deficits in lung function growth related to air quality are permanent or reversible. Data from several cross-sectional prospective studies suggest that lung function may recover if an individual breathes cleaner air, either because of improvements in air quality or because the person moves to an area with cleaner air.

Italian researchers examined respiratory function in almost 2000 schoolchildren who lived in urban areas before and after an improvement in air quality *(102)*. They also evaluated 160 children living in a suburban area as controls. In the first survey, the FEV_1 and MMEF of children from urban areas were significantly lower than those of controls. In a second survey, they were not significantly different. The slopes over time of FEV_1 and MMEF, adjusted for sex and anthropometric variables, were closely related to decreases in the concentration of pollutants.

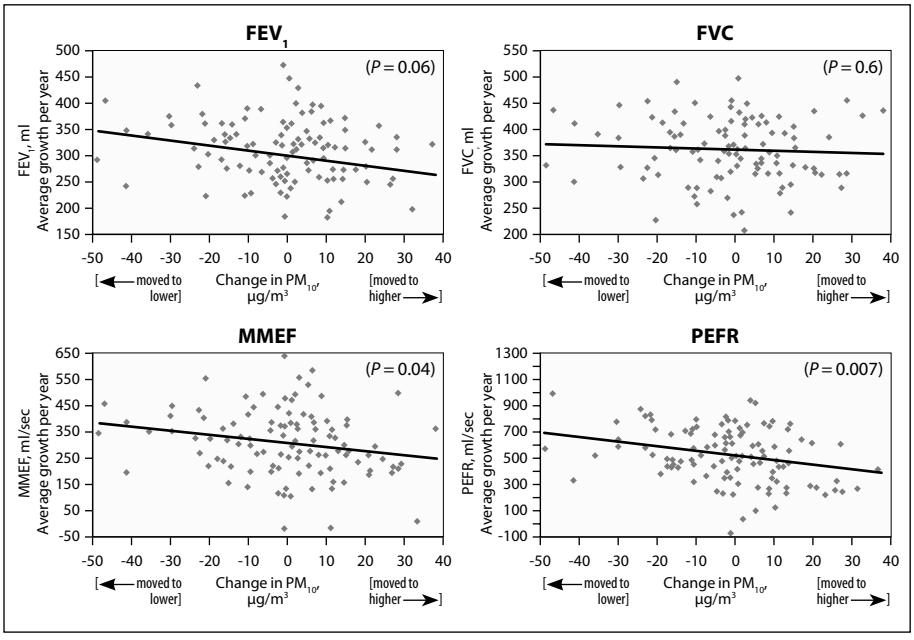
Substantial improvements in air quality in the area of the former German Democratic Republic following reunification in 1990 were associated with im-

provements in children's lung function. Consecutive cross-sectional surveys of almost 2500 schoolchildren aged 11–14 years from three communities in eastern Germany were performed in 1992–1993, 1995–1996 and 1998–1999. During this period, as the annual mean concentration of TSP fell from 79 to 25 μg/m^3 and that of sulfur dioxide fell from 113 to 6 μg/m^3, increases were observed in mean FVC and FEV_1 *(49)*. For each 50-μg/m^3 decrease in TSP, the adjusted increase in the geometric mean of FVC was 4.7%. For each 100-μg/m^3 decrease in sulfur dioxide, FVC increased by 4.9%.

Investigators with the Children's Health Study in Southern California examined respiratory function in 110 children enrolled in the 10-year study who moved from the cohort communities. Subjects who moved to areas with lower levels of PM_{10} showed improvements in lung function growth, while those who moved to areas with a higher PM_{10} level showed impairment of lung function growth (Fig. 4) *(103)*. The longer the child lived in the new community, the stronger the trend.

Data from these studies of responses to improving air quality or migration from areas of high concentrations of air pollutants to ones with lower concentrations suggest that recovery of lung function growth is possible.

Fig. 4. Effect of changes in PM_{10} on adjusted annual lung function growth for FEV_1, FVC, MMEF and PEFR in all subjects who moved from one of the 12 communities in the Southern California Children's Health Study



Source: Avol et al. *(103)*.

Note: Annual lung function growth rates were adjusted for sex, race, year of entry into the study, annual average changes in height, weight and body mass index, and interaction of sex with change in height.

IMPACT OF SPECIFIC TOXICANTS

While studies on the effects of mixtures of ambient pollutants on lung function development and decline have been reported, they have not clearly identified the constituent or characteristic of the air pollution mixture that accounts for the associations. Our lack of understanding of which pollutants are important, and what levels of exposure are safe, inhibits rational approaches for control. Among the large number of chemical species that occur in ambient air, ozone, nitrogen dioxide, acid vapours, respirable particulates (PM_{10} and $PM_{2.5}$), sulfur dioxide and acid aerosols have been identified as candidate pollutants for adverse effects on lung function *(19)*. Evidence for effects of each of these pollutants on lung function growth and decline are reviewed below.

Ozone and lung function development

There is substantial evidence that short-term exposures to ozone are associated with acutely reduced lung function. In a pooled analysis of six summer camp studies *(70)*, each 100-μg/m^3 increase in daily ozone concentration was associated with a 51-ml decrease in FEV_1 and a 29-ml/sec decrease in PEF. In a meta-analysis of 29 panel studies of children *(97)*, each 100-μg/m^3 increase in ozone was associated with a 2.2% decrease in FEV_1 and a 3.4% decrease in PEF.

The acute effects of ozone on lung function, airway hyper-responsiveness and airway inflammation in humans and animal models has led to the hypothesis that living in regions with high levels of ambient ozone is associated with chronic deficits in lung function caused by reduced growth and a faster decline in lung function *(104)*. Much of the evidence derives from cross-sectional studies of attained lung function and retrospectively assessed lifetime exposure *(61,63,105–107)*.

Schwartz *(63)* studied the effect of air pollution on lung function in a cross-sectional analysis of children and young people aged 6–24 years who participated in NHANES II. In these subjects, community ozone level was associated with decrements in FVC and FEV_1. Kuenzli and colleagues *(106)* studied the effects of ozone exposure on lung function in 130 college students. Using a residence-based exposure assignment for ozone, they observed a strong relationship between lifetime ambient ozone exposure and mid- and end-expiratory flows. No associations with FEV_1 or FVC were found, which is consistent with biological models of chronic effects of ozone in the small airways. In a study on another group of college students, using a similar design, lung function was lower in the group exposed to higher levels of ozone *(107,108)*. Deficits were observed for FEV_1 (–3.1%; 95% CI –0.2% to –5.9%) and MMEF (–8.1%; 95% CI –2.3% to –13.9%). However, after considering the effects of PM_{10} exposure, the investigators concluded that living for four or more years in regions of the country with high levels of ozone and related co-pollutants was associated with lower lung function, but that the effects were more strongly associated with PM_{10} levels than with ozone levels *(107,108)*. Cross-sectional analysis of the Children's Health Study also found

an effect of ozone on PEF ($r = -0.75$, $P<0.005$), and $PM_{2.5}$ on MMEF ($r = -0.80$, $P<0.005$). Ozone exposure was associated with decreased FVC and FEV_1 in girls with asthma, and between-peak ozone exposures were associated with lower FVC and FEV_1 in boys spending more time outdoors *(109)*. The effects of ozone were larger for exposures earlier in life. The cross-sectional studies suggest that high lifetime ozone exposure is associated with deficits in small airway function.

In Austria, Frischer et al. *(45)* prospectively investigated the effects of ozone on children's lung function growth. They conducted repeated pulmonary function tests over a three-year period on children in nine Austrian cities, and reported associations between ozone and reduced lung function growth. It must be noted, however, that the ozone findings may be confounded by contemporaneous exposure to other pollutants.

In the first Children's Health Study cohort, ozone was not significantly associated with growth of FVC, FEV_1 or MMEF among school-age children *(99)*. In the second cohort of fourth-grade students, however, ozone was associated with reduced growth of PEF and some evidence for reduced growth in FVC and marginally in FEV_1 ($P = 0.053$) in the group of children spending more time outdoors *(100)*.

Putting the results of longitudinal and cross-sectional studies together, the evidence is consistent with an age-dependent effect of ozone on the growth of small airway function that is largest during preschool ages.

Nitrogen dioxide and lung function development

Because nitrogen dioxide is a common indoor air pollutant, arising from natural gas combustion, the effect of nitrogen dioxide on lung function has been examined free from the effects of other ambient pollutants *(19)*. Although a meta-analysis of panel studies of nitrogen dioxide exposures determined that each 100-$\mu g/m^3$ increase was associated with a 0.7% decrease in FEV_1, the association was not statistically significant *(97)*. This highlights the inconsistency of the data collected to date.

In a prospective study of Dutch children followed over a two-year period with serial lung function measurements, nitrogen dioxide showed a weak negative association with MMEF. There was not, however, a consistent relationship between growth of lung function and a single measurement of indoor nitrogen dioxide *(110)*. In early analyses of data from the Six Cities Study, lower levels of FEV_1 and FVC were observed in children living in homes with gas stoves *(111,112)*, but in subsequent analyses there was no evidence that lung function growth was correlated with gas stoves *(44)*. In a subsample of children from the Six Cities Study for whom indoor nitrogen dioxide was measured in homes, there was no effect of nitrogen dioxide on lung function level *(113)*. Other studies of the effect of indoor sources of nitrogen dioxide on lung function in children have also been inconsistent *(19)*. The data from these studies and the Children's Health Study suggest that

nitrogen dioxide at ambient levels may not have an independent effect on lung function level or growth. It is possible, however, that ambient nitrogen dioxide level may be associated with lung function growth in the context of the other pollutants that occur with ambient nitrogen dioxide. In this regard, it is uncertain whether nitrogen dioxide itself is the active pollutant that interacts with other pollutants, such as ozone, or whether it serves as a surrogate for high levels of fresh emissions from combustion sources such as motor vehicles.

Particulates and lung function

As illustrated in Fig. 2, brief exposures to particulate air pollution have been associated with acute decreases in lung function. In an early meta-analysis, Dockery & Pope *(95)* reported a 1.5% decrease in FEV_1 and a 0.8% decrease in PEF associated with each 100-μg/m^3 increase in PM_{10}. Zmirou et al. *(97)* found similar decreases of 2.2% in FEV_1 and 0.7% in PEF for the same increment in particle concentration. In a recent meta-analysis, Ward & Ayres *(96)* reported a 3.3 l/min decrease in PEF associated with each 100-μg/m^3 increase in PM_{10}.

Although cross-sectional associations of PM_{10} and $PM_{2.5}$ mass concentrations with lung function have been inconsistent, TSP level has been associated with decreased lung function growth in children in Poland *(51)* and PM_{10} and $PM_{2.5}$ levels have been associated with decreased lung function in children in Utah *(62)* and Southern California *(99,100)*.

The effect of particulates may be due, in part, to particle acidity. Particle strong acidity, characterized by sulfur dioxide-derived acidic sulfate particles, has been associated in a cross-sectional study with lung function level *(61)*. In the Children's Health Study, a strong association was observed between vapour phase acids and deficits in lung function growth. This association was not due to particle acidity, as Southern California had low concentrations of sulfur dioxide and acidic sulfate particles during the study period. In Southern California, high ambient concentrations of nitrogen dioxide were the primary source of nitric acid vapour. These findings suggest that the effects of gaseous nitric acid and acid sulfate aerosols on lung function level and growth may be mediated, in part, by the hydrogen ion concentrations produced in the lung; however, the findings in the Children's Health Study suggest that vapour acids may be a surrogate marker for other species that occur in a polluted atmosphere in which vehicle emissions have undergone significant photo-oxidation.

Other ambient pollutants and lung function

Although motor vehicle exhaust is the primary source of many of the ambient air pollutants associated with adverse effects on lung function, the role of high levels of exposure to freshly emitted motor vehicle exhaust on lung function level or growth is an important unanswered question. There is some evidence supporting an effect of fresh exhaust on lung function based on experimental studies, stud-

ies of children who live near highways with heavy traffic volumes, and studies of exposures in tunnels. In a cross sectional study of 1191 Dutch children living near busy roads, deficits in lung flow rates were observed in children living within 300 metres of a such a road. The deficits were larger for traffic counts of trucks (powered primarily by diesel fuel) than for cars (powered primarily by petrol) and were stronger for girls than for boys *(54)*. In a study of 4320 fourth-grade children in Munich, using a variety of measures, traffic density was associated with diminished lung function *(114)*. In a cross sectional study of preschool children in Leipzig, exposure to heavy traffic was associated with lower FVC and FEV_1 *(47)*. In contrast, a study using repeated cross-sectional surveys of 200 non-smoking women living in each of three areas in Tokyo – within 20 metres of major roads, 20–150 metres from the same roads, and in a separate suburban low-traffic neighbourhood –exposure to traffic was not associated with lung function *(115,116)*.

Although the effects of living near heavily used roads may be related to nitrogen dioxide exposure, a number of other pollutants that are emitted in exhaust are of interest, including diesel exhaust and ultrafine particles. Diesel exhaust is a traffic-related pollutant that contains high levels of nitrogen dioxide, fine particles and organic compounds. Diesel exhaust appears to have acute and chronic effects on lung function *(117)*. In the Children's Health Study, elemental carbon levels (a marker for diesel exhaust) were associated with reduced lung function growth in children *(100)*. Further work is needed to investigate the components or characteristics of diesel exhaust that affect lung function development and decline. Urban particulates exist in three sizes: ultrafine particles <0.1 μm in diameter, accumulation mode particles between 0.1 μm and 2.5 μm in diameter, and coarse particles between 2.5 μm and 10 μm in diameter. The fine particle mass <2.5 μm in diameter ($PM_{2.5}$) includes both the ultrafine and accumulation mode particles. Ultrafine particles contribute very little to the overall mass of fine particles but are very high in number, especially within 100 metres of roads. These particles are of interest because they have high deposition in the distal lung, have large surface areas coated in organic compounds and transition metals, and have the ability to induce oxidative stress and inflammation in the lung *(118)*.

To date, no investigations of the chronic effects of ultrafine particles on lung function growth have been reported. Although ultrafine particles may be important, determining the size distribution of fine particles in general may be required. For example, the number of accumulation mode but not ultrafine particles was consistently inversely associated with PEF in a study of 54 adult asthmatics in Helsinki with whom approximately 8000 daily morning, afternoon and evening PEF measurements were performed at home *(119,120)*. In that study, no associations were observed with large particles or particle mass. Given the biological effects of ultrafine particles on the lung, studies of the effects on lung function are a priority.

SUSCEPTIBILITY TO AMBIENT POLLUTANTS AND LUNG FUNCTION DEVELOPMENT

Because airway defences to inhaled oxidants are interacting systems, a number of host and genetic factors may contribute to the response of fetal and children's lung function to air pollutants. Asthma and other respiratory conditions appear to be important determinants of lung function growth, which declines following exposure to elevated levels of air pollutants. Time–activity patterns and sex may also modify the effects of air pollution on lung function growth and development. Dietary factors may affect both lung growth and responses to air pollutants *(121–124)*. A growing number of susceptibility genes have been identified as participants in the pathogenesis of persistent lung damage *(125,126)*. Genotypes that result in a higher-intensity oxidative stress, inflammatory responses or altered tissue response to damage appear to be associated with increased susceptibility to respiratory effects from acute and chronic exposure to air pollution.

CONCLUSIONS

Studies of lung function in children suggest that:

- living in areas of high air pollution is associated with lower lung function;
- chronically elevated air pollution is associated with lower rates of lung function growth;
- improvement in air pollution leads to improvements in lung function level and/or growth rate;
- acute exposures to air pollution are associated with apparently reversible deficits in lung function; and
- children who spend a significant amount of time outdoors in polluted environments or those with poor nutrition may be more strongly affected by air pollution.

These effects of air pollution are modest, accounting for only a few per cent of the deficit in average lung function. Nevertheless, the studies suggest that the effects can be cumulative over a 20-year growing period, and there is uncertainty over whether the chronic effects are reversible. Furthermore, even a small shift in average lung function can yield a substantial increase in the fraction of children with "abnormally" low lung function, that is, small changes in the population mean can reflect large changes in a susceptible subgroup of the population.

RESEARCH QUESTIONS OR AREAS REQUIRING STUDY

Better understanding of the impacts of air pollutants on lung development requires further research, in particular focused on the following issues:

- characteristics that make children more sensitive to air pollution;
- the effects of prenatal and early life exposures to air pollution (the lungs are not fully developed at birth, and early life challenges may have more serious and more long-lasting impacts);

- major components of air pollution (e.g. acids or particles) that affect the growing lung, and determining the important particle size implicated in any effect on lung function growth; and
- determining whether the effect of air pollution on lung growth is truly reversible and, if so, whether this is due to "catch up" lung growth or to some other mechanism when pollution is removed or reduced.

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ASSOCIATION OF SCHOOL ABSENTEEISM WITH AIR POLLUTION

Mark Everard

Indirect evidence that there may be an association between levels of atmospheric pollutants and adverse affects on the health of children has been sought over the past four decades in a number of studies assessing levels of school absenteeism, predominantly in young children. These studies have been based on the assumption that significant increases in school absenteeism may reflect the health effects of short-term increases in levels of pollutants. The design and interpretation of such studies is challenging because of the many social, behavioural and medical factors that are known to influence school absenteeism. These include the day of the week, season, temperature, relationship to holidays, family dynamics, the presence of family members with respiratory disease, exposure to tobacco smoke, and epidemics of respiratory and other infectious diseases. It is also possible that less quantifiable factors such as individual perception of pollutant levels influence these figures *(1,2)*.

Despite these difficulties, most (though not all) published studies appear to indicate that the ambient level of certain pollutants may have a small but discernible association with school absenteeism *(3,4)*. However, there are a number of conflicting results regarding individual pollutants. Some studies, for example, suggest that there is a positive association between PM_{10} levels and school absence *(5,6)*, while others suggest that there is a negative correlation *(7)* or are unable to identify an effect *(8,9)*. Other pollutants such as ozone *(5,7,8,10)*, carbon monoxide *(7)* and sulfur dioxide *(5,11)* have also been linked to increases in school absence. As with PM_{10} there are conflicting data regarding nitrogen dioxide and nitrogen oxides, with positive short-term associations being reported in one study *(9)* but not in others *(5,8)*. The causes of these discrepancies are unclear but may be attributable to a threshold effect, with variations in a particular pollutant having no discernable adverse effect below a certain level. The effect of other pollutants may act as confounders in some studies, particularly those where the possible impact of only one pollutant has been assessed. Other factors such as differences in methodology, differences in assessing exposure, differences in analysis or simple chance may also have a bearing.

In general, earlier studies used absenteeism alone as the end-point but more recent studies have tried to assess the impact of the pollutants under consideration on total illness-related absenteeism and on absenteeism related to respiratory illness. Gilliland et al. *(8)* specifically sought to identify types of illness associated

with school absence in Southern California. The results indicated that a 40-μg/m^3 increase in ozone levels appeared to be associated with a self-reported increase in absenteeism due to respiratory-related symptoms of 82.9% (95% CI 3.9–222%), with a 45% (95% CI 21.3–73.7%) increase in upper airways illness, and a 173.9% (95% CI 91.3–292.3%) increase in lower respiratory illness with a wet cough. However, their study was unable to demonstrate an association between rates of school absenteeism and nitric oxide or PM_{10} levels. The increase in respiratory symptoms associated with increases in ozone levels was noted by days 2–3 and the peak effect was noted with a lag time of approximately 5 days. The impact of surges in the level of ozone was most notable in those residing in areas with the lowest PM_{10} concentrations. Similar results were obtained by Romieu et al. *(10)*, who found a 49% increase in absenteeism following exposure to medium levels (260– 440 μg/m^3) of ozone and a 92% increase in those exposed to high levels (460–680 μg/m^3). This study also found a significant correlation with absences attributed to respiratory tract symptoms. However, a study in rural Canada in areas with low levels of particulates and other pollutants did not find evidence that moderately elevated levels of ozone or inhaled sulfates were associated with an increase in respiratory illnesses leading to absence from school *(3)*.

Ransom & Pope *(6)* specifically studied the potential effects of PM_{10} in a heavily industrialized area of Utah where steelmaking was the dominant industry. They noted an increase in absenteeism of approximately 40% when the moving 28-day average of PM_{10} increased by 100 μg/m^3, resulting in an increase of approximately 2% in the total percentage absent. Their data indicated that the effect was present even at relatively low levels and that the association was strengthened by observing absenteeism rates before, during and after a strike, during which production of PM_{10} fell then rose again. Their data is consistent with that of Gilliland et al., who found a positive correlation between school absences and PM_{10} levels. However, they found that the number of absences due to respiratory complaints did not increase significantly and they concluded that PM_{10} (unlike ozone) did not contribute to increased school absence due to respiratory illness. PM_{10} was also found to be positively associated with school absenteeism in a study from South Korea *(5)*. This study also found an increase in respiratory illnesses leading to school absence associated with PM_{10}, levels with a relatively linear relationship observed across the range of observed values. However, as noted above, these findings have not been replicated in all studies, and indeed Chen et al. *(7)* found that PM10 levels were negatively correlated with school absenteeism. In this study, ambient levels of PM_{10} were relatively low.

In those studies showing a positive correlation between absenteeism and increasing levels of atmospheric pollutants the effect is generally small. However, the ability to detect such effects does add to the body of evidence suggesting that pollutants do indeed affect children's health and that the major impact is on respiratory health. These epidemiological studies are unable to shed light on the

mechanisms that might be operating, and to date they have not explored important outcomes such as quality of life and academic achievement. It does not appear possible from these studies to determine whether the impact of exposure to atmospheric pollutants is confined to a small "vulnerable" group (such as those with pre-existing respiratory illness, including those with asthma or cystic fibrosis) *(12)* or is borne by the whole population. If confined predominantly to the former group, this would potentially have a greater cumulative impact on individuals than if the effect were spread evenly across the population. Overall academic attainment by the majority of asthmatic children does not appear to be impaired when compared with "healthy controls" *(13,14)* but to date studies have not attempted to explore the possible interaction of factors such as atmospheric pollutants on academic achievement and quality of life in these vulnerable groups.

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AIR POLLUTION AND CHILDHOOD CANCER

Ole Raaschou-Nielsen

INTRODUCTION AND BIOLOGICAL CONSIDERATIONS

Incidence of childhood cancer

The incidence of all cancers in childhood (0–14 years of age) varies little among populations of Caucasian origin. The incidence is 120–150 per year per million population among boys and 110–140 per year per million among girls in the countries of Europe, North and South America, Australia and New Zealand, where incident cancer cases are registered routinely *(1)*.

Leukaemias are the most common cancers affecting children, accounting for between 25% and 35% of malignancies in most populations *(2)*. Acute lymphocytic leukaemia (ALL) accounts for the overwhelming majority of cases. Acute non-lymphocytic leukaemia is the only other subtype occurring regularly in children. Tumours of the central nervous system (CNS) are the second most frequent form of cancer in children in most populations, comprising 17–25% of all childhood cancers in North America, Europe and Australia and among non-Maori populations in New Zealand. In other populations, CNS tumours are considerably rarer. The group of childhood lymphomas contains several different types with distinctive epidemiological features. These can be categorized as Hodgkin's disease, Burkett's lymphoma and other non-Hodgkin's lymphoma (NHL). The frequency of lymphomas differs substantially in different populations, with lymphomas contributing 10–15% of all childhood cancers in North America, Europe, Australia and non-Maori populations of New Zealand but 20–60% in many other parts of the world. More rare types of childhood cancer include: neuroblastomas, contributing 6–10% of cancers in North America, Europe and Australia but probably less in other parts of the world; retinoblastomas, accounting for 2–4% of childhood cancers in many populations; renal tumours, comprising around 5–6% in populations in Europe and Australia and among white Americans, less in populations in Asia and Central and South America, but more among black Americans and African populations; hepatic tumours (1–3%); malignant bone tumours (3–5%); soft-tissue sarcomas comprising 4–8% in most populations but 8–16% in most of Africa; and finally carcinomas and other malignant epithelial neoplasms, accounting for less than a few per cent of childhood cancers in most populations *(2)*.

Temporal trends have been more thoroughly investigated for leukaemia than for any other type of childhood cancer. Most of the studies, which considered all leukaemias together, found no evidence of any increase in incidence over the last 3–4

decades *(2)*. Studies considering subgroups of leukaemia showed inconsistent results, being difficult to interpret because of changes over time in diagnostic methods and classification schemes *(2)*. For lymphomas, the picture is unclear with no indication of increasing incidence. In contrast, an increasing incidence of childhood CNS tumours has been evident in most reported series in Europe, Australia, Japan and the United States; the possibility is being discussed of the being an artefact caused by changes in reporting practice and improved diagnostic methods *(2,3)*.

Exposure and risk factors

The age-dependent incidence strongly indicates that factors early in life contribute to the development of a large proportion of childhood cancers, and it has been clear for decades that risk factors operating during pregnancy, or even before conception, are of importance *(4–6)*.

The possible routes of exposure and mechanisms involved in the development of childhood cancers may change with developmental stage. Factors that might operate before conception include transgenerational genetic aberrations and mutations in sperm, oocytes or their germ cells caused by environmental or endogenous factors. During pregnancy, environmental factors may affect the risk of fetal mutations if they are not prevented from crossing the placental barrier. Moreover, physical factors such as ionizing radiation might reach the fetus directly. The possible routes of exposure during childhood are similar to those in adults, but the sensitivity and biological response of children may differ because of rapid cell division and functionally immature organs.

The etiology of childhood cancers is largely unknown. While as many as half of the cases of the rare retinoblastoma are hereditary, arising through germ-line mutations in tumour-suppressor genes, only a small fraction of all childhood cancers are expected to be hereditary *(2,7–9)*. Few risk factors have been established. These include some known inherited genetic alterations, intrauterine and postnatal exposure to ionizing radiation, treatment of pregnant women with diethylstilbestrol, and infection with Epstein-Barr virus and probably hepatitis B virus, but these factors explain only a small proportion of childhood cancers. Suspected or suggested risk factors include other infections, parental occupational exposures (in particular to hydrocarbons and infections), parental smoking, birth order, maternal age, birth weight, (unknown) factors related to socioeconomic status of the family and the residential community, (unknown) factors related to degree of urbanization, diet, medication, electromagnetic fields, radon and air pollution from traffic *(2)*.

Air pollution and childhood cancer

In many parts of the world, road traffic is the major source of ambient air pollution in urban areas, where most people live. Traffic-related air pollution is a com-

plex mixture of many chemicals, of which many are known or suspected carcinogens. In 1987 the International Agency for Research on Cancer (IARC) classified diesel and gasoline exhaust as, respectively, probably (Group 2A) and possibly (Group 2B) carcinogenic to humans, mainly on the basis of animal experiments and epidemiological studies on exposed adults *(10)*. In 1989, however, a case-control study performed in Denver in the United States showed elevated risk of cancer among children living near streets with high traffic density *(11)*. Since then a number of epidemiological studies have addressed the hypothesis that air pollution from traffic causes cancer, particularly leukaemia, in children.

Benzene is one of the traffic-related air pollutants and occurs in the urban atmosphere due to evaporation from and incomplete combustion in petrol engines, as well as evaporation related to petrol stations and the refuelling of cars. The importance of ambient concentrations and proximity to petrol engines for the exposure of children to benzene has been documented *(12)*. Occupational studies have shown that exposure to benzene causes acute myeloid leukaemia (AML) *(13)* and probably also other histological subtypes of leukaemia in adults *(14)* and may also, therefore, be suspected of causing leukaemia in children. The fact that benzene concentrations in children's environments are much lower than those in the work environment of the studied workers may be counterbalanced by a possibly higher susceptibility in childhood *(15)*. Also, it is unknown whether there is a lower threshold concentration below which benzene does not cause leukaemia. Although benzene has been in focus, however, air pollution is in fact a complex mixture of many chemicals, and other pollutants than benzene may contribute to the development of cancer in children. Nevertheless, apart from the known association between benzene and adult leukaemia, pollutants present in ambient air have not been shown to cause in adults the same types of cancer that occur during childhood.

It is the aim of this chapter to evaluate the epidemiological literature for support for the hypothesis that ambient air pollution, in particular that from traffic, causes childhood cancer.

EVIDENCE IDENTIFICATION

A search of the PubMed database up to January 2004, by entering "air pollution and childhood cancer" and "traffic and childhood cancer" as the search criteria, yielded 118 and 23 hits, respectively. Of these, 9 papers were selected that reported results of original epidemiological research, were written in English, considered ambient air pollution as the exposure (studies of indoor air pollution such as radon and second-hand tobacco smoke were excluded), considered exposure of the child (studies of, for example, parental occupational exposure were excluded), dealt primarily with cancers diagnosed before age 15 years, and were full papers (conference abstracts were excluded). The literature lists of these papers were reviewed, leading to another 6 papers fulfilling the same criteria. Thus, a total of 15 papers have been included in this evaluation.

Each paper was reviewed, and information on aims, design, population, setting, exposure assessment, results and the potential for bias was evaluated in order to determine whether the study provided evidence in support of the hypothesis that air pollution, particularly that from traffic, causes childhood cancer. In making this judgement, the criteria used related to (*a*) the results for the main types of childhood cancer (as opposed to more rare types and histological subtypes), (*b*) the statistical significance of the results, (*c*) the presence of a dose–response pattern, (*d*) the magnitude of the relative risk estimates and (*e*) the potential for bias.

EVIDENCE REVIEW

In 1979, Wertheimer & Leeper *(16)* reported an excess of electrical wiring near homes of children who died from cancer, suggesting magnetic fields to be involved in the etiology of the disease. The study included 344 cases and 344 controls in the area of Denver, United States. Street congestion was among the potential confounding factors considered. Findings for high electrical currents were independent of proximity of the addresses to roads with a high density of traffic, but in fact the data indicated a mild excess of case addresses near such roads. A total of 491 and 472 addresses were identified among cases and controls, respectively. Both birth and death address information was available for about 40% of the children; for the remainder only one address was available, which could be either that at birth or that at death (or both for those with stable residence). Seventy-four of the case-addresses and 48 of the control addresses were found to be located within 40 metres of a street having a daily traffic count of more than 5000 vehicles. On the basis of these numbers, an odds ratio of 1.6 (95% CI 1.1–2.3) has been calculated by other authors (Table 1) *(17)*.

This study was the first to link childhood cancer to proximity to traffic, but the odds ratio and confidence interval should be treated with caution because it is based on addresses, not persons. In this calculation, a case can contribute both as exposed and as unexposed (and the same for controls), and the proportion of children who moved and contributed two addresses was higher among cases than among controls.

To address the hypothesis that electromagnetic fields cause childhood cancer, Savitz et al. *(18)* set up a case-control incidence study. Although it was also based on cases and controls in the Denver area, there was no overlap with the study of Wertheimer & Leeper *(16)*. Again, traffic density was considered as a possible confounder, and again it was noted that traffic density seemed to be associated with childhood cancer, although no exact results were reported in this study *(17)*. In 1989, however, Savitz & Feingold *(11)* reported the results for traffic density in a separate paper. The analyses were based on 328 cases and 262 population-based referents selected by random digit dialling. Traffic flow data was obtained for streets at the addresses occupied at the time of diagnosis. The results showed a roughly double risk for all cancers, leukaemias and CNS tumours for those living

Table 1. Fifteen studies on air pollution and childhood cancer

Reference, location and year of publication	Design	Cases: number and definition	Period and study area	Air pollution exposure assessment method
Wertheimer & Leeper, Colorado, USA, 1979 *(16)*	Case-control	N=344, all cancers, 0–18 years, mortality	1950–1973, Denver area	Traffic counts at home address at birth and/or at death
Savitz & Feingold, Colorado, USA, 1989 *(11)*	Case-control	N=328, all cancers, 0–14 years, incidence	1976–1983, Denver area	Traffic counts at home address at diagnosis
Alexander et al., United Kingdom, 1996 *(19)*	Ecological: observed-to-expected ratios were correlated with prevalence of car ownership in 3270 small-area units	N=438, acute lymphocytic leukaemia (ALL), 0–14 years, incidence	1984–1989, England and Wales	Information on car ownership derived from 1981 census data
Knox & Gilman, United Kingdom, 1997 *(20)*	Ecological: observed-to-expected numbers of deaths were compared for areas of different distance from potential hazard sites	N=22 458, all cancers, 0–15 years, mortality	1953–1980, whole of Great Britain	Identification of location of major industrial sites, transportation routes and airborne drift, as well as home addresses at birth and death of cancer patients
Nordlinder & Järvholm, Sweden, 1997 *(24)*	Ecological: incidence compared between municipalities	N=982, leukaemia and lymphoma, 0–24 years, incidence	1975–1985, whole of Sweden	Car density in the municipality of residence

Indicator for exposure	Exposure difference evaluated	Relative risk estimate (95 % CI)	Comments
Home within 40 m of a street with more than 5000 vehicles per day	Yes vs No	1.6 (1.1–2.3) [a]	No adjustment; traffic only considered as a potential confounder
Number of vehicles per day	More vs less than 500: All cancers: Leukaemia: CNS tumour: Lymphoma: More than 10 000 vs less than 500: All cancers: Leukaemia:	 1.7 (1.0–2.8) 2.1 (1.1–4.0) 1.7 (0.8–3.9) 0.7 (0.2–3.0) 3.1 (1.2–8.0) 4.7 (1.6–13.5)	Match on age, sex and area; no adjustment
Proportion of households with no car	More than 44% (fewest cars) vs less than 17% (most cars): ALL:	 1.4 (0.8–2.5)	Adjusted for socioeconomic status and degree of isolation on the area level No trend
Distance from potential environmental hazard sites	Residence within up to 5 km of a hazard site	Significantly elevated case density ratios were observed for areas close to about 30 different types of potential hazard Ratios mostly between 1.10 and 1.20	No adjustment The number of postcodes used to calculate expected number of cases; actual population at risk unknown
Cars per km^2		Incidence per 10^6 person-years	No adjustment
	ALL: <5 cars/km^2 ≥20 cars/km^2 AML: <5 cars/km^2 ≥20 cars/km^2 CML: <5 cars/km^2 ≥20 cars/km^2 NHL: <5 cars/km^2 ≥20 cars/km^2	 21.1 18.6 3.4 5.5 0.5 1.3 3.2 3.5	The difference in incidence rates was significant only for AML ALL: acute lymphocytic leukaemia AML: acute myeloid leukaemia CML: chronic myeloid leukaemia NHL: non-Hodgkin's lymphoma

[a] Odds ratio and 95% confidence intervals calculated by Feychting et al. (17). These should be treated with caution because the calculations were based on addresses, and one child may contribute two addresses (both that at birth and that at diagnosis).

Table 1. Fifteen studies on air pollution and childhood cancer (continued)

Reference, location and year of publication	Design	Cases: number and definition	Period and study area	Air pollution exposure assessment method
Feychting et al., Sweden, 1998 *(17)*	Case-control	N=142, all cancers, 0–15 years, incidence	1976–1983, children living within 300 m of high-voltage power lines in Sweden	Modelled peak concentrations of nitrogen dioxide Based on the latest address
Harrison et al., United Kingdom, 1999 *(22)*	1. Case-control: solid tumours used as controls 2. Observed-to-expected numbers of cases were compared for areas close to benzene sources	N=381, solid tumour and leukaemia, 0–15 years, incidence	1990–1994, West Midlands	Distance from home to main roads and petrol stations inferred from GIS operations Based on postcodes of the home address at time of diagnosis
Pearson et al., Colorado, USA, 2000 *(23)*	Case-control	N=320, all cancers, 0–14 years, incidence	1976–1983, Denver area	Traffic counts at the most highly trafficked street within 1500 feet of the home address at diagnosis Traffic density was (inversely) weighted by distance from the street
Raaschou-Nielsen et al., Denmark, 2000 *(26)*	Case-control	N=1989, leukaemia, CNS tumour and lymphoma, 0–14 years, incidence	1968–1991, whole of Denmark	Traffic density and modelled air pollution concentrations at residence Based on all home addresses from time of conception to time of diagnosis
Reynolds et al., California, USA, 2001 *(27)*	Case-control	N=90, leukaemia, 0–4 years, incidence	1988–1994, San Diego	Distance-weighted traffic counts at streets within 550 feet of home address at birth

Indicator for exposure	Exposure difference evaluated	Relative risk estimate (95 % CI)	Comments
The 99th percentile of 1-hour means of nitrogen dioxide over a year in µg/m³	More than 50 vs less than 40:		Match for year of birth, geographical area and residence near the same power line
	All cancers:	2.7 (0.9–8.5)	
	Leukaemia:	2.7 (0.3–20.6)	
	CNS tumour:	5.1 (0.4–61.2)	Adjustment for electromagnetic fields and socioeconomic status.
Residence within 100 m of a main road or petrol station (Yes/No)	Main roads:		No adjustment
	Leukaemia	1.2 (0.7–1.7)	
	CNS tumour	0.8 (CI not given)	Uncertainties in population numbers and age and sex distribution used to calculate expected numbers of cases
	Petrol stations:		
	Leukaemia	1.5 (0.7–2.9)	
	CNS tumour	0.8 (CI not given)	
Number of vehicles per day (distance weighted)	More than 20 000 vs less than 500:		Match on sex, age and area; no adjustment
	All cancers	5.9 (1.7–20.6)	
	Leukaemia	8.3 (2.1–32.8)	This study used the same material as that of Savitz et al. (18) but the exposure assessment method was modified and the reported exposure categories were changed
			No dose–response across the 5 exposure categories below 20 000 vehicles per day
Number of vehicles per day during childhood	More than 10 000 vs less than 500:		Match on sex, age and calendar time
	All cancers	1.0 (0.7–1.6)	
	Leukaemia	1.1 (0.6–2.2)	Adjusted for urban development, geographical region, type of residence, electromagnetic fields, mother's age and birth order
Cumulated nitrogen dioxide concentrations during childhood	CNS tumour	0.9 (0.4–1.8)	
	Lymphoma	1.3 (0.4–4.8)	
	Highest 1% vs lowest 50%:		No significant dose–response trend for any of these results
	All cancers	1.2 (0.6–2.3)	
	Leukaemia	0.4 (0.1–1.3)	
	CNS tumour	1.0 (0.3–3.1)	
	Lymphoma	4.7 (1.2–17.6)	
Number of cars per day	More than 20 000 vs less than 10 000:		Matched for sex and birth year
	Nearest street:	0.9 (0.4–2.1)	Adjusted for race/ethnicity and median family income in the local area
	All streets:	1.6 (0.8–3.3)	

Table 1. Fifteen studies on air pollution and childhood cancer (continued)

Reference, location and year of publication	Design	Cases: number and definition	Period and study area	Air pollution exposure assessment method
Reynolds et al., California, USA, 2002 *(28)*	Ecological: incidence compared between areas with different traffic load	N=7143, all cancers, 0–14 years, incidence	1988–1994, whole of California	Different traffic measures were allocated to each of 21 519 small-area units Allocation of cases to blocks based on home address at time of diagnosis
Langholz et al., California, USA, 2002 *(29)*	Case-control	N=212, leukaemia, 0–10 years, incidence	1978–1984, Los Angeles County	Sum of traffic counts at all streets within 1500 feet of home address where child had resided longest A distance-weighted metric was used
Reynolds et al., California, USA, 2003 *(30)*	Ecological.: Incidence rates were compared between areas with different air pollution levels	N=6989, all cancers, 0-14 years, incidence	1988-1994, the whole of California	Mean concentrations for carcinogenic air pollutants were modelled for each census tract and weighted with cancer potency in an exposure score index
Crosignani et al., Italy, 2004 *(31)*	Case-control	N=120, leukaemia, 0–14 years, incidence	1978–1997, Province of Varese 1988–1997	Modelled concentration of benzene outside the residence at time of diagnosis
Reynolds et al., California, USA, 2004 *(32)*	Case-control	N=4369, all cancers, 0–4 years, incidence		Road density and traffic density based on traffic counts and length of roads within 500 feet of address at time of birth

on streets with a traffic density of more than 500 vehicles per day, but no increase for lymphomas. For all cancers and leukaemias there were indications of a dose–response relationship. In a subset of 71% of cases and 80% of controls, adjustment for sex, age, year of diagnosis, type of residence, location at birth, mother's age, father's education, per capita income and wire configuration code at diagnosis had little effect on the odds ratios.

Although this association between traffic and childhood cancer had already been noted in the previous electromagnetic field study using the same study material *(18)*, and was thus not a result of an independent a priori hypothesis, the results were persuading. Nevertheless, selection bias may have occurred owing to

Indicator for exposure	Exposure difference evaluated	Relative risk estimate (95 % CI)	Comments
Vehicle miles travelled per day per square mile	More than 320 701 (upper 10%) vs less than 33 291 (lower 25%):		Adjusted for age, race/ethnicity and sex on the ecological level
	All cancers:	1.08 (0.98–1.20)	No indication of increased risk for two other measures of traffic load, namely vehicles per square mile and miles of road per square mile
	Leukaemia:	1.15 (0.97–1.37)	
	Glioma (CNS):	1.14 (0.90–1.45)	
Number of vehicles per day (distance-weighted)	More than 28 497 (upper 20%) vs less than 2.301 (lower 20%):		Match on gender and age Adjustment for wire codes No evidence of dose–response
	Leukaemia	1.4 (0.7–3.0)	
Exposure scores in relation to different emission sources	Mobile source exposure scores: highest 10% versus lowest 25%:		Adjusted for age, race/ethnicity and sex on the ecological level; little effect of further adjustment for socioeconomic status
	All cancers	1.04 (0.95-1.14)	
	Leukaemia	1.18 (0.98-1.41)	
	Glioma	1.02 (0.83-1.26)	Uncertainties in population numbers No indication of dose–response
Annual mean	More than 10 versus less than 0.1 mg/m^3		Match by age and gender Significant dose–response trend across three exposure groups
	Leukaemia:	3.9 (1.4–11.3)	Match for age and sex
1. Road density in miles per square mile 2. Traffic density in vehicle miles travelled per square mile	Traffic density: highest 10% vs lowest 25%:		Adjustment for race/ethnicity; little effect of further adjustment
	All cancers	0.92 (0.80–1.06)	
	Leukaemia	0.92 (0.73–1.15)	No indication of dose–response
	CNS tumour	1.22 (0.87–1.70)	

non-respondents (8% of cases and 25% of controls). There appears to have been a dearth of controls of low socioeconomic status, and this might have produced a spurious association with a marker of low socioeconomic status, such as residential traffic density *(2)*.

Alexander et al. *(19)* used an ecological study in England and Wales to determine whether increased rates of ALL, which had been reported in isolated areas, could be attributed to higher proportions of households owning cars and related exposure to benzene during car use. In 3270 electoral wards, socioeconomic status, degree of isolation and proportion of households with no car was estimated using 1981 census data and digital maps. Both crude and adjusted analyses

showed a 30–40% higher risk (insignificant) for ALL in areas with the fewest cars. Adjusted (though not crude) analyses for the age group 1–7 years showed a significantly higher risk of ALL in areas with the fewest cars (RR = 2.1, 95 % CI 1.1–4.6). The study provides evidence that incidence of childhood ALL is not higher in areas of England and Wales where more households possess cars.

Knox & Gilman *(20)* further explored a previous observation that childhood cancers in the United Kingdom seemed to occur in small geographical clusters. In an ecological study, they identified all deaths from childhood cancer in England, Wales and Scotland between 1953 and 1980 and the addresses at birth and death for these children. A wide range of potential environmental hazards were identified, including factories involved in the production of such items as paper, beer, cotton, oil products, cars, bricks, steel products and power, and transport routes such as motorways and railways, and areas at different distances from these potential hazards were defined. The observed number of cases was enumerated within a series of defined areas at specified distances from each type of hazard, and the expected number was calculated on the basis of the number of postcodes within the same areas. The actual number of person-years at risk within the areas was unknown. Case density ratios were obtained from the observed and expected numbers within the areas. The results showed that childhood cancers were geographically associated with sources of atmospheric pollution by (*a*) petroleum-derived volatiles and (*b*) kiln and furnace smoke and gases. Most density ratios were only slightly increased (10–20%) in proximity to these sources. No tumour specificity for the different sources was apparent. No evidence was found of an association with proximity to benzene-emitting plants. Concerning traffic-related air pollution, the results showed increasing case density ratios from 300 to 1000 metres and decreasing ratios from 1000 to 7000 metres from motorways. This result is not in line with a carcinogenic effect of air pollution from traffic, as the concentration of primary pollutants from traffic is expected to decrease exponentially with distance, such that background levels are already reached at about 500 metres from a motorway with high traffic load *(21)*. Other studies estimate that background levels are reached at even shorter distances from such ground level sources *(22)*.

A limitation of and potential for bias in the study of Knox & Gilman relates to the calculation of expected numbers of cases. No population data were available for the small area units required for the study, and the number of postcodes was used as proxy for the childhood population at risk. Although efforts were made to handle the potential problem as well as possible, uncertainty remains as to what degree small-scale demographic structuring related to proximity to the hazard sites influenced the results. Altogether, this study provides no support for an association between air pollution from traffic or benzene-emitting plants and childhood cancer. Slightly (10–20%) higher density ratios were found in the proximity of other air pollution sources, but the results should be interpreted with great cau-

tion given the magnitude of the risk estimate, the number of associations evaluated, the methodological uncertainties and the lack of tumour specificity.

Pearson et al. *(23)* studied childhood cancer and traffic density at place of residence in the Denver area. Basically, their study was identical with that of Savitz & Feingold *(11)*, except that the exposure assessment method was modified and the reported exposure categories were changed. The rationale for the study was that, if air pollution from traffic at place of residence were the cause of the increased odds ratios in the Savitz study, then a more precise exposure assessment method would produce higher odds ratios. Pearson et al. improved the exposure assessment by (*a*) using the most highly trafficked street near the house of residence at the time of diagnosis (not simply the street of address) and (*b*) by taking into account the reduction in air pollution concentration with distance from the street. The results showed no effect of (distance-weighted) traffic density on all cancers or leukaemia across five exposure categories ranging from 0 to 19 999 vehicles per day, but a markedly higher risk for all cancers (OR = 5.9, 95% CI 1.7–20.6) and leukaemia (OR = 8.3, 95% CI 2.1–32.8) for the top exposure category "20 000 or more vehicles per day", which was somewhat higher than those obtained when this top category was applied to the Savitz material (all cancers, OR = 3.4; leukaemia, OR = 7.4). The authors interpreted this result as evidence suggesting an association between living near a highly trafficked street and increased incidence of childhood cancer, particularly leukaemia. This is not surprising, as the study is a re-analysis of the original hypothesis-generating study by Savitz.

However, when data were re-analysed using exactly the same exposure categories as those in the study by Savitz & Feingold *(11)*, which would be a natural a priori approach, the new exposure assessment method provided lower odds ratios. Savitz & Feingold reported odds ratios of 1.3 and 3.1 for all cancers and 1.4 and 4.7 for leukaemia in association with the categories "500–10 000 vehicles/day" and "above 10 000 vehicles/day" compared with 0–500 vehicles/day. A recalculation from the data presented by Pearson et al. *(23)* showed odds ratios of 1.3 (95% CI 0.9–1.8) and 1.8 (95% CI 1.0–3.2) for all cancers and 1.2 (95% CI 0.8–2.0) and 1.6 (95% CI 0.7–3.6) for leukaemia in association with the same exposure categories. Thus, in this case, the assumed more precise exposure assessment method provided weaker associations between traffic at the residence and the occurrence of childhood cancer, indicating that traffic-related air pollution is not the causal factor. In conclusion, the main feature of this study was the development of the exposure assessment method. Concerning the possible association between traffic-related air pollution and childhood cancer, this study provided no clear evidence beyond that of the Savitz study.

Nordlinder & Järvholm *(24)* conducted an ecological study in Sweden on whether environmental exposure to benzene from petrol and car exhaust was associated with leukaemia in children and young adults (0–24 years). The 277 municipalities in Sweden were divided in four groups on the basis of car density,

i.e. the number of cars per area, with cut-off points at 5, 10 and 20 cars per km^2. Incidence rates were calculated for each group on the basis of registry data for incident cancer cases and population size. The incidence of NHL, ALL and chronic myeloid leukaemia did not differ significantly between the groups with the lowest and highest car densities. The incidence of AML, however, was significantly higher in the group of municipalities with the highest car density than in that with the lowest car density. However, no dose–response pattern was evident as AML incidence was virtually identical in the three municipality groups with higher car densities (5.4, 5.4 and 5.5 per million person-years). Simple addition of incidence rates for the three types of leukaemia, to estimate rates for all leukaemias combined, provides almost identical rates for the lowest and highest exposure groups. Further, as noted by the authors, the significant result for AML must be regarded with caution as uncontrolled confounding may have occurred in this ecological study. Moreover, the lack of a dose–response pattern argues against a causal interpretation of the finding. In conclusion, the study yielded no support for a higher incidence of all leukaemias combined or NHL in areas with a higher car density.

Feychting et al. *(17)* used a nested case-control design in a study in Sweden. The study base, which was originally defined for another study, comprised children living within 300 metres of high-voltage power lines. For the latest address of 142 cases and 550 controls, information was traced on traffic density, street type, speed limit, street width, distance between the house and the street, and other relevant information. An outdoor air pollution model was used to calculate the 99th percentile of 1-hour averages over a year of nitrogen dioxide (i.e. peak concentrations). When referents were children living at addresses with nitrogen dioxide concentrations below the median (40 $\mu g/m^3$), the third (40–50 $\mu g/m^3$) and fourth (>50 $\mu g/m^3$) quartile were associated with relative risks of 1.3 (95% CI 0.4–4.3) and 2.7 (0.9–8.5) for all cancers combined, 1.7 (0.2–14.6) and 2.7 (0.3–20.6) for leukaemias, and 1.0 (0.1–12.7) and 5.1 (0.4–61.2) for CNS tumours. For all cancers combined, a cut-off point at 80 $\mu g/m^3$ yielded a relative risk of 3.8 (1.2–12.1) compared with those below the median. Thus, except for the last-mentioned analyses, based on only eight exposed cases, no significant results were found. Despite the limited sample size and the mostly insignificant results, however, the high risk estimates may indicate an association between childhood cancer and motor vehicle exhaust.

Harrison et al. *(22)* investigated the hypothesis that exposure to benzene from main roads and petrol stations may influence the incidence of childhood leukaemia. Of a total of 130 cases of leukaemia and 251 cases of solid tumour identified in the West Midlands, United Kingdom, 24 children with leukaemia and 31 with a solid tumour lived within 100 metres of a main road, and 8 children with leukaemia and 8 with a solid tumour lived within 100 metres of a petrol station at the time of diagnosis. These 71 children were considered to be exposed to benzene. In the first analytical approach, solid tumours were used as controls for leukaemia

cases, providing odds ratios of 1.6 (0.9–2.9) for proximity to main roads and 2.0 (0.7–5.4) for proximity to petrol stations, indicating a different distribution of cancer types within and outside the 100-metre borderline. In the second analytical approach, incidence rates for the District Health Authority as a whole, together with an estimated childhood population at risk in the much smaller postcode districts within 100 metres of a benzene source, were used to calculate expected numbers of cases near the benzene sources. Incidence ratios (calculated as the ratio of observed to expected cases) for leukaemia were 1.2 (0.7–1.7) and 1.5 (0.7–2.9), respectively, for proximity to main roads and petrol stations; for solid tumours the incidence ratio was 0.8 (no CI given) for proximity both to main roads and to petrol stations. Thus, no significant results were found in this study, based on few exposed cases.

Raaschou-Nielsen et al. *(25)* included 1989 cases and 5506 controls in a population-based case-control study in Denmark. The residential history of each child was traced from 9 months before birth to the time of diagnosis, resulting in 18 440 identified addresses. Concentrations of benzene and nitrogen dioxide were calculated for each address separately for the pregnancy and the childhood periods by use of a validated model *(26)*. Input data for these calculations related to the characteristics of traffic, streets and buildings at the address, emission factors for Danish cars, meteorological variables and the background air pollution concentration. When using the same exposure categories as Savitz & Feingold *(12)* there were no significant associations between childhood cancer and traffic density at the place of residence during either the pregnancy or the childhood period. This applied to leukaemia, CNS tumours, lymphoma and all these types combined. Neither were calculated concentrations of benzene and nitrogen dioxide significantly associated with leukaemia, CNS tumours or all childhood cancers combined.

Higher concentrations of nitrogen dioxide were associated with an increased risk of lymphomas, but benzene concentration was inversely associated with lymphomas. No significant trend was seen for these associations, and the inverse risk pattern for the two indicators for traffic-related air pollution needs to be interpreted with caution. Concentrations during the pregnancy period of both indicators for traffic-related air pollution showed a barely significant trend with lymphomas, such that the risk for lymphomas increased by 25% and 51%, respectively, for a doubling of the concentration of benzene and nitrogen dioxide. These associations were restricted to Hodgkin's disease, showing a relative risk of 4.3 (95% CI 1.5–12.4) and 6.7 (95% CI 1.7–26.0) for benzene and nitrogen dioxide, respectively, when concentrations above the 90th percentile were compared with concentrations below the median. A significant trend was present for both indicators. However, the authors drew attention to the unexpected nature of the finding and the fact that there is no specific biological explanation. In conclusion, the risks for leukaemia, CNS tumours and all selected cancers combined did not appear to be linked to traffic-related air pollution.

Reynolds et al. *(27)* compared the traffic pattern around the home addresses at birth of 90 children who developed leukaemia before the age of 5 and 349 control children born in the same urban area of California. The aim was to evaluate the potential of traffic density and socioeconomic status to confound apparent associations between wire codes and childhood cancer. The authors used a variety of measures of traffic density within 168 metres of the home addresses, including total traffic counts on all streets, traffic count at the nearest street regardless of the distance, highest traffic count at a street within 168 metres and traffic count at the nearest street. The latter two indicators were calculated with and without weights inversely proportional to the distance to the streets. The results showed a marked pattern of higher traffic volume in areas of lower socioeconomic status, but no significant associations between any of the traffic measures and childhood leukaemia. The study provides little or no evidence to suggest a risk association between traffic exposures and early childhood leukaemia.

In a subsequent study, Reynolds et al. *(28)* extended their study area to the whole of California and included 7143 incident childhood cancer cases. Incidence rates and traffic load measured by spatial information on neighbourhood vehicle density, road density and traffic density were computed for the 21 519 small area block groups of California. The case children were allocated to block groups by residence at time of diagnosis. The traffic measures were validated against fixed site monitoring results, showing correlation coefficients of 0.57–0.70 between traffic density and the three primary pollutants from traffic (carbon monoxide, benzene and 1,3-butadiene) but poorer correlations for the two others measures of traffic load (nitrogen dioxide and PM_{10}). Traffic density above the 90th percentile showed rate ratios of 1.08 (95% CI 0.98–1.20) for all cancers combined, 1.15 (95% CI 0.97–1.37) for leukaemias and 1.14 (95% CI 0.90–1.45) for gliomas compared with traffic density below the 25th percentile. There was no clear trend through the five exposure categories. There was also little or no evidence for rate differences in areas characterized by high vehicle or road density. Also, for Hodgkin's disease and all lymphomas combined, no exposure–response relationship was observed with any of these measures of exposure at the time of diagnosis. Thus, this large study provided relatively precise rate ratio point estimates very close to 1.0, indicating that childhood cancer rates are not higher in neighbourhoods with high traffic densities.

Langholz et al. *(29)* evaluated traffic density near 212 incident cases of leukaemia and 202 controls in the Los Angeles area. Taking the address where the child had lived for the longest period, traffic counts on all streets within 457 metres of the home were converted to a distance-weighted count equivalent to the situation had there been a single street at the side of the home. The distance weight was used to take account of the dilution of air pollution with increasing distance from the source. The results showed no statistically significant increase in risk in association with distance-weighted traffic density. The rate ratio for the 5th quintile was 1.4 (95% CI 0.7–3.0) but no indication of a dose–response relationship was

seen across the quintiles. In fact, the highest relative risk (1.6) was seen for the second quintile, and a dose–response curve using adjusted spline estimates showed similar rate ratios for the lowest and highest traffic densities. In conclusion, this study, for one of the most heavily trafficked areas of the United States, showed no evidence of an association between traffic density and childhood leukaemia.

Reynolds et al. *(30)* included 6989 incident childhood cancer cases between 1988 and 1994 from the whole of California in an exploratory ecological analysis, taking census tract as the unit of area. Each case was allocated to a census tract using the address at the time of diagnosis. For each census tract, the population at risk during the study period was estimated from 1990 census data multiplied by growth factors for the California population. The exposure was assessed as exposure scores for a number of potentially carcinogenic hazardous air pollutants (HAP) released from a variety of sources. The assessment, developed by the US Environmental Protection Agency, was based on emission inventories for mobile sources (cars, aircraft, trains and ships), for area sources (e.g. dry cleaning premises, petrol stations, chemical use in the home and application of pesticides to fields) and for point sources (large industrial manufacturing facilities) combined with meteorological data and dispersion modelling, leading to estimated HAP mean concentrations for each census tract. Comparison of modelled and measured concentrations indicated good agreement. Further, each HAP contributed to an exposure index with a weight corresponding to the cancer potency of the HAP. The rate ratios for all types of cancer, leukaemias and gliomas were all close to 1.0, were insignificant and showed no dose–response pattern in association with HAPs from *mobile and area sources*. The rate ratio was 1.32 (95% CI 1.11–1.57) for leukaemia and 1.13 (95% CI 1.03–1.23) for all cancers combined when the 10% of census tracts with the highest exposures from *point sources* was compared with the 25% of census tracts with the lowest exposures. A significant trend was found for these results for point sources.

In addition to the general limitations of ecological studies, the potential for bias in this large study includes uncertainty about the precise population at risk; growth rate factors for the Californian population as a whole were used in calculations for each census tract, and bias could occur if the population growth rate differed by density of or distance to HAP sources. Moreover, exposure scores based on the emission source correlated with Spearman coefficients of between 0.6 and 0.7, but risk estimates for the emission sources were not mutually adjusted. In conclusion, this study provides no support for the hypothesis that traffic-related air pollution causes childhood cancer. Slightly but significantly elevated rate ratios were found in association with exposure scores related to large industrial manufacturing facilities, but the explorative study approach, the magnitude of the risk estimates and the potential for bias demands a cautious interpretation.

Crosignani et al. *(31)* conducted a case-control study of 120 incident leukaemia cases in the province of Varese, Italy, and 480 control children living in the same

area. Main roads within 300 metres of the home address at the time of diagnosis were considered in the exposure assessment. On the basis of traffic density on the roads and distances from roads to the home, the benzene concentration at the address was estimated. Benzene concentrations above 10 μg/m^3 were associated with a rate ratio of 3.9 (95% CI 1.4–11.3) when compared with concentrations below 0.1 μg/m^3, and a significant trend was present across the three exposure categories. Increase in risk was more strongly associated with distance from roads than with the traffic density; the rate ratios were almost identical for the categories "<10 000 vehicles per day" and ">10 000 vehicles per day". This study indicates a relationship between exposure to traffic exhaust emissions and childhood leukaemia.

Reynolds et al. *(32)* reported the results of a large case-control study in California. They included 4369 cases reported to the statewide population-based cancer registry between 1988 and 1997. A total of 8730 controls were identified from California birth certificates and matched to cases by birth date and sex. Exposure was estimated as the road density and traffic density for the area within 152 metres of each address at birth. The traffic density measure was validated against fixed site monitoring for benzene, providing a correlation coefficient of 0.67. Cut-off points at the 25th, 50th, 75th and 90th percentiles defined five exposure groups. All results showed point estimates very close to 1.0. Compared with the lower exposure category, the highest was associated with relative risk estimates of 0.92 (95% CI 0.80–1.06) for all cancers, 0.92 (95% CI 0.73–1.15) for leukaemia and 1.22 (95% CI 0.87–1.70) for CNS tumours. Similar negative results were obtained when "road density" was used as the exposure. There was no indication of a dose–response trend through the five exposure groups for all cancers combined, leukaemias or CNS tumours in association with any of the two traffic measures. Similar results were obtained for the histological subgroups ALL and acute non-lymphocytic leukaemia. Adjustment for maternal age, birth weight, neighbourhood income level and county-level benzene emissions had little effect on the results.

Compared with the previous study of Reynolds et al. *(28)*, this study included another three years of diagnosis, focused on young children, was changed from an ecological to a case-control design, based exposure assessment on the address at the time of birth (which differed from that at the time of the diagnosis for about half of the children), and improved the geographical precision of the area considered in the exposure assessment from block groups to the area within 152 metres of the address. Thus, despite some degree of overlap between the populations under study, the results (showing no evidence for increased cancer risk among children born in high-traffic areas) are considered as new evidence of importance for the hypothesis.

EVIDENCE SYNTHESIS

Of the 15 studies included, 8 were conducted in the United States and 7 in different European settings. The predominant study design was case-control, with 6 of the studies using an ecological design.

The first two studies to report associations between road traffic and childhood cancer were both from the Denver area, and both associations were noted as a subsidiary finding in studies of electromagnetic fields and childhood cancer *(11,16)*. Although these associations as such can be considered as hypothesis-generating rather than hypothesis-testing, it is indeed noteworthy that the same finding appeared in these two independent studies. Among the 13 later studies, one is positive and provides clear support for the hypothesis *(31)*, one shows high but mainly insignificant point estimates *(17)*, one improved on the exposure assessment method of a previous study but provided no really new evidence *(23)*, and the remaining 10 studies were mainly negative. The two studies providing new support for the hypothesis were both relatively small, including 142 and 120 cases, respectively, whereas the five largest studies to date by far are all considered to have given negative results with respect to traffic-related air pollution *(20,25,28,30,32)*.

The main methodological challenges in studies of the hypothesis relate to the exposure assessment. All studies assess exposure in relation to the home address of the children, but the timing of the assessed exposure differs between studies. Because little is known about the causes of and mechanisms leading to childhood cancer, it is not clear which time windows of exposure could be most important. The home address at the time of diagnosis or death was used for most studies, and only one retrieved the full residential history as the basis for the exposure assessment. Using the address at one point in time implies a risk of bias owing to differential movement patterns for cases and controls. The geographical precision in the exposure assessment also differed between studies. The ecological studies used measures for air pollution in relation to geopolitically defined areas, whereas the case-control studies estimated air pollution within a smaller defined distance of the address of the child. The latter approach is preferred because air pollution concentrations may differ substantially within even a small area. Air pollution measures differed among the studies assessing exposure at an exact address, the crudest measure being a simple traffic count at the street. More sophisticated approaches include distance-weighted traffic counts and extensive air pollution models, which required comprehensive input data. Irrespective of the method used, more weight should be attached to results based on a validated exposure assessment method.

The possibility of confounding is always an aspect to be considered in epidemiology. The descriptive epidemiology of childhood cancer shows different incidence rates between the sexes and striking differences in incidence rates for leu-

kaemias and lymphomas in different age groups. Thus, it is important to control the potential confounding from these factors, either by matching or by adjustment, which was done in most of the studies reviewed. Moreover, a number of suspected risk factors, such as mother's age, birth order, socioeconomic status and electromagnetic fields, may have the potential to be confounders, and the more such suspected risk factors are adjusted for the better. Half of the included studies adjusted for factors other than age and sex.

Table 2 summarizes the studies with respect to the methodological issues discussed above. The choice and the relative weight of categories is a matter of debate, and it is not always clear how a study should score in a given category. Nevertheless, the scores may provide a general index of quality. Moreover, the table indicates which studies are considered positive (i.e. providing evidence in support of the hypothesis) and which are not according to the review of each study (see Evidence review section above). Table 2 shows that the positive studies are mostly found among those with a low total score, whereas studies with a high total score were mostly negative.

Publication bias is expected to occur if small positive studies have greater chances of being published than small negative studies. The fact that all studies considered positive are also small (Table 2) indicates that publication bias may have occurred.

Assuming that traffic-related air pollution in fact causes childhood cancer, the difference between positive and negative studies may be caused by higher concentrations or a more hazardous composition of air pollution at the settings of the positive studies. This interpretation of the literature review, however, seems problematic, in part because road traffic is the primary source considered in almost all studies and pollution from traffic largely comprises the same pollutants everywhere in the developed world. Moreover, it seems unlikely that the exposure of children to traffic-related air pollution was substantially higher in Denver, Sweden and Varese (Italy) than in Los Angeles, California, Denmark and the United Kingdom. An indirect comparison between several of the study locations shows that it is unlikely that differences in traffic levels can explain why some studies are positive and others negative *(32)*.

Although the majority of the identified studies, and those scoring highest in the simple index of quality, showed no convincing association between childhood cancer risk and traffic-related air pollution at the place of residence, epidemiological studies are usually unsuitable to refute weak associations. This is due to methodological limitations related to exposure assessment and study size. Moreover, the reviewed literature was not consistently negative. Also, two ecological studies indicated that a slightly increased childhood cancer risk might be associated with air pollution from other sources than traffic *(20,30)*.

A literature review may benefit from a meta-analysis or a pooled data analysis. In this case, however, the substantial differences between studies as to design,

Table 2. Characteristics of the included studies

Study	Study considered mainly positive (+) or negative (–)[a]	Hypothesis generating (G) or testing (T)	More than 200 cases of childhood leukaemia	Exposure assessment method				Match or adjustment for age and sex	Further match or adjustment	Total score
				Based on total address history	Based on precise address (as opposed to an area)	Estimation at address more sophisticated than traffic counts (e.g. distance-weights)	Validation of method reported			
Wertheimer & Leeper *(16)*	+	G	0	0	1	0	0	0	0	1
Savitz & Feingold *(11)*	+	G	0	0	1	0	0	1	0[b]	2
Alexander et al. *(19)*	–	T	1	0	0	0	0	1[c]	1[d]	3
Knox & Gilman *(20)*	–	T	1	0	0	0	0	0	0	1
Nordlinder & Järvholm *(24)*	–	T	1	0	0	0	0	1	0	2
Feychting et al. *(17)*	+	T	0	0	1	1	0	1[e]	1	4
Harrison et al. *(22)*	–	T	0	0	0	0	0	0	0	0
Pearson et al. *(23)*	[f]	T	0	0	1	1	0	1	0	3
Raaschou-Nielsen et al. *(26)*	–	T	1	1	1	1	1	1	1	7
Reynolds et al. *(27)*	–	T	0	0	1	1	0	1	1	4
Reynolds et al. *(28)*	–	T	1	0	0	0	1	1[d]	1[d]	4
Langholz et al. *(29)*	–	T	1	0	1	1	0	1	1	5
Reynolds et al. *(30)*	–	T	1	0	0	0	1	1[d]	1[d]	4
Crosignani et al. *(31)*	+	T	0	0	1	1	0	1	0	3
Reynolds et al. *(32)*	–	T	1	0	0	0	1	1	1	4

[a] See Evidence identification section for criteria and Evidence review section for the review of each study. The 0/1 scores in the table indicate the absence/presence of the study characteristics listed in the table header.

[b] Adjustment for a number of variables in a subset of data indicated no major effect on the risk estimates.

[c] No information given on whether expected numbers were based on age- and sex-specific rates (they probably were).

[d] Adjustment on the ecological level.

[e] Match on year of birth and stratum-specific analyses for age and sex.

[f] The study used the same material as that of Savitz & Feingold (11) and provided no real new evidence of relevance for the hypothesis.

exposure assessment method, type of cancer and age group make a formal meta-analysis less meaningful.

Many pollutants are present both in air pollution from traffic and in tobacco smoke. A number of studies have addressed a possible association between childhood cancer and maternal tobacco smoke, which can be regarded either a measure for maternal exposure during pregnancy or exposure of the child to environmental tobacco smoke. The fact that no consistent association between maternal smoking and childhood cancer has been found *(2)* would be consistent with an interpretation of the epidemiological evidence for traffic-related air pollution as mainly negative.

Even if air pollution may not cause childhood cancer, exposure of children may well contribute to development of cancers later in life. There is evidence that exposure to air pollution during adulthood increases the risk of lung cancer in adults *(33–38)*.

CONCLUSIONS

The hypothesis that ambient air pollution causes childhood cancer has been studied almost entirely in relation to air pollution from traffic. The hypothesis was generated by two studies from Denver in the United States, but only 2 out of 13 additional studies identified yield new support for the hypothesis. Studies ranking highest on an index of quality were mostly negative.

The weight of the epidemiological evidence to date indicates that no increased risk of childhood cancer is associated with traffic-related air pollution at home. Nevertheless, the low number of studies, the methodological limitations of epidemiological research and the absence of full consistency across the study results preclude a firm conclusion of no effect.

The epidemiological evidence is insufficient to infer a causal relationship between ambient air pollution and childhood cancer.

Future studies may help clarify the hypothesis, particularly if a successfully validated exposure assessment method is applied and if exposure during different periods from the time of conception to the time of diagnosis is considered.

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NEURODEVELOPMENTAL AND BEHAVIOURAL EFFECTS

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INTRODUCTION

The brain is a target for several environmental substances that may or may not be primarily airborne. Neurodevelopment and neurobehaviour largely reflect brain development and its chemically induced modification, with resulting delays or deficits in development. It is generally believed that the developing brain is a particularly vulnerable target for chemical insult, and that such insult may have long-lasting or even irreversible developmental consequences.

Among the groups of environmental chemicals for which neurodevelopmental and neurobehavioural effects in children are to some extent documented are some heavy metals and polyhalogenated aromatic hydrocarbons (PHAHs). The former primarily include lead, mercury and (less frequently) manganese, whereas the most extensively studied PHAH species include the polychlorinated biphenyls (PCBs); although the dioxins are also of relevance, there is typical co-exposure with the PCBs such that it is almost impossible to distinguish between PCBs and dioxins in paediatric cohort studies.

The focus of this chapter is on these environmental contaminants, which are also covered in the WHO monograph *Air quality guidelines for Europe (1)*. For the large and heterogeneous group of organic solvents (e.g. trichloroethylene, tetrachloroethylene, toluene and xylene), neurotoxicity has mainly been studied in occupational settings or in cases of inhalation abuse rather then in environmental exposure settings involving children.

For the chemicals covered here, inhalation is not the main route of exposure. Nevertheless, atmospheric transport typically contributes indirectly to general environmental exposure, which in most cases is dietary. Therefore, the main pathways and degree of childhood exposure will be discussed briefly before the neuroepidemiological evidence from studies in paediatric populations is presented and evaluated.

BIOLOGICAL CONSIDERATIONS

A brief account of some basic principles of human brain development may help to better understand why and how prenatal or early postnatal environmental exposure to chemicals may give rise to adverse neurobehavioural alterations in infants and children postnatally. This brief overview can only be elementary; for a more detailed account the reader is referred to standard textbooks.

The maturation of the central nervous system (CNS) is often described under the four headings of gross morphology, proliferation and migration of neurons and glial cells, neuronal differentiation, and myelinization. By the end of the embryonal stage (12th week of gestation) the organogenesis of the brain already shows marked progress. Following the formation of the neural tube in the first three gestational weeks, the division of the prosencephalon into two hemispheres occurs together with a pronounced enlargement of the thalamus and an initial formation of the cerebellum. Towards the end of the 12th week of gestation, separate ventricles occur but the brain surface is still smooth. Its structuring into lobes through the formation of primary sulci (folds) occurs in the 4th month of gestation, such that the main lobes (frontal, parietal, occipital and temporal) become discernible. Among the deeper structures the main hemispheric connections, namely the corpus callosum and the commissurae anterior and posterior, also develop early. Brain damage during these early stages of CNS development gives rise to gross structural anomalies. Following the formation of the primary sulci, secondary sulci are formed during the last three months of gestation, whereas tertiary sulci develop postnatally until the end of the 2nd year of life.

It is important to note that the place of origin of neurons and glial cells is different from their final destination in the brain. Cells migrate to form, for example, the six cortical layers and the architecture of other brain structures. Besides migration, the maturation of neurons from their precursor cells, the neuroblasts, is another important developmental principle. Maturation includes enlargement of the cell body, storage of Nissl substance, formation of neurofibrils, arborization of axons and apical dendrites, and finally the increasing number of synaptic contacts between neurons. Although neuronal differentiation begins prenatally (the six cortical layers, for example, being already present around the 28th gestational week), much neuronal maturation extends into the first two postnatal years, such as the arborization of dendrites and synapse formation. Also, much of the myelinization of fibres occurs postnatally. Thus, both the prenatal and early postnatal phases of CNS development offer opportunities for chemical insult.

It must finally be pointed out that many of the above-mentioned developmental processes and their timely orchestration, namely proliferation, migration, differentiation and myelinization of neurons, are partly under endocrine control *(2)*. One prominent example is the hypothalamic-pituitary-thyroid (HPT) axis *(3)*. Clinical observations show that severe congenital or dietary hypothyroid conditions during pregnancy or in the neonatal stage, if untreated, often result in cretinism associated with mental retardation. This is one mechanistic possibility of how chemicals interacting with endocrine systems may also interfere with brain development and associated dysfunctional neurobehavioural development postnatally.

EVIDENCE IDENTIFICATION

Comprehensive bibliographic databases such as PubMed were consulted for studies published in the past five years. Additionally, recent reviews for lead *(4)*, methylmercury *(5)* and PCBs *(6)* were considered. This, together with the research experience of the author, should provide an up-to-date and pertinent coverage of the field.

EVIDENCE REVIEW

Lead

Pathways and degree of exposure

Typical air lead levels are between 0.15 and 0.5 μg/m^3 in most European cities *(1)*. The relationship between lead in children's blood and in air has been estimated to be 19 μg/l for each 1 μg/m^3 in air, exhibiting downward curvilinearity *(1)*. The transient behavioural habit of children of putting inedible objects into their mouths (hand-to-mouth activity or, if clinically relevant, "pica") makes lead in airborne dust or urban house dust an important additional source of childhood lead exposure. Average lead concentrations in urban house dust in Germany have been found to range from 5.9 μg/g *(7)* up to 127.9 μg/g *(8)*. Lead levels in surface soils and road/pavement dust also vary from below 100 μg/g to over 600 μg/g *(9)*. It has therefore been estimated that an increase of lead in air also increases the uptake of lead by indirect routes, such that 1 μg/m^3 may contribute to 50 μg/l blood *(1)*. This also contributes to dietary lead exposure. Diet is the single most important route of lead exposure for children. Duplicate diet studies for children aged between 1.5 and 8 years found lead intake to vary between 2.1 and 6.4 μg/kg body weight, corresponding to 8% and 25% of the provisional tolerable weekly intake, respectively *(10,11)*. Lead in drinking-water from lead pipes in old houses may add substantially to the dietary lead exposure of children.

Neurodevelopmental and behavioural effects of inorganic lead

Children rather than adults are considered a sensitive risk group for lead because, on a body weight basis, their dietary intake, absorption and total retention are markedly higher. In addition, the blood–brain barrier is not yet fully developed in young children, and specific behavioural characteristics such as hand-to-mouth and playground activities put them at higher risk of exposure. For these reasons, both cross-sectional and prospective epidemiological studies have been done in order to test the assumption that children are particularly at risk for neurodevelopmental effects at even low environmental levels of exposure to inorganic lead.

Intelligence and sensorimotor performance

Blood lead concentrations (PbB) and/or lead concentrations in shed deciduous teeth (PbT) have been used as markers of internal dose or body burden in such studies. Children with different degrees of environmental lead exposure, namely

airborne lead from traffic or lead in drinking-water, or with more specific exposure due to lead-emitting industrial sources such as lead-zinc smelters, have already been studied in the early and mid-1970s using neuropsychological tests for the objective assessment of neurobehavioural deficit within cross-sectional or clinical studies.

Following the pioneering work of Needleman et al. *(12)*, a second generation of cross-sectional and prospective studies was initiated characterized by more sophisticated study designs, particularly a careful control over relevant confounding. Both cognitive and sensorimotor outcome measures have been used to characterize lead-related neurobehavioural deficit in these studies. In most cases, cognitive measures were partial or full-size clinical tests of mental/motor development or intelligence, such as the Bayley Scales of Infant Development, the Wechsler Intelligence Scale for Children or the Wechsler Preschool and Primary Scale of Intelligence, the British Ability Scales, and the Stanford-Binet Intelligence Scale. Measures of sensorimotor performance typically include different types of simple and choice reaction time paradigms, tapping speed and memory for design-tasks, such as the Benton test or the Bender Gestalt test. A characteristic superior feature of the prospective studies relative to the cross-sectional ones is the sequential collection of blood samples and testing over a prolonged period of time, which allows for separation of the pre- and postnatal impact of lead exposure, and the systematic effort to include both genetic and home environment determinants of development among the set of confounding variables.

Several meta-analyses have been conducted to better summarize the somewhat heterogeneous outcome of these second-generation cross-sectional and prospective studies in a more systematic manner. The most comprehensive are those by Pocock et al. *(13)* and by the International Programme on Chemical Safety (IPCS) *(14)*. Both focus on IQ as the outcome measure, because the standardized nature of this measure allows for better comparability of results across different studies. The common conclusion of both meta-analyses, for both cross-sectional and prospective studies, was that the effect of lead was highly significant but rather small: for a typical doubling of PbB from 100 μg/l to 200 μg/l, one could expect a drop in IQ of 1–3 points. In addition, IPCS *(14)* pointed out that 100 μg/l appeared to be a lower effect limit, although it was also noted that there was an indication of some adverse neurobehavioural effect of lead below that limit; nevertheless, methodological difficulties related to exposure and effect assessment must be considered as limiting factors for producing valid observations below 100 μg/l. IPCS *(14)* also emphasized that the size of the effect is based on groups rather than on individuals, and that such averages can only be applied to the individual child in a stochastic manner.

It should also be mentioned that IQ, despite its advantages of comparability and interpretability, may not be the most sensitive target variable for the detection of low-level effects of lead. Indeed, results from the European Multicenter Study covering individual studies from eight European countries (Bulgaria,

Denmark, Greece, Germany, Hungary, Italy, Romania and the former Yugoslavia) tied together by a common study protocol with some quality assurance elements, suggest that measures of attention and sensorimotor performance may exhibit stronger association with PbB than IQ *(15)*. As pointed out by Bellinger *(16)*, however, despite such observations a consistent behavioural signature of lead still remains to be established.

Efforts to document associations between environmental lead exposure and IQ have continued in both cross-sectional and prospective studies up to the present. The outcome from cross-sectional studies in 6–16-year-old children from six countries, namely China (Province of Taiwan) *(17)*, Croatia *(18)*, Mexico *(19)*, Pakistan *(20)*, Saudi Arabia *(21)* and the United States *(22)* was mixed: four found significant or borderline negative associations between PbB and IQ and two found no effect.

More consistent results were recently reported from ongoing prospective cohort studies. A publication from the Yugoslavia Prospective Lead Study, covering 390 children aged 3, 4, 5 and 7 years *(23)*, reported significant negative associations between both prenatal (maternal blood during pregnancy and at delivery) and postnatal PbB and IQ up to 7 years of age. A recent report from the Mexico City Prospective Lead Study *(24)*, covering 436 children up to 5 years of age, described significant negative associations between postnatal PbB levels and IQ, whereas prenatal PbB had no effect. Children from the Port Pirie Lead Smelter Study, based on a cohort of 375 children, have now been followed up to 13 years of age *(25)*. Again, there was a significant negative correlation between IQ and lifetime average PbB levels, which was more pronounced in girls than in boys, and there was a tendency for socially disadvantaged children to be more affected than children from more privileged families.

A recent report of a cohort study run in the city of Rochester, New York, has received particular interest because it demonstrated lead-related IQ deficits extending below the presumed critical level of 100 µg/l blood *(26)*. The study cohort comprised 240 children. Blood was collected at 6-monthly intervals from 6 to 60 months of age, and the Stanford-Binet intelligence test was administered at 3 and 5 years of age. After careful adjustment for a set of predetermined confounders, an overall significant negative correlation between lifetime average PbB concentration and IQ was observed, with an effect size of 0.46 point deficit for each 10 µg/l. For a subset of 101 children whose postnatal PbB had never exceeded 100 µg/l, the effect size was also negative and significant and even more pronounced than for the full cohort. This peculiar feature of the dose–effect curve is, of course, counterintuitive and may be due to oversampling of a group of children with low PbB but high IQ. Apart from this peculiarity, the importance of this study lies in the fact that it clearly extends the level of concern for environmental lead exposure below 100 µg/l blood. Other evidence in this respect has been reported before, but in a less convincing manner.

Delinquent and antisocial behaviour

Several studies have attempted to relate lead exposure to deviant behaviour in young and adolescent boys. Using in vivo X-ray fluorescence to measure lead in the bones of 301 primary-school boys, Needleman et al. *(27)* reported an association between bone lead levels and antisocial behaviour as rated by teachers, parents and the boys themselves. No actual bone lead levels are given in the report, however, and no PbB levels were available. In a later case-control study, the same group of researchers *(28)* compared 194 youths aged 12–18 years who had been arrested and convicted for delinquency with 146 non-delinquent age-matched controls from high schools in Pittsburgh. Again, bone lead levels were measured using X-ray fluorescence, but no PbB levels were available. After controlling for confounding, the delinquent youths were found to be four times more likely to have markedly elevated bone lead levels than the controls. Dietrich et al. *(29)* also studied the relationship between environmental lead exposure (prenatal and postnatal) and antisocial/delinquent behaviour in 195 inner-city adolescents from their Cincinnati cohort study. Deviant behaviour was assessed by means of parental ratings and self-reporting. After controlling for confounding, prenatal lead exposure (mean PbB = 89 μg/l) was associated with parent-reported deviant behaviour, while prenatal and postnatal lead levels were associated with higher self-reported antisocial/delinquent behaviour.

Studies of this kind are interesting and attractive from an overall societal point of view. However, their interpretation is extremely difficult, owing both to the complexity of the endpoints and, even more so, to the likelihood of high and almost uncontrollable reverse causality. It is not unlikely that hyperactive, aggressive youths are prone to expose themselves to environments and activities associated inter alia with higher levels of lead contamination.

Ototoxicity

Based on audiometric data from a subsample of 4519 children and adolescents aged 4–19 years from the second National Health and Nutrition Examination Survey (NHANES II), Schwartz & Otto *(30,31)* found a highly significant linear increase in pure tone hearing thresholds between 0.5 and 4 kHz, and confirmed this in 3262 subjects aged 6–19 years from the Hispanic Health and Nutrition Survey. An increase of PbB from 70 to 180 μg/l was associated with about 2 dB loss of pure tone hearing at frequencies between 0.5 and 4 kHz.

A more recent study conducted in the industrial area of Katowice, Poland, extends these observations to even lower levels of PbB and younger ages *(32)*. The PbB levels in 155 children aged 4–14 years ranged from 19 to 281 μg/l (median 72 μg/l). Hearing thresholds increased significantly with increasing PbB levels at all investigated frequencies (0.5–8 kHz) and even remained significant for PbB concentrations below 100 μg/l. These functional deficits were partly accompanied by lead-associated prolonged latencies in the brainstem auditory evoked potential.

Mercury

Pathways and degree of exposure

Like lead, mercury belongs to those metals known to, and used by, humans since ancient times. Mercury has three valence states, namely Hg^0, Hg^{1+}, Hg^{2+}, and is found in the environment in the metallic form and in various inorganic and organic complexes. Hg^0 is the predominant species in air. According to WHO *(1)*, atmospheric mercury levels in areas remote from industry are about 2–4 ng/m^3, and in urban areas about 10 ng/m^3. Thus the daily amount of mercury absorbed by inhalation is about 32–64 ng in remote areas and about 160 ng in urban areas *(1)*. This is almost negligible vis-à-vis the estimated daily exposure to mercury vapour from dental amalgam fillings, which varies between 3000 and 17 000 ng *(1)*.

From a neuropaediatric perspective, organic mercury complexes (particularly methylmercury compounds) are of greater concern than metallic mercury *(33)*. Methylation of mercury by microorganisms occurs in the marine environment, and biomagnification in the aquatic food chain may give rise to elevated methylmercury exposure in selected fish-eating populations. Although direct airborne exposure to methylmercury is negligible, an indirect contribution from mercury in the atmosphere following deposition on soils and sediments in the aquatic environment through subsequent methylation must be considered *(1)*.

Neurodevelopmental and behavioural effects of methylmercury

Much of the current evidence is summarized in a recent monograph from the National Research Council *(5)*. Initial knowledge about the neurological and neurobehavioural consequences of high methylmercury exposure was primarily gained in two episodes of mass poisoning in the Minamata Bay area of Japan in 1950 and in Iraq 20 years later. Methylmercury exposure in the Minamata tragedy was through contaminated fish and in Iraq through eating bread made from seed grain treated with a phenylmercury-containing fungicide. In both incidents several thousand victims were hospitalized, neurological signs and symptoms were predominant, and effects were generally more pronounced in the children born to poisoned mothers.

Relatively few studies have been conducted in infants and children exposed to low-level environmental methylmercury, but one was performed in New Zealand *(34,35)*, one in the Seychelles *(36)* and two on the Faeroe Islands *(37,38)*. Each of the study populations was characterized by a high proportion of marine food in the diet.

Both reports from the New Zealand study are based on relatively small groups of 4- (n = 31) and 6-year-old children (n = 61) paired with control children. A cross-sectional approach was used. Cases were selected on the basis of markedly elevated methylmercury levels in the hair of their mothers during pregnancy. The Denver Developmental Screening test revealed significant methylmercury-related deficits in the 4-year-old children, whereas at 6 years of age significant or bor-

derline inverse associations were reported between maternal hair mercury levels and outcome for language development and general intelligence. The largest deficit was seen for children with maternal mercury hair levels exceeding 10 ppm.

The Seychelles study was a prospective cohort approach based on 779 mother–infant pairs, representing about 50% of all live births during the recruitment period. Neurodevelopmental and neurobehavioural examinations were performed at several ages up to 66 months. Prenatal exposure to mercury was estimated from a hair segment of the mother taken during pregnancy, and postnatal exposure was assessed from a hair segment from each child taken at 66 months of age. At no age was any significant exposure-related neurodevelopmental or neurobehavioural deficit observed.

The two prospective Faeroe Islands cohort studies were based on 182 infants at two weeks of age *(38)* and 917 children at 7 years of age *(37)*, respectively. Both methylmercury in maternal hair during pregnancy and in umbilical cord serum served as the exposure markers. In the smaller study, a significant inverse association between mercury in cord blood and neurological optimality was observed. In the larger cohort with children of school age, significant inverse associations were found between mercury in cord blood and outcome in a number of neurobehavioural tests, covering the functional domains of attention, motor speed, hand–eye coordination, memory and language processing. In general, children's performance was more closely associated with mercury in cord blood than with either mercury in maternal or children's hair collected at 1 or 7 years of age.

The two large cohort studies on neurodevelopmental and neurobehavioural effects of methylmercury in fish-eating populations obviously produced different results. The reasons for this are unclear, because neither suffered from serious methodological flaws. A recent risk assessment presenting a benchmark dose estimate was based on the Faeroe Islands studies alone *(5)*.

Manganese

Manganese is known as an essential trace element that, with excessive exposure, induces signs and symptoms of CNS involvement.

Pathways and degree of exposure

Problems with manganese are typically restricted to occupational exposure of adults, with inhalation being the main exposure pathway. In general, environmental manganese levels in air are typically low. According to WHO *(1)* they are mainly in the range of 0.01–0.07 μg/m^3, but may reach air concentrations higher than 0.5 μg/m^3 in the vicinity of ferro- and silico-manganese plants. Concern has also been raised about possible airborne exposure to manganese in the context of the use of the organomanganese petrol additive MMT *(39)*. Apart from inhalation, significant manganese exposure may occur in rare circumstances through excessive levels in drinking-water *(40)*.

Neurodevelopmental and behavioural effects

Most of what is known about the neurotoxicity of manganese comes from neurological and neurobehavioural studies in exposed workers. Such studies have typically shown high inhalation exposure to be associated with sensorimotor deficit compatible with deficient extrapyramidal functions (tremor, postural instability, muscular dysthonia), resembling but not identical with the symptoms of Parkinson disease.

Little is known about neurodevelopmental and behavioural effects of manganese in children. A diminished rate of neurodevelopment, and correspondingly elevated hair manganese levels, were found in children in an area irrigated with sewage containing a high level of manganese; memory and manual dexterity scores were lower in these children than in children from a control area, and were negatively associated with hair manganese levels *(41)*. More recent findings have been reported from a cohort study covering 247 healthy mother–child pairs from the general population in Paris *(42)*. Children were studied at 9 months and at 3 and 9 years of age, and observations were related to manganese concentrations in maternal and cord blood. Although neither a covariate-adjusted developmental index nor the McCarthy general cognitive index correlated with prenatal/neonatal manganese levels, significant negative associations with manganese in cord blood were found for attention and verbal memory scores at 3 years and with hand skill in boys at the same age, but no longer at 9 years of age. Negative correlations were also observed between manganese levels in maternal blood during pregnancy and monoamine metabolite levels at birth. Multiple regression modelling included cord PbB concentration, in addition to other cofactors.

Although these findings are suggestive of subtle effects of manganese at environmental levels of exposure, they still represent isolated observations that will have to be confirmed independently.

Polychlorinated biphenyls

The PCBs belong to the larger family of structurally related PHAHs, which also include the dibenzo-*p*-dioxins and dibenzofurans. It is likely, and has indeed been shown, that under environmental conditions of exposure the different PHAH members – at least the PCBs and the dioxins – often occur together. Thus in typical epidemiological studies it is difficult or even impossible to distinguish the possible relative contributions of these groups of compounds. This review will nevertheless focus on the PCBs, because almost all paediatric neuroepidemiological studies have been conducted taking PCBs rather than dioxins as the exposure marker, mainly because of the analytical difficulties of measuring dioxins in small volumes of blood.

Pathways and degree of exposure

PCBs are a family of 209 congeners with two linked phenyl rings and variable chlorination. Because of their toxicity and biopersistence, their production and

use was forbidden in most industrialized countries in the late 1970s and environmental levels are, therefore, decreasing. For toxicity reasons, the dioxin-like (coplanar) and non-dioxin-like PCBs are to be distinguished. Although this distinction is of toxicological interest, however, it has little relevance to the studies described later, since for analytical reasons the coplanar PCB congeners are rarely measured in such studies.

The main exposure pathway is dietary. Over 90% of PCBs found in the body are of dietary origin and, because PCBs are highly lipophilic, derive mainly from the consumption of animal fat and milk products. According to WHO *(1)*, the daily intake of total PCBs in Nordic countries has been estimated as varying between 0.05 and 0.24 μg/kg body weight. Breastfeeding is an important source of PCB exposure in infants.

PCB levels in ambient air are low and may range from 0.003 ng/m^3 in nonindustrial areas to about 3 ng/m^3 in urban or industrial areas *(1)*. Indoor air levels can be substantially higher if PCB-containing building materials such as paints or sealants have been used. Levels of up to 7500 ng/m^3 and higher have been reported *(1)*. It must be pointed out, however, that such PCBs mostly belong to the lower chlorinated congeners exhibiting sufficient vapour pressure for degassing. These undergo rapid metabolism and excretion such that it has been difficult to detect elevated PCB levels in the blood, even in those exposed to high indoor air levels such as in schools.

To quantify childhood PCB exposure in neurodevelopmental and behavioural studies in human infants and children, some typical or abundant PCB congeners are usually measured in body fluids at different ages, such as in maternal or cord serum or in maternal milk shortly after birth. Since studies differ both in this respect and also in terms of analytical method, an effort has been made to compare the levels of PCB exposure of different childhood PCB studies in terms of the most abundant congener, PCB 153 *(43)*. These median values are given in Table 1 and may help to better understand the degree of childhood PCB exposure in the various neurodevelopmental studies described below.

Table 1. Measured or estimated serum levels of PCB 153 in studies relating paediatric PCB levels to neurodevelopment in children

Reference	Study area	Period of sample collection	Median (ng/g lipid)
Rogan et al. *(44)*	USA (North Carolina)	1978–1982	80
Jacobson & Jacobson *(45)*	USA (Michigan)	1980–1981	120
Patandin et al. *(46)*	Netherlands (Rotterdam/Groningen)	1990–1992	100
Darvill et al. *(47)*	USA (New York)	1991–1994	40
Walkowiak et al. *(48)*	Germany (Düsseldorf)	1993–1995	140
Steuerwald et al. *(38)*	Denmark (Faeroe Islands)	1994–1995	450[a]

[a] Level influenced by the high proportion of marine food in the diet.
Source: Longnecker et al. *(43)*. Reproduced with permission from Environmental Health Perspectives.

Neurodevelopmental and behavioural effects of PCBs

Apart from two mass poisoning events – in Yusho (Japan) in 1968 and Yucheng (Taiwan, China) in 1979, each with between 1000 and 2000 adults accidentally exposed to high levels of PCBs (and other PHAHs) through contaminated rice oil – at least six groups of cohort studies have now been undertaken relating measured PCB concentrations at environmental background concentrations in relevant body fluids to developmental (mainly neurobehavioural) outcomes.

Despite the high levels of exposure and the possible contribution of other PHAHs (e.g. PCDFs), both the Yusho and Yucheng incidents provide sufficient neurodevelopmental information to deserve attention in the present context. In a subset of children who were followed for several years after the Yusho incident, persistent growth retardation, movement disorders, generalized slowness and substantial IQ deficits (average IQ of around 70) were found. In the Yucheng incident, the overall picture was similar to that in Yusho, but babies born to mothers exposed during pregnancy were followed over a longer period of time and compared with carefully matched controls *(44)*. Small but systematic IQ deficits, prolonged P300 latencies (a "cognitive" component of event-related brain potential with a latency of around 300 ms after onset of stimulus), and higher frequencies of behavioural disorders were reported, but there was no correlation between the degree of deficit and the PCB levels of the mothers *(45)*. Since pregnant mothers were advised by their doctors not to breastfeed, PCB exposure probably occurred only prenatally.

At least six groups of cohort studies are available in which measures of internal dose at environmental levels have been related to neurobehavioural outcome. These are two early American studies conducted in Michigan *(46)* and North Carolina *(44)*, an ongoing American study from Oswego, New York *(47)* and three forming part of a European coordinated effort: the Dutch breast milk study *(48)*, the Faeroe Islands study *(38)* and the Düsseldorf study *(49)*. In the Michigan study, healthy mother–infant pairs were recruited from families with different levels of consumption of Lake Michigan fish, whereas the other five studies are general population studies. All of them are characterized by background PCB levels measured in different biological matrices, namely maternal serum, umbilical cord serum and/or maternal milk collected shortly after birth.

In the Michigan study *(46)*, 313 out of over 8000 mothers who had given birth to a healthy child were recruited for the study. These comprised mothers who had reported consuming different quantities of fish over the previous six years, and a control group who reported no consumption of Lake Michigan fish. PCB levels were measured in maternal and umbilical cord serum and in the milk of breastfeeding mothers, while PCB values were available for cord serum in only about 30% of cases. Subsequent neurobehavioural testing took place at birth and at 5 and 7 months and 4 and 11 years of age. The overall outcome was as follows.

- Fish consumption, though not PCB levels in cord serum or breast milk, was correlated with delayed motor development and hyporeflexia.
- Neither fish consumption nor PCB levels in cord serum or breast milk was associated with mental/motor development at 5 months of age.
- Visual recognition memory at 7 months was negatively related to PCB levels in cord serum but not to those in breast milk.
- At 4 years of age memory performance was negatively correlated with PCB levels in cord serum.
- At 11 years of age full-scale and verbal IQ still exhibited a negative association with a composite exposure index constructed from PCB levels in maternal or cord serum and breast milk *(50)*.

In the North Carolina study *(44)*, 880 mother–infant pairs were recruited from the general population over 700 of whom were available for follow-up until the infants were 5 years of age. Since PCBs were not detectable in cord serum, they were measured in the milk of nursing mothers shortly after birth and on later occasions for up to 12 months. Neurobehavioural development of the children was measured at regular 6- and 12-month intervals after birth for up to 5 years. Hyporeflexia, hypotonicity and delayed motor development were related to the prenatal PCB body burden of the mothers as indexed by PCBs in early milk samples taken up to 24 months postnatally. Mental and psychomotor development was not affected at any age.

In the ongoing Oswego study, 212 children were studied from birth until 54 months of age and PCB concentrations were measured in cord serum and maternal milk *(47,51,52)*. In contrast to the early Michigan study mentioned above, possible co-exposure to methylmercury was considered and a large set of potential confounders was taken into account in the statistical analysis. At 6 and 12 months of age visual recognition memory showed negative associations with perinatal PCBs (51), and at 38 months of age – but no longer at 54 months – results from the McCarthy general cognitive index were also negatively correlated with PCB levels in cord blood. The sum of the most persistent highly chlorinated congeners, 170–206 (15 congeners altogether), served as the marker for prenatal PCB exposure.

In the Dutch breast milk study *(48,53)*, 200 healthy mother–infant pairs were recruited in both Groningen and Rotterdam. Half of the mothers were breastfeeding, the other half were using infant formula. Four PCB congeners were measured in maternal and cord plasma and other PCBs, as well as a number of dioxins, were measured in early breast milk samples. Neurological status according to the Touwen/Prechtl examination, as well as psychomotor and mental development, was assessed at 2 weeks and at 3, 7 and 18 months of age. The main results were as follows.

- Neurological status (hypotonia) was negatively associated with PCBs in maternal plasma but not with PCBs/dioxins in milk at 2 weeks and 7 months of age.
- Psychomotor development was delayed at 3 and 7 months in relation to PCBs in maternal plasma.
- At 18 months, the overall neurological status and fluency of movement was negatively association with PCBs in cord plasma.
- No impairment of visual recognition memory was found to be associated with neonatal PCBs at 3 and 7 months.

In the European PCB study, in addition to the two Dutch cohorts described above, two additional cohorts of about 170 healthy mother–infant pairs each were recruited in the Faeroe Islands *(38)* and in Düsseldorf *(49,54)*. The two cohorts were studied between 2 weeks and 42 months of age for neurodevelopment, for visual recognition memory at 7 months, for psychomotor/mental development at 7, 18 and 30 months, and for early intelligence at 42 months. In the Faeroe Islands study, PCBs were measured in maternal serum and milk collected at about 2 weeks of age. In the German cohort, PCBs were measured in umbilical cord blood and in maternal milk also collected at about 2 weeks of age. The two existing Dutch cohorts were reassessed for neurodevelopment, language development and intelligence at 42 months of age. The common denominator for prenatal and neonatal exposure was PCBs in cord and/or maternal plasma, as well as in early (two weeks) breast milk samples. Both measures of exposure are highly correlated. The first results from this study suggest the following.

- Cognitive development is negatively associated with PCBs in breast milk between 7 and 42 months of age (significantly at 30 and 42 months) *(49)*.
- Visual recognition memory does not relate to neonatal PCB at 7 months of age *(54)*.
- Both cognitive development and language development exhibit negative associations with PCBs in maternal plasma but not in cord plasma at 42 months of age *(55)*.
- Neither the German *(56)* nor the Dutch study *(57)* found persistent effects of PCBs between 72 and 77 months of age for the group as a whole, although in the Dutch study negative PCB associations were still reported for socially disadvantaged mothers.

Gender-specific behaviour and sex-role identity in relation to prenatal/neonatal exposure to PCBs

Steroid hormones, like thyroid hormones, exert an organizational role in brain development. Experimental studies have shown PCBs to interact with the estrogen/androgen systems and, in doing so, to have long-lasting or irreversible effects in altering gender-specific behaviour. Recently, the first such observations have also been reported in children. The mothers of 190 children from the Rotterdam

cohort were asked to characterize their children by means of a questionnaire in terms of preferred toys, play activities and male/female characteristics, using a set of five-point scales (never to very often). These were used to place the children on masculinity/femininity scales. The rating of boys by their mothers as being significantly less masculine was associated with cord serum PCB levels; there was also a tendency for girls to be rated more masculine, but this was not statistically significant.

REVIEW SYNTHESIS

Environmental exposure to some toxic metals, namely inorganic lead, organic mercury and manganese, as well as to some persistent organic pollutants (PCBs), has been found to be associated with neurobehavioural deficit in children. Although exposure to these compounds is not primarily by way of inhalation, but rather dietary, atmospheric transport may contribute substantially to indirect exposure of children.

For inorganic lead, the most consistent evidence is from prospective studies and the primary outcome measure has been the IQ. Despite considerable confounding, subtle loss of IQ of up to 3 points was found to be related to a typical doubling of PbB from 100 to 200 μg/l. Early postnatal exposure appears to be more effective than exposure prenatally. Although most findings are consistent with a lower effect level of 100 μg/l, some well-conducted studies observed IQ loss at even lower PbB levels. Such effects are group averages and refer to the individual child only in a stochastic manner. This is also true for lead-related hearing loss, which is subtle but also well documented. Reports relating lead exposure to antisocial behaviour in children and adolescents are less well documented; reverse causality is a real possibility here.

Organic mercury can primarily be considered a risk factor for neurobehavioural deficit in children from fish-eating populations. Inorganic forms of mercury reaching the marine environment, either by way of atmospheric deposition or by direct discharge of industrial sewage effluents, are converted into methylmercury by microorganisms and bioaccumulate in the marine food chain. Two large cohort studies in the Seychelles and the Faeroe Islands came up with differing results: whereas neurodevelopmental toxicity was observed in infants and children from the Faeroes, no such effect was found in the cohort from the Seychelles. If findings from some smaller cohort studies are also taken into account, however, there is good reason to accept methylmercury as being a neurodevelopmental risk factor. This evaluation is also in line with a recent benchmark dose analysis of the US National Research Council.

Manganese is primarily an occupational risk factor. In such settings, neurological symptoms in adult workers following exposure to airborne manganese were found to resemble Parkinson disease, although mechanistic studies do not support a common etiopathology. Little information exists concerning neurobehav-

ioural effects of manganese in environmentally exposed children. One such study provides for suggestive evidence in this respect, but more research is needed in order to come up with definitive conclusions.

PCBs belong to the large family of polyhalogenated aromatic hydrocarbons, which also includes the dibenzo-*p*-dioxins. PCBs are synthetic oils that have been used in large amounts in open and closed systems until the early 1980s. Their production and use has been banned in most industrialized countries ever since. Nevertheless, owing to their resistance to biodegradation they are still detectable in the environment, and primarily reach humans via animal fat and milk products, although some degree of atmospheric transport has been reported and inhalation exposure indoors may occur from PCB-containing building materials. This, however, is restricted to the lower chlorinated congeners, which, in contrast to the higher chlorinated congeners, are easily metabolized. In addition to the two mass poisoning episodes resulting from PCB contamination of rice oil in China (Province of Taiwan) and Japan, four out of five published cohort studies in infants and young children have reported some degree of developmental neurotoxicity, primarily in relation to prenatal exposure to background levels of environmental PCBs. Psychomotor, neurological and cognitive development were found to be compromised, but the matrix (maternal or cord serum or early breast milk) differs between studies. Also, the degree of persistence of developmental delay is still controversial and the mechanisms need to be clarified. Interactions of PCBs with endocrine systems, particularly the thyroid and the estrogen/androgen systems, have been shown experimentally to be plausible but have not yet been proven *(58)*. Since co-exposure of humans to PCBs and dibenzo-*p*-dioxins occurs, it is difficult or even impossible to characterize the relative contribution of both these to the observed developmental effects.

CONCLUSIONS

Lead. Primarily based on the large number of well-controlled prospective studies covering prenatal and postnatal exposure, there is considered to be *sufficient* evidence that neurobehavioural deficit in terms of cognitive impairment is caused by developmental exposure at low environmental levels.

Organic mercury. The evidence that developmental exposure is causally linked with neurobehavioural deficit is considered to be *suggestive*. This is due to the fact that two large prospective studies in children from fish-eating populations arrived at conflicting findings.

Manganese. The evidence for a link between developmental exposure of children at environmental levels and neurobehavioural adversity is considered *insufficient*, owing to the limited data is available to date.

Environmental PCBs. The evidence from prospective cohort studies linking early developmental exposure to neurobehavioural deficit in terms of cognitive, neurological or psychomotor development is considered *suggestive*. This evaluation considers the fact that, (*a*) not all of the published studies have documented a coherent spectrum of neurobehavioural deficit; (*b*) neurodevelopmental adversity has been documented relative to PCB levels in different matrices (e.g. milk, cord serum and maternal serum); and (*c*) owing to inevitable co-exposure to other members of the PHAH family, such as the dibenzo-*p*-dioxins, it is difficult to clearly identify the PCBs as the only causative agent.

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CONCLUSIONS

There is evidence implicating air pollution in adverse effects on children's health. Effects of air pollution have mainly been investigated in relation to lung development and function, pregnancy outcomes, respiratory diseases such as asthma, bronchitis and cough, allergies, rates of infection in smaller children, incidence of cancer, and deficits in neurobehavioral development. This review evaluates the strength of the evidence for a causal link between air pollution and these outcomes.

The developing fetal lung, as well as the infant lung, is more susceptible to injury by lung toxicants (including air pollutants) at doses below the no-effect level for adults. There may be a multitude of factors influencing susceptibility, but some have been investigated. The time-dependent efficiency of detoxification systems during a child's lung development influences susceptibility to the health impact of air pollutants. Also, polymorphic variation in susceptibility genes, which protect against tissue injury or drive repair mechanisms, may explain some of the variation in the greater response of children.

Lung function is a well-studied outcome in respect to air pollution exposure. The large differences in lung function among adults are due to attained lung function at maturity. Thus, factors that affect development of lung function in childhood are important in determining the level of lung function in adulthood. Studies on lung function development in children have shown that living in areas with high levels of air pollution is associated with reduced lung function. Animal studies also indicate that intrauterine and postnatal exposure to pollutants can lead to impaired lung growth. Furthermore, chronically elevated air pollution levels are associated with lower rates of lung function development. Lower air pollution levels result in improved lung function and/or growth rates, and acute exposures to air pollution are associated with apparently reversible deficits in lung function. A small shift in average lung function may yield a substantial increase in the proportion of children with "abnormally" low lung function. In addition, small changes in the population mean may reflect large changes in a susceptible subgroup of the population.

The evidence for the impact of air pollution on infant mortality, primarily due to respiratory deaths in the post-neonatal period, seems to be solid. Less consistent though still suggestive of a causal link to air pollution are lower birth weight, a higher incidence of preterm births and intrauterine growth retardation.

The available evidence on the prevalence and incidence of cough and bronchitis is sufficient to suggest a causal link between air pollution and these out-

comes. The same holds true for increases in hospital admissions or emergency department visits for asthma, for increased medication use among children with asthma and for exacerbation of wheezing and coughing during extended periods of air pollution. Interestingly, the prevalence and incidence of asthma cannot be linked as strongly to air pollution, although there seems to be a causal relationship between air pollution and asthma symptoms if people live close to traffic. Furthermore, a link is suggested between traffic-related air pollution and the prevalence and incidence of hay fever.

Many of the upper and lower respiratory symptoms in children studied as health outcomes, such as bronchitis, wheeze, cough and stuffy nose, seem to be accompanied by infections of mixed but largely viral etiology. Most data therefore suggest a significantly increased risk of respiratory infections following long-term exposure to air pollutants.

In respect to the development of cancer in children, the weight of the epidemiological evidence to date is insufficient to infer a causal link with air pollution. Nevertheless, exposure needs to be considered during different periods in the child's development, and diagnosis of disease might be made later in life. Thus exposure of children to air pollution and the occurrence of cancer in childhood and adulthood have to be investigated more thoroughly in the same context.

Neurobehavioral outcomes following exposure to air pollution have also been studied. The link between exposure to lead and cognitive impairment in children is considered to be sufficient for a causal relationship. A causal link is suggested for exposure to organic mercury and PCBs, whereas for manganese exposure the evidence is insufficient to draw firm conclusions at the moment. Although inhalation is typically not the main route of exposure to these contaminants, their emission to the air and subsequent atmospheric transport constitutes an important source.

Although this review has attempted to pinpoint the role of single pollutants in different health outcomes, current scientific evidence in general does not allow an association to be made between exposure to specific pollutants and specific outcomes. More research is needed to better understand the role of the various air pollutants and their interaction with individual susceptibility. Nevertheless, the data already available provide strong evidence that the respiratory health of children, particularly those with increased susceptibility such as children with asthma, will benefit substantially from a reduction in current levels of air pollution, especially that from motor vehicle exhausts.

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Concerns about the adverse effects of air pollution on children's health and development are important determinants of environmental and public health policies. To be effective, they must be based on the best available evidence and research. This book presents an assessment of research data gathered over the last decade, and provides conclusions concerning the risks posed by ambient air pollutants to various aspects of children's health. The authors of this evaluation, constituting a WHO Working Group, comprise leading scientists active in epidemiology, toxicology and public health. They summarize research into the effects of air pollution common in contemporary European cities on infant health, the development of lung function, childhood infections, the development and severity of allergic diseases (including asthma), childhood cancer and neurobehavioural development. On all of these health issues, the Working Group formulates conclusions regarding the likelihood of a causal link with air pollution.

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