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AB AC

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

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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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

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

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

BACKG D

Concerns about children's health and the factors that affect it are important de-

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.

CE F E A I G HE G A H

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 *( )*. 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) *( )*. 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

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,

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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 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 rer55(s t)655(o)169ildr, al(, r006 hi3.6(a58T(tib2 w)7s7(

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I D C I

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

from indices of domestic and industrial pollution *( )*. The study found significant correlations between air pollution and infant mortality, particularly infant respiratory mortality. The Nashville Air Pollution Study conducted in the 1950s *( )* 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 . The si3s addr-5.83ae6(u)8.als -ee(ed is) in 117

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 $\mu g/m^3$ 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

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

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

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

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 *(37)* 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

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. *(3)* 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.

AI LE I A DBI H DEFEC

At present, evidence on the relationship between outdoor air pollution and birth defects is limited to only one report. Ritz et al. *(3)* 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 ( ) 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 ( ) 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).

DI C I

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.

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

In addition, there appears to be an interaction between PAH exposure and genotype to produce DNA adducts *(5, 24)*. 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 epide-

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the induction and maturation of their relevant enzyme systems *(11)*. Differential

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 under-

tern of lung development 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 *(3 3)* and the response of the airways and alveoli to environmental insults associated with chronic diseases such as asthma *(3 42)*.

I FLU E CE F LU A U GDE EL E

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 (e did)20.003(o)huife

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 *(3)*. 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 *(3)*. 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 iden-ep77eigt orltir lo3.6(i)3lo3.(j)9. 18.4(t).2(ir .2(e a)a1.4(n.l-0.4(n3under)7.n(lo3.g.2(ir)m5.7(h)

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 growu2.2(h(t)-0 0I.6(c)6((d t)6.3wi)12.3(r)6s3(n a)9n2(h)4d.3(-1(t)5y3(w)18(t)6.3o)1

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for the health consequences of ambient air pollution. The ability of DEPs to enhance allergic responses is highly repeatable within individuals *(2)* 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 *(6)*. 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 *(6)* and ozone *(6)*.

C CL I

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

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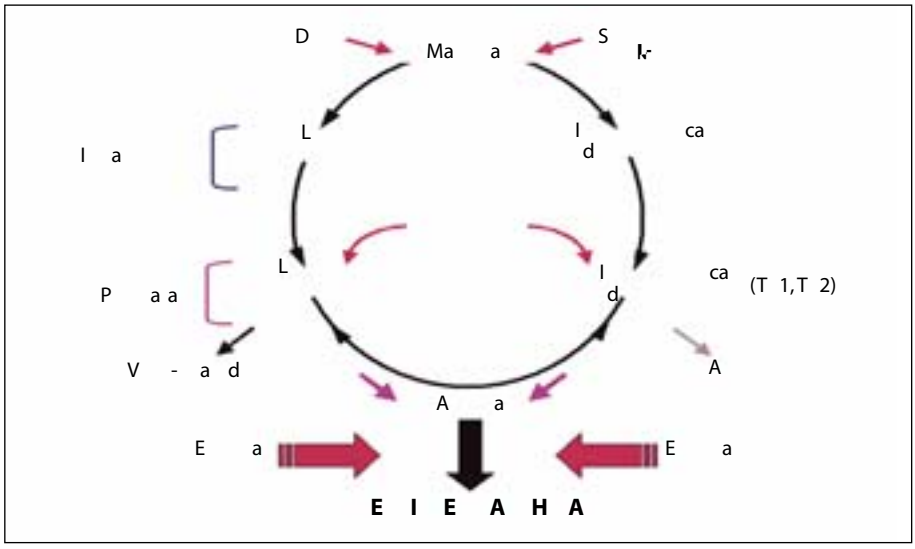

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air pollutants may exert deleterious effects. With the knowledge that air pollutants can also enhance pro-allergic pathways in those genetically at risk, additional plausibility is provided for the potentially injurious effects of ambient air pollutants 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

the structural elements as well as involve immune or inflammatory cells *(0)*. The importance of air pollutants alone or in concert with other environmental insults such as respiratory virus infections *(1, 2)*, allergen exposure *(44, 3, 4)* 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.

A

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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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.

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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 pollutf(-9.1(ob 8 Twc[(o)15.9(v)O)2.4(sk 141-9(o(6(-9.1.2(

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.

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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)*.

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 proinflammatory 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.

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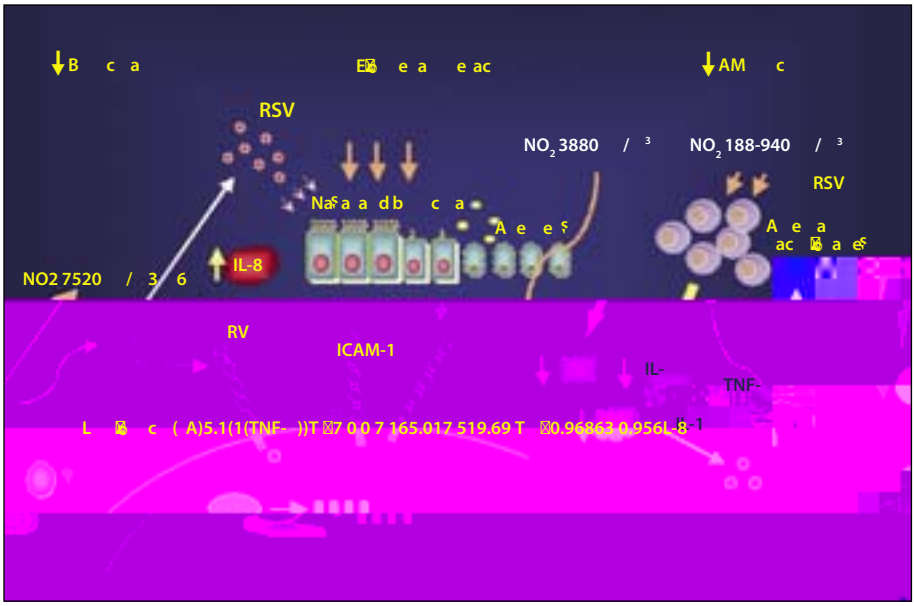
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alveolar macrophages were obtained by lavage and incubated with influenza virus *(24)*. Alveolar macrophages from four of the nine people showed depressed

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 *(2 ,30)*, hospital admissions *(31,32)*, mortality *(33,34)*, increased symptoms *(3 ,36)*, school absenteeism due to respiratory illness *(3)* and reduced lung function *(3 ,3)*.

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 analalth eft stu8.4(t511.8(f)n(i)11.1(t)-d TDc-0.,al)fs.2t12.3(fr)1 s

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

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 between1.5(ds5T]TJ
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tory illness *(6)*. 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-μg/m^3 increase in PM10 *(6)*; the other evaluated both symptomatic and asymptomatic children, revealing non-significant increases in upper and lower respiratory symptoms in both groups *(0)*. 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 *(1)*. 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 *(2)*.

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 *(3)*. O.2(uded)]TJcTS(. O.2al.5(

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 *(4)*.

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 *( )*. 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

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}

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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 ( ) or ( ) 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.

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.

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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 par1o 10.7

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}.

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)*

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 schools).

Other studies assessed exposure to traffic by inquiring about the density of truck traffic in the street of residence *(42, 44)*

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 *( )*. Random samples of school-children (n = 7509, grades 1 and 4) were studied using parental questionnaires, skin-prick tests and measurements of serum IgE and lung function. This study

Investigators in the Netherlands examined the relationship between traffic-re-

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).

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. *(2)* 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 *(3)* 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 *(4)* in Vancouver, Pope *( )* in the Utah Valley, Schwartz et al. *(6)* in Seattle and Burnett et al. *( )* 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 *( )*, Mexico City *( )* and New Brunswick, Canada *(0)* found a strong and statistically significant effect of ozone. White et al. *( )* 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 *(1)*. 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. *(2)* 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 (= 0.75). Associations between daily visits, PM_{10} and ozone were reported, with consistent results across all models.

In São Paulo, Brazil, Gouveia & Fletcher *(3)* 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 *(4)*. 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 *( )*,
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Particulate matter. All the studies that considered BS were conducted in

In summary, the overall results of the time-series studies suggest an effect from

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,

et al. *(10)* 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 nitcts

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. *(126,12)* 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. *(12)* 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. *(12)* 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

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

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.

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[1] R f c 139 a d 140 a a a d C a 3.3, a a ab a 89.

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 , 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 ( ). 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 ( ). 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 (,) and all-cause mortality *(10 1)*.

Many factors influence lung function and its growth during fetal and neonatal

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

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 effects of maternal smoking are important *(2 ,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.

EFFEC FE I E AL ICA L GH C I G H A DDECLI E

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

C EC I AL DIE

Studies examining lung function at specific points in time from Europe *(4, 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)*.

E DIE

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.

L GI DI AL DIE

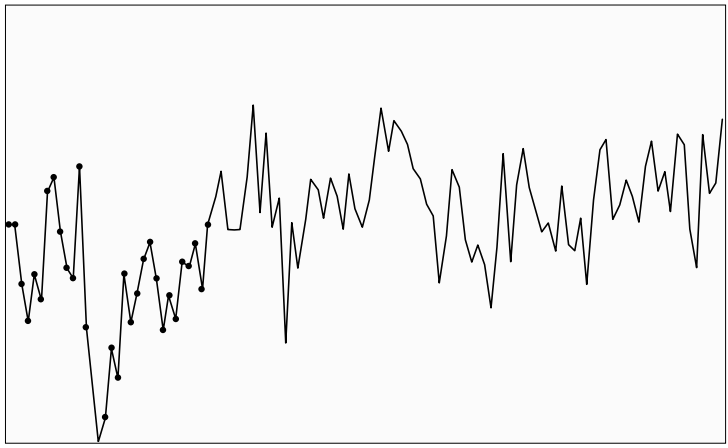
Longitudinal cohort studies offer a number of advantages for examining the association between air pollution and lung function and growth. Repeated assessments can establish the temporal sequence between exposure and disease. Repeated measurement of children's lung function over several weeks or months (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)*.

In one of the first panel studies, lung function of children was measured weekly before, during and after air pollution episodes in Steubenville, Ohio *(6)*. 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 *(6)*.

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 *(0 6)*. 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 *( )*. 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 *(4)*, North America *(1)* and other continents *(2, 3)*.

Meta-analyses of these panel studies have found acute, apparently reversible decreases in lung function associated with short-term air pollution exposures *(4)*



(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.

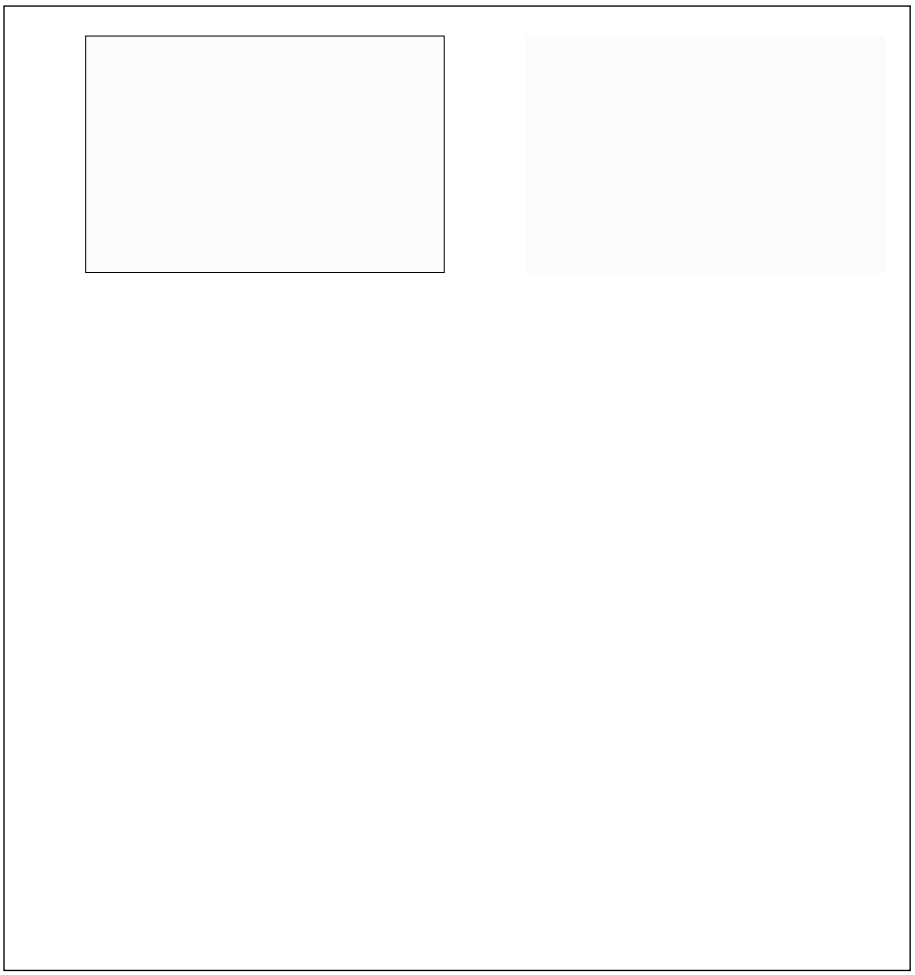
After an additional year of follow-up of 975 schoolchildren from eight of these communities in Lower Austria, these investigators reported a slower increase in FEV_1 and MMEF with age in children exposed to higher summer PM_{10} *(46)*. After adjusting for potential confounders, an increase of summer 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 *( )*. 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-



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 *( )*. 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.

provements in children's lung function. Consecutive cross-sectional surveys of

I AC F ECIFIC ICA

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 *(1)*. Evidence for effects of each of these pollutants on lung function growth and decline are reviewed below.

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 *(0)*, 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 *( )*, 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)*

an effect of ozone on PEF (= –0.75, <0.005), and $PM_{2.5}$ on MMEF (= –0.80, <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 *(10)*. 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. *(4)* 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 *( )*. 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 (= 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.

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 *(1)*. Although a meta-analysis of panel studies of nitrogen dioxide exposures determined that each 100-µg/m^3 increase was associated with a 0.7% decrease in FEV_1, the association was not statistically significant *( )*. 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, however1(v)7.8()-8.2(C l)11.1o10.9(t)5(v)(e)0.39rio ltii lt

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 *(4)*. 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 *(4)*. 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 *(11 ,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

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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

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.

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I D C I A DBI L GICAL C IDE A I

I

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

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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

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

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F c a ., S d , 1998 *(1)*	Ca -c	N=142, a ca c , 0 15 0(c)6( )29/704 Tcc -0.0424 T 0 Tc -0.0a
Ha a ., U d K d , 1999 *(22)*	1. Ca -c : d d a c 2. Ob d- - c d b f ca c a df a a c b c	
P a a ., C ad , USA, 2000 *(23)*	Ca -c	
Raa c - N a ., D a , 2000 *(2)*	Ca -c	
R d a ., Ca f a, USA, 2001 *(2)*	Ca -c	

Tab e 1. F ee S de S a M a dc d dca ce (c ed)

R d a., Ca f a, USA, 2002 *(28)*	Ec ca: c d c c a d b a a dff af c ad	N=7143, a ca c , 0 14 a , c d c	1988 1994, f C 24 a	Dff af c a ca d ac f 21519
La a., Ca f a, USA, 2002 *(2)*	Ca -c	N=212, a a, 0 10 a , c d c	1978 1984, L A C	
R d a., Ca f a, USA, 2003 *(30)*	Ec ca .: I c d c a c a d b a a dff a	N=6989, a ca c , 0-14 a , c d c	1988-1994, f C 24 a	
C a a., I a , 2004 *(31)*	Ca -c	N=120, a a, 0 14 a , c d c	1978 1997, P c f Va 1988 1997	
R d a., Ca f a, USA, 2004 *(32)*	Ca -c	N=4369, a ca c , 0 4 a , c d c		

V c

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,

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. *(2)* 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. Nghe chrs foils iS co6(f)·

Reynolds et al. *(2)* 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. *(2)* 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. *(2)* 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

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

E IDE CE HE I

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 *(1)*, 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 *(20,2 ,2 ,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

kaemias and lymphomas in different age groups. Thus, it is important to control

Tab e 2. C a ac e ? G e c ded? d e?

S d	Study considered mainly positive (+) or negative (–)[a]	Hypothesis generating (G) or testing (T)	More than 200 cases of childhood leukaemia	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
W &L *(1)*	+	G	0	0	1	0	
Sa &F d *(11)*	+	G	0	0	1	0	
A a d a . *(1.)*		T	1	0	0	0	
K &G a *(20)*		T	1	0	0	0	
N d d &d *(2)*		T	1	0	0	0	
F c a . *(1)*	+	T	0	0	1	1	
Ha a . *(22)*		T	0	0	0	0	
P a a . *(23)*	[f]	T	0	0	1	1	
Raa c -N a . *(2)*		T	1	1	1	1	
R d a . *(2)*		T	0	0	1	1	
R d a . *(2)*		T	1	0	0	0	
La a . *(2.)*		T	1	0	1	1	
R d a . *(30)*		T	1	0	0	0	
C a a . *(31)*	+	T	0	0	1	1	
R d a . *(32)*		T	1	0	0	0	

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

36. Nyberg F et al. Urban air pollution and lung cancer in Stockholm. , 2000, 11:487–495.
37. Pope CA III et al. Lung cancer, cardiopulmonary mortality, and long-term exposure to fine particulate air pollution. , 2002, 287:1132–1141.
38. Nafstad P et al. Lung cancer and air pollution: a 27 year follow up of 16 209 Norwegian men. , 2003, 58:1071–1076.

I D C I

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 *(1)*. For the large and heterogeneous group of organic solvents (e.g. trichloroethylene, tetrachloroethylene,0.5(t)-6cound xylene), neurotoxicity has mainly been studied in occupational settings or in cases of inhalation abuse rather thvironmental

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 prima.3(e f,)(e)0.8((.(o)12n)4

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

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 *(1)*. 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) *(1)*, Croatia *(1)*, Mexico *(1)*, 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 co-

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(2)

D

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. *(2)* 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 *(2)* 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

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 *(3)* and 917 children at 7 years of age *(3)*, 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 is known as an essential trace element that, with excessive exposure, induces signs and symptoms of CNS involvement.

P

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 *(3)*. Apart from inhalation, significant manganese exposure may occur in rare circumstances through excessive levels in drinking-water *(40)*.

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

N PCB

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.

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 *(0).*

5

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

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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

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- -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

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 . This evaluation considers the fact that, ( ) not all of the published studies have documented a coherent spectrum of neurobehavioural deficit; (

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