4. Studies on health effects of transport-related air pollution

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Key points

Facts

Evidence from epidemiological and toxicological studies on the effects of transport-related air pollution on health has increased substantially, although it is only a fraction of the total evidence on the effects of urban air pollution on health. A review of this evidence indicates that transport-related air pollution affects a number of health outcomes, including mortality, non-allergic respiratory morbidity, allergic illness and symptoms (such as asthma), cardiovascular morbidity, cancer, pregnancy, birth outcomes and male fertility. Transport-related air pollution increases the risk of death, particularly from cardiopulmonary causes, and of non-allergic respiratory symptoms and disease. Experimental research indicates that the effects are linked to changes in the formation of reactive oxygen species (ROS), changes in antioxidant defence, and increased non-allergic inflammation, thus articulating some parameters of susceptibility. While laboratory studies indicate that transport-related air pollution may increase the risk of developing an allergy and can exacerbate symptoms, particularly in susceptible subgroups, the evidence from population studies that supports this conclusion is inconsistent.

Though only a few studies have been conducted, a significant increase in the risk of heart attack (myocardial infarction) following exposure to transport-related air pollution has been reported. Other studies and the experimental evidence indicate changes in autonomic nervous system regulation and increased inflammatory responses, as a result of exposure. Cancer, too, is a problem. A few studies suggest an increased incidence of lung cancer in people exposed to transport-related air pollution for a long time. An elevated incidence of cancer in children with high or prolonged exposure to air pollution cannot be excluded, though the supporting evidence is less consistent than that for adults. Certain occupational groups, such as professional drivers...
Health effects of transport-related air pollution and railway workers show increased incidence of and mortality from lung cancer, especially in instances of long exposure. Finally, some studies suggest that transport-related air pollution has adverse outcomes on pregnancy, such as premature birth and low birth weight, but the available evidence is inconsistent.

Only a few intervention studies have been conducted, most of them not specific to transport-related air pollution. They show, however, that reducing such pollution may directly reduce acute asthma attacks and related medical care for children. They also show that long-term decreases in air pollution levels are associated with a gain in life expectancy and with declines in bronchial hyperactivity, the average annual trend in deaths from all causes, and respiratory and cardiovascular diseases.

Possible indicators of exposure
Often, the effects observed in epidemiological studies cannot be attributed to the specific indicators addressed, but to a mixture of pollutants. Fine PM (including black smoke) and ozone are associated with increased risks of mortality and respiratory morbidity, while exposure to nitrogen dioxide, ozone and PM has been linked to allergic responses. Other indicators of exposure to transport-related air pollution, such as residence near or distance to major roads and, in part, self-reported traffic intensity at a residence, were associated with several adverse health outcomes. A drawback of self-reported transport-related air pollution exposure, however, is that it might overestimate the effect of self-assessed health.

Introduction
This assessment of the health risks associated with air pollution is based on combined scientific evidence from epidemiology and toxicology. WHO’s recent systematic review of the health aspects of air pollution in Europe assessed this evidence, focusing on the health effects of PM, ozone and nitrogen dioxide (WHO Regional Office for Europe, 2003, 2004a). This valuation provides the background for the analysis of transport-related air pollution, but does not offer a specific response to the risks created by transport. Though PM, ozone and nitrogen dioxide are produced by traffic, other emission sources also contribute to the population’s exposure and the effects on health. Only some of the many studies conducted are specific to the assessment of transport-related air pollution. In addition, the WHO review project did not consider the variety of other pollutants, including carcinogens, emitted by motor-vehicle engines, tyres and brakes.

Both epidemiology and toxicology have advantages and limitations in studying the adverse effects of air pollution on health. The advantage of epidemiological studies is their relevance to real life, in terms of both exposure patterns and coverage of target populations. These studies may include subjects differing in age and health status, performing normal activities in their everyday environment, sometimes for a prolonged period. This characteristic, however, is also a limitation when exposure to pollution from a specific source, such as transport, is considered. The air-pollution mixture experienced by subjects in most epidemiological
studies is generated by a variety of sources, so it is difficult to attribute the effects of exposure on health to a particular source.

Specific epidemiological approaches reduce the problem of identifying the source and help indicate the extent to which transport contributes to the observed adverse effects on health. Each of the following examples of approaches to assessing exposure to transport-related air pollution has specific limitations and strengths. Some studies have concentrated on the components emitted by transport sources, although, in most cases, other processes also generate them. Measured traffic-related combustion pollutants (such as carbon dioxide, nitrogen oxides, benzene, black smoke, soot and PM2.5) or modelled exposure to these pollutants could be used to study possible adverse effects on health. Other studies have explored the spatial or temporal patterns of pollution's composition and level, to link the exposure to transport. Still others have used indirect indicators of transport-related air pollution, such as distance to roads of a certain traffic intensity and type. Several studies have used self-reported traffic intensity, street type or frequency of traffic jams at residences as exposure surrogates. The authors of this book consider these surrogates as subjective measures of exposure. Moreover, some studies have used data on traffic counts on roads nearest a residence, GIS-derived distances of homes from busy roads, or a combination of both, as proxies for exposure to transport-related air pollution. Consideration of the special situation of subjects with occupational exposure also contributes to the evidence on transport-related air pollution.

Toxicological studies comprise experimental studies of human volunteers, different animal species and strains and cell cultures derived from human or animal lungs or airways. Toxicological studies can examine the effects of specific components, such as those from transport emissions, combined exposures to defined pollutants or exposures to ambient mixtures. The human studies are usually limited in duration, concentration range and the assessment of the end-points of the effects of exposure. They often include healthy volunteers, but more recently have also tested subjects with some degree of disease. Most recently, they have employed novel techniques, using particle concentrators, to expose people to concentrated particles of ambient air pollution; several of these studies have focused on the effects of typical transport-related pollutants, such as diesel particles. Many experimental studies have identified the reactive effects of transport-related air pollution in the airways and cardiovascular system, and the sections that follow discuss the possible mechanisms of the effects indicated by these findings.

Both animal studies and cell-culture studies contribute to the body of evidence on the hazardousness of transport-related air pollution. Animal studies permit the investigation of larger concentration ranges, longer exposure times, more end-points and a wider range of pollutants. Extrapolating findings to the human situation, however, is difficult, whether healthy or diseased animals are used. The data reviewed here come from studies on concentrated PM collected from urban air, diesel particles, some gases and VOCs.
Cell-culture studies are useful for experiments to identify hazards and explore the mechanisms of disease development, and may support results from other model systems. The compounds reviewed include different types of particles (such as those emitted from diesel, diesel alternatives or petrol combustion, ultrafine particles or particle mix from urban air), gases, VOCs and PAHs. As with animal experiments, extrapolation from in vitro effects to the human situation is difficult, so the results are most useful in support of other approaches, such as hypotheses of mechanisms and plausibility arguments.

The different end-points of toxicological research – such as inflammation, production of IgE, cell death, DNA damage, fibrinogen and vasoconstriction – are discussed under different disease outcomes, but the reader should remember that toxicological outcomes are very often indicators of biological/pathological responses or of susceptibility, but not necessarily of disease. Further, many of the toxicological studies described below used exposure concentrations of pollutants well above the levels routinely experienced by people in Europe and North America. These concentrations are essential for identifying the hazards of pollutants, but they must be interpreted along with the evidence from epidemiological and exposure-assessment studies to yield a risk assessment.

This chapter summarizes the combined epidemiological and toxicological evidence on the possible links of various indicators of health to air pollution generated by transport, and focuses on the studies that specifically attribute the exposure to transport. The evidence from various types of studies is presented for each of the health outcomes considered, and the combined evidence is used to draw conclusions.

**Mortality**

Epidemiological studies on the adverse effects of air pollution on health most frequently use mortality as an indicator. It is routinely registered and reported in most populations, fairly well standardized and readily available. Numerous studies conducted in Europe, North America and other parts of the world indicate the association of death, particularly from cardiopulmonary causes, with various indicators of air pollution, and point to the important role of fine PM and ozone (WHO Regional Office for Europe, 2003). The effects of both long-term exposures, observed in cohort studies, and short-term (daily) changes in pollution levels have been reported.

Most of the evidence, however, comes from studies on the effects of the pollution mix generated by a variety of sources, which include traffic, communal and industrial combustion, and long-range transport of air pollution. Identifying the effects related specifically to the pollution created by transport is a challenge. In this respect, international and multi-city studies provide an opportunity to link disparate patterns of associations detected in various cities with differences between cities in the contribution of various sources to pollution.
Measured compounds

Studies have investigated the association between transport-related air pollution and mortality. The multinational, EC-funded APHEA2 (Air Pollution and Health: a European Approach 2) project included data from 29 European cities (Katsouyanni et al., 2001). It reported the combined estimate for an increase in the daily number of deaths associated with a 10-µg/m³ increase in daily black smoke concentrations as 0.6% (95% confidence interval (CI): 0.3–0.8%). In the two-pollutant model, considering black smoke with nitrogen dioxide, the estimated effect of black smoke was lower, although it remained significant. The effect was slightly higher in cities with high concentrations of nitrogen dioxide. These results could be interpreted as meaning that nitrogen dioxide might serve as an indicator of the presence of more toxic particles, such as traffic-related particles. In contrast, the National Morbidity, Mortality, and Air Pollution Study (NMMAPS) in the United States found no evidence for modification of the association between PM and daily mortality by nitrogen dioxide (Samet et al., 2000).

Other studies associated black smoke more strongly with respiratory and cardiovascular mortality than with other causes of death (Zmirou et al., 1998; Ballester et al., 2002; Le Tertre et al., 2002). In a case-crossover analysis of a group of men and women with pre-existing chronic obstructive pulmonary disease, who had died during 1990–1995, Sunyer et al. (2000) found that black smoke levels were associated with mortality for all causes. For an increase of 20 µg/m³ (the interquartile change) in daily mean level of black smoke, the odds ratio (OR) adjusted for temperature, humidity and influenza was 1.112 (95% CI: 1.017–1.215). The association was stronger for mortality from respiratory causes (OR: 1.182; 95% CI: 1.025–1.365), but was not significant for cardiovascular causes (OR: 1.077; 95% CI: 0.917–1.264). Also, the risk of dying associated with black smoke was greater for older women admitted to intensive care units and for people with a higher rate of emergency room visits due to chronic obstructive pulmonary disease.

Modelled exposure

Modelled exposures have been used to associate transport-related air pollution with mortality. A recent reanalysis (Schwartz et al., 2002) of the data from the Six Cities study in the United States, using source apportionment techniques, showed that PM2.5 from traffic-related particles has a linear association with mortality. The relationship was a 3.4% increase in mortality per 10-µg/m³ increase in traffic-related PM2.5, compared with no major effects for non-combustion-derived particles, with about half of that effect for PM2.5 in general. An earlier reanalysis of the Six Cities study (Laden et al., 2000) suggests that daily mortality was associated mostly with air pollution from such combustion sources as traffic, coal and residual oil. The study looked at pollution data obtained in the 1980s, when lead could still be used as a tracer for traffic exhausts, so the results are relevant for a
mixture of transport-related air pollution for which lead is a tracer. It is uncertain, however, whether these results are still representative of present-day mixtures.

**Subjective and indirect indicators of exposure**

The distance from a residence to a road was used as an indicator of traffic exposure in both time-series and cohort studies of mortality. A time-series study for Amsterdam estimated increased adverse effects of air pollution on people living close to major roads (Roemer & van Wijnen, 2001). A cohort study in the Netherlands showed an increased risk of death for people living close to major roads, in addition to the impact of the background level of black smoke and nitrogen dioxide (Hoek et al., 2002); the study also found that the effects on cardiopulmonary mortality were the most pronounced. The increased risk of death from cardiopulmonary causes was estimated to be 1.34 (95% CI: 0.68–2.64) per 10-µg/m³ increment of black smoke and 1.95 (95% CI: 1.09–3.51) for living near a major road.

**Occupational exposure**

Several epidemiological studies showed associations between mortality and occupational exposure to emissions from transport, though not all found a statistically significant excess in risk. The studies were both retrospective and prospective.

A retrospective study of the effects of occupational exposure to carbon monoxide on mortality from heart disease (Stern et al., 1988) found that tunnel officers had higher mortality from arteriosclerotic heart disease than people in the general population of New York City (standardized mortality ratio (SMR): 135; 90% CI: 109–168). Tunnel officers also had a higher risk of mortality from arteriosclerotic heart disease than the less-exposed bridge officers, which leads to the hypothesis that motor exhaust might increase the risk of myocardial infarction.

A prospective study on mortality of professional drivers in London – particularly lorry drivers – showed excess deaths from stomach cancer, lung cancer, bronchitis, emphysema and asthma, although there were significantly fewer deaths than expected from all causes and circulatory diseases (Balarajan & McDowall, 1988). This pattern, however, could not be confirmed in taxi drivers. The possible relationship between occupational exposure to vehicle exhaust and cancer risk was studied in a Danish cohort (Hansen, 1993); lorry drivers were followed for cause-specific mortality for a ten-year period, and increased mortality from lung cancer (SMR: 160; 95% CI: 126–200) could be shown, indicating that exposure to diesel exhaust may have contributed to the observed increased risk of lung cancer. Alfredsson et al. (1993) compared mortality from myocardial infarction and other causes for all male bus drivers in Sweden was with that of other employed men over a fifteen-year period; they found a 50% increase in mortality from myocardial infarction among drivers in the counties with the largest cities. Another study identified a significantly increased risk of mortality from ischaemic heart disease in bus drivers working in an area with high traffic
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intensity (Netterstrom & Suadicani, 1993). A cohort study in Rome explored the mortality pattern of taxi drivers exposed to vehicle exhaust (Borgia et al., 1994). An increased SMR was observed for lung cancer (123; 95% CI: 97–154). Owing to statistical uncertainty, however, the results did not clearly indicate an association between the risk of lung cancer and exposure to vehicle exhaust among taxi drivers.

In Italy, Lagorio et al. (1994) compared the mortality in a cohort of petrol-station attendants with that in the regional population. Data analysis indicated some increased risks for oesophageal cancer (SMR: 241; 90% CI: 82–551) and brain cancer (SMR: 195; 90% CI: 77–401); this also applied to the attendants of small stations with a small number of employees and those working at stations with a high number of sales of petrol per full-time employee (SMR: 351; 90% CI: 120–803 and SMR: 266; 90% CI: 105–559, respectively). A historical cohort study of police officers in Rome showed mortality from cardiovascular diseases that was higher than expected, though that from respiratory conditions was lower than expected; no statistically significant excess mortality from lung and other types of cancer was found (Forastiere et al., 1994).

In summary, the few available studies that focus on transport-related air pollution indicate that it contributes substantially to the increased risk of death (particularly from cardiopulmonary causes) from exposure to air pollution.

**Respiratory morbidity**

**Non-allergic respiratory morbidity**

**Measured compounds**

Studies have sought an association between measured transport-related air pollution compounds and non-allergic respiratory morbidity. In the Netherlands, Steerenberg et al. (2001) compared children attending a school located near a busy motorway in Utrecht (mean black smoke levels: 53 µg/m³) with children in suburban areas attending a school located in the middle of a green area (mean black smoke levels: 18 µg/m³). The former showed significantly higher mean levels of inflammatory nasal markers (interleukin-8 (IL-8 – +32%), urea (+39%), uric acid (+26%), albumin (+15%), nitric oxide metabolites (+21%)), as well as a slightly lower (although not significant) peak expiratory flow (−5.3 ml/min). Associations of several inflammatory markers and peak expiratory flow with measured black smoke level were more pronounced in the urban than suburban children.

Janssen et al. (2003) reported on 24 schools located within 400 m of busy motorways in the Netherlands; the study included 2503 schoolchildren aged 7–12 years. PM2.5, soot and nitrogen dioxide were measured in the schools for a year. Non-allergic respiratory symptoms (such as current phlegm and current bronchitis) were increased near motorways with high traffic counts of lorries, not cars. The adverse effects on health were mostly restricted to allergic, sensitized or
bronchial-hyperreactive children. Lung-function changes and bronchial hyper-reactivity, however, were not related to the pollution.

A questionnaire-based survey of 6109 adults who lived close to 55 centrally located air-quality monitoring stations was conducted in Sweden (Forsberg et al., 1997b). Exposure to sulfur dioxide (range of six-month averages: 1.7–16.0 µg/m³) was most consistently related with cough, phlegm, and upper-respiratory symptoms. While exposure to nitrogen dioxide was related significantly to cough and throat or nose irritation, black smoke was not. The strongest associations (statistically significant for all outcomes considered), however, were found between self-reported exposures to traffic and self-reported respiratory health parameters.

A study of 5421 children aged 5–11 years in a 1-km² grid in Dresden, Germany, showed that all measured traffic-related pollutants (such as nitrogen dioxide, carbon monoxide and benzene) increased the risks of morning cough and bronchitis (Hirsch et al., 1999). Impaired lung function was seen only in children with high exposure to benzene, while bronchial hyperreactivity was lower in children exposed to higher levels of nitrogen dioxide and carbon monoxide (Hirsch et al., 1999).

A study of 843 children from 8 Austrian communities measured nitrogen dioxide as a traffic indicator (Studnicka et al., 1997). Increased prevalence of cough (apart from cold), but not bronchitis, was associated with high levels of nitrogen dioxide.

Two Norwegian time-series studies demonstrated an increased risk of hospital admissions for respiratory diseases in days with higher levels of benzene, formaldehyde and toluene—the air pollutants that come mainly from traffic (Hagen et al., 2000; Oftedal et al., 2003).

**Modelled exposure**

Studies using models have also sought an association between transport-related air pollution and non-allergic respiratory morbidity. Exposure to transport-related air pollution at residences was assessed by a combination of measurements and GIS-based models in the Dutch part of the EU-funded international project on the effect of transport-related air pollution on childhood asthma (TRAPCA). In the project, the Dutch birth cohort of 4000 children showed significantly increased risks of ear, nose and throat infections, as well as influenza (Brauer et al., 2002), but a weak association with cough and bronchitis. The German sister study in the TRAPCA project included nearly 2000 children living in Munich. Children with higher estimated exposure to transport-related air pollution showed a statistically significant increase in risk of cough without infections and dry cough at night, but not of respiratory infections (Gehring et al., 2002).

Exposure to soot, benzene and nitrogen dioxide was modelled using traffic counts and GIS data in 7509 children in Munich (Nicolai et al., 2003). Morning cough was more common in children with higher estimated exposure to these
pollutants. After adjusting for hereditary influences and environmental tobacco smoke (including during pregnancy), Pershagen et al. (1995) found positive associations between modelled outdoor nitrogen dioxide concentrations and the respiratory health of young children. The adjusted relative risk (RR) for wheezing bronchitis was 2.7 (95% CI: 1.1–6.8) for the category of high exposure among girls less than 48 months old. This association, however, was not found among boys.

In adults, in Toronto, Canada, modelled exposure to transport-related air pollution was associated with bronchitis, chronic obstructive pulmonary disease, pneumonia and hospital admission (Buckeridge et al., 2002). In Norway, Clench-Aas et al. (2000) found associations between self-reported symptoms and traffic-related pollutant concentrations, estimated by using a source-oriented air-pollution model; in this study, the risk of a number of symptoms was increased by 20–40% for an interquartile range in indicator pollutants: nitrogen dioxide or PM2.5. In a Dutch study, only mild dyspnoea was more prevalent in adults living along busy streets than in residents of quiet areas, while such associations were seen for most respiratory symptoms in children (Oosterlee et al., 1996).

A study by Northridge et al. (1999) on diesel exhaust exposure and lung function among 24 adolescents in Harlem, New York City, showed that 76% of the children had detectable levels of 1-OH-pyrene, a marker of diesel exhaust exposure, 13% (3 children) had a forced mid-expiratory flow (FEF25–75%) of less than or equal to 80% of their predicted measurements, and 17% (4 children) had 80–90% of the predicted value; no relation was apparent between FEF25–75% and urinary 1-OH-pyrene levels. The authors suggested that further studies of larger numbers of adolescents in multiple sites were needed for a better understanding of the relationship between the burden of asthma (exacerbation, predisposition or both) and diesel exhausts.

**Subjective and indirect indicators of exposure**

A number of studies reported the associations of bronchitis and cough with different self-reported and surrogate indicators of exposure to transport-related air pollution. High exposure to transport-related air pollution was associated with:

- increased prevalence of bronchitis in children (Braun-Fahrländer et al., 1992) and adults (Nitta et al., 1993);
- cough in children (Braun-Fahrländer et al., 1992; Bruneckreef et al., 1997; van Vliet et al., 1997; Ciccone et al., 1998) and adults (Nitta et al., 1993); and
- wheeze in children (Venn et al., 2001).

A few studies, however, did not find associations between traffic-related exposures and specific non-allergic symptoms, such as bronchitis and cough in
adults or children (Wjst et al., 1993; Lercher et al., 1995) and wheeze in children (Venn et al., 2000), or did not report effects for these symptoms, even though the data were probably collected. The associations between traffic-related surrogate variables and non-allergic respiratory outcomes are more consistent in children than adults.

**Occupational exposure**
Several studies found an increased risk of respiratory symptoms or disease in people with occupational exposure to vehicle exhausts. A study of highway tollbooth workers reported an increased number of acute irritative symptoms in exposed people, such as headache, nasal congestion, eye irritation and dry throat (Yang et al., 2002). Bus drivers, conductors and taxi drivers in Shanghai showed higher prevalence of respiratory symptoms and chronic respiratory diseases than controls not exposed to vehicle emissions (Zhou et al., 2001). The adjusted ORs were 1.95 for throat pain (95% CI: 1.55–2.46), 3.90 for phlegm (95% CI: 2.61–5.81), 1.96 for chronic rhinitis (95% CI: 1.11–3.46) and 4.19 for chronic pharyngitis (95% CI: 2.49–7.06).

A questionnaire-based study in Denmark (Raaschou-Nielsen et al., 1995) investigated the prevalence of respiratory diseases and other disease symptoms in street cleaners in Copenhagen. The street cleaners showed a significantly higher prevalence of chronic bronchitis and asthma than cemetery workers, who are exposed to lower levels of pollution and served as controls. In the statistical analysis, adjusted for smoking and age, ORs for chronic bronchitis (2.5; 95% CI: 1.2–5.1) and asthma (2.3; 95% CI: 1.0–5.1) were significantly elevated for street cleaners.

A five-year survey of Swiss customs officers investigated the adverse effects on health of occupational chronic exposure to diesel-engine emissions on respiratory mucous membranes (Glück et al., 2003). It showed that officers that cleared diesel lorries had significantly higher goblet cell hyperplasia, with increased metaplastic and dysplastic epithelia, and an increase in leukocyte counts.

**Controlled studies of human exposure**
Using particle concentrators, several studies evaluated the impact of exposure to transport-related air pollution on respiratory symptoms or on indicators of inflammation of the respiratory system. Ghio et al. (2000) exposed 38 healthy exercising subjects, for 2 hours, to either filtered air or concentrated ambient particles (CAPs) originating mainly from motor-vehicle exhaust (CAPs: 207 µg/m³) in an exposure chamber connected to a Harvard particle concentrator. The subjects were unable to identify any increased symptoms following the exposures, and lung function was not changed. Bronchoscopy was performed at 18 hours after exposure, and cell counts displayed a mild increase in neutrophils in both bronchial and alveolar fractions in the people with greatest CAP exposure, as
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compared with those exposed to filtered air. The concentrations of inflammatory mediators IL-6, IL-8, prostaglandin $E_2$, $\alpha_1$-antitrypsin and fibronectin were unchanged. This combination of markers indicates mild airway inflammation. In the quest to identify the chemical components in the ambient PM responsible for inflammatory responses to the exposures, a sulfate/iron/selenium factor was reported as associated with an increase in the percentage of bronchoalveolar lavage neutrophils. These chemical components are usually associated with other pollution sources than traffic (Huang et al., 2003).

In another study, the larger particles were filtered out and the remaining particles, mostly primary particles originating from motor vehicles, were concentrated. Healthy and asthmatic subjects were exposed to these fine CAPs during rest and exercise intervals (Gong et al., 2003). The average PM$_{2.5}$ concentration during exposures was 174 $\mu$g/m$^3$ (range: 99–224 $\mu$g/m$^3$). Relative to filtered air, CAPs tended slightly to worsen cardiorespiratory symptoms four hours and two days after the exposure. The changes were generally small. Inflammatory cells were unchanged, as were concentrations of IL-6 and IL-8. Analysis of induced sputum showed a decrease of columnar epithelial cells by about 50% in healthy and asthmatic subjects at one day after exposure, suggesting that CAPs induced a direct epithelial response. This was not accompanied by an increase in inflammatory cells one day after exposure. Methods that use induced sputum to detect epithelial and inflammatory cell infiltration may be less sensitive than those that use bronchoscopies with lavages and biopsies. As compared with diesel exhaust exposures, the response of healthy subjects in this experiment may be slightly less pronounced (Nordenhäll et al., 2000). An earlier occurrence of a transient inflammatory response, such as that shown by Salvi et al. (1999), cannot be excluded.

Other studies investigated the effect of exposure to freshly generated diesel exhaust by inhalation, or to resuspended diesel exhaust particles by nasal instillation; the effects were assessed by studying indices of airway inflammation in induced sputum, bronchoalveolar lavage and bronchial mucosal biopsies. Four studies that used inhalation of diesel exhaust demonstrated increases in inflammatory parameters (a significant increase in neutrophils, and CD4$^+$ and CD8$^+$ lymphocytes) in bronchoalveolar lavage several hours after exposure (Rudell et al., 1990, 1994, 1996, 1999). Symptoms in the eyes and nose, and unpleasant smells, increased during exposures. Both airway resistance and specific airway resistance increased significantly during exposures to diesel exhaust, as compared with exposures to filtered air. The presence of a ceramic particle trap reduced the particle numbers almost by half. This reduction, however, was insufficient to produce any significant beneficial effect in the population of 12 healthy young people investigated (Rudell et al., 1996). A follow-up study (Rudell et al., 1999) demonstrated that diesel exhaust, as compared with exposure to air, significantly increased the total number of alveolar macrophages and reduced their capacity to ingest yeast particles in vitro; also, the number of neutrophils increased while...
the number of CD3+ and CD25+ lymphocytes decreased. Statistically, the cer-amic particle trap did not result in a significant reduction in the inflammatory response in the airway after exposure to diesel exhaust, compared with exposure to unfiltered exhaust. The insignificant trends all pointed towards a slightly smaller response after exposure to the filtered exhaust. Because the number of subjects in the study was relatively small, the power to detect a protective effect of the use of the ceramic particle trap was also small (Rudell et al., 1999).

In a subsequent study, healthy human subjects, performing intermittent moderate exercise, were exposed for 1 hour to diesel exhaust with 300 μg/m³ PM. Bronchial wash and bronchoalveolar lavage demonstrated increases in neutrophils and B-lymphocytes, as well as increased secretion of histamine and fibronectin. Bronchial mucosal biopsies demonstrated significant increases in neutrophils, mast cells, and CD4+ and CD8+ T-lymphocytes; they also demonstrated up-regulated intercellular adhesion molecule 1 (ICAM-1) and vascular cell adhesion molecule 1 (VCAM-1), as well as increased leukocyte function-associated antigen 1 (LFA-1)-positive cells in the bronchial mucosal tissue. Moreover, significant increases in neutrophils and platelets were demonstrated in peripheral blood after exposure (Salvi et al., 1999, 2000). In a follow-up study, Stenfors et al. (2004) investigated a lower exposure concentration of diesel exhaust (108 μg/m³ PM) in 24 healthy and 15 mildly asthmatic subjects. Diesel exhaust and filtered air exposures were performed in random order, at least three weeks apart. Both mildly asthmatic and healthy subjects showed increased airway resistance of similar magnitude. The healthy subjects showed signs of airway inflammation, with an increase in IL-8 protein and up-regulation of endothelial adhesion molecules. In contrast, the asthmatic subjects did not show any increase in neutrophilic or basal asthmatic inflammation. Instead, they experienced a fivefold increase in the expression of anti-inflammatory cytokine IL-10 in the bronchial epithelium, compared with a reduction by half in the healthy subjects. It was suggested that this cytokine in the asthmatic subjects might possibly enhance later IgE-production and thus enhance the T-helper type-2 cytokine (Th-2) response (Stenfors et al., 2004).

Nordenhäll et al. (2001) published a study supporting that assumption, in which a group of asthmatics who inhaled corticosteroids (on average, 1200 μg per day) were exposed under similar conditions to diesel exhaust with PM10 (300 μg/m³) for an hour. The asthmatic subjects showed an increase in bronchial hyperresponsiveness 1 day after exposure. Bronchial hyperresponsiveness is a key marker and symptom of asthma and relates to its exacerbation. Consequently, this could link the association of enhanced symptoms and exacerbations in asthmatics with periods of higher concentrations of PM in ambient air.

Nightingale et al. (2000) demonstrated an alternative model for diesel exhaust exposure. Cyclone collectors at the exhaust of a stationary diesel engine accumulated exhaust. A commercial powder disperser was then used to resuspend
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the collected diesel powder in an exposure chamber. Ten healthy, non-atopic, nonsmoking volunteers (mean age: 28 years), with normal lung function and absence of bronchial hyperresponsiveness, participated. The subjects were exposed to resuspended diesel particles and clean air, with a four-week interval, in a randomized sequence. The diesel particle concentration was approximately 200 µg/m³ PM10 during the two-hour exposure. Sputum was induced at 4 and 24 hours after exposure. At the time of the first induction after exposure to diesel particles, induced sputum neutrophils and myeloperoxidase increased significantly, as compared with clean air. No changes in lymphocytes, eosinophils or epithelial cells were detected, and lung function and peripheral blood markers of inflammation were unchanged. The level of exhaled carbon monoxide almost doubled after exposure.

Controlled animal exposure studies

Controlled animal exposure studies have also sought an association between transport-related air pollution and non-allergic respiratory morbidity. In the United States, Clarke et al. (1999) treated healthy rats and rats with chronic bronchitis (induced by over 500 mg/m³ sulfur dioxide) with CAPs from Boston air. The CAP treatment (206–733 µg/m³ for 5 hours a day, for 3 days) induced a significant increase in tidal volume (the volume of air inhaled and exhaled at each breath) in both sets of animals and an increase in peak expiratory flow in the bronchitic animals. The CAP treatment also induced inflammation in both groups, as indicated by neutrophil, lymphocyte and protein content of lavage fluid measured 24 hours after the exposure. In a study by the same group, Saldiva et al. (2002) also treated healthy and bronchitic rats with CAPs from Boston air. Short-term exposure again induced a significant inflammatory reaction, as indicated by neutrophils in bronchoalveolar lavage, and this inflammation was dose dependent, but varied according to the CAP composition. Of the parameters measured, only vanadium and bromine concentrations correlated with both neutrophil counts in the bronchoalveolar lavage and in the alveolar walls at the bronchoalveolar junction and periphery. In another study, Zelikoff et al. (2003) treated aged rats with a single dose of PM2.5 CAPs (about 65 µg/m³) from New York City and investigated the effect on them of infection with Streptococcus pneumoniae. The study identified no significant effect in healthy animals treated subsequently with the bacteria. Exposure of previously infected animals, however, led to an increase in bacterial burden and a decrease in the lavageable neutrophils and cytokines from the lungs.

Inflammatory cell-derived oxidants have been implicated in the mutagenic effects of particles (Driscoll et al., 1997), and hydroxyl radicals have been detected in the lungs of rats exposed to diesel exhaust particles (DEPs) (Han et al., 2001). There is also evidence of 8-hydroxy-2’-deoxyguanosine (8-OHdG) adducts in rats chronically exposed to DEPs (Jing et al., 1996; Tsurudome et al., 1999;
Iwai et al., 2000). The source of the hydroxyl radical may be Fenton chemistry (the chemistry that occurs when metal ions in water interact with peroxide), as a consequence of the metals associated with the particles or the accumulation of endogenous iron around the DEPs in the lung tissue (Ghio et al., 2000). Cassee et al. (2002) demonstrated that treating rats with concentrated, freshly generated diesel PM induced oxidative stress, as indicated by the raised glutathione content in the bronchoalveolar lavage fluid.

In studies with various minerals that may be found as components of road dust, Schwarze and co-workers demonstrated the inflammatory potential of stone particles with differing mineral and metal composition (Becher et al., 2001; Schwarze et al., 2002). Of the different stone particles studied, mylonite (median size: 8 µm) caused a stronger inflammation than did quartz 20 hours after exposure, while the mineral plagioclase in feldspar caused the least inflammation. This suggests that some mineral components of road dust present in PM10 could be important in mediating inflammation.

**Mechanistic cell-culture studies**

The mechanisms by which transport-related air pollution induces respiratory morbidity have also been investigated. Inhaled particles encounter the epithelial lining fluid, which contains antioxidants that may alter the effects of these particles. The antioxidants are depleted in the presence of at least some particles, though this has not yet been shown for urban-air particles (Zielinski et al., 1999). As with many other particles, CAPs induce oxygen radical-mediated lesions in cell-free DNA and intact cells, as measured by different methods (Donaldson et al., 1997; Smith & Aust, 1997; Prahalad et al., 2001; Knaapen et al., 2002; Shi et al., 2003). For PM10 or finer particles collected in different locations, non-enzymatic and enzymatic antioxidants reduced the formation of oxidants in most samples. Some studies showed that trivalent cations are associated with the oxidative effect (Upadhyay et al., 2003). In addition to metal ions, organic compounds (such as semiquinone radicals derived from the PM2.5 fraction) seem to be able also to contribute to redox (oxidation–reduction) cycling (Dellinger et al., 2001). Such compounds would be expected on combustion particles, including diesel particles. Two studies showed that the coarse fraction was more potent in damaging DNA than was the fine fraction, but antioxidants ameliorated the particle-induced effect (Greenwell et al., 2002; Shi et al., 2003). Both soluble and insoluble metals seemed to contribute to the formation of radicals. Samples from Hettstedt and Zerbst, Germany, varied in potency over different weeks of sampling, indicating variations in emissions and PM composition over time (Shi et al., 2003). Also, CAPs induced oxidative DNA damage in epithelial cells. The DNA damage was much greater in the presence of particles of residual oil fly ash than in the presence of the CAPs tested (Prahalad et al., 2001). In line with the temporary variations of oxidative potential in the Hettstedt and Zerbst samples,
different PM10 particles from Mexico City exhibited spatial variation of concentration-dependent DNA damage. The particles from the southern part of the city were the least potent, while CAPs from the northern part were the most potent (Alfaro-Moreno et al., 2002). Particles from all regions of the city were found to induce apoptosis in different types of cells. In macrophages, the apoptotic effect of standardized reference material (SRM) 1648 (St Louis particles) seemed to be mediated by the activation of scavenger receptors, not by the soluble fractions of the particles (Obot et al., 2002).

Pro-inflammatory mediators are involved in the development of inflammation, which is an important factor in many diseases. Different epithelial cells and macrophages exposed to ambient particles up-regulate ribonucleic acid (RNA) levels, protein release of pro-inflammatory mediators or both; the pro-inflammatory mediators include IL-8, tumour necrosis factor alpha (TNF-α), IL-1β, IL-6, monocyte chemoattractant protein 1 (MCP-1), granulocyte-macrophage colony-stimulating factor (GM-CSF) and ICAM-1 (Stringer et al., 1996; Kennedy et al., 1998; Fujii et al., 2001; Soukup & Becker, 2001; Huang et al., 2003). The effects of the particles seem to be related to soluble factors in some cases (Huang et al., 2003; Kennedy et al., 1998), but not all (Fujii et al., 2001). In some studies, the coarse fraction elicited a stronger response than the fine fraction. This response was most prominent with the insoluble coarse fraction and was to some extent attributable to endotoxin. Another study found a response to both endotoxin and soluble metal (Bonner et al., 1998). In other cells, however, the PM1.0 fraction elicited a stronger response than did the larger fractions (Huang et al., 2003). Both the coarse and fine fraction of CAPs collected near a busy highway in Downey, California decreased the ratio of reduced-to-oxidized glutathione in macrophages. Also, haem oxygenase 1 was induced by the particles, and this response seemed to depend on PAHs, rather than on metals (Li et al., 2002). Long et al. (2001) compared CAPs from the Boston area, sampled indoors and outdoors; they found that endotoxin appears to play a significant role in eliciting cytokine release, but other components may also be involved. Also, particles in indoor air tended to be more potent than those in outdoor air.

The in vitro data on combined exposure to microbial factors and particles do not render a clear picture. Particles still might increase an inflammatory response to microbes to a degree that damages the lung cells or inhibit the inflammatory response, and thus facilitate microbial attack.

DEPS sampled from different engines and the standard diesel particles, SRM1650, have been used in in vitro studies, such as those of Steerenberg et al. (1998), Takizawa et al. (1999) and Boland et al. (2001). Boland et al. (2001) observed that the SRM1650 particles and their own DEPs elicited similar effects on airway epithelial cells, while DEPs from an engine with an oxidation catalyst seemed less toxic. DEPS induced cell death in normal human bronchial epithelial cells, which were more sensitive to them than the other cell types tested. The
cytotoxicity of DEPs increased with decreasing glutathione content in the cells. Antioxidants, metal chelators and inhibitors of nitrogen oxide synthase reduced DEP cytotoxicity (Matsuo et al., 2003). A comparison of the effects of DEPs indicated that epithelial cells were less protected against oxidant damage than macrophage cells.

The organic fraction of DEPs has induced more cell death in epithelial cells than in macrophages. In macrophages, this response was partly reversed in the presence of the antioxidant N-acetylcysteine (Li et al., 2002). Both the aromatic and the polar fraction appeared to contribute to the response. PAHs, which are abundant on DEPs, increase oxidative stress in several different cell types (Burchiel & Luster, 2001; Garcon et al., 2001). Benzo[a]pyrene increased the oxidative DNA damage induced by ultraviolet light in two different mammalian cell types (Shyong et al., 2003). On the other hand, neutrophils amplified the formation of benzo[a]pyrene-DNA adducts in human blood neutrophils (Borm et al., 1997). PAHs were found to induce apoptosis in lymphocytes, thus exerting an immunosuppressive effect (Yamaguchi et al., 1997; Page et al., 2002). Apoptosis induced by benzo[a]pyrene metabolites seemed to depend on the activation of a receptor and induction of a PAH-metabolizing enzyme. In addition, protein kinases involved in both survival and death pathways inside the cell were activated (Chen et al., 2003; Solhaug et al., 2004). In another study, the apoptosis induced by PAHs was found to be distinguishable from clonal deletion, since some signal proteins involved in clonal deletion were not activated (Ryu et al., 2003). Suppression of mitogenesis of lymphocytes and inhibition of differentiation of monocytes to macrophages have also been reported. These effects seemed to be receptor dependent (Davila et al., 1996; van Grevenynghe et al., 2003).

DEPS and organic compounds from them have elicited the release of proinflammatory cytokines (IL-6, IL-8, GM-CSF IL-1β and eotaxin) from different types of epithelial cells and macrophages (Ohtoshi et al., 1998; Steerenberg et al., 1998; Boland et al., 1999; Bonvallot et al., 2001; Li et al., 2002; Takizawa et al., 2003). In contrast, macrophages (in BALB/c mice) and monocytes (RAW264.7) exposed to DEPs (300 µg/m³) exhibited reductions in protein or RNA levels of TNF-α and IL-12, with no changes in IL-18 (Saito et al., 2002). Li et al. (2002) found that the effect of the extracts depended on the induction of metabolizing enzymes and that the concentration-dependent changes in IL-8 production were modulated by the induction of apoptosis in the epithelial cells. Bonvallot et al. (2001) demonstrated that GM-CSF production was elicited most strongly by the organic fraction of DEPs, while stripped DEPs exhibited only a small effect. The effect appeared to depend on a ROS-sensitive signal pathway. Upon exposure to benzene extracts of DEPs, an immortalized human bronchial epithelial cell line, BEAS-2B cells, produced increased amounts of IL-8 RNA and protein. Also, this study indicated the involvement of the transcription factor NF-κB and ROS (Kawasaki et al., 2001). A DNA microarray analysis revealed the increase of four
oxidant defence-related genes in macrophages exposed to extracts of DEPs. An increase in enzymes possibly related to DNA repair was also noted (Koike et al., 2002).

The finest particles in ambient air, the ultrafine particles, have received attention only recently. Ultrafine CAPs from Los Angeles were found to generate ROS in epithelial cells and macrophages and to induce haem oxygenase, an enzyme involved in defence against ROS. The ultrafine particles and, to a lesser extent, the fine ones localized to mitochondria, where they might cause further damage (Li et al., 2003). In the Netherlands, ultrafine particles (50 µg/ml) induced considerably less IL-6 release from macrophages than the coarse fraction, and less than the fine fraction. Ultrafine particles did not affect CD11b expression, yeast-induced oxidative burst and phagocytosis, while these functions were reduced in the presence of the coarse fraction and, to a lesser extent, the fine fraction. The effects of the coarse and fine fractions seemed to be partly mediated by endotoxin (Becker et al., 2003). Similar samples from Biltoven, the Netherlands induced a concentration-dependent increase (up to 400 µg/ml) in IL-8 and IL-6 release from A549 cells. Although there was no significant difference between the size fractions’ ability to elicit IL-8 release, the ultrafine particles were most potent in inducing IL-6 release. At higher concentrations, the coarse and ultrafine particles were apparently more toxic than the fine fraction. Surprisingly, ultrafine particles were not able to induce cytokine release from primary rat type-2 cells, in contrast to the coarse and fine fraction or St Louis dust (Hetland et al., 2004). In New York, human bronchial epithelial cells responded to ultrafine ambient particles (up to 100 µg/ml) with an increased release of GM-CSF (Reibman et al., 2002). The ultrafine particles appeared to exert a stronger effect than the larger size fractions, and the effect varied with collection period. Activation of protein kinases involved in survival and death signalling seemed necessary for the increased release of GM-CSF. Another study, using ultrafine carbon and epithelial cells, described increases in certain transcription factors and the involvement of factors associated with apoptosis (Timblin et al., 2002). Stone et al. (2000) observed that the ultrafine carbon effect was related to the influx of extracellular ionic calcium.

In some areas, the use of studded tyres leads to greatly increased abrasion of the road pavement, which results in substantial increases in PM10 and a much smaller increase in PM2.5. Most of the abrasion-generated PM consists of mineral particles (Hetland et al., 2000). Such particles include a variety of different minerals, such as quartz and amphiboles. Hetland et al. (2000) and Becher et al. (2001) showed that a mineral type, such as plagioclase, had little potential to induce the release of pro-inflammatory cytokines in different human and rat epithelial cells and macrophages. In contrast, stone types, such as mylonite and gabbro, and PM from a tunnel in which the pavement consisted of these stone types, were very efficient in eliciting pro-inflammatory responses. Though some of the minerals in these stones were rich in metals and produced some ROS, these
factors could not explain the differences in inflammatory potential (Hetland et al., 2001). Thus, some pavement abrasion particles may elicit inflammation in the lungs. Other known components of dust generated by road transport are tyre debris, including latex, and vehicle wear particles, but no in vitro information on them is available.

The antioxidant defence system of such compounds as certain vitamins and the radical-removing enzymes, such as superoxide dismutase, may be important markers of susceptibility. The growing evidence of the involvement of ROS in particle effects corroborates this notion. ROS, such as those generated by particles, might exert their effects at the cell surface by lipid peroxidation, through activation of nicotinamide adenine dinucleotide phosphate hydrogen oxidase or other enzymes, or stimulation of mitochondrial ROS production; in these two cases, the effects of ROS might be secondary to some other reactions. These reactions may involve the activation of certain cell surface receptors, downstream signalling through different types of protein kinases (such as tyrosine kinases and mitogen-activated protein kinases) and transcription factors (Samet et al., 1999; Sauer et al., 2001; Baulig et al., 2003; Brown et al., 2004). Secondary effects might be elicited, including autocrine effects of released mediators. The components of the surfactant are other factors that modulate the inflammatory response to particles influencing susceptibility (Hohlfeld et al., 2002–2003). Höhr et al. (2001) observed a reduced release of inflammatory cytokines, when epithelial cells and macrophages were exposed to particles in the presence of a phospholipid component of surfactant. Surfactant proteins are also deemed important for lung defence, and reduced release of these proteins would conceivably exacerbate pathological conditions in the lungs (Bridges et al., 2000; Hohlfeld et al., 2002–2003; Augusto et al., 2003). Oxidant gases (such as ozone and nitrogen dioxide) and ROS (hydrogen peroxide and ferrous chloride) have been shown to reduce the normal activity of surfactant proteins – either the antimicrobial activity of surfactant protein (SP) A/D or the reduction in surface tension by the concerted activity of SP-B, SP-C and SP-A (Putman et al., 1997; Wu et al., 2003).

Conclusions

In summary, rather substantial evidence points to transport-related air pollution's increasing the risk of non-allergic respiratory symptoms and suggests that inflammatory processes are related to exposure to such pollution. Fine PM (especially black smoke) and ozone were associated with the risk of morbidity, and similar outcomes were seen in studies that used different indicators of exposure. All size fractions of PM and different types of transport-related air pollution elicited inflammatory responses, which are associated with different diseases. In experimental studies, the organic fraction of DEPs appeared to produce more important reactive responses than did other types of particles. In general, however,
the different effects of various particle types could not be attributed to specific components of PM. Antioxidants and possibly surfactant components may be important determinants of susceptibility.

**Allergic illness/symptoms including asthma**

**Measured and modelled exposure**

Studies have sought an association between transport-related air pollution and allergic respiratory illness or symptoms. Using models for exposure, Brauer et al. (2002) detected associations with increased incidence of asthma in the first two years of life. Although not statistically significant, this association was in general robust, because the ORs were not altered to any great extent by the inclusion of potential confounding variables in the regression models or the sensitivity analyses. One must consider that the children observed were too young to have a reliable diagnosis of asthma, but the determination of wheeze, and its association with transport-related air pollution (also detected in this study), supports this diagnosis. The German part of the TRAPCA project, in which only a few asthma cases were reported, however, found no association of asthma incidence with transport-related air pollution (Gehring et al., 2002).

Considering wheeze as a possible key asthma-related symptom, and less related to doctors’ diagnoses, does not make the picture clearer. While some studies found positive associations between traffic surrogate variables and the prevalence of wheeze in children (Oosterlee et al., 1996; Studnicka et al., 1997; Venn et al. 2001; Nicolai et al., 2003) and adults (de Marco et al., 2002), others did not (Hirsch et al., 1999; Wyler et al., 2000; Venn et al., 2000). The reasons for these inconsistent results remain unclear. Even within a single study, results on asthma and wheeze are inconsistent.

Other studies of adults also give inconsistent results. While some found increased reporting of asthma in subjects exposed to transport-related air pollution (Edwards et al., 1994; Duhme et al., 1996; van Vliet et al., 1997; Guo et al., 1999; Lin et al., 2002; Zmirou et al., 2004), others found no increased prevalence (Braun-Fahrländer et al., 1992; Nitta et al., 1993; Lercher et al., 1995; Waldron et al., 1995; Ciccone et al., 1998; Wilkinson et al., 1999).

No consistent association was found in the few studies that explicitly analysed associations between measured or modelled traffic exposure (or both) and hay fever. Studies in metropolitan areas (Hirsch et al., 1999; Lee et al., 2003) or urban metropolitan areas (Krämer et al., 2000) found increased reporting of hay fever, in relation to a high level of exposure to transport-related air pollution. Several other studies conducted in large communities, however, reported no statistically significant associations with hay fever (Forsberg et al., 1997a; Wyler et al., 2000; Janssen et al., 2003; Nicolai et al., 2003). Even when the methods of the International Study of Asthma and Allergies in Childhood (ISAAC) were
applied in two cities in one country, the results on hay fever and traffic exposure were different (Hirsch et al., 1999; Nicolai et al., 2003).

With the review restricted to studies that used measured or modelled exposure to indicators of transport-related air pollution and allergic sensitization assessed by antibody measurements or skin-prick testing, the overall results remain inconsistent. While some studies reported a positive association between allergic sensitization and exposure to nitrogen dioxide (Krämer et al., 2000; Wyler et al., 2000; Janssen et al., 2003) others did not (Hirsch et al., 1999; Nicolai et al., 2003).

**Controlled exposure studies**

Important insights can be gleaned from a tunnel study in which subjects were exposed for a relatively short time to a high concentration of a real traffic-related pollution mix; 20 allergic asthmatic subjects were exposed during rest for 30 minutes in a busy city road tunnel, to study the effects of air pollution on allergen responsiveness (Svartengren et al., 2000). In the tunnel, the median levels of pollutants were 303 µg/m³ nitrogen dioxide (range: 203–362 µg/m³), 170 µg/m³ PM10 (range: 103–613 µg/m³) and 95 µg/m³ PM2.5 (range: 62–218 µg/m³). Four hours after exposure, an allergen provocation was performed and lung function responses measured. Subjects exposed to nitrogen dioxide levels of 300 µg/m³ or more had a significantly greater early reaction following allergen exposure, as well as lower lung function and more asthma symptoms during the late phase, compared to the reference exposure. Subjects exposed to 100 µg/m³ PM2.5 or more also had a slightly increased early reaction, compared to control subjects. It was suggested that the enhanced response of the asthmatics to the allergens in the tunnel was related causally to the nitrogen dioxide and PM2.5 content of the tunnel air pollution. A response to other potentially reactive compounds generated by motor vehicles is possible.

A series of studies by Diaz-Sanchez and colleagues have clearly indicated a modulating effect on the nasal mucosa by DEPs instilled at several hundred micrograms locally. Because the local deposition of PM per surface area in the nose is clearly high, the data are very interesting. Also, the data suggest that DEPs potentiate an allergy-related (Th-2) response, IgE production, and neo-sensitization in human nasal mucosa. Four days after a local nasal instillation challenge with 0.30 mg DEPs, a significant increase in nasal IgE, but not in other immunoglobulin classes, was demonstrated (Diaz-Sanchez et al., 1994). The number of IgE-secreting cells in nasal lavage also increased, but no increase was observed in IgA-secreting cells. Healthy, nonsmoking human volunteers were exposed to DEPs by intranasal instillation, and cytokines in the nasal lavage were estimated after 18 hours by an indirect approach using messenger RNA (Diaz-Sanchez et al., 1996). Before the challenge, most subjects had detectable messenger RNA levels of only a few cytokines (interferon gamma (IFN-γ), IL-2 and IL-13). After
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the challenge, the levels of these three and a number of additional cytokines (IL-4, IL-5, IL-6 and IL-10) increased. An increase in such nasal cytokine expression after exposure to DEPs could again contribute to enhanced local IgE production.

Diaz-Sanchez et al. (1997a) also suggested that a nasal provocation with DEPs could act as an adjuvant to an allergen. In a group of ragweed-sensitive subjects, a nasal challenge was performed with 0.30 mg DEPs, the ragweed allergen Amb a I or both. The provocation with ragweed caused an increase in IgE and IgG4, as well as ragweed-specific IgE in the nasal lavage. A challenge with allergen and DEPs induced a sixteenfold greater increase in ragweed-specific IgE than DEPs alone. DEPS alone increased total IgE but, in combination with the allergen, antigen-specific IgE increased, as did the expression of Th-0 and Th-2 type cytokines: IL-4, IL-5, IL-6, IL-10 and IL-13. These studies suggest that DEPs can enhance B-cell differentiation. Fujieda et al. (1998) obtained similar results. A nasal challenge with a combination of DEPs and the allergen induced larger ragweed-specific IgE and IgG4 responses, compared with DEPs alone, but with similar total IgE levels (Diaz-Sanchez et al., 1997b). The cytokine pattern also changed, favouring allergic sensitization. DEPs and natural allergens may have a synergism that is a key to increasing allergen-induced respiratory allergic disease. Recently, this group demonstrated a role for genetic polymorphism in DEP-enhanced allergen response (Gilliland et al., 2004). This was associated with a polymorphism in the detoxifying enzyme glutathione S-transferase M1 and suggests a clearer focus for new genetic aspects.

Chronic inflammation in mice, caused by multiple installations of DEPs, showed similarities to asthmatic inflammation – inflammation of the airway wall, goblet cell hyperplasia, eosinophils and airway narrowing – even in the absence of a concomitant allergic stimulus (Sagai et al., 1996). Concomitant exposure to DEPs enhanced the allergic inflammatory response in the airways of mice primed with ovalbumin (OVA); this appeared as increased local production of cytokines, such as IL-5 and GM-CSF, as well as increased infiltration of eosinophils and lymphocytes into the airways, along with goblet cell hyperplasia (Takano et al., 1997). Similar adjuvant effects for IgG and IgE were found with the more common allergen timothy grass pollen (Steerenberg et al., 1999). Anthracene, fluoranthene and benzo[a]pyrene in DEPs also enhanced the IgE response to model allergens (Kanoh et al., 1996). Studies with instilled carbon black and DEPs, and their effect on OVA-specific IgE and IgG in a rat instillation model, demonstrated that the particles are more important than the organic component, as the effect could be mimicked by carbon black (Al-Humadi et al., 2002). In studies of mice, both CD4+ and CD8+ lymphocytes drove these effects, since depletion of either subset decreases the extent of the adjuvant effect of DEPs on OVA allergy (Lovik et al., 1997). In the mouse footpad/popliteal lymph node model, the dominant role of particles over organics was again demonstrated, since carbon black had complementary qualities similar to those of DEPs, and yet a very
low level of organic contamination (Lovik, et al., 1997). Selective depletion of organics from DEPs resulted in complex changes in the ability of DEPs to affect Th-1 and Th-2 pathways following intranasal instillation, and different organic fractions modulated the two different pathways. Whole body plethysmography identified the role of GM-CSF in mediating DEP-induced airway hypersensitivity to acetylcholine in mice (Ohta et al., 1999). The hyperresponsive effect was mediated by muscarinic receptors and could be decreased by a beta-2-adrenergic agonist. DEPs may act as a carrier for allergens and deliver them to the lungs, and so enhance any adjuvant effects (Sagai, et al., 1996; Knox et al., 1997).

An exposure of basophils to DEP extract and an allergen resulted in an increase in IL-4 release. DEP extract and allergen were not synergistic in their effects, but the effect of the former lasted longer than that of the latter (Devouassoux et al., 2002). Kepley et al. (2003) did not observe a release of IL-4 from basophils when exposed to DEPs extract alone, but observed an increased release in the presence of PAHs, when the IgE receptors were cross-linked. The particle component and the organic fraction of DEPs may exert somewhat different effects, but combined they stimulate a Th-2-mediated response with the production of allergen-specific IgE and an eosinophilic inflammation (Ma & Ma, 2002).

Conclusion
Rather substantial evidence from controlled human exposure studies and animal experiments indicates that transport-related air pollution can increase the risk of allergy development and exacerbate allergic reaction. The evidence from population studies to support this observation is weak, however, because the results of several available studies that focus on transport-related air pollution are inconsistent. Further, identifying the component(s) of transport-related air pollution responsible for the allergic responses is still not possible, though nitrogen dioxide and ozone have been linked to these responses.

Lung function
Only two studies reported an association between lung function and transport-related air pollution. A Dutch study of children aged 7–12 years showed a significant association between lung function and the density of lorry traffic in the area of residence, but only a weak association with total traffic volume (Brunekreef et al., 1997). Living close to motorways and measured high concentrations of black smoke in schools were also associated with diminished lung function. These effects were stronger in girls than in boys. The ISAAC study of children in Dresden aged 5–7 and 9–11 years measured transport-related air pollution (nitrogen dioxide, carbon monoxide and benzene) in school areas and residential areas, based on pollution means in 1-km² grid cells, and found lower lung function in children with a high level of exposure to benzene, but no such association for carbon monoxide or nitrogen dioxide (Hirsch et al., 1999).
A few studies investigated the relation of bronchial hyperreactivity to surrogate variables for traffic-related pollutants, and found no positive associations. Hirsch et al. (1999) reported a statistically significant negative association between bronchial hyperreactivity and nitrogen dioxide and carbon monoxide in a large study, while a further study on children in Munich did not find any association between bronchial hyperreactivity and traffic volume in residential areas (Wjst et al., 1993).

**Cardiovascular morbidity**

**Measured compounds**

Several time-series studies assessed the association of daily changes of urban, mostly traffic-related air pollution with the variation in hospital admissions for cardiovascular diseases. These associations, with black smoke used as the pollution indicator, were especially evident in elderly people (Atkinson et al., 1999) in the hotter semester (Ballester et al., 2001). Poloniecki et al. (1997) did not find any detectable association with all circulatory diseases and angina, but observed a significant association with acute myocardial infarction. In eight large European cities in the APHEA2 project (Le Tertre et al., 2002), the pooled percentage increases associated with a 10-µg/m³ increase in black smoke concentrations were 1.1% (95% CI: 0.4–1.8%) in cardiac admissions for people of all ages, 1.3% (95% CI: 0.4–2.2%) in cardiac admissions for people aged over 65 years, and 1.1% (95% CI: 0.7–1.5%) in ischaemic-heart-disease admissions for people over 65. The effect of black smoke was unchanged when the analysis controlled for carbon monoxide, but somewhat reduced when it controlled for nitrogen dioxide.

A case-crossover study of hospital admission for myocardial infarction in Rome showed statistically significant effects for exposure to nitrogen dioxide and marginally significant effects for exposure to carbon monoxide (D’Ippoliti et al., 2003). Transport is the main source of both pollutants in the city.

A study in Helsinki, where traffic is a major source of particulate air pollution, found that increases of fine and ultrafine PM concentrations increased the risk of ischaemia two days after exposure, as indicated by ST-segment depressions on electrocardiograms (ECG) (Pekkanen et al., 2002).

A recently published panel study of nine healthy state troopers in North Carolina investigated the possible physiological effects of in-vehicle, roadside and ambient PM2.5 before, during and after a patrol shift (Riedecker et al., 2004). In-vehicle exposure was associated with a decrease in lymphocyte count (–11% per 10 µg/m³) and increased red blood cell indices (+1% mean corpuscular volume), increased neutrophils (+6%), increased C-reactive protein (+32%), increased von Willebrand factor (+2%), increased length of the heart beat cycle next morning (+6%), and increased heart rate variability and ectopic beats (+20%). The authors concluded that in-vehicle PM2.5 might cause pathophysiological changes
that involve inflammation, coagulation and cardiac rhythm. While the finding on blood inflammatory markers is quite consistent with previous results on the effects of air pollution, as summarized by the WHO Regional Office for Europe (2003), the results on increased heart rate variability are not.

**Indirect exposure indicators**

A recent paper assessed whether time spent in traffic can trigger myocardial infarction (Peters et al., 2004). This prospective case-crossover study included 691 subjects who survived myocardial infarction for at least 24 hours. The time spent in traffic one hour before the onset of myocardial infarction was associated with the increased risk (OR: 2.9; 95% CI: 2.2–3.8). Time spent in cars, public transport and on bicycles was consistently connected with an increased risk. The authors concluded that transient time spent in traffic might pose a risk to people vulnerable to myocardial infarction. Other traffic-related factors than transport-related air pollution, however, might have contributed to the elevated risk observed in this study.

**Occupational exposures**

A number of studies investigated the risk of coronary heart disease in professional drivers. This risk seems to be elevated, but the underlying causes are not well understood. Studies that specifically investigate the role in coronary diseases of occupational exposure to motor exhaust are rare. A case-referent study investigated the risk of myocardial infarction from occupational exposure to motor-vehicle exhaust, other combustion products, organic solvents, lead and dynamite (Gustavsson et al., 2001). The RR of myocardial infarction was elevated for people exposed to combustion products from organic material, but the previously demonstrated increased risk of myocardial infarction in professional drivers, especially bus drivers, could not be clearly confirmed. Individual risk factors and the psychological demands of the profession may explain a large part of the increased risk in this group, making it difficult to assess the additional risk due to the increased exposure to transport-related air pollution (Bigert et al., 2003).

**Controlled exposure studies**

Several recent studies examined the response of the cardiovascular system to exposure to CAPs. A significant increase in blood fibrinogen was observed in subjects exposed to CAPs, as compared with controls exposed to air, but no evident dose–response relationship was noted (Ghio, 2000; Harder et al., 2001). No effect on lymphocyte subsets in peripheral blood was found but increased blood fibrinogen was associated with a copper/zinc/vanadium factor. This gives some support to the hypothesis that metals, which are also present in transport-related air pollution, may be important in the reactive and cardiorespiratory responses to air pollution.
Gong et al. (2003) reported on controlled exposures to concentrated fine particles, mostly from motor vehicles, in healthy and asthmatic subjects. In summary, exposures to CAPs elicited different biological end-points, with statistically significant differences between CAPs and filtered air. The observed changes in blood parameters and heart rate variability were consistent with systemic (rather than respiratory) effects of exposure.

Brook et al. (2002) measured cardiovascular changes due to exposure to PM and ozone. The subjects were exposed for two hours on two separate occasions with at least a two-day interval between exposures; they were exposed once to filtered air and once to CAPs with about 150 µg/m³ PM2.5 and 240 µg/m³ ozone. Within 10 minutes after the exposure to the pollutants, a significant vasoconstriction occurred in the brachial artery, compared with the exposure to filtered air.

**Controlled animal response studies**

Gordon et al. (1998, 2000) used normal rats and rats treated with monocrotaline (MCT) to investigate the effects of CAPs on the pulmonary and cardiovascular systems. The CAP treatment induced an increase in the percentage of neutrophils and a decrease in the percentage of lymphocytes in the blood of both groups of animals, which is indicative of systemic inflammation. Neither group showed changes in cardiac rhythm, and the changes in cardiac function observed in the study were not statistically significant.

In experiments with dogs, Godleski et al. (2000) observed the effects of CAPs from Boston air on the cardiac system. The findings are complex, but in essence they suggest that CAPs disturbed autonomic balance, as indicated by changes in heart rate variability, either directly or through the respiratory system. The study also involved occlusion of the coronary artery and found that exposure to CAPs decreased the time from occlusion to ST-segment elevation in an ECG. The authors suggest that these changes could be caused by endothelial dysfunction, altered cardiac metabolism and responses to organic aerosol components. The study identified considerable variation between animals and in the same animal from day to day, possibly owing to variations in particle composition and dose.

Several experimental studies have shown that a small portion of ultrafine particles of various materials can enter the bloodstream, following deposition in the lungs (Nemmar et al., 2001, 2002; Kreyling et al., 2002). In an early study, chronic exposure to high levels of diesel soot produced marked thickening of the pulmonary artery wall in exposed rats, compared with controls (Vallyathan et al., 1986), although no mechanism was advanced. In a hamster model, instilled DEPs caused an increase in peripheral thrombus formation and platelet aggregation in vivo (Nemmar et al., 2003). The doses used produced pulmonary inflammation, so it was impossible to determine whether the mechanism was inflammation-driven or a consequence of bloodborne particles. Rats exposed by inhalation to resuspended diesel soot showed an elevation of plasma endothelin-3 at 36 hours.
Health effects of transport-related air pollution

after exposure (Vincent et al., 2001); a similar exposure to carbon black had no effect. Studies have been conducted on rats pretreated with MCT, to induce a model of pulmonary hypertension. Such animals demonstrate hypertrophy of the media of the pulmonary muscular arteries, but this was not affected by concentrated, freshly generated, DEPs (Cassee et al., 2002). The MCT-treated animals did demonstrate an increase in bromodeoxyuridine labelling of Clara cells in the terminal bronchioles, which was enhanced by treatment with DEPs. This treatment also induced a significant increase in plasma fibrinogen (Cassee et al., 2002).

Accumulated experimental evidence suggests that combustion-related particles can penetrate to the bloodstream and can directly affect the cardiovascular system, but there is no evidence that particles specifically from transport-related air pollution become bloodborne. The effects of transport-related air pollution particles on the cardiovascular system could also be caused by inflammatory mediators that originate in the lungs. Such particles could also affect the regulation of the nervous system.

Conclusion

Only recent studies have focused on PM and explored the effects of exposure to transport-related air pollution on diverse indicators of cardiovascular diseases or functions of the cardiovascular system. While an epidemiological study reports a strong, significant increase of risk of myocardial infarction following exposure, other studies and the experimental evidence show changes in various cardiovascular parameters without providing a consistent explanation of the possible mechanisms involved.

Cancer

Measured or modelled compounds

Several Scandinavian studies on cancer used nitrogen dioxide or benzene as indicators of transport-related air pollution. In a study of Stockholm residents, Nyberg et al. (2000) found that the risk of lung cancer was associated with retrospectively assessed long-term exposure to transport-related air pollution, indicated by nitrogen dioxide averaged over 30 years. An RR of 1.2 (95% CI: 0.8–1.6) was found for the top decile of exposure, adjusted for tobacco smoking, socioeconomic status, residential radon and occupational exposures. The authors suggest a latency period, since the RR for the top decile of average exposure to traffic-related nitrogen dioxide 20 years earlier was higher: 1.4 (95% CI: 1.1–2.0).

Nafstad et al. (2003) reported the results of the analysis of data from a twenty-seven-year follow-up study on cardiovascular risk factors among 16 209 men (aged 40–49 years in 1972/1973) from Oslo. Those data were linked with information from the Norwegian cancer and death registers. To derive average annual air pollution levels at the participants’ home addresses from 1974 to 1998, concentrations
of nitrogen oxides and sulfur dioxide from industry and from heating and traffic sources were estimated, using a combination of models and monitoring data. Controlling for age, smoking habits and length of education, the adjusted risk ratio for developing lung cancer was 1.08 (95% CI: 1.02–1.15) per 10-µg/m³ increase in average concentration of nitrogen oxides at a home address between 1974 and 1978. The corresponding figure per 10-µg/m³ increase in sulfur dioxide was 1.01 (95% CI: 0.94–1.08).

Studies of children are less consistent than those of adults in indicating the association of cancer risk with exposure to transport-related air pollution or air pollution in general.

A study by Feychting et al. (1998) reported an increasing risk of all types of cancer, leukaemias and tumours of the central nervous system with increasing indicators of exposure to transport-related air pollution, though the increase in risk was not significant in most exposure categories. The RR, however, achieved a statistically significant level (3.8; 95% CI: 1.2–12.1) in a small group of children with the largest exposure, indicated by a nitrogen dioxide level over 80 µg/m³, compared with that for children exposed to transport-related air pollution below median concentrations.

For estimated exposures to benzene or nitrogen dioxide during pregnancy or childhood, a study by Raaschou-Nielsen et al. (2001) of Danish children did not observe an increase in the risk of developing leukaemia, tumours of the central nervous system or all selected types of cancer combined. The risk of lymphomas increased by 25% (P (for trend) = 0.06) and 51% (P (for trend) = 0.05) for a doubling of the concentrations of benzene and nitrogen dioxide, respectively, during pregnancy. Analyses by morphologic subtype showed that the increased risk of lymphomas associated with exposure to benzene and nitrogen dioxide in utero was restricted to Hodgkin’s disease. In the adjusted analysis, the highest categories of exposure to benzene and nitrogen dioxide resulted in 4.3 and 6.7 times higher risks of Hodgkin’s disease, respectively, than those of the lowest exposure category.

**Indirect indicators of exposure**

Harrison et al. (1999) studied living close to (within 100 m of) a main road or a petrol station in relation to the onset of childhood leukaemia in the United Kingdom. In comparison with the incidence of leukaemia in the general population, that among those living close to transport-related air pollution sources was slightly elevated: the RR was 1.16 (95% CI: 0.74–1.72) for those living close to a road and 1.48 (95% CI: 0.65–2.93) for those living close to a petrol station, but neither reached the level of statistical significance. In a recently reported Californian study, no increased cancer risks (for all cancer sites combined or leukaemia) were found among the offspring of mothers living in areas with a high density of traffic (Reynolds et al., 2004).
Occupational exposure

Most epidemiological studies on the adverse effects on health of occupational exposure to transport-related air pollution have been performed for professional drivers, such as lorry, bus and taxi drivers. A major population-based case–control study conducted in the 1980s in the United States investigated the association between employment with potential exposure to motor exhaust and the risk of bladder cancer (Silverman et al., 1986). A statistically significant trend in cancer risk with increased duration of lorry driving was observed. This risk was highest for lorry drivers and delivery staff, and lower for taxi and bus drivers, indicating, overall, a role for exposure to motor exhaust in bladder cancer etiology.

In another major study, a pooled analysis of two case–control studies on lung cancer in Germany investigated the association between diesel motor emissions and elevated risk of lung cancer (Brueske-Hohlfeld et al. 1999). An elevated OR adjusted for smoking was found for professional drivers (1.43; 95% CI: 1.23–1.67). An even higher risk was found for the subgroup of heavy equipment operators (OR: 2.31; 95% CI: 1.44–3.70). The risk of lung cancer for tractor drivers increased with duration of employment and reached statistical significance for exposures above 30 years (OR: 6.81; 95% CI: 1.17–39.51). Drivers in other occupations exposed to traffic-related diesel motor exhausts also showed an elevated OR for lung cancer (1.53; 95% CI: 1.04–2.24).

Several studies investigated the risk of cancer in Danish professional drivers. Based on a nationwide case–control study, Hansen et al. (1998) reported an increased risk of lung cancer among professional drivers. Taxi drivers showed the highest risk (OR: 1.6; 95% CI: 1.2–2.2); bus and lorry drivers had a somewhat lower but still increased OR value (1.3; 95% CI: 1.2–1.5). The risk of lung cancer increased with the duration of employment as a driver, with a highest OR of 3.0 (95% CI: 1.2–9.8) for more than 10 years as an active taxi driver. Another study, based on a large retrospective cohort (Soll-Johanning et al., 1998), reported an increased incidence of lung cancer in bus drivers and tramway employees (standardized incidence ratio (SIR): 1.6; 95% CI: 1.5–1.8). It also reported increased incidence of other types of cancer – such as pharyngeal (SIR: 1.9; 95% CI: 1.2–2.8), kidney (SIR: 1.6; 95% CI: 1.3–2.0), liver (SIR: 1.6; 95% CI: 1.2–2.2) and bladder cancer (SIR: 1.4; 95% CI: 1.2–1.6) – in bus drivers and tramway operators employed for more than three months. A more recent case–control study conducted by the same research group found a decreasing risk of lung cancer with increasing years of employment as a bus driver (RR: 0.97; 95% CI: 0.96–0.99), when the analysis controlled for confounders relevant to lung cancer risk, such as smoking (Soll-Johanning et al., 2003). Thus, taking the findings of the two studies together, one cannot attribute the excess risk of lung cancer observed among bus drivers to employment as such. For the other types of cancer for which increased risks were observed in the retrospective study (Soll-Johanning et al., 1998), no firm conclusion could be drawn based on the more recent case–control study, which investigated cases of lung and bladder cancer only.
Urban drivers – such as taxi drivers and short-haul lorry drivers – were reported to have a higher risk (RR: 2.0; 95% CI: 1.5–2.6) of lung cancer when they were compared with colleagues from rural areas of Sweden (Jakobsson et al., 1997). For the short-haul lorry drivers, the RR remained high, even after adjusting for smoking. The contribution of exposure to an increased risk of lung cancer was also indicated by a ten-year follow-up study on the mortality of lorry drivers (SMR: 160; 95% CI: 126–200) (Hansen, 1993), as well as by an exposure–response analysis, adjusted for smoking, among workers in the road-haulage industry (Steenland et al., 1998). The latter study was based on estimates of unknown past exposures and therefore should be characterized as rather exploratory. A recent major study on the incidence of cancer and mortality among lorry drivers exposed to diesel exhaust in Sweden (Jarvholm & Silverman, 2003) indicated an increased incidence of lung cancer (61 cases versus 47.3 expected) and prostate cancer (124 cases versus 99.7 expected). The higher mortality in the drivers was statistically significant for lung cancer only.

Many of the available epidemiological studies on the risk of cancer, particularly lung cancer, in professional drivers lack information on subjects’ smoking habits; this complicates the interpretation of their results. The studies that could control for confounding by smoking (such as Damber & Larsson, 1985; Jakobsson et al., 1997; Brueske-Hohlfeld et al., 1999), however, indicate that the occupational exposure of drivers to exhaust fumes may affect the elevated risk of lung cancer.

Studies that investigated the links between transport-related air pollution and cancer included other professional groups besides drivers. Two major early studies investigated the risk of lung cancer from exposure to diesel exhaust among railroad workers (Garshick et al., 1987, 1988). Both indicate that such exposure may result in an elevated risk of lung cancer. A study of traffic police in Rome (Forastiere et al., 1994) suggested an increased risk of various cancer types: cancer of the colon, male breast, endocrine glands, bladder and kidney, and non-Hodgkin’s lymphoma, but not lung cancer.

A study of another group, road construction workers, indicated a statistically significant increase in the risk of lung cancer (adjusted for smoking) in workers exposed to diesel engine exhaust (Brueske-Hohlfeld et al., 2000). Data from the Danish census in 1970 identified more than 4000 men (mostly petrol station attendants) as having indicated retail sale of oil and petrol as their employment. A significant excess of respiratory cancer (SMR: 158; 95% CI: 125–200) could be shown when compared with all men gainfully employed at the time of the census (Grandjean et al., 1991).

**Occupational exposures and biomarkers**

A few studies on the effects of exposure to air pollution have considered DNA damage as an end-point, particularly “bulky” DNA adducts, which are related to exposure to aromatic compounds, including PAHs. Studies in western Europe
have shown that the levels of white blood cell DNA adducts were higher among subjects heavily exposed to air pollutants. This has been observed in police officers (Peluso et al., 1998), newspaper vendors exposed to urban traffic (Pastorelli et al., 1996), residents in a highly industrialized area in the United Kingdom (Farmer et al., 1996) and bus drivers in Denmark (Nielsen et al., 1996).

Based on the assumption that oxidative DNA damage might be involved in the increased risk of cancer associated with exposure to urban air pollution, a biomarker for oxidative DNA damage (CYP1A2) in bus drivers was determined (Loft et al., 1999). In a comparison between bus drivers from central Copenhagen and drivers from rural/suburban greater Copenhagen, the urban Copenhagen drivers excreted an increased amount of this biomarker, indicating that exposure to ambient air pollution may cause oxidative DNA damage.

A cross-sectional study among fuel system maintenance personnel showed that they had significantly higher counts of white blood cells, neutrophils and monocytes than a group with low exposure, after adjustment for relevant covariates (Rhodes et al., 2003). This indicative study, however, needs to be followed by results on whether a modulation of the immune system takes place in these people.

**Experimental exposure studies**

At sufficiently high levels of exposure, DEPs cause pathogenic effects, including cancer in rats (Mauderly et al., 1994; Nikula, 2000; Kato et al., 2000). It is plausible, however, that these effects are attributable to high levels of exposure and rat lung overload and therefore might not be generally applicable to relatively low levels of human exposure (ILSI Risk Science Institute Workshop Participants, 2000). Several studies have shown that filtering out the particles, but leaving the gases, abolished the carcinogenicity of diesel exhaust, clearly identifying a role for the particles (Nikula, 2000). Other studies, using carbon black as a surrogate for DEPs without their organic fraction, have found that the particles, not the organic fraction, are the main source of DEPs’ carcinogenic (Nikula et al., 1995) and mutagenic (Bond et al., 1990) effects. DEPS with the organic fraction removed, however, caused fewer tumours than the parent DEPs in an instillation study (Dasenbrock et al., 1996).

Inflammatory cell-derived oxidants have been implicated in the mutagenic effects of particles (Driscoll et al., 1997). Hydroxyl radicals have been detected in the lungs of DEP-exposed rats (Han et al., 2001), and there is evidence of 8-OHdG adducts in chronically exposed rats (Jing et al., 1996; Tsurudome et al., 1999; Iwai et al., 2000). The source of the hydroxyl radical may be Fenton chemistry, as a consequence of metals associated with the particles or the accumulation of endogenous iron around the DEPs in the lung tissue (Ghio et al., 2000). Gallagher et al. (1993) found that diesel exhaust extracts, particularly nitrated PAHs and benzo[a]pyrene, formed DNA adducts in human lymphocytes. Cyclopenta-fused
PAHs, benz[a]aceanthrylene, benz[j]aceanthrylene and benzo[a]pyrene were metabolized in rat and rabbit primary lung cells, Clara cells, type-2 cells and macrophages, and formed DNA adducts in all these cell types from both species (Holme et al., 1993; Johnsen et al., 1997). Also, the lungs retain inhaled PAHs for a longer time when these compounds are associated with DEPs (Sun et al., 1984).

Air toxics are volatile toxic organic molecules found in air pollution in various circumstances. Those derived in greatest quantity from vehicle emissions are acetaldehyde, benzene, 1,3-butadiene and formaldehyde. All are considered to be carcinogenic in some animals and all are classified by the International Agency for Research on Cancer (IARC) as carcinogenic for human beings, with varying degrees of certainty. Considering ambient concentrations, however, the risk is rather low.

Conclusions
A wide range of studies indicates an increased risk of various types of cancer in people with prolonged exposure to higher levels of transport-related air pollution. Such effects have been measured or modelled mainly in subgroups that are susceptible or have higher levels of exposure than average, such as those with higher occupational exposure. A few studies estimating the general population’s exposure to transport-related air pollution, however, suggest an increased incidence of lung cancer associated with increased exposure.

For certain occupational groups, such as professional drivers and railway workers, increased incidence of and mortality from lung cancer has been reported, and the increases are greater in people with long histories of exposure. Increased cancer rates were also observed in animals exposed to diesel exhaust.

Biomarker assessments in human beings and animals suggest that oxidative stress and DNA damage are linked to exposure to transport-related air pollution, which may play a role in the development of cancer. Both particles and semi-volatile compounds at current concentrations may affect the induction of cancer. For the volatile compounds, the ambient levels are in general so low that the risk of effects is low.

Pregnancy outcomes and male fertility
Pregnancy outcomes
Fetuses are considered to be highly susceptible to a variety of toxicants, because of their exposure pattern and physiologic immaturity (Perera et al., 1999; Šrám, 1999). Their developing organ systems can be more vulnerable to environmental toxicants during critical periods, due to higher rates of cell proliferation or changing metabolic capabilities.

Several studies have shown the adverse effects of ambient air pollution on pregnancy outcomes, including an increase in post-neonatal infant mortality
Health effects of transport-related air pollution (WHO Regional Office for Europe, 2004b). Only a few studies, however, have sought more specific associations between these outcomes and transport-related air pollution.

**Modelled exposure**

In Seoul, the Republic of Korea, Ha et al. (2001) examined the associations between low birth weight and exposure to transport-related air pollution at the mother’s residence during pregnancy. The adjusted RR of low birth weight was 1.08 (95% CI: 1.04–1.12) for interquartile increase in carbon monoxide concentration during the first trimester of pregnancy. The RRs were 1.07 (95% CI: 1.03–1.11) for nitrogen dioxide, 1.06 (95% CI: 1.02–1.10) for sulfur dioxide and 1.04 (95% CI: 1.00–1.08) for total suspended particles—all for interquartile increases in exposure. Also, several studies conducted by Ritz and colleagues in Los Angeles indicate that the risk of an adverse outcome at birth, such as premature birth and low birth weight, may be affected by exposure to transport-related air pollution, as indicated by the distance-weighted traffic density (Ritz & Yu, 1999; Ritz et al., 2000; Wilhelm & Ritz, 2003).

**Experimental exposure studies**

Diesel exhaust fosters abnormal delivery in pregnant mice and affects the growth of their young. Tsukue et al. (2002) reported that exposure of pregnant female mice to 0.3 mg/m^3, 1.0 mg/m^3 and 3.0 mg /m^3 DEPs resulted in 9.1%, 10.0% and 25.0% abnormal deliveries, respectively. The offspring of exposed females showed significantly lower body weights at the ages of 6 and 8 weeks, and delayed sexual maturation. Watanabe & Kurita (2001) exposed female rats to diesel engine exhaust from day 7 to day 20 of pregnancy and observed that the differentiation of the testis, ovary and thymus was delayed and disturbed. Maternal testosterone and progesterone levels were significantly higher in the exposed pregnant rats than in controls.

**Male fertility**

Levels of transport-related air pollution may also affect male fertility, although the number of studies that address this hypothesis is rather small. De Rosa et al. (2003) compared male motorway toll-gate workers with men living in the same area. The results showed that sperm count and serum levels of follicle-stimulating hormone, leuteinizing hormone and testosterone were within the normal range in both groups, while total motility, forward progression, functional tests and sperm kinetics were significantly lower in the toll-gate workers than in controls. The finding that blood methaemoglobin and lead were inversely correlated with sperm parameters indicates that nitrogen oxide and lead may adversely affect semen quality.

In experimental studies, Fredricsson et al. (1993) exposed human spermatozoa to DEP extracts and found that the pollutant interfered with sperm motility in a
dose–response fashion. In male mice, daily sperm production per gram of testis decreased dose dependently when the animals were exposed to diesel exhaust for six months (Yoshida et al., 1999). A study by Watanabe & Oonuki (1999) indicates that spermatogenesis in growing rats was inhibited after exposure to diesel engine exhaust. In exposed animals, serum levels of testosterone and estradiol were significantly higher, and sperm production and activity of testicular hyaluronidase were significantly reduced.

**Conclusion**

There is evidence that implicates ambient air pollution in adverse effects on pregnancy, birth outcomes and male fertility. Modelled studies on exposure to traffic-related air pollutants suggest that they are a risk factor for adverse birth outcomes, but further studies are needed that estimate this exposure more precisely, in terms of both pollution components and timing.

**Intervention studies**

Intervention studies address the health benefits of improvements in air quality and provide useful information to decision-makers and air-quality managers. Unfortunately, these studies are very rare, particularly when restricted to the adverse effects on health related to transport. The few examples that exist can be classified as describing short-term and long-term interventions.

**Short-term changes in air-pollution levels**

The implementation of a modified transport strategy, to reduce traffic congestion during the 1996 Summer Olympic Games in Atlanta, Georgia, United States provided the opportunity to study the health impact of a short-term change in levels of transport-related air pollution (Friedman et al., 2001). For a total of more than 10 weeks (4 weeks before, 17 days during and 4 weeks after the Games), data were registered for: the number of medical emergency visits, the number of hospitalizations for asthma and non-asthma events, air quality, weather conditions, and traffic and public transportation. The air-quality data included measurements of PM10, nitrogen dioxide and ozone.

The results of the analysis show a significant decrease in the number (41.6%) and incidence of acute care events for asthma (RR: 0.48; 95% CI: 0.44–0.86) during the Olympic Games. In the same period, air quality improved, with significant reductions in ozone (from 163 µg/m³ to 117 µg/m³ mean of one-hour daily maximum), carbon monoxide (from 1.80 mg/m³ to 1.47 mg/m³, eight-hour means) and PM10 (from 36.7 µg/m³ to 30.8 µg/m³ daily mean) concentrations. The peak weekday morning traffic counts were reduced by 22.5% from the baseline period. The peak daily ozone concentration was significantly correlated with traffic counts (correlation coefficient $r = 0.36$).
These results suggest that reductions in car emissions and the associated ozone and PM levels, resulting from changes in city transportation systems can prevent disease and lead to a reduced number of asthma exacerbations that require medical attention. This study, however, has some noticeable weaknesses that should be considered. They include low statistical power (only one of the four sources of medical data taken into consideration provided statistical significance), a limited number of air-pollution monitoring sites and a non-optimal traffic counting system. Moreover, due to the high correlation between the levels of PM10 and ozone, it is impossible to determine which pollutant's reduction was responsible for the decrease in asthma events, although ozone levels were reduced further (28%) than that PM levels (16%). The study supports the general perception that the change in car emissions contributed to the improvement in air quality – not the weather conditions, which remained relatively constant during the observation period.

Despite the limitations of the study, the immediate implications are of major importance and indicate the need to introduce changes in traffic that improve air quality and reduce the morbidity associated with air pollution.

**Long-term changes in air-pollution levels**

Very few published intervention studies assess the health impact of long-term changes in traffic-related air pollution.

**Regulation of traffic**

Various long-term changes can be made to reduce the adverse effects on health of exposure to transport-related air pollution. One increasingly used option is the regulation of traffic by, for example, building tunnels, diverting traffic to different routes, constructing roundabouts and regulating speed. Environmental evaluation reports often document the impact of traffic regulation in terms of changes in air-pollution levels, living conditions and the well-being of local residents. The number of published epidemiological studies that assess the effect on health of traffic regulations is very small, however.

A few studies have been published in connection with the construction of two tunnels in Norway. They were constructed to reduce the effect of traffic on the urban environment in Oslo. Bartonova et al. (1999) used a dispersion model to estimate the effect of these changes on the residents’ levels of exposure. After both tunnels were in use, the average exposure to nitrogen dioxide decreased from 51 µg/m³ to 40 µg/m³ (Bartonova et al., 1999). Another study investigated the effect of the tunnels on the self-reporting of symptoms of reduced health and on the well-being of adults living in Oslo (Clench-Aas et al., 2000). The decrease in the levels of nitrogen dioxide reported by Bartonova and co-workers was related to a decrease of about 5–10% in the risk of being bothered by fatigue (Clench-Aas et al., 2000). Finally, Klaeboe et al. (2000) studied the combined effect of
changes in air pollution and noise level on annoyance, caused by the construction of these tunnels. This study indicated that the higher the levels of road-traffic noise to which people are exposed, the more likely they are to be annoyed by the smell of traffic exhaust at a specified level of air pollution.

**Changes in fuel composition**

Improving technology, such as emission controls or changes in fuel composition, is another option that might benefit health. In 1990, a fuel restriction was introduced in Hong Kong, requiring that all power plants and road vehicles use fuel oil with a sulfur content of not more than 0.5% by weight. In the first year after introducing this intervention, the mean reduction in sulfur dioxide was 53%, and this reduction was sustained at 35–53% for 5 years (Hedley et al., 2002). No significant change was noted in mean PM10 and nitrogen dioxide concentrations, but a significance increase in ozone was noted over this period (Hedley et al., 2002).

Studies examined the effect of this intervention on the differences between two districts in changes in bronchial responsiveness (Wong et al., 1998) and in immediate and long-term health benefits (Hedley et al., 2002). A comparison of measurements made before the intervention with those made a year later showed that both the bronchial hyperreactivity slope and the bronchial reactivity slope declined from 29% to 16% and from 48% to 39%, respectively, in the polluted district, and from 21% to 10% and from 42% to 36%, respectively, in the less polluted district (Wong et al., 1998). Comparing measurements made in 1991 (a year after the intervention) with those in 1992, only the polluted district showed a significant decline, from 28% to 12% and from 46% to 35% for bronchial hyperreactivity and bronchial reactivity slopes, respectively (Wong et al., 1998).

Also, an immediate reduction in cool-season deaths was reported, which suggests that, in the first year, many people survived who would have otherwise died (Hedley et al., 2002). The intervention led to significant declines in the average annual trend in deaths from all causes (2.1%; \( P = 0.001 \)), respiratory causes (3.9%; \( P = 0.0014 \)) and cardiovascular diseases (2.0%; \( P = 0.0214 \)) (Hedley et al., 2002). Reductions in risks for overall mortality were greater in districts that had large reductions in sulfur dioxide than in those that did not (Hedley et al., 2002). Differences in age-specific death rates before and after the intervention suggest that it resulted in an average gain in life expectancy of 0.73 years for men aged 25–100 years, because of a 10-µg/m³ reduction in exposure to sulfur dioxide for 15 years (Hedley et al., 2002).

Since the 1970s, a series of regulations on the lead content of petrol has been adopted. Modelled data from a recently published German study (von Storch et al., 2003) shows that atmospheric lead concentrations in Europe increased heavily until the 1970s and fell strongly in the following years, largely because of the reduced lead content of petrol. Many studies investigated the impact of
this fuel change on levels of lead in blood. Thomas et al. (1999) examined 17 of these studies, and found a strong linear correlation between lead concentrations in petrol and lead levels in blood. They also reported that lead levels in blood in the population decreased from the late 1970s to the early 1990s, and that average levels in the population of about 30 µg/l are widely achievable.

A more recently published study (Lou et al., 2003) provides additional support for the beneficial effects of this change in fuel composition on levels of lead in blood in China. In 1998, petrol stations in the city of Shantou were prohibited from selling leaded petrol. The effects of this intervention on the levels of lead in children’s blood were investigated for three consecutive years, when the average levels declined from 104 µg/l in 1999 to 94 µg/l in 2000 and 79 µg/l in 2001. These decreases were all statistically significant. The current standard elevated level of lead in blood for children, set by the Centers for Disease Control and Prevention in the United States, is 100 µg/l. Lou et al. (2003) found that the percentage of children in Shantou with levels above this standard was reduced by 35.8% in 2000 and 23.0% in 2001. These numbers indicate that prohibiting the sale of leaded petrol in the city had beneficial effects. With regard to transit traffic, the implementation of similar regulations in other parts of China might reduce these numbers even more. Nevertheless, one should remember that elevated levels of lead in blood can have other sources, although automobile emissions from the combustion of leaded petrol have been recognized as one of the major sources of widespread environmental lead contamination.

Relocation to less polluted areas

A more invasive way to protect human health against transport-related air pollution is for people to move from more to less polluted areas. Within a large follow-up study in southern California, 110 children changed their place of residence, providing an opportunity to investigate whether changes in air quality due to relocation were associated with changes in growth rates of lung function (Avol et al., 2001). As a group, subjects who had moved to areas of lower PM10 showed an increased growth rate of lung function; those who moved to communities with higher PM10 showed a decreased growth rate. A stronger trend was found for subjects who had migrated at least 3 years before the follow-up visit than for those who had moved in the previous 1–2 years (Avol et al., 2001).

Conclusions and outlook

Intervention studies can provide valuable information that aids in understanding the epidemiology of respiratory disease associated with air pollution and in evaluating the observable health benefits of air-quality regulations and control measures, and the emission sources involved. As stated earlier, such studies are unfortunately rare, and more should be encouraged (for example, HEI, 2003). The only short-term intervention study performed so far prudently suggests that
a reduction in transport-related air pollution may have a direct health benefit in reducing acute asthma attacks and related medical care, as observed in children. The intervention studies of long-term changes reported several health benefits, such as a decline in bronchial hyperactivity, a decline in the average annual trends in deaths from all causes and from respiratory and cardiovascular diseases, and a gain in life expectancy. Owing to the limited amount of evidence, however, one should still be reluctant to draw firm conclusions about the health benefits of these particular changes.

Discussion
The available scientific evidence suggests that transport-related air pollution affects several health outcomes, including mortality and respiratory morbidity. This evidence is supported by both epidemiological studies using various designs and experimental studies (Table 4.1).

In the numerous epidemiological time-series studies conducted in urban areas, mortality and morbidity were associated with black smoke. Especially for diesel exhaust, black smoke is likely to be a good indicator of transport-related air pollution. In studies on the adverse effects on health of chronic exposures to transport-related air pollution, it was also a good predictor of mortality and morbidity. Black smoke, however, is not the sole indicator associated with effects on health. Others – such as nitrogen dioxide, carbon monoxide, sulfur dioxide and different indicators of PM – were also correlated with the adverse effects studied. The various pollutants examined are often highly correlated with each other. This is the case for black smoke, carbon monoxide and nitrogen dioxide, and, to a lesser extent, PM10 and PM2.5. The fraction of the air pollution mixture emitted by traffic that adversely affects health therefore remains unclear.

One strength of time-series studies of daily mortality and morbidity is that they use daily concentrations that are widely, consistently and, for the most part, completely recorded. Although these studies have been extremely helpful in assessing the role of air pollution in acute effects on health in urban populations, they are less helpful in quantifying the role of traffic, which they were seldom designed to do. Most of the studies measured air pollution at a single site and made no distinction between spatial variation in levels of traffic-related air pollution or exposure. Sometimes, however, these studies can help improve the understanding of the role of transport-related air pollution in acute effects on health. A good example is the finding in the APHEA2 study that the slope of the relationship between PM and health was higher in areas with relatively high nitrogen dioxide concentrations, providing some evidence of the enhanced toxicity of PM emitted by mobile sources.

A few panel studies conducted in urban and rural areas suggest that adverse effects on health (symptoms, reduced lung function, medication use) were associated with transport-related air pollution. Most of them made additional air pollution measurements, which better represent the real exposure of study
Table 4.1. Summary of health studies of transport-related air pollution

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<th>Health outcome</th>
<th>Population studies</th>
<th>Experimental studies</th>
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<td>Pollutant</td>
<td>Evidence</td>
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<td>Mortality</td>
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<td>Respiratory diseases (allergic)</td>
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<td>Nitrogen dioxide</td>
</tr>
<tr>
<td>Cardiovascular diseases</td>
<td>Black smoke</td>
<td>Some</td>
<td>CAPs</td>
</tr>
<tr>
<td>Cancer</td>
<td>Nitrogen dioxide</td>
<td>Some</td>
<td>Diesel exhaust</td>
</tr>
<tr>
<td></td>
<td>Diesel exhaust</td>
<td>Some</td>
<td>VOCs</td>
</tr>
<tr>
<td>Reproductive outcomes</td>
<td>Nitrogen dioxide</td>
<td>Equivocal</td>
<td>Diesel exhaust</td>
</tr>
<tr>
<td></td>
<td>Carbon monoxide</td>
<td>Equivocal</td>
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</tr>
<tr>
<td></td>
<td>Sulfur dioxide</td>
<td>Equivocal</td>
<td></td>
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<tr>
<td></td>
<td>Total suspended particles</td>
<td>Equivocal</td>
<td>Diesel exhaust</td>
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participants than do the data from existing measurement sites. Another advantage of this design, compared with time-series studies, is that the statistical analyses could compensate for the individual potential confounders.

A substantial part of current knowledge about the health effects of transport-related air pollution comes from cross-sectional or cohort studies, in which exposure to indicators of transport-related air pollution were measured, modelled or assessed by questionnaire, or indirect indicators of transport-related air pollution (such as distance to nearest street or traffic count) were used. Because long-term epidemiological studies were often started for reasons other than assessing the effects of air pollution or its transport-related portion, they are not designed optimally for contrasts in exposure and for end-point and confounder information.

Some studies were designed to achieve a contrast in exposure to transport-related air pollution. It is therefore likely that differences in health between study subjects can be attributed to differences in this exposure. Although such studies address the issue of the role of road traffic better than time-series and panel studies, they have other limitations.

Cross-sectional studies that used subjective, self-reported exposures or measures of health effects may suffer from responder bias, resulting in positive associations between exposure and adverse effects on health. Studies that use measured or modelled exposures and objective measures of adverse effects are less influenced by responder bias. Another limitation of cross-sectional studies is the absence of historical data on exposure, which limits the possibility of establishing the temporal order of cause and effect.

Important information on the association between disease and exposure to the products of fossil-fuel combustion can be extracted from epidemiological studies on groups with occupational exposure. Though other factors may also contribute to the increased risk in these groups, the studies consider air pollution from motor-vehicle emissions an important risk factor for coronary and respiratory diseases, as well as for several types of cancer.

Toxicological studies provide supportive arguments for the peril from transport- or traffic-related air pollution. They report the expression of many biological and pathological responses and, in some cases, the onset or exacerbation of disease. The lowest concentrations studied, however, are still in the range of episodes of high concentrations of pollutants. Also, the human subjects in the studies do not represent the most susceptible subpopulations, and extrapolations from animal and cell studies are difficult. Thus, the studies do not provide exposure–response functions, and it is unclear whether more susceptible individuals may experience effects at average ambient concentrations. Modified animal and cell-culture models could be used to a greater extent to investigate the effects of lower concentrations and the influence of pre-existing disease.

Overall, the toxicological studies lend support to the epidemiological findings. Several pollutants that show associations in epidemiological studies on adverse
effects on health also provoke biological or pathological reactions, or both, in experimental settings. These reactions are involved in the development or exacerbation of diseases investigated in epidemiological studies. Inflammation is an important response, often investigated in toxicological studies of the effects of air pollution. Though inflammation is a useful process for eliminating intruding pathogens, it may also cause damage to surrounding tissue and thus exacerbate pre-existing disease, if not resolved by a defensive process of the tissue. In particular, subjects with chronic lung disease would be expected to experience a negative effect from increased inflammation. Also, although the epidemiological evidence is weak in suggesting the involvement of air pollution in the development and exacerbation of respiratory allergy and allergic asthma, the toxicological results suggest such an involvement.

Toxicological studies have also observed cardiovascular effects, but the evidence here is just accumulating. The relative importance of possible pathways of adverse effects on health has not been clarified. Whether the cardiovascular effects are mediated through inflammation of the lungs, stimulation of the nervous system or a direct effect (for example, of ultrafine particles on the blood or heart) still remains to be elucidated. Toxicological studies of cancer have indicated the importance of diesel exhaust and PAHs at high concentrations and thus support epidemiological studies. Only the latter studies, using indicators, however, have found associations between relatively low levels of ambient pollution and cancer.

Attempts have been made to clarify which component of PM plays the most important role in eliciting adverse effects on health. The studies on this problem have been unable to single out specific components responsible for specific responses, except for the ability of PAHs to cause DNA damage and cancer. The diverse results show, depending on the particles sampled, the involvement of different components; this may indicate that a particular component, common in all or many types of particles, will not be found. The production of ROS seems to be important in the responses observed; in connection with this, the antioxidant status of the lung seems to be one crucial factor of susceptibility to effects in this organ. Other important factors may be lung SPs. Further, allergic asthmatics and people with a pre-existing cardiovascular disease may be at higher risk than healthy people. The data on likely or possible susceptibility traits are still far from sufficient, however, and there is still insufficient data on the importance of age.

Are the pollutants from traffic unique in exerting their effects or are their effects in keeping with those of pollutants from other sources? A number of studies on pollution from other sources have been carried out, including those on quartz and asbestos in occupational settings, residual oil fly ash, pollution from several industrial areas and pollution from domestic heating. Several sources produce the same components of pollution as those produced by traffic, but with quantitative variations. The greatest differences seem to be found in the composition of
particle fractions from different sources. Though there are many differences in
the effects of particles from these sources, some principles seem to prevail between
all of them. The formation of ROS seems to be an important factor, and has been
tied to the activity of some surface or soluble element. It is linked to increased
inflammation, which again is associated with disease. Though composition may
vary considerably, the effect of PM pollution seems to change relatively little across
many studies, even though some differences in estimates of effects between differ-
ettent cities have been reported, for example, in the APHEA studies. Also, the health
benefits observed from reducing pollution from non-traffic sources – shown for
example in studies in Utah Valley, United States and Dublin, Ireland (Pope et al.,
1996; Clancy et al., 2002) – have to be considered.

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