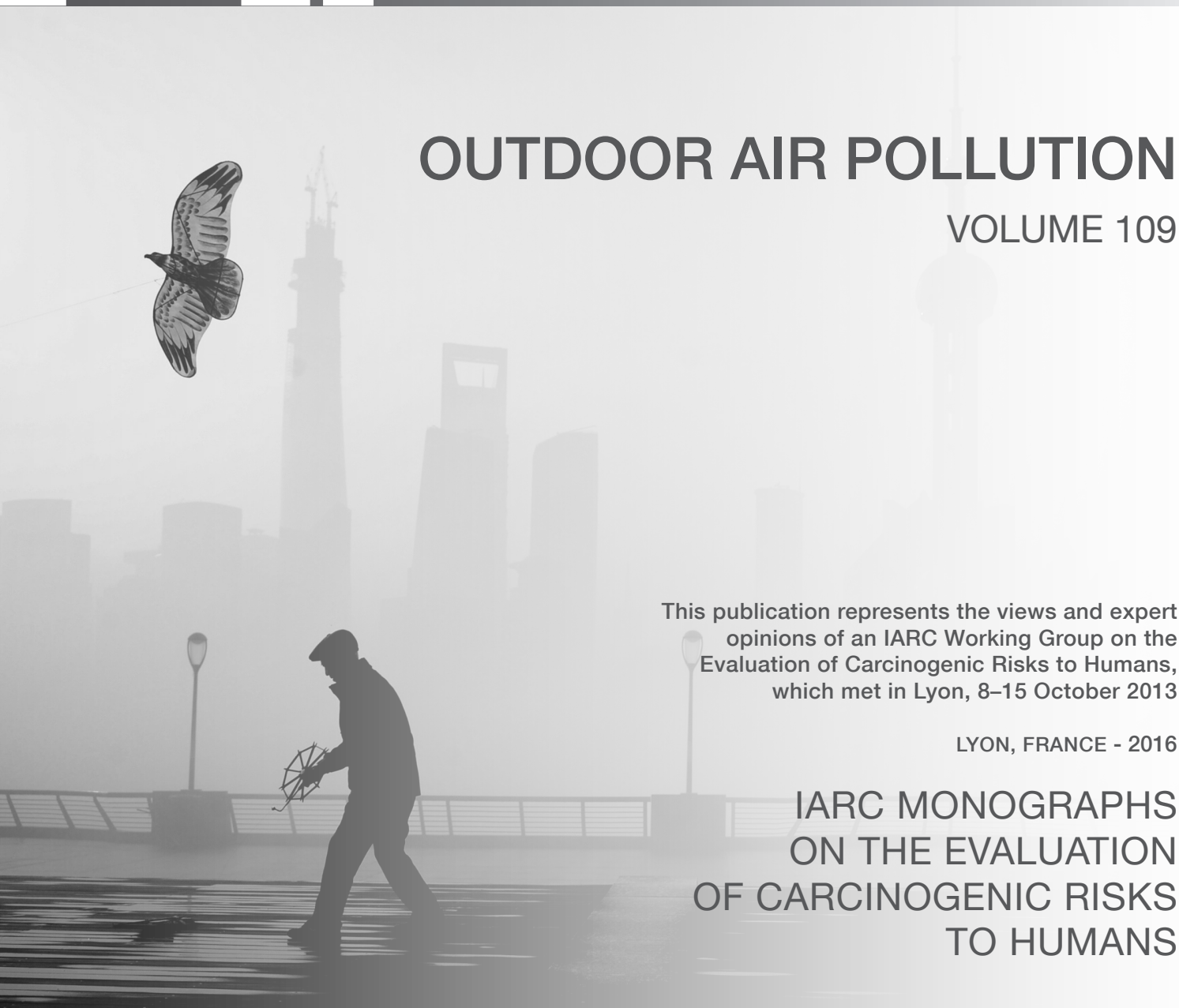
IARC MONOGRAPHS



OUTDOOR AIR POLLUTION

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IARC MONOGRAPHS ON THE EVALUATION OF CARCINOGENIC RISKS TO HUMANS

International Agency for Research on Cancer

World Health Organization

5. SUMMARY OF DATA REPORTED

5.1 Exposure data

5.1.1 The agent and its components

Air pollutants are ubiquitous – from anthropogenic activities and natural processes – and global, and cross international boundaries. Levels of individual contaminants can vary dramatically between locations, due to the contributing sources and atmospheric processing, which mixes and transforms pollutants and transports them across great distances. Several important species are formed in the atmosphere and are not directly emitted. Air pollution is a mixture of mixtures, which can be viewed from source-oriented or component-oriented perspectives. Any outdoor air pollution mixture includes gases and suspended particles that are constantly interacting. Gaseous pollutants include photochemical oxidants, numerous organic compounds, carbon monoxide (CO), volatile metals, and nitrogenous and sulfurous species. Suspended particles (a heterogeneous mixture of liquids and solids referred to as particulate matter [PM]) are also a very complex mixture, with variable and dynamic chemical composition and physical characteristics. Many of the individual species and mixtures present in air have been classified by IARC as Group 1 (e.g. benzene, benzo[*a*]pyrene, chromium (VI), and dioxin) and Group 2A carcinogens.

5.1.2 Sources

Although there are many sources of outdoor air pollution, the largest contributors of air pollutants in many locations are: mobile sources; stationary power generation; other industrial and agricultural emissions; residential heating and cooking; re-emission from terrestrial and aquatic surfaces; the manufacturing, distribution, and use of chemicals; and natural sources. The distribution of these sources, the implementation of emissions control technologies, and the resulting emissions vary considerably between and within regions. Many of these sources have diurnal, weekly, and seasonal patterns in emissions. Some important regional trends in source contributions to air pollution include: (1) substantial contributions from residential burning of solid fuels in developing countries in Asia, Africa, and parts of South America; (2) substantial contributions from coal-fired power plants in China; (3) substantial contributions from stationary sources in heavily industrialized cities where advanced emissions controls are not present; (4) large episodic dust storms in Asia, Africa, and the Middle East; and (5) mobile sources, which contribute to varying degrees in urban areas.

5.1.3 Measurement methods

A wide variety of measurement methods are applied to measure concentrations of air pollutants. Therefore, comparisons of measurements across space or time need to consider

these differences. Most methods for regulated gaseous pollutants, such as CO, nitrogen dioxide (NO_2), sulfur dioxide (SO_2), and ozone, use in situ continuous monitors for hourly averaged (or shorter-duration) concentrations, whereas PM is most often measured using integrated sampling systems on filter substrates for air passed through size-selective inlets to determine mass concentration and major components such as multi-elements, ions, and carbon. Passive sampling is increasingly used to assess spatial variation, particularly for gases. With specified standard operating procedures and quality assurance/quality control, within- and between-network consistency may be achieved.

5.1.4 Environmental occurrence

In some countries outdoor air quality is monitored routinely in networks. Measurement methods and site selection differ between networks, partially limiting comparisons between countries. Satellite-based approaches provide global estimates, filling the gaps for a limited number of pollutants (e.g. PM with particles of aerodynamic diameter < 2.5 μm [$PM_{2.5}$], NO_2, SO_2, and formaldehyde). Network and satellite data have shown large variability across countries of concentrations of PM with particles of aerodynamic diameter < 10 μm (PM_{10}), $PM_{2.5}$, NO_2, and other pollutants. Annual average $PM_{2.5}$ concentrations range from below 10 μg/m^3 to well above 100 μg/m^3. In many areas, World Health Organization (WHO) air quality guidelines for $PM_{2.5}$ are substantially exceeded. High $PM_{2.5}$ concentrations are observed in South and East Asia and North Africa. High NO_2 concentrations are observed in areas with high population density and traffic density. Within countries, high concentrations are observed in urban areas and around traffic sites and industrial locations. Significant spatial variability is present, related to urban–rural differences and proximity to sources or source areas.

Trends differ by pollutant and region of the world. In North America and Europe, concentrations of major pollutants such as PM, SO_2, and NO_2 have decreased substantially in the past 30 years. In many developing countries, concentrations have increased with rapid economic development.

5.1.5 Exposure assessment in epidemiological studies

Epidemiological studies of relationships between air pollution exposure and cancer require long periods of observation and large populations. Therefore, it is almost impossible with currently available approaches to assess exposure via personal monitoring. Rather, epidemiological studies use measured or modelled concentrations of outdoor air pollution as the primary basis for exposure estimation. Air quality monitoring is usually limited to measurements of a relatively small number of indicator pollutants collected at discrete locations. Epidemiological studies have typically used centrally located outdoor monitors or geostatistical averaging of multiple measurements within a single study area in analyses of between-area variation in exposure, and various modelling techniques (e.g. atmospheric transport and land-use regression models), sometimes in combination with detailed spatial and temporal measurements, to assign individual estimates of exposure. Evaluation of these models indicates that they can accurately estimate outdoor concentrations at residential locations. More recently, satellite-based estimates, sometimes in combination with land-use information, have been used to produce relatively high resolution and compatible estimates of concentrations at national (and even global) scales, including rural areas, where in situ measurements are generally not available. Since it is important to estimate exposures over long time periods, assessments can be improved by using both estimates of air pollution concentrations for extended time

periods and residential histories for the study population of interest.

5.1.6 Personal exposure

Personal exposure is typically not used to assess exposure in epidemiological studies of air pollution and cancer but can be used to assess the agreement with outdoor exposure estimates. Human biomarkers of exposure provide information about individual exposures that may be used in evaluation studies.

There is strong evidence that temporal variation of outdoor concentration is correlated with temporal variation of personal exposure to fine particles. The few studies that have evaluated the agreement between average outdoor concentration estimated at a fine scale and personal exposure have generally found a moderate agreement, which differed between pollutants and studies. A few studies comparing personal exposure of subjects in cities with different outdoor air pollution concentrations have shown a strong correlation between average personal exposure and city-average outdoor concentration.

Personal exposure to air pollution is determined by the pollutant concentration in the microenvironment and by the time–activity patterns and location of individuals, including outdoors, indoors, and in transit. Personal exposures differ from those estimated based solely on outdoor concentrations because of time–activity patterns, variable infiltration of outdoor air pollution into indoor environments, and indoor sources. Thus, for studies of health effects of outdoor air pollution, the contributions from indoor and outdoor sources to total personal exposure should be considered separately.

People generally spend a large fraction of their time indoors (typically about 80–90%). A substantial fraction of the time spent indoors is spent in the home, supporting the assessment of exposure based upon the residential address. Because of the high fraction of time spent indoors, infiltration of outdoor pollution indoors is an important factor that modifies exposure. Infiltration varies substantially between pollutants and homes/buildings and by season. Relatively high infiltration factors (≥ 0.5) have generally been found for fine particles (particularly sulfate and elemental carbon) and CO. Lower infiltration factors have been found for ultrafine and especially coarse particles, NO_2, and ozone. For pollutants with lower infiltration factors, the potential for misclassification of exposure based on outdoor concentrations is higher. Infiltration factors are affected strongly by air exchange rates, which differ between homes and by season. Despite the typically small fraction of their time (< 10%) that people spend in traffic, the contribution to average personal exposure may be substantial because of the high concentrations found in traffic areas. Outdoor workers such as street vendors, traffic police, and toll booth operators experience long exposure durations and elevated exposure levels.

5.1.7 Guidelines and regulations

Given the chemical complexity of outdoor air pollution and the large number of anthropogenic sources, air pollution is managed with a combination of air quality standards for selected pollutants, regulation of sources, emissions permitting, and indirect control of sources, such as land-use regulation. Although the regulatory framework for outdoor air pollution control differs considerably across countries and across local government agencies within countries, most regions of the world have air quality standards for key air pollutants (ozone, SO_2, NO_2, CO, and PM, although there is limited specification on the components of PM). The control of these pollutants has beneficial consequences for the control of other pollutants. Useful air quality regulations include an indicator, a specified averaging time, and a statistical form, which is effectively the number of exceedances that are allowed. In

some locations where air quality standards have not been developed, WHO guidelines are used as a reference for air quality management. In many locations around the world, compliance with air quality standards and WHO guidelines is not achieved.

5.2 Human carcinogenicity data

5.2.1 Cancer of the lung

The association of exposure to outdoor air pollution with lung cancer risk has been examined in cohort and case–control studies conducted in countries in Europe, North America, Asia, and Oceania. Several of these are large studies of general population cohorts with individual-level information on cancer risk factors, including tobacco smoking, and with quantitative estimates of exposure to outdoor air pollution. Some relevant information is also available from studies of workers exposed to outdoor air pollution in their jobs. Other studies have evaluated the occurrence of lung cancer in populations potentially exposed to emissions from various specific sources and industries.

In evaluating the evidence from these epidemiological studies, the Working Group placed the greatest weight on cohort studies with quantitative exposure data within the general population. The most commonly examined pollutant in these studies was $PM_{2.5}$. The studies provided information on other indicators of atmospheric PM, including PM_{10}, total suspended particles, and black smoke, and other common components of air pollution, including nitrogen oxides (NO_x), NO_2, SO_2, and ozone. Several studies included indicators of exposure to traffic based on proximity to roads or traffic volume. The spatial and temporal scale at which the exposures were assessed in these studies varied widely, and few studies specifically considered exposure-time–response relationships.

Large cohort studies have been conducted almost exclusively in high-income countries, mostly in North America and Europe, and results of some studies have been reported in numerous publications. The follow-up of these studies extends from as early as the 1970s through 2010. During that period, outdoor air pollution levels generally declined in North America and Europe. The Working Group judged that among the North American studies, the Harvard Six Cities Study, the analyses of the American Cancer Society (ACS) cohort (especially the results for never-smokers), and the California Teachers Study (particularly its analysis for never-smokers) were the most informative for the evaluation of carcinogenicity. Among the European cohort studies, those judged to be most informative were studies conducted in Oslo (Norway), the Netherlands, Denmark, and Rome (Italy), and a Europe-wide study of 17 cohorts from the ESCAPE study. Of studies in other areas of the world, one study from New Zealand and two studies from Japan were considered to be the most informative because of the detailed exposure assessment or adjustment for potential confounders, including indoor air pollution.

Two large cohort studies – the European ESCAPE study and the ACS study in the USA – are particularly informative for their large scale, exposure assessment based on actual measurements, the broad range of exposures considered, very detailed information about potential confounders (e.g. duration and intensity of smoking), and standardization of methods. In addition, the ESCAPE study had incidence data and histological classification of lung cancer cases.

The Working Group also considered case–control studies in Europe and North America. Considering study design, availability of quantitative exposure estimates, sample size, and ability to control for confounders, the Working Group judged that population-based studies conducted since 1990 in Canada, Poland, and Sweden were informative.

Earlier case–control studies (before 1990) had several limitations: some were based on

deceased subjects, had a low response rate among controls, had a small sample size, used rather crude exposure assessment methods, and lacked adjustment for smoking as a possible confounder. Consequently, the Working Group gave these studies little weight.

Other case–control studies of populations potentially exposed to local sources of industrial emissions were reviewed but were considered to be less informative of a relationship between the general air pollution mixture and lung cancer risk because of the unique nature of the exposure sources and methodological limitations similar to those of the group of studies mentioned previously.

Overall, studies with quantitative measures of outdoor air pollution showed positive associations with lung cancer in both sexes and in cohort and case–control studies from all regions, with the potential confounding and effect modification by tobacco smoking accounted for by adjustment or stratification. A large number of potential individual- and area-level confounders were considered in the most informative studies, and overall there was no evidence of a substantial impact of these factors on the estimated associations. Some studies provided analyses stratified by smoking or restricted to never-smokers, and associations of lung cancer with outdoor air pollution were similarly observed in these studies.

Most cohort and case–control studies estimated relative risks using multiplicative models with a continuous variable for exposure, which assumes a linear exposure–response relationship. Evaluation of alternatives to a linear exposure–response model (i.e. smoothed terms or categorical modelling) was reported in the Harvard Six Cities Study, the ACS study, the Canadian case–control study, the Rome study, and the ESCAPE study. All studies that assessed smoothed exposure–response relationships found no statistically significant deviation from linearity. The results obtained with these approaches were consistent with those described previously, generally indicating increasing risk of lung cancer with increasing levels of exposure.

The available studies used a range of quantitative or qualitative estimates of exposure. Quantitative estimates were mainly for PM ($PM_{2.5}$ or PM_{10}) and NO_2 or NO_x. Qualitative or semi-quantitative estimates included traffic density or distance from heavy-traffic roads. The relative risk estimates for $PM_{2.5}$ and PM_{10} were indicative of positive associations in almost all the studies. When exposure–response relationships were examined, these generally indicated increasing risk of lung cancer with increasing levels of exposure to PM. There also was a suggestion of increasing risk with increasing levels of exposure to NO_2 and/or NO_x, but results were inconsistent.

In summary, both cohort and case–control studies with exposures assessed in the population setting, involving millions of subjects and many thousands of lung cancer cases in different parts of the world, consistently showed an association between exposure to **outdoor air pollution** and the risk of lung cancer, in both sexes and after adjustment for the main potential confounders. The association was present in almost all studies that specifically investigated the association of lung cancer and outdoor air pollution among never-smokers. Positive exposure–response relationships were reported in several studies. Although all of the studies are subject to error in estimating exposure, the most likely effect of such error is attenuation of the risk estimates. While not definitive in themselves because of the limitations noted previously, the findings of occupational cohort studies suggesting an association between professional driving and risk of lung cancer are supportive.

In addition to considering **particulate matter in outdoor air** as an indicator of the overall air pollution mixture, the Working Group also evaluated PM as a causal agent using the same body of epidemiological evidence. Because most evidence for an association between outdoor air

pollution and cancer comes from results for PM, the evidence for PM and lung cancer is generally similar to that for outdoor air pollution as a whole. Positive exposure–response relationships have been observed, and confounding and other forms of bias can be excluded with reasonable confidence for the reasons described previously. A challenge in interpreting the observed associations for PM lies in determining whether they are an effect of PM as a causal agent or of PM as a surrogate for the outdoor air pollution mixture or other components of it. One hypothetical alternative to PM as a causal agent is the existence of gas-phase carcinogens, highly correlated with PM concentration, that are the actual cause of lung cancer attributed to PM. However, this alternative is unrealistic and is contradicted by the known presence of multiple carcinogens in airborne PM. Furthermore, associations have been observed in multiple locations with different pollution mixtures, and lung cancer risk increases with increasing concentrations of mass-based PM indicators.

The Working Group also considered the evidence on traffic in relation to the risk of lung cancer. These studies used diverse approaches to estimate exposure to traffic. Six studies used measures of traffic intensity or distance from heavy-traffic roads as surrogate measures of exposure to traffic-related air pollution, and the reported associations with lung cancer were inconsistent. Four studies, including one that also reported associations for qualitative indicators of traffic exposure, explicitly modelled NO_2 or NO_x from traffic using dispersion models. Three other studies labelled NO_2 estimates as indicators of exposure to traffic, but the Working Group did not consider them exclusively as such because the estimates also included other sources of NO_2. The Working Group considered the evidence on pollution from traffic sources as supportive of an overall relationship between lung cancer and outdoor air pollution.

5.2.2 Cancer of the urinary bladder

Seven studies with cohort or case–control designs directly evaluated the association of cancer of the bladder with metrics of exposure to outdoor air pollution, traffic, or traffic fumes. In several studies, some of which adjusted for tobacco smoking, an increased risk of bladder cancer was associated with these exposure metrics.

Several studies also demonstrated a higher risk among people who were occupationally exposed to potentially high levels of outdoor air pollution after accounting for tobacco smoking. Since these studies involved occupations (specifically taxi, bus, and truck drivers) as surrogate indicators of exposure to outdoor air pollution, and specific air pollutants were not measured, the Working Group did not place as much weight on these studies in its evaluation.

5.2.3 Other cancer sites

The Working Group also reviewed in detail studies of breast cancer, leukaemia and lymphoma, and several other cancers in addition to those of the lung and bladder. The evidence of carcinogenicity for these sites was based on a relatively small number of informative studies, and the observed associations were inconsistent.

However, the Working Group noted that weak associations with childhood leukaemia (especially acute lymphoblastic leukaemia) could not be ruled out. Some of these were reported in studies that were informative because they were large, were population-based, used incidence as the end-point, used validated exposure assessment methods, had no potential for recall bias, and had no or limited potential for selection bias. Although the associations with childhood leukaemia were suggestive, they were inconsistent. There was also a tendency for stronger associations to be published in the smaller studies, indicating evidence for potential publication bias.

5.3 Animal carcinogenicity data

5.3.1 Studies of air pollutants evaluated in previous IARC Monographs

The Working Group reviewed and updated studies in experimental animals of the carcinogenicity of several components of air pollution that were evaluated in previous *IARC Monographs*. Inhalation exposure to emissions from combustion of coal caused high incidence of malignant lung tumours in two studies in mice and one study in rats. Emissions from combustion of wood caused an increased incidence of lung tumours (mainly adenocarcinomas) in one study in mice but not in another study in rats. Four skin application or subcutaneous injection studies using coal-derived soot extracts in mice and two subcutaneous injection studies using wood smoke extracts in mice showed increased incidences of lung cancers or skin tumours. Only one new skin application study using wood smoke extract in mice (judged inadequate for the evaluation) and no new studies on emissions from combustion of coal were available to the Working Group since the previous *IARC Monographs* evaluation.

It has been shown in 11 studies in rats that whole diesel engine exhaust from engines produced before 2000 caused an increased incidence of benign and/or malignant lung tumours after long-term inhalation exposure. All studies in mice exposed to whole diesel engine exhaust were negative except one, which showed inconsistent results. No increase in the incidence of lung tumours was observed in hamsters exposed to whole diesel engine exhaust. The gas phase of diesel engine exhaust (i.e. without particles) did not cause an increase in lung tumours in mice, rats, or hamsters. Diesel engine exhaust particles caused malignant lung tumours in rats after intratracheal instillation in one study. Extracts of diesel engine exhaust particles caused malignant lung tumours in rats after intrapulmonary implantation in one study and malignant fibrous histiocytomas in mice after subcutaneous injection in another study. Only one new skin application study using diesel engine exhaust particle extract in mice (a negative study) was available to the Working Group since the previous *IARC Monographs* evaluation.

In previous studies, no lung tumours were observed in rats, hamsters, or dogs after inhalation exposure to whole gasoline engine exhaust. However, gasoline engine exhaust condensates induced malignant tumours of the skin in three skin application studies in mice, malignant lung tumours in one intrapulmonary implantation study in rats, and pulmonary adenomas in one intratracheal instillation study in hamsters. No new studies on gasoline engine exhaust were available to the Working Group since the previous *IARC Monographs* evaluation.

5.3.2 Inhalation studies of exposure to outdoor air

In one study in male and female mice, in a first experiment, traffic-related outdoor air pollution in São Paulo, Brazil, caused an increase in the incidence of lung adenoma and increased the incidence and multiplicity of urethane-induced lung adenoma. In a second experiment, traffic-related outdoor air pollution promoted urethane-induced lung adenoma incidence in a dose-dependent manner. In another study in female mice, exposure to traffic-related outdoor air pollution in São Paulo increased the average number of lung adenomas per urethane-exposed animal. In a third study in mice exposed to traffic-related outdoor air pollution in São Paulo, there was no increase in the multiplicity of urethane-induced lung adenomas.

A study in male and female mice exposed to outdoor air in Los Angeles, USA, which gave inconsistent results, was judged inadequate for the evaluation.

A study in male and female rats exposed to outdoor air in Los Angeles gave negative results.

5.3.3 Non-inhalation studies of exposure to outdoor air

In a subcutaneous injection study in male and female mice, the crude benzene extract of PM sampled from outdoor air increased the incidence of injection-site tumours (mainly sarcomas and fibrosarcomas). In a second study in mice, a benzene extract increased the incidence of local fibrosarcomas. In a third study in female mice, several benzene extracts increased the incidence of injection-site sarcomas. In a fourth study in pre-weaned mice, a benzene extract increased the incidence of pulmonary adenocarcinoma and of multiple pulmonary adenoma in male and female mice. In a fifth study in newborn mice, a benzene extract of PM sampled from outdoor air increased the incidence of hepatoma in male mice and of multiple pulmonary adenoma in male and female mice. In a sixth study in newborn mice, different fractions of a benzene extract increased the incidence of tumours in male and female mice. In a seventh study in newborn mice, a neutral fraction of outdoor air particulates increased the incidence of pulmonary adenoma in male and female mice. Two studies in mice were judged inadequate for the evaluation.

In a skin application study in male and female mice, the benzene extract of PM sampled from outdoor air increased the incidence of skin papilloma and squamous cell carcinoma. Another skin application study in male and female mice was judged inadequate for the evaluation. In two two-stage carcinogenesis studies in mice, skin application of dichloromethane extracts initiated skin papillomas promoted by 12-*O*-tetradecanoylphorbol-13-acetate (TPA). A study on the role of aryl hydrocarbon receptor (AhR) using $AhR^{+/+}$ and $AhR^{-/-}$ female mice was judged inadequate for the evaluation.

One intraperitoneal injection study of benzene extract of PM sampled from outdoor air in mice and one intravenous injection study of PM sampled from outdoor air in mice were negative.

One intratracheal instillation study in male rats exposed to an extract of PM sampled from outdoor air was judged inadequate for the evaluation.

5.4 Mechanistic and other relevant data

5.4.1 Toxicokinetic considerations, including inhalation, deposition, clearance, and metabolism

The toxicokinetics of several classes of compounds that contribute to outdoor air pollution have been described in earlier *IARC Monographs* (see Section 4.1).

Some PM present in outdoor air is poorly soluble in water and may thus persist in the respiratory tract, producing effects associated with particle toxicity, such as inflammation and oxidative stress. The deposition of particles in the respiratory tract depends primarily on the size of the inhaled particle, the route of breathing, and the breathing pattern. Particles that deposit in the tracheobronchial region are cleared by mucociliary clearance; for particles that deposit in the alveolar region, the primary mechanism of clearance is phagocytosis by alveolar macrophages, followed by migration of the macrophages to the terminal bronchioles and subsequent mucociliary clearance. Particles that are cleared via the mucociliary escalator, whether from the tracheobronchial region or the alveolar region, can then be swallowed or expectorated. If swallowed, they will pass through the gastrointestinal tract and will subsequently be eliminated via the gut.

The deposition and clearance of particles can vary across individuals, depending on age, sex, tobacco smoking status, and pre-existing diseases such as asthma or chronic obstructive pulmonary disease.

Inhaled lipophilic organic vapours and gases readily distribute throughout the respiratory tract and are absorbed into the blood. Organic

compounds in PM or adsorbed to atmospheric PM can be extracted by biological fluids.

Many studies in humans that investigated the exposure and metabolism of organic substances adsorbed to PM in outdoor air have used measurements such as urinary concentrations of hydroxylated polycyclic aromatic hydrocarbons (PAHs) as indicators of exposure and metabolism. These studies have demonstrated the ability of humans to be exposed to carcinogenic organic pollutants such as PAHs and, moreover, to adsorb, distribute, metabolize, and excrete the metabolites. Additional studies have described haemoglobin adducts of nitro-PAHs and low-molecular-weight alkenes. Collectively, the results showed that urinary 1-hydroxypyrene and haemoglobin adducts (hydroxyethyl-valine and hydroxypropyl-valine) were present in populations exposed to outdoor air pollution.

5.4.2 Genetic and related effects of outdoor air pollution

(a) In humans

Studies have investigated the ability of unaltered outdoor air to induce genetic and related effects in humans and experimental systems that are mechanistically linked to cancer. Studies of people exposed to outdoor air pollution in occupational settings (e.g. traffic police, mail carriers, and newspaper vendors) or by living in areas with elevated levels of outdoor air pollution have shown enhanced frequencies of genetic damage (chromosomal aberrations and micronuclei) in lymphocytes of exposed individuals compared with controls. In addition, studies have shown an association between selected genetic polymorphisms, such as glutathione *S*-transferase M1 (*GSTM1*) null, and an increased frequency of genotoxic damage. A single observational study of newborns in an area with elevated levels of outdoor air pollution showed an increased frequency of somatic mutations in lymphocytes. These studies, which cover several countries, collectively confirm the induction of end-points that are empirically and mechanistically linked to increased risk of cancer in humans.

Many studies have shown significant elevation in the levels of DNA adducts in lymphocytes of humans exposed to elevated levels of outdoor air pollution in occupational and urban settings. These findings are supported by a more limited number of studies detecting blood protein adducts.

Studies that examined humans exposed to elevated levels of outdoor air pollution have also documented epigenetic alterations such as changes in DNA methylation patterns and telomere shortening.

(b) In experimental systems

(i) Experimental animals

Experimental studies of rodents exposed to outdoor air in situ provided evidence that outdoor air pollution in urban/industrial areas, especially the particulate fraction, induces heritable germ-cell mutations and cytogenetic damage. Experimental studies of plants exposed to outdoor air pollution at a range of locations also showed induction of mutations and cytogenetic damage.

There is also strong evidence that outdoor air PM or samples derived from outdoor air PM can induce increases in cytogenetic damage in animals.

(ii) Human and animal cells

There is strong evidence that organic extracts, aqueous extracts, or suspensions of outdoor air PM collected from a range of locations induce mutations and cytogenetic effects (chromosomal aberrations, aneuploidy, micronuclei, and sister chromatid exchanges), bulky DNA adducts, DNA strand breaks, oxidatively generated DNA lesions, and formation of reactive oxygen species in cultured human lymphocytes, human cell lines, cultured animal primary cells, animal cell lines in vitro, and naked DNA. Evidence from

source apportionment studies indicates that contributions from mobile-source emissions and residential heating combustion emissions are significant; chemical fractionation of PM extracts revealed contributions from several chemical classes, including non-polar compounds (e.g. PAHs), semipolar compounds (e.g. nitro-PAHs and quinones), and polar compounds (e.g. organic acids and hydroxy-polycyclic aromatic compounds).

(c) In bacteria

There is strong evidence that organic solvent extracts of outdoor air PM representing a wide range of locations, source emissions, seasons, and meteorological conditions induce mutations in bacteria. Published results generally show less than 10-fold variation in the mutagenic potency of PM extracts, expressed per milligram of PM or per microgram of extractable organic matter, across a wide range of locations and site conditions (i.e. source contributions, weather, season, and land use). In contrast, atmospheric mutagenic activity expressed per cubic metre varies by more than 5 orders of magnitude across locations and site conditions (i.e. season, source contributions, and land use), and increased atmospheric mutagenic activity is empirically related to increased levels of atmospheric PM. A large portion of the observed spatial and temporal variations in atmospheric mutagenic activity expressed per cubic metre can be attributed to variations in measured levels of suspended PM.

The atmospheric mutagenic activity at locations described as urban and/or industrial is generally about 2-fold higher compared with locations described as rural and/or residential. Similarly, the atmospheric mutagenic activity measured during colder months is generally about 2-fold higher compared with warmer months. High atmospheric mutagenic activity has been associated with emissions from both mobile and stationary combustion sources, and has been shown to be positively associated with higher levels of NO_x, PAHs, nitro-PAHs, lead, and SO_2. Chemical fractionation studies have noted that a significant portion of the mutagenic activity of organic extracts of outdoor air PM is associated with the moderately polar and polar organic fractions, and includes a wide range of substances, many of which have not been well characterized. Analyses of the non-particulate semivolatile organic compounds (SVOCs) fraction of outdoor air indicate that a significant fraction of the mutagens associated with the solvent-extractable portion of PM from polluted outdoor air may occur as organic vapours.

5.4.3 Other data relevant to carcinogenicity

Some studies have documented increased levels of DNA fragmentation in sperm in young men exposed to polluted outdoor air in an urban location. In addition, human observational studies have shown that exposure to polluted outdoor air in urban/industrial areas or outdoor occupational settings altered the expression of genes involved in DNA damage repair, cell-cycle control, inflammation, and response to oxidative stress.

One experimental exposure of human subjects to concentrated PM from outdoor air showed significant induction of inflammation, a physiological change that has been linked to tumour progression.

Several studies have demonstrated that organic solvent extracts of PM collected from urban environments cause oncogenic transformation of cultured animal cells. Moreover, cells transformed by in vitro exposures to organic solvent extracts of urban PM formed malignant tumours when injected into immunocompromised mice. There is also evidence that exposure of animal cells to PM induces inflammatory reactions, assessed mainly as secretion of cytokines and chemokines, and experimental evidence has linked the inflammation reaction in cultured cells to oxidative stress and metal-catalysed

production of reactive oxygen species. This association between exposure to PM and secretion of cytokines is observed especially in lung epithelial cells and macrophages.

5.4.4 Susceptibility

The available scientific information indicates that certain groups of individuals, such as the elderly, children, and individuals with conditions such as emphysema, bronchitis, and cardiovascular illness, are especially sensitive to the health effects of toxicants in outdoor air. It is recognized that obstructive pulmonary disorders increase lung cancer risk via abnormal immune system regulation and chronic inflammation. The risk of human cancer is related to age and sex via differences in PM deposition patterns and in the capacity to metabolize organic compounds adsorbed to PM.

Polymorphisms in carcinogen-metabolizing genes have been studied as part of human biomonitoring studies investigating the frequency of cytogenetic damage in individuals exposed to polluted outdoor air, and polymorphisms such as the *GSTM1* null genotype, alone or in combination with *CYP1A1* polymorphisms, are associated with an increased risk of genetic and related effects linked to cancer.

5.4.5 Mechanistic considerations

In conclusion, there is *strong mechanistic evidence* for the ability of outdoor air pollution, as well as many of its components, to induce a myriad of genetic and related effects in humans and a wide range of experimental systems. Well-documented genotoxic effects include bulky DNA adducts, DNA strand breaks, oxidatively damaged DNA bases, genetic mutations and chromosomal damage in somatic cells, gametic mutations, and oncogenic transformation in vitro. Molecular epidemiology studies in humans have documented significant empirical associations between the frequencies of DNA damage (i.e. adducts in lymphocytes) and cytogenetic damage (e.g. chromosomal translocations and micronuclei) and exposures to PM in outdoor air and/or levels of carcinogenic PAHs in outdoor PM. In addition, several studies in humans provide evidence of an empirical association between the frequency of stable adducts in lymphocytes of individuals occupationally exposed to outdoor air and levels of outdoor PM or levels of PAHs associated with outdoor PM. Bulky adducts and cytogenetic damage have been shown to be predictive of cancer in humans. Documented changes in gene expression in response to exposures to PM or organic solvent extracts of PM include genes involved in metabolism and activation of mutagenic carcinogens, responses to DNA damage and oxidative stress, alterations of cell-cycle control, and inflammation. The multiplicity of substantiated effects documented in humans as well as in experimental systems in vivo and in vitro supports the assertion that outdoor air pollution, as well as many of its components, is capable of initiating the development of human pulmonary cancers via a genotoxic mechanism and, moreover, of promoting the progress of tumour development via oxidative stress, responses to oxidative stress, and sustained inflammation.