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Chemical Carcinogens

JOHN C. LARSEN AND POUL B. LARSEN

1 Introduction

Although the dominant risk factor in lung cancer is cigarette smoking, epidemiological studies over the last half century have suggested that general ambient air pollution may contribute to increased rates of lung cancer. This evidence is derived from comparisons of urban and rural populations in a number of cohort and case-control studies. Studies on occupational groups have provided strong supportive evidence.[1–3] Cohort studies from several countries have shown relative risks of lung cancer in urban areas of the order of 1.5 or lower, when adjusted for smoking. These findings mainly relate to male smokers. In a number of case-control studies, the evidence of increased relative risks for lung cancer in urban areas was also recorded primarily in male smokers. Increased risks for females and non-smokers in urban areas have only been indicated in a few studies, because the number of cases were too small to provide meaningful differences.[3] A smoking-standardized relative lung cancer risk of 1.5 was found among men and of 1.2 among women living in highly polluted areas of Poland.[4] It was estimated that 4.3% of the lung cancers in men and 10.5% in women could be attributed to air pollution.

Ambient air in densely populated urban areas contains a variety of organic chemicals, including known carcinogens such as benzo[*a*]pyrene (BaP) and benzene. Humans are thus exposed to complex mixtures which also include carbon-based particles that absorb organic compounds, oxidants such as ozone, sulfuric acid in aerosol form, and inorganics such as arsenic and chromium. In this paper, only the organic chemicals which most often have been implicated in cancer risk from general air pollution are considered, notably benzene, 1,3-butadiene, formaldehyde and, in particular, polynuclear aromatic hydrocarbons (PAHs).

Chemical carcinogenesis is a multistage process including initiation, promotion

[1] A. J. Cohen and C. A. Pope III, *Environ. Health Perspect.*, 1995, **103**, 219.
[2] G. Pershagen and L. Simonte, in *Air Pollution and Human Cancer*, ed. L. Tomatis, Springer, Heidelberg, 1990, p. 63.
[3] K. Hemminki and G. Pershagen, *Environ. Health Perspect.*, 1994, **102**, 187.
[4] W. Jedrychowski, H. Becher, J. Wahrendorf and Z. Basa-Cierpialek, *J. Epidemiol. Commun. Health*, 1990, **44**, 114.

and progression. In the initiation step, which may involve procarcinogen activation to genotoxic species, a genotoxic agent interacts with DNA and induces mutations in the target cells. If not repaired by the endogenous DNA repair systems the mutations may be fixed in initiated daughter cells. During promotion the initiated cells experience growth advantages, resulting in increased cell proliferation and the development of (benign) neoplasia. The promotion can be stimulated by many chemicals acting on enzymes controlling cell homeostasis, by respiratory tract irritants and by tissue injury and inflammation. Promotion is not thought to involve genotoxic mechanisms. During the progression phase the cells become malignant and capable of invading other tissues (metastasis). Genotoxic events are thought to play a role during progression.

Data from epidemiological studies of occupationally exposed workers or animal studies may be used to estimate risks from chemicals at the much lower levels normally encountered in ambient air. From a theoretical point of view, there is no threshold dose for the carcinogenic effect of a genotoxic agent below which there is no risk. Risks at low levels of exposure have to be estimated by extrapolation. In most cases, linear dose–response relationships are assumed, and a unit risk factor can be calculated. Normally, unit risk is the probability (95% upper confidence limit) of developing cancer from continuous lifetime inhalation of 1 $\mu g\,m^{-3}$ of the airborne chemical. In the case of compounds that produce cancer by non-genotoxic mechanisms, it is believed that threshold exposures for the carcinogenic effect can be established.

There seems to be a genetic predisposition in the individual susceptibility to lung cancer, at least for cigarette smoking. Of the many steps involved in carcinogenesis, most toxicological information on differences in susceptibility points to the proximate procarcinogen metabolism steps. The major classes of organic chemical carcinogens present in ambient air undergo oxidation (phase I) and conjugation steps (phase II). During phase I, intermediates can be bioactivated to potential carcinogens, while they are detoxified during phase II. Genetic polymorphisms seem to exist for both phase I and phase II enzymes, and an individual's susceptibility to lung cancer may be conferred by the balance between the capacity to activate inhaled procarcinogens to ultimate carcinogens and detoxify proximate/ultimate carcinogens.[5]

2 Benzene

Sources and Levels in Ambient Air

Benzene is a colourless liquid with a boiling point of 80 °C and a high vapour pressure. Benzene constitutes about 1–5% of gasoline. The major release of benzene into the environment ($> 80\%$) comes from automobile exhaust, where benzene accounts for about 5% of the total hydrocarbon emissions.[6,7] Background levels of benzene at remote and rural areas have been reported at 0.5–1.5 $\mu g\,m^{-3}$.

[5] S. D. Spivack, M. J. Fasco, V. E. Walker and L. S. Kaminsky, *Crit. Rev. Toxicol.*, 1997, **27**, 319.
[6] IPCS, *Benzene*, Environmental Health Criteria 150, International Programme on Chemical Safety, World Health Organization, Geneva, 1993.
[7] L. Wallace, *Environ. Health Perspect.*, 1996, **104**, 1129.

Average levels of 5–15 $\mu g\,m^{-3}$ have been found in Western European and North American cities. However, at the kerbside of busy streets, levels of 30 $\mu g\,m^{-3}$ or higher have been measured.[6,8] Measurements of benzene concentration at 20 sites in California showed a decreasing time trend from an average level of about 9 $\mu g\,m^{-3}$ in 1986 to about 4 $\mu g\,m^{-3}$ in 1994.[7] Levels were found to be about twice as high in the winter compared to the summer. In Sweden, winter levels (1993/1994) in 22 towns were reported at 2.6–7.4 $\mu g\,m^{-3}$.[8]

Human Exposure

About 40% of the average daily benzene exposure of non-smokers can be attributed to benzene in outdoor air, while indoor air may account for about 31% (levels of about 3–8 $\mu g\,m^{-3}$). Driving a vehicle may account for about 19%, as the average level inside cars is about 40 $\mu g\,m^{-3}$.[7] At petrol stations, one may be exposed to a benzene level of about 1 $mg\,m^{-3}$ during refuelling.[8] Cigarette smoke is an important additional source of benzene, and smokers are exposed to about 55 μg of benzene per cigarette. Further, cigarette smoke significantly contributes to indoor benzene levels, as the levels in homes of smokers are generally 3.5–4.5 $\mu g\,m^{-3}$ higher than in homes with no tobacco smoke.[7]

Overall, inhalation of benzene accounts for about 98–99% of the total daily benzene exposure, and the average intake is estimated to about 200 μg for non-smokers and 2 mg for smokers. Oral ingestion, *i.e.* through food and drinking water, does not significantly contribute to benzene intake ($< 1\%$).[7]

Toxicokinetics

Inhaled benzene is readily absorbed from the lungs. In humans at exposure levels of 163–326 $mg\,m^{-3}$, about 50% of the inhaled benzene was reported to be absorbed. The highest levels of benzene are obtained in lipid-rich tissues, and benzene is known to cross the placental barrier.[6,8] Benzene metabolism is similar in humans and experimental animals. Benzene is metabolized mainly in the liver by the cytochrome P450 2E1 enzyme system and involves formation of the unstable intermediate benzene oxide. The major metabolites formed are phenol, catechol and hydroquinone. Benzoquinone and muconaldehyde are minor metabolites considered to contribute to the toxicity of benzene. In rodents, the formation of these metabolites appears to be saturable, resulting in proportionally higher fractions of these toxic metabolites at lower levels. Mice were found to be most active in converting benzene to benzoquinone and muconaldehyde.[6,8]

In humans, benzene is eliminated unmetabolized with the expiratory air, whereas metabolites are excreted in urine, primarily as the sulfate and glucuronide conjugates of phenol.[6]

Toxicological Effects

The primary acute reponses to benzene by humans involve narcotic symptoms

[8] WHO, *Benzene*, in *WHO Air Quality Guidelies for Europe*, 2nd edn., World Health Organization, Regional Office for Europe, Copenhagen, 1998.

from the central nervous system, such as dizziness, headache, drowsiness and nausea. Headache, lassitude and weakness have been reported at benzene levels between 160 and 480 mg m^{-3}. However, short-term exposure to benzene at levels of 1600–3200 mg m^{-3} (500–1000 ppm) are tolerated by humans without serious adverse effects.[6,9]

The main toxic manifestations from repeated occupational exposure to benzene are bone marrow depression with anaemia, leucopenia or thrombocytopenia. The effects follow a clear dose–response relationship down to an exposure level of about 32 mg m^{-3} (10 ppm). It has been suggested that it is the combined effects of several of the benzene metabolites that adversely affect the functioning of bone marrow cells and lead to pancytopenia and aplastic anaemia.[6]

Many studies have reported structural and numerical chromosomal aberrations in lymphocytes and bone marrow cells from workers exposed to benzene, and in some cases at exposure levels as low as 4–7 mg m^{-3}. Benzene has not induced gene mutations *in vitro*, but in animal studies benzene exposures have caused a variety of chromosomal aberrations which support the view that benzene is a clastogenic agent.[8] The mechanism of action is not fully understood. Metabolic data suggest that several reactive metabolites may form adducts with DNA and proteins. Binding to protein components of the spindle apparatus may inhibit the mitosis of the cell, while binding to DNA may be an initiating event in carcinogenesis.[6]

Carcinogenicity

Results from carcinogenicity testing of benzene in experimental animals have revealed the induction of various types of lymphomas/leukaemias. However, most neoplasms found were of epithelial origin, *i.e.* in the Zymbal gland, liver, mammary gland and oro-nasal cavity. A carcinogenic effect was still found at 320 mg m^{-3} in inhalation studies and at a dose of 25 mg kg^{-1} of body weight per day by gavage. Thus, in experimental animals, benzene was not only a specific leukaemogenic agent as in humans (see below), but rather a multipotent carcinogen.[6]

Epidemiological Data

Several epidemiological studies have consistently shown a positive relationship between benzene exposure and leukaemia. The most thorough study involves a group of workers in the rubber film industry (the Pliofilm cohort). A total of 1212 workers employed between 1940 and 1965 were followed up to 1987. The cohort was unique because of the high quality data with respect to exposure history and medical surveillance. In the latest up-date a total of 14 cases of leukaemia and four cases of multiple myelomas had occurred. The standard mortality rate (SMR) for all lymphatic and haematopoietic cancers (SMR = 221) and for leukaemia (SMR = 360) were significantly increased. A strong positive trend was found between leukaemia mortality and increased cumulative exposure.[6,8]

[9] D. J. Paustenbach, R. D. Bass and P. Price, *Environ. Health Perspect.*, 1993, **101**, 177.

Evaluation and Risk Assessment

Based on the epidemiological evidence, benzene was considered a human carcinogen (group 1) by the IARC, the International Agency for Research on Cancer.[10]

The WHO, in its update of the Air Quality Guidelines for Europe, used data from the updated Pliofilm cohort and models based on relative risk and cumulative exposure to calculate unit risks for benzene in the range of $4.4–7.5 \times 10^{-6}$ per $\mu g\,m^{-3}$, with a geometric mean of 6×10^{-6} per $\mu g\,m^{-3}$. Based on this, the WHO concluded that the average concentration of airborne benzene associated with an excess lifetime cancer risk of 10^{-6} was $0.18\,\mu g\,m^{-3}$.[8] Thus, at an average urban air level of $5–15\,\mu g\,m^{-3}$ this risk estimate predicts 30–90 extra cases of leukaemia among 1 million exposed for their lifetime.

3 1,3-Butadiene

Sources and Levels in Ambient Air

1,3-Butadiene is a colourless gas, only slightly soluble in water. The two conjugated double bonds in the molecule make it highly reactive.[11,12]

Traffic exhaust is the primary source of 1,3-butadiene in ambient air. 1,3-Butadiene is emitted at an average vehicle rate of $5.6–6.1\,mg\,km^{-1}$ and comprises roughly 0.35% of the hydrocarbons in the exhaust (exhaust contains about $44–72\,\mu g\,m^{-3}$ 1,3-butadiene). In general, average long-term exposure levels of 1,3-butadiene in urban air are around $1\,\mu g\,m^{-3}$. The mean level in 19 cities in the USA was reported to be $1.4\,\mu g\,m^{-3}$.[11,12]

1,3-Butadiene is rapidly transformed in the atmosphere by reaction with hydroxyl radicals, ozone and nitrogen trioxide radicals. These reactions generate formaldehyde, acrolein and organic nitrates. In the daytime during the summer the residence time of 1,3-butadiene in the atmosphere is estimated to be less than one hour, while in the winter on cloudy days it may exceed one day.[11]

Human Exposure

The general public is exposed to concentrations of 1,3-butadiene in the low $\mu g\,m^{-3}$ range through ambient and indoor air. Indoor cigarette smoke may significantly contribute to the exposure (0.2–0.4 mg per cigarette in sidestream smoke) and smoky indoor levels of $10–20\,\mu g\,m^{-3}$ have been reported. An

[10] IARC, *Benzene*, in *Overal Evaluations of Carcinogenicity*: *An Updating of IARC Monographs Volumes 1 to 42*, IARC Monographs on the Evaluation of Carcinogenic Risks to Humans, suppl. 7, International Agency for Research on Cancer, Lyon, 1987, p. 120.

[11] US EPA, *Motor Vehicle-Related Air Toxics Study*, Technical Support Branch Emission Planning and Strategies Division, Office of Mobile Sources, Office of Air and Radiation, US Environmental Protection Agency, 1993.

[12] WHO, *1,3-Butadiene*, in *WHO Air Quality Guidelines for Europe*, 2nd edn., World Health Organization, Regional Office for Europe, Copenhagen, 1998.

additional source of exposure is inhalation of gasoline vapours at petrol stations and inside cars.[12,13]

Toxicokinetics

In animal studies the degree of absorption following inhalation of 1,3-butadiene depends on the species tested and the exposure level used. At a (low) exposure level of 1.77 mg m^{-3}, 20% of the inhaled dose was retained by mice, while only 6% was retained by rats. At a higher exposure level of 2210 mg m^{-3} (1000 ppm), 4% was retained by mice and 2.5% by rats.[14] Studies in monkeys indicate a lower uptake in this species than in rats and mice.[15]

Metabolic conversion to the genotoxic metabolites 1,2-epoxy-3-butene and 1,2: 3,4-diepoxybutane by cytochrome P450 enzymes is regarded as the crucial event for the carcinogenic potential of 1,3-butadiene. Large species differences have been found with respect to the formation and degradation of these active metabolites. Thus, at a similar exposure level, considerably higher levels of 1,2-epoxy-3-butene and 1,2: 3,4-diepoxybutane were measured in the blood from mice than from rats.[16] This may explain why the mouse is more susceptible to the carcinogenic effect of 1,3-butadiene than the rat. There is evidence that primates generate 1,2-epoxy-3-butene to a lesser extent than rodents; however, the extent to which 1,2: 3,4-diepoxybutane is produced in primates is not known.[16]

Toxicological Effects

1,3-Butadiene is of low acute toxicity in experimental animals with LD_{50} values above 221 000 mg m^{-3} (100 000 ppm). Exposure levels of several thousand ppm may cause respiratory tract and eye irritation in humans. In long-term experiments, 1,3-butadiene exposure has caused testicular atrophy in male mice at 1380 mg m^{-3} and ovarian atrophy in female mice at 13.8 mg m^{-3} and higher levels. In reproductive and developmental studies, decreased foetal weight (exposure level 88.4 mg m^{-3}), extra ribs (442 mg m^{-3}) and sperm head abnormalities (2210 mg m^{-3}) have been reported in mice. In the rat, skeletal variations (2210 mg m^{-3}) and skeletal abnormalities (17 600 mg m^{-3}) have been observed.[13]

1,3-Butadiene and its metabolites, 1,2-epoxy-3-butene and 1,2: 3,4-diepoxybutane, have shown genotoxicity in a variety of *in vitro* and *in vivo* studies. 1,3-Butadiene was particularly active in studies using mice, owing to the high capacity of this species to bioactivate 1,3-butadiene to the genotoxic metabolites.[13,17]

[13] M. W. Himmelstein, J. F. Acquavella, L. Recio, M. A. Medinsky and J. A. Bond, *Crit. Rev. Toxicol.*, 1997, **27**, 1.

[14] J. A. Bond, A. R. Dahl, R. F. Henderson, J. S. Dutcher, J. L. Mauderly and L. S. Birnbaum, *Toxicol. Appl. Pharmacol.*, 1986, **84**, 617.

[15] A. Dahl, J. D. Sun, L. S. Birnbaum, J. A. Bond, W. C. Griffith, J. L. Mauderly, B. A. Muggenburg, P. J. Sabourin and R. F. Henderson, *Toxicol. Appl. Pharmacol.*, 1991, **110**, 9.

[16] R. F. Henderson, J. R. Thornton-Manning, W. E. Bechtold and A. Dahl, *Toxicology*, 1996, **113**, 17.

[17] IARC, *1,3-Butadiene*, IARC Monographs on the Evaluation of Carcinogenic Risks to Humans, vol. 54, International Agency for Research on Cancer, Lyon, 1992, p. 237.

Carcinogenicity

1,3-Butadiene has been tested for carcinogenicity in one rat study and four mouse studies using inhalation exposures in the range of 14 to 17 600 mg m^{-3}. In all studies and at all exposure levels, increased incidences of tumours were found.

In rats tested at 2200 and 17 600 mg m^{-3} (6 h per day, 5 days per week for up to 111 weeks), females had exposure-related increased rates of mammary gland adenomas/carcinomas, thyroid follicular cell adenomas, uterine sarcomas and Zymbal gland sarcomas, while males had increased incidences of testicular Leydig cell tumours and pancreatic exocrine adenomas.[13] The mouse was found more susceptible to the carcinogenic effects of 1,3-butadiene exposure than the rat. Exposure at levels of 13.8, 44.2, 138, 442 and 1380 mg m^{-3} (6 h per day, 5 days per week for up to 2 years) resulted in treatment-related increased incidences of lymphocytic lymphomas, haemangiosarcomas of the heart, and neoplasms of the lung, forestomach, Harderian gland, preputial gland, liver, mammary gland and ovary. Significant increases in lung adenomas/carcinomas were observed down to the lowest exposure level of 13.8 mg m^{-3}.[18]

Epidemiological Data

The most important epidemiological data include cohort mortality studies of butadiene monomer (BDM) workers and styrene butadiene rubber (SBR) workers. In a recent update of a cohort of 2795 BDM workers with occupational exposure solely to 1,3-butadiene, an increased standardized mortality rate (SMR) of 147 (95% confidence limit: 106–198) was found for lymphohaematopoietic cancers (LHC). However, many of the LHC cases were seen in workers engaged fewer than five years at the plant and therefore might have been exposed to other agents in previous occupations. Furthermore, only very rough exposure indices were available as measurements of 1,3-butadiene occupational levels were not performed.[19]

An increased SMR of 131 (95% confidence limit: 97–174) for leukaemia was found in a recent update of a cohort of 15 649 SBR workers from seven plants. Even higher SMRs were found for leukaemia in subgroups with a long duration of employment, and for workers occupied at sites and processes with high levels of styrene and 1,3-butadiene.[20] From estimated individual cumulative exposure indices, a positive relationship was found between 1,3-butadiene exposure and increased SMR values for leukaemia.[21] In these studies, no increased SMR was found for other types of lymphohaematopoietic cancer.

[18] R. L. Melnick, J. Huff, B. J. Chou and R. A. Miller, *Cancer Res.*, 1990, **50**, 6592.
[19] B. J. Divine and C. M. Hartman, *Toxicology*, 1996, **113**, 169.
[20] E. Delzell, N. Sathiakumar, M. Hovinga, M. Macaluso, J. Julian, R. Larson, P. Cole and D. Muir, *Toxicology*, 1996, **113**, 182.
[21] M. Macaluso, R. Larson, E. Delzell, N. Sathiakumar, M. Hovinga, J. Julian, D. Muir and P. Cole, *Toxicology*, 1996, **113**, 190.

Evaluation and Risk Assessment

The IARC has evaluated 1,3-butadiene as probably carcinogenic to humans (group 2A), based on sufficient evidence for carcinogenicity from experimental animal data and limited evidence for carcinogenicity from human data.[17]

Owing to uncertainties as to which animal species and extrapolation models should be used for risk assessment, the WHO in its update of the Air Quality Guidelines for Europe did not recommend a risk estimate for 1,3-butadiene as a basis for a guidance value. The WHO expressed the view that despite the fact that there is some evidence of the carcinogenicity of 1,3-butadiene in humans, albeit equivocal, decisions regarding ambient air standards should be made with prudence.[12]

In a review of seven risk assessments of 1,3-butadiene performed by different agencies and organizations, the calculated risk estimates for an occupational level of 1 ppm (2.21 mg m^{-3}) 1,3-butadiene ranged from 0 to 2613 extra deaths per 10 000 exposed workers. This reflects the large differences between the assessments in selecting and utilizing experimental data (using rat or mouse data, and how to scale from animal dose to human dose) and in the use of models for low-dose level extrapolation. In general, considerably lower risk estimates were obtained when the data from the rat study were used. However, at present there is no general agreement upon which experimental animal species (rat or mouse) should be used for the extrapolation to humans.[13]

4 Formaldehyde

Sources and Ambient Air Levels

Formaldehyde is a very water soluble and reactive gas with a pungent odour. Formaldehyde is formed by photooxidation of hydrocarbons in the troposphere, where naturally occurring methane is the most important source. Background levels of formaldehyde are below 1 $\mu g\,m^{-3}$.[22,23] Traffic emissions are by far the most important sources of formaldehyde in ambient air in urban areas. Gasoline engines may emit several hundred mg of formaldehyde per litre of combusted fuel and diesel engines about 1 g formaldehyde per litre of fuel. The use of exhaust catalytic converters reduces the formaldehyde emission to less than one-tenth of those levels.[22] Levels in urban areas with anthropogenic hydrocarbon and aldehyde emissions from traffic are reported to be 1–20 $\mu g\,m^{-3}$. However, peak levels up to 100 $\mu g\,m^{-3}$ may occur during severe inversion episodes.[22,23]

In air, formaldehyde photolyses and reacts rapidly with free radicals. The half-life in sunlight is a few hours. Owing to the high water solubility, formaldehyde may also be eliminated with rain. Levels in rainwater have been reported to be 0.1–0.2 mg kg^{-1}.[22]

[22] IPCS, *Formaldehyde*, Environmental Health Criteria 89, International Programme on Chemical Safety, World Health Organization, Geneva, 1989.

[23] IARC, in *Wood Dust and Formaldehyde*, IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Humans, vol. 62, International Agency for Research on Cancer, Lyon, 1995, p. 217.

Human Exposure

In humans and other mammals, formaldehyde is an essential metabolic intermediate in all cells, *e.g.* in the biosynthesis of purines, thymidine and certain amino acids. The concentration of formaldehyde in the blood of humans not exposed to exogenous formaldehyde has been reported to be $2.6\,mg\,kg^{-1}$.[23] Humans are mainly exposed to formaldehyde by inhalation from ambient and indoor air. Levels in indoor air may be much higher than in ambient air owing to evaporation of formaldehyde from furniture, painting and building constructions. Levels between 10 and 1000 $\mu g\,m^{-3}$ have been reported. The contribution from various atmospheric environments to the average human daily intake has been calculated to be $0.02\,mg\,d^{-1}$ for outdoor air, 0.5–$2\,mg\,d^{-1}$ for indoor conventional buildings and up to 1–$10\,mg\,d^{-1}$ for buildings with sources of formaldehyde. Smoking 20 cigarettes per day contributes an additional exposure of about 1 mg formaldehyde.[22]

Toxicokinetics

Formaldehyde is almost completely retained after inhalation; however, no incease in blood formaldehyde has been measured after exposure of humans or experimental animals. This may be explained by the high reactivity of formaldehyde. After retention of the highly hydrophilic substance in the mucus layer of the upper respiratory tract, formaldehyde either rapidly reacts with macromolecules in the mucus layer or the surface structures of the epithelial cells or is rapidly metabolized to formic acid and carbon dioxide by formaldehyde dehydrogenase and other enzymes, and becomes a source for the one-carbon biosynthetic pathways. In the rat, retention of formaldehyde takes place primarily in the nasal cavities, while in primates, formaldehyde may pass deeper into the respiratory tract and be retained in the trachea and the proximal regions of the major bronchi.[22,23]

Toxicological Effects

Exposure to formaldehyde vapour causes sensory irritation of the mucous membranes of the eyes and the upper respiratory tract. In humans the threshold of irritation is considered to be $0.1\,mg\,m^{-3}$ for the average population, while hyperreactive persons may experience irritation at lower levels.[22,24]

Formaldehyde reacts readily with macromolecules and has produced genotoxic effects *in vitro* and *in vivo*. DNA damage and mutations have been observed in bacterial assays, and DNA single-strand breaks, chromosomal aberrations, sister chromatid exchanges and gene mutations have been seen in assays using human cells. Studies have shown DNA–protein cross links in the nasal mucosa of rodents and monkeys, and chromosomal anomalies in lung cells of rats.[23]

[24] WHO, *Formaldehyde*, in *WHO Air Quality Guidelines for Europe*, 2nd edn., World Health Organization, Regional Office for Europe, Copenhagen, 1998.

Carcinogenicity

Several studies have demonstrated that long-term exposure to formaldehyde vapour by inhalation produces squamous cell carcinomas of the nasal epithelium of rats and mice.[23] The rat was found particulary sensitive, showing a steep dose–response relationship for the development of tumours in the exposure range of 7–18 mg m^{-3}.[25,26] As an example, when 120 rats of each sex were exposed to 0, 2.5, 6.9 or 17.6 mg m^{-3} (6 h per day, 5 days per week for up to 24 months), 2 of 235 animals at the medium exposure level (6.9 mg m^{-3}) and 103 of 232 animals at the high exposure level (17.6 mg m^{-3}) developed nasal squamous cell carcinomas.[25]

Much research has been done to clarify the mechanisms behind the carcinogenic effect of formaldehyde. It is recognized that nasal squamous cell carcinomas have only been observed at formaldehyde levels higher than those producing cytotoxic effects in the same tissue. In the rat, formaldehyde has induced cytotoxic responses and increased cell proliferation at exposure levels down to 2.5 mg m^{-3}.[25,27] Thus, the development of squamous cell carcinomas at higher exposure levels in animal experiments is considered a consequence of prolonged, repeated exposure to cytotoxic formaldehyde levels that produce inflammation, cell damage and increased cell proliferation.[23,28,29]

Epidemiological Data

More than 30 epidemiological studies have been performed on the relationship between exposure to formaldehyde and cancer in humans. From two meta-analyses a causal relationship was suggested for occupational exposure to formaldehyde and elevated risks for development of sinonasal and nasopharyngeal cancers.[30,31] On the basis of the overall human database, the IARC in 1995 concluded that there was only limited evidence for carcinogenic effects of formaldehyde in humans. However, the suggested relationship between formaldehyde exposure and cancer of the nasopharynx and the nasal cavities was noticed.[23]

Recent epidemiological data add further support to a causal relationship between formaldehyde exposure and nasal cancer. Among 3304 cancer patients having worked more than 10 years in 265 identified companies where formaldehyde was used, the only increased cancer risk was found for nasal cancer [RR for men: 2.3 (1.3–4.0, 95% confidence limit); RR for women: 2.4 (0.6–6.0, 95% confidence limit)]. In a subgroup of workers with no probable combined exposure to formaldehyde and wood-dust (a major confounder for nasal cancer), a relative risk for nasal cancer of 3.0 (1.4–5.7) was obtained.[32]

[25] W. D. Kerns, K. L. Pavkov, D. J. Donofrio, E. J. Gralla and J. A. Swenberg, *Cancer Res.*, 1983, **43**, 4382.
[26] T. M. Monticello, J. A. Swenberg, E. A. Gross, J. R. Leininger, J. S. Kimbell, S. Seilkop, T. B. Starr, J. E. Gibson and K. T. Morgan, *Cancer Res.*, 1996, **56**, 1012.
[27] E. Roemer, H. J. Anton and R. Kindt, *J. Appl. Toxicol.*, 1993, **13**, 103.
[28] H. A. Heck, M. Casanova and T. B. Starr, *Crit. Rev. Toxicol.*, 1990, **20**, 397.
[29] K. T. Morgan, *Toxicol. Pathol.*, 1997, **25**, 291.
[30] A. Blair, R. Saracci, P. A. Stewart, R. B. Hayes and C. Shy, *Scand. J. Work Environ. Health*, 1990, **16**, 381.
[31] T. Partanen, *Scand. J. Work Environ. Health*, 1993, **19**, 8.
[32] J. Hansen and J. H. Olsen, *Ugeskrift for Læger*, 1996, **158**, 4191 (in Danish with English summary).

Evaluation and Risk Assessment

The IARC has evaluated formaldehyde as probably carcinogenic to humans (group 2A), based on sufficient evidence for carcinogenicity from experimental animal data and limited evidence for carcinogenicity from human data.[23]

Based on data from a rat study[25] and using the linearized multistage model for cancer risk extrapolation, the US EPA in 1987 estimated a human inhalation unit risk of 1.6×10^{-2} per ppm of formaldehyde (corresponding to a unit risk of 1.3×10^{-5} per $\mu g\,m^{-3}$). In 1991, the US EPA re-evaluated this risk estimate in order to account for differences between rodents and primates in the anatomical structure of the nasal cavities. Using data from tissue dosimetry (formaldehyde-induced formation of DNA–protein cross links in target tissue of rats and monkeys), a human unit risk value of 3.3×10^{-4} per ppm was calculated (corresponding to a unit risk of 2.75×10^{-7} per $\mu g\,m^{-3}$). This was an overall 50-fold reduction of the previous risk estimate.[33,34] With this estimate an average level of formaldehyde in urban air of $10\,\mu g\,m^{-3}$ corresponds to 2–3 extra cases of nasal cancer among 1 million exposed during a lifetime.

The WHO, in its updating of the Air Quality Guidelines for Europe, did not recommend any unit risk level for the carcinogenicity of formaldehyde. It was concluded that formaldehyde exposure below the cytotoxic level may only represent a negligible cancer risk, as cytotoxicity and repeated cell damage were considered closely linked to the development of nasal cancer. Thus, a guideline value of $100\,\mu g\,m^{-3}$ to protect against sensory irritation was considered adequate to protect also against carcinogenic effects.

5 Other Aldehydes

Acetaldehyde is another aldehyde that has shown carcinogenicity in experimental animals. Acetaldehyde induced tumours in the nasal cavities in rats after long-term exposure by inhalation to $1350\,mg\,m^{-3}$, *i.e.* at much higher levels than formaldehyde. The lowest observed effect level for cytotoxicity in the nasal mucosa of rats was reported to be $275\,mg\,m^{-3}$; thus acetaldehyde may be considered much less potent than formaldehyde. Levels of acetaldehyde in urban ambient air average about $5\,\mu g\,m^{-3}$.[35] Based on this, the carcinogenic potential of acetaldehyde in ambient air seems far less problematic compared to formaldehyde.

Acrolein has higher potency than formaldehyde with respect to irritative effect and cytotoxicity. No carcinogenicity testing has been performed with acrolein. Acrolein has shown genotoxicity *in vitro*. The reported levels in ambient air tend to be somewhat lower than those of formaldehyde (about three times).[36]

[33] US EPA, *Formaldehyde Risk Assessment Update*, Office of Toxic Substances, US Environmental Protection Agency, Washington, 1991.

[34] O. Hernandez, L. Rhomberg, K. Hogan, C. Siegel-Scott, D. Lai, G. Grindstaff, M. Henry and J. A. Cotruvo, *J. Hazard Mater.*, 1994, **39**, 161.

[35] IPCS, *Acetaldehyde*, Environmental Health Criteria 167, International Programme on Chemical Safety, World Health Organization, Geneva, 1995.

[36] IPCS, *Acrolein*, Environmental Health Criteria 127, International Programme on Chemical Safety, World Health Organization, Geneva, 1992.

6 Polynuclear Aromatic Hydrocarbons (PAHs)

Sources and Levels in Ambient Air

PAHs are formed by incomplete combustion of organic materials and in natural processes such as carbonization. Major sources are residential heating (coal, wood, oil), automobile exhaust, industrial power generation, incinerators, the production of coal tar, coke, asphalt and petroleum catalytic cracking, cooking and tobacco smoking. Of the many hundreds of PAHs, the best known is benzo[*a*]pyrene (BaP), which often is used as a marker for PAHs in ambient air. In addition to the 'classical' PAHs, a number of heterocyclic aromatic compounds (*e.g.* carbazole, acridine), as well as derivatives of PAHs, such as nitro-PAHs and oxygenated PAHs, can be generated by incomplete combustion and from chemical reactions in ambient air. The contributions from the different important sources are difficult to estimate, and may vary from country to country. Stationary sources account for a high percentage of the total annual PAH emission. However, in urban or suburban areas, mobile sources are additional major contributors to PAH releases to the atmosphere. In air, PAHs are mainly attached to particles.[37–39] In the 1960s the annual average concentration of BaP was reported to be higher than 100 ng m^{-3} in several European cities.[37] In most developed countries, PAH concentrations have decreased substantially during the last 30 years owing to improved combustion technologies, increased use of catalytic converters in motor vehicles, and replacement of coal with oil and natural gas as energy sources. BaP levels below 1 ng m^{-3} are normally found at rural sites, while the levels in urban areas and areas with heavy traffic generally are 1–10 ng m^{-3}. PAH levels are higher during winter than summer.[39,40] In Copenhagen, the mean BaP concentration (January to March 1992) at a petrol station in a busy street was found to be 4.4 ng m^{-3}.[41]

Human Exposure

Human exposure to PAHs from inhalation of ambient air varies according to the degree of urbanization, traffic and industrialization. In terms of daily BaP intake the range could normally cover from less than 10 ng to more than 100 ng. Additional contributions from tobacco smoking and the use of unvented heating sources can increase PAH concentrations in indoor air, in certain cases to very high levels. Very high concentrations of PAHs can also occur in workplaces, such as coke-oven batteries, retort houses of coal-gas works and in the metal smelting industry.[37,42]

[37] WHO, *Polynuclear Aromatic Hydrocarbons (PAH)*, in *Who Air Quality Guidelines for Europe*, 2nd edn., World Health Organization, Regional Office for Europe, Copenhagen, 1998.

[38] ATSDR, *Toxicological Profile for Polycyclic Aromatic Hydrocarbons (PAHs): Update*, US Department of Health and Human Services, Public Health Services, Agency for Toxic Substances and Disease Registry, Atlanta, 1994.

[39] S. O. Baek, R. A. Field, M. E. Goldstone, P. W. Kirk, J. N. Lester and R. Perry, *Water Air Soil Pollut.*, 1991, **60**, 279.

[40] H. U. Pfeffer, *Sci. Total Environ.*, 1994, **146/147**, 263.

[41] T. Nielsen, H. E. Jørgensen, M. Poulsen, F. Palmgren Jensen, J. C. Larsen, M. Poulsen, A. B. Jensen, J. Schramm and J. Tønnesen, *Traffic PAH and Other Mutagens in Air in Denmark*, Miljøprojekt 285, Danish Environmental Protection Agency, Copenhagen, Denmark, 1995.

However, food is considered the major source of human exposure to PAH owing to the formation of PAH during cooking and from atmospheric deposition of PAHs on grains, fruits and vegetables. When human exposure to eight carcinogenic PAHs (benz[*a*]anthracene, chrysene, benzo[*b*]fluoranthene, benzo[*k*]fluoranthene, BaP, indeno[1,2,3-*cd*]pyrene, dibenz[*a,h*]anthracene and benzo[*ghi*]perylene) was estimated for a 'reference man', a mean total intake of 3.12 $\mu g\,d^{-1}$ was estimated for non-smokers, of which food contributed 96.2%, air 1.6%, water 0.2% and soil 0.4%. Smokers consuming one pack of non-filtered cigarettes per day had an estimated additional intake of 1–5 $\mu g\,d^{-1}$.[43]

Toxicokinetics

PAHs are highly lipid-soluble and are absorbed from the lung, gut and skin. Studies in rats given microcrystalline PAHs or PAHs in solution have indicated that PAHs are efficiently cleared from the respiratory tract. For several PAHs, greater than 85% of the initial dose was cleared with a half-time of less than 1 hour.[37] Prolonged retention and extensive metabolism and activation of BaP was found to take place in the tracheobronchial epithelium of dogs.[44] When BaP is adsorbed on particles, the respiratory uptake rate is much lower, but the particles are retained for a long period of time in the respiratory tract. When radioactively labelled BaP adsorbed onto diesel engine exhaust particles or urban air particles was inhaled by rats, the lung clearance of the inhaled particle-associated radioactivity occurred in two phases: an initial rapid clearance and a long-term component that represented 50% of the radioactivity initially deposited in the lungs. Inhalation of [^{14}C]BaP adsorbed on carbon black particles resulted in 100-fold higher levels of ^{14}C in lungs at the end of a 12-week exposure than did inhalation of pure BaP.[37]

Irrespective of the route of administration, PAHs are rapidly and widely distributed throughout the organism. The highest levels are obtained in the liver.[45,46] Owing to the rapid metabolism of PAHs, no significant accumulation takes place in body fat. Studies show that BaP can readily cross the placental barrier of rats and mice. Following metabolism, hepatobiliary excretion and elimination through the faeces, and to a minor extent urinary excretion, are the major routes by which BaP metabolites are removed from the body, independent of the route of administration.[37,46–48]

[42] P. L. Lioy, J. M. Waldman, A. Greenberg, R. Harkov and C. Pietarinen, *Arch. Environ. Health*, 1988, **43**, 304.
[43] C. A. Menzie, B. B. Potocki and J. Santodonato, *Environ. Sci. Technol.*, 1992, **26**, 1278.
[44] P. Gerde, B. A. Muggenburg, J. R. Thornton-Manning, J. L. Lewis, K. H. Pyon and A. R. Dahl, *Carcinogenesis*, 1997, **18**, 1825.
[45] IARC, *Polynuclear Aromatic Compounds. Part 1. Chemical, Environmental and Experimental Data*, IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Humans, vol. 32, International Agency for Research on Cancer, Lyon, France, 1983.
[46] H. Foth, R. Kahl and G. F. Kahl, *Food Chem. Toxicol.*, 1988, **26**, 45.
[47] J. R. Withey, J. Shedden, F. C. Law and S. Abedini, *J. Appl. Toxicol.*, 1993, **13**, 193.
[48] J. A. van de Wiel, P. H. Fijneman, C. M. Duijf, R. B. Anzion, J. L. Theuws and R. P. Bos, *Toxicology*, 1993, **80**, 103.

Metabolism and Activation

The biotransformation and activation of BaP and other PAHs have been studied intensively.[45,49–52] PAHs are metabolized by the microsomal cytochrome P450 system, which converts the non-polar PAHs into polar hydroxy and epoxy derivatives. Isozymes belonging to the P450 1A (in particular), P450 2A, P450 3A and P450 2B superfamilies are the major forms thought to be involved in the metabolism and activation of PAHs. These enzymes are widely distributed in cells and tissues of humans and animals. The highest metabolizing capacity is present in the liver, followed by the lung, intestinal mucosa, skin and kidneys.[37] In human lung, P450 1A1 seems to be the only inducible form of the P450 1As present. The P450 1A related activities in human lung are approximately 1–4% of those in the liver.[5]

BaP is initially oxidized to several arene oxides and phenols. The arene oxides may rearrange spontaneously to phenols, undergo hydration (catalysed by microsomal epoxide hydrolases) to the corresponding *trans*-dihydrodiols, or may react covalently with glutathione, either spontaneously or catalysed by cytosolic glutathione *S*-transferases. The phenols can be further oxidized to quinones. The phenols, quinones and dihydrodiols can all be conjugated to form glucuronides and sulfate esters, and the quinones also form glutathione conjugates. In addition, secondary epoxides are derived from the phenols and the dihydrodiols (resulting in diol epoxides) following further oxidation by the cytochrome P450 system.[45,53]

BaP and other PAHs stimulate their own metabolism by inducing cytochrome P450s and epoxide hydrolases. The induction of P450 1A1 is mediated by binding to a cytosolic receptor protein, the Ah receptor.[54] Numerous studies have shown that this induction leads to an enhanced turn-over of PAHs and enhanced generation of the active metabolites that bind to cellular macromolecules.[50,55]

Mechanism of Action

PAHs exert their mutagenic and carcinogenic activity through biotransformation to chemically reactive intermediates which bind covalently to cellular macromolecules (*i.e.* DNA).[45,49–53,56–59] Systematic studies indicate that vicinal

[49] W. Levin, A. Wood, R. Chang, D. Ryan and P. Thomas, *Drug Metab. Rev.*, 1982, **13**, 555.
[50] A. H. Conney, *Cancer Res.*, 1982, **42**, 4875.
[51] P. L. Grover, *Xenobiotica*, 1986, **16**, 915.
[52] A. Dipple, in *DNA Adducts: Identification and Biological Significance*, ed. K. Hemminki, A. Dipple, D. E. G. Shuker, F. F. Kadlubar, D. Segerbäck and H. Bartsch, IARC Scientific Publications 125, International Agency for Research on Cancer, Lyon, 1994, p. 107.
[53] A. Graslund and B. Jernstrom, *Q. Rev. Biophys.*, 1989, **22**, 1.
[54] D. W. Nebert, A. Puga and V. Vasiliou, *Ann. N. Y. Acad. Sci.*, 1993, **685**, 624.
[55] C. S. Cooper, P. L. Grover and P. Sims, in *Progress in Drug Metabolism*, ed. J. W. Bridges and L. F. Chasseaud, Wiley, Chichester, 1983, vol. 7, p. 295.
[56] D. H. Phillips and P. L. Grover, *Drug Metab. Rev.*, 1994, **26**, 443.
[57] F. A. Beland and M. M. Marques, in *DNA Adducts: Identification and Biological Significance*, ed. K. Hemminki, A. Dipple, D. E. G. Shuker, F. F. Kadlubar, D. Segerbäck and H. Bartsch, IARC Scientific Publications 125, International Agency for Research on Cancer, Lyon, France, 1994, p. 229.
[58] G. R. Shaw and D. W. Connell, in *Reviews of Environmental Contamination and Toxicology*, ed. G. W. Ware, Springer, New York, 1994, vol. 135, p. 1.

(bay-region) diol epoxides are the ultimate mutagenic and carcinogenic species of alternant PAHs. The BaP-7,8-dihydrodiol is oxidized to the bay-region BaP-7,8-dihydrodiol 9,10-epoxide (BPDE), which binds (*via* the C-10 position) predominantly to the exocyclic amino group of guanine (N^2), and the N^2-guanine adduct seems to be the most important mutagenic lesion in the case of BaP.[55,56]

Non-alternant PAHs, such as the benzofluoranthenes and indeno[1,2,3-*cd*] pyrene, differ in their metabolic activation from the alternant PAHs in exerting their genotoxic effects through reactive metabolites others than simple diol epoxides.[56] The mononitro-PAHs, by oxidative metabolism, form metabolites similar to the products formed from their parent PAH, but in addition undergo reductive metabolism at the nitro group to *N*-hydroxylamines which yield reactive, DNA-binding species. Dinitropyrenes do not appear to be activated through oxidative pathways but rather by reduction of one of the nitro groups. The *N*-hydroxylamines from nitro-PAH predominantly form DNA adducts by binding to C^8 of guanine.[57] PAHs can also form free radicals owing to the action of peroxidating enzyme systems in several different tissues. Free radicals of PAHs, including BaP, bind to C^8 and N^7 in guanine and N^7 of adenine in DNA, leaving apurinic sites in DNA.[60] However, the significance of this pathway for PAH carcinogenicity is unclear.[61] The structures of stereoisomeric covalent PAH DNA adducts have recently been reviewed.[62]

Use of Biomarkers

A number of methods have been used for monitoring of human exposure to PAHs (biomarkers of exposure and effect).[63] Plasma levels of BaP and metabolites were reported higher in humans living in an urban–industrial area than in outer suburban subjects. Smokers also had higher levels than non-smokers.[64] Urinary 1-hydroxypyrene finds increasing use as a marker of exposure to PAHs. Pyrene is normally abundant in complex PAH mixtures, and elevated urinary levels of the metabolite 1-hydroxypyrene have been found in smokers, patients cutaneously treated with coal tar, workers exposed to creosote oil, coal tar distillery workers, road paving workers, coke-oven workers, and workers exposed to bitumen fumes. Significant correlations were obtained between urinary 1-hydroxypyrene of coke-oven workers and city residents and levels of pyrene and BaP in the ambient air.[64–66] In studies on PAH exposure of the

[59] W. E. Bechtold, J. D. Sun, R. K. Wolff, W. C. Griffith, J. Kilmer and J. A. Bond, *J. Appl. Toxicol.*, 1991, **11**, 115.

[60] E. L. Cavalieri and E. G. Rogan, *Xenobiotica*, 1996, **25**, 677.

[61] A. P. Reddy, D. Pruess Schwartz, C. Ji, P. Gorycki and L. J. Marnett, *Chem. Res. Toxicol.*, 1992, **5**, 26.

[62] N. E. Geacintov, M. Cosman, B. E. Hingerty, S. Amin, S. Broyde and D. J. Patel, *Chem. Res. Toxicol.*, 1997, **10**, 111.

[63] G. Talaska, P. Underwood, A. Maier, J. Lewtas, N. Rothman and M. Jaeger, *Environ. Health Perspect.*, 1996, **104**, 901.

[64] J. Larden, *Toxicology*, 1995, **101**, 11.

[65] B. E. Moen, R. Nilsson, R. Nordlinder, S. Øvrebø, K. Bleie, A. H. Skorve and B. E. Hollund, *Occup. Environ. Med.*, 1996, **53**, 692.

[66] P. Strickland, D. Kang and P. Sithisarankul, *Environ. Health Perspect.*, 1996, **104**, 927.

general population from air pollution, intake of PAHs from foods is a serious confounder.[67,68]

The ^{32}P-postlabelling assay is highly sensitive for detection and quantization of carcinogen–DNA adducts.[69,70] ^{32}P-Postlabelling analyses have been used to detect DNA adducts in the skin of mice and humans exposed to components of complex mixtures of PAHs, including coal-tar and fuel exhaust condensates.[37] The principal methods that have been developed for the detection of PAH adducts to white blood cell DNA and blood proteins (haemoglobin, albumin) have been reviewed.[69,71,72] Higher levels of PAH–DNA adducts in lymphocytes of occupationally exposed workers, bus drivers[73] and smokers have frequently been found. In several studies, significant correlations between the estimated PAH exposures and adduct levels were obtained, while in other studies no such correlations were found.[74] Large inter-individual variations in DNA adduct formation and persistence have been found in freshly isolated lymphocytes. Dietary sources, such as ingestion of charcoal-broiled beef, may greatly influence the level of PAH–DNA adducts in white blood cells, making it very difficult to monitor the effect of air pollution in the general population.[75,76] Another complicating factor is that the DNA adduct level only correlates to the PAH level at low to moderate exposures, while at high exposure levels, such as cigarette smoke or coke-oven fumes, saturation and non-linearity is observed, resulting in a lower DNA-binding potency.[77]

The effect of environmental pollution on DNA adducts in humans has been measured in a highly industrialized area of Poland. Local controls exhibited adduct levels and patterns similar to those of coke workers, while the levels in rural controls were 2–3 times lower. The results showed that the levels of aromatic adducts in white blood cell DNA did not linearly relate to ambient air levels of PAHs and that other sources such as food might be important contributors.[78] Seasonal variations, with much higher levels of DNA adducts in the winter time, were observed in all groups.[79]

[67] A. Vyskocil, Z. Fiala, D. Fialova, V. Krajak and C. Viau, *Hum. Exp. Toxicol*., 1997, **16**, 589.
[68] P. Sithisarankul, P. Vineis, D. Kang, N. Rothman, N. Caporaso and P. Strickland, *Biomarkers*, 1997, **2**, 217.
[69] K. Hemminki, H. Autrup and A. Haugen, *Toxicology*, 1995, **101**, 41.
[70] D. H. Phillips, *Mutat. Res*., 1997, **378**, 1.
[71] M. dell'Omo and R. R. Lauwerys, *Crit. Rev. Toxicol*., 1993, **23**, 111.
[72] M. C. Poirier and A. Weston, *Environ. Health Perspect*., 1996, **104**, 883.
[73] P. S. Nielsen, N. de Pater, H. Okkels and H. Autrup, *Carcinogenesis*, 1996, **17**, 1021.
[74] K. Yang, L. Airoldi, R. Pastorelli, J. Restano, M. Guanci and K. Hemminki, *Chem.-Biol. Interact*., 1996, **101**, 127.
[75] N. Rothman, M. C. Porier, R. A. Haas, A. Correa Villasenor, P. Ford, J. A. Hansen, T. O'Toole and P. T. Strickland, *Environ. Health Perspect*., 1993, **99**, 265.
[76] K. Hemminki, C. Dickey, S. Karlsson, D. Bell, Y. Hsu, W.-Y. Tsai, L. A. Mooney, K. Savela and F. Perera, *Carcinogenesis*, 1997, **18**, 345.
[77] J. Lewtas, D. Walsh, R. Williams and L. Dobias, *Mutat. Res*., 1997, **378**, 51.
[78] K. Hemminki, E. Grzybowska, M. Chorazy, K. Twardowska Saucha, J. W. Sroczynski, K. L. Putman, K. Randerath, D. H. Phillips, A. Hewer, R. M. Santella *et al*., *Carcinogenesis*, 1990, **11**, 1229.
[79] E. Grzybowska, K. Hemminki and M. Chorazy, *Environ. Health Perspect*., 1993, **99**, 77.

Toxicological effects

Haematological effects, including bone marrow toxicity, have been observed in animals following oral exposure to high doses of PAHs.[80] Data on the reproductive toxicity of PAHs are scarce. BaP is a potent reproductive toxicant adversely affecting the reproductive performance of pregnant rats and mice. *In utero* exposure to BaP has also produced several serious effects in the progeny of mice, such as testicular atrophy and interstitial cell tumours, immunosuppression and tumour induction.[37] A number of PAHs have an immunosuppressive effect in mice.[81]

A large number of PAHs and nitro-PAHs, as well as emissions containing these compounds, have shown genotoxicity and mutagenicity *in vitro* and *in vivo*.[38,45,82] The Ames test using various strains of *Salmonella typhimurium* has been widely used to monitor the mutagenic activity of PAHs and other mutagens present in complex environmental mixtures. Standard reference materials have been developed for mutagenicity assays of various combustion-related complex environmental mixtures.[83]

Carcinogenicity

A number of PAHs produce tumours in experimental animals. BaP has been used for many years as a model compound in studies of chemical carcinogenesis. When administered by the oral route, BaP and several other PAHs have produced tumours of the forestomach, liver, lungs and mammary glands of rodents,[45,84] while mono- and dinitropyrenes produced pituitary and mammary gland tumours.[85] BaP and other PAHs produce liver and lung tumours within half a year following intraperitoneal or subcutaneous injection to newborn animals.[45,84,86–89] In addition, nitro-PAHs produce leukaemia and tumours of the mammary glands and colon.[82,90] The study of skin tumours after dermal application of PAHs to mice has provided much of the background for the initiation/promotion theory in chemical carcinogenesis.[37,45,84]

[80] V. Anselstetter and H. Heimpel, *Acta Haematol. Basel*, 1986, **76**, 217.
[81] K. L. J. White, H. H. Lysy and M. P. Holsapple, *Immunopharmacology*, 1985, **9**, 155.
[82] IARC, *Diesel and Gasoline Engine Exhaust and Some Nitroarenes*, IARC Monographs on the Evaluation of Carcinogenic Risks to Humans, vol. 46, International Agency for Research on Cancer, Lyon, France, 1989.
[83] T. J. Hughes, J. Lewtas and L. D. Claxton, *Mutat. Res.*, 1997, **391**, 243.
[84] IARC, *Certain Polycyclic Aromatic Hydrocarbons and Heterocyclic Compounds*, IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Humans, vol. 3, International Agency for Research on Cancer, Lyon, France, 1973.
[85] K. Imaida, M. S. Lee, C. Y. Wang and C. M. King, *Carcinogenesis*, 1991, **12**, 1187.
[86] K. L. Platt, E. Pfeiffer, P. Petrovic, H. Friesel, D. Beermann, E. Hecker and F. Oesch, *Carcinogenesis*, 1990, **11**, 1721.
[87] W. F. J. Busby, E. K. Stevens, C. N. Martin, F. L. Chow and R. C. Garner, *Toxicol. Appl. Pharmacol.*, 1989, **99**, 555.
[88] W. F. J. Busby, E. K. Stevens, E. R. Kellenbach, J. Cornelisse and J. Lugtenburg, *Carcinogenesis*, 1988, **9**, 741.
[89] E. J. Lavoie, J. Braley, J. E. Rice and A. Rivenson, *Cancer Lett.*, 1987, **31**, 15.
[90] K. Imaida, C. Uneyama, H. Ogasawara, S. Hayashi, K. Fukuhara, N. Miyata and M. Takahashi, *Cancer Res.*, 1992, **52**, 1542.

Several studies have confirmed the lung carcinogenicity of single PAHs and nitro-PAHs after direct application into the respiratory tract of rats and hamsters.[37,45,84,91–97] BaP is the only PAH that has been tested following inhalation. After long-term inhalation of 10 mg BaP per m^3, cancer of the respiratory tract occurred in 35% of golden hamsters.[37,98,99]

Dibenzo[*a*,*h*]anthracene, dibenzo[*a*,*h*]pyrene, dibenzo[*a*,*l*]pyrene, BaP, benzo[*b*]fluoranthene, 5-methylchrysene, 7*H*-dibenzo-[*c*,*g*]carbazole, 6-nitrochrysene and the dinitropyrenes and dinitrofluoranthenes are the strongest carcinogenic PAHs in animal bioassays. The benzofluoranthenes are moderately carcinogenic, while benz[*a*]anthracene and chrysene are relatively weak carcinogens.[37]

Carcinogenicity of PAH-containing Emissions

The 4–7 ring PAH fraction of condensate from car exhaust (gasoline, diesel), domestic coal stove emissions and tobacco smoke contains almost all the carcinogenic potential of PAHs. This has been found in a series of important studies using skin painting, subcutaneous injection and intrapulmonary implantation of different fractions (see refs. 37, 41). It can be concluded from the skin painting tests of different condensates that BaP represents about 5–15% of the carcinogenic potency of the exhaust condensates from petrol-driven vehicles and coal-fired domestic stoves. When tested by lung implantation in the rat, BaP contributed a somewhat lower percentage of the total carcinogenicity.

In rats exposed by inhalation to coal tar/pitch condensation aerosol containing either 20 or 46 $\mu g\,m^{-3}$ BaP, a dose-related lung carcinogenic effect was observed. The lifetime lung tumour risk for rats exposed to 1 $\mu g\,m^{-3}$ BaP as a constituent of this complex mixture was calculated to be 2%. In comparison, the estimated unit lung cancer risk for BaP based on epidemiological data from coking plants was 7–9%. It was suggested that in the evaluation of the lung carcinogenicity of PAHs attached to inhaled fine particles, the likely enhancing properties of the inflammatory effects of particles on lung tissue should be considered.[100]

Epidemiological and experimental inhalation studies indicate that cigarette smoke contains about 100 times less BaP, and diesel exhaust about 1000 times less BaP, than the exhaust from coke ovens or heated tar pitch which yield the

[91] R. Wenzel Hartung, H. Brune, G. Grimmer, P. Germann, J. Timm and W. Wosniok, *Exp. Pathol.*, 1990, **40**, 221.
[92] T. Maeda, K. Izumi, H. Otsuka, Y. Manabe, T. Kinouchi and Y. Ohnishi, *J. Natl. Cancer Inst.*, 1986, **76**, 693.
[93] R. P. Deutsch Wenzel, H. Brune, G. Grimmer, G. Dettbarn and J. Misfield, *J. Natl. Cancer Inst.*, 1983, **71**, 539.
[94] R. P. Deutsch Wenzel, H. Brune and G. Grimmer, *Cancer Lett.*, 1983, **20**, 97.
[95] M. Iwagawa, T. Maeda, K. Izumi, H. Otsuka, K. Nishifuji, Y. Ohnishi and S. Aoki, *Carcinogenesis*, 1989, **10**, 1285.
[96] S. Sato, H. Ohgaki, S. Takayama, M. Ochiai, T. Tahira, Y. Ishizaka, M. Nagao and T. Sugimura, *Dev. Toxicol. Environ. Sci.*, 1986, **13**, 271.
[97] K. Horikawa, N. Sera, T. Otofuji, K. Murakami, H. Tokiwa, M. Iawagawa, K. Izumi and H. Otsuka, *Carcinogenesis*, 1991, **12**, 1003.
[98] J. Thyssen, J. Althoff, G. Kimmerie and U. Mohr, *J. Natl. Cancer Inst.*, 1981, **66**, 575.
[99] J. Pauluhn, J. Thyssen, J. Althoff, G. Kimmerle and U. Mohr, *Exp. Pathol.*, 1985, **28**, 31.
[100] U. Heinrich, M. Roller and F. Pott, *Toxicol. Lett.*, 1994, **72**, 155.

same lung tumour incidence.[101] When results from inhalation studies with rats exposed to diesel engine exhaust (4 mg m^{-3}) were compared with results from studies with rats exposed to coal-oven flue gas mixed with pyrolysed pitch, it was concluded that diesel exhaust had more lung tumour promotional effect than PAH-enriched coal-oven flue gas, which in turn was a more complete carcinogen.[102] The high levels of diesel exhaust used in the animal bioassays produce overloading of the lungs with particulate matter, resulting in severe inflammatory changes, while the lungs of rats exposed to coal-oven flue gas mixed with pyrolysed pitch had much less severe inflammatory changes. This suggests that the lung tumour response seen in rat inhalation bioassays using high level exposures to diesel soot is predominantly a non-specific effect, and to a lesser extent related to the genotoxic substances (*e.g.* PAHs, nitro-PAHs) present in diesel particulates. In support, it has been shown that fine carbon black particles and titanium dioxide particles, almost completely free of organic substances, were able to produce tumours in the rat lung after chronic inhalation exposure with particle mass concentrations in the exposure atmosphere of 6 mg m^{-3}.[103,104] The inhalation of titanium dioxide and metallic iron was also shown to produce impaired pulmonary clearance and persistent inflammation in the lungs of rats.[105]

Epidemiological Data

Epidemiological studies have focused on occupational exposures to PAHs. Occupational exposure to PAH-containing emissions from coke production, coal gasification, aluminium production, iron and steel founding, coal tars and coal tar pitches, and soots have produced lung cancer in humans, and coal tars and coal tar pitches, non-refined mineral oils, shale oils and soots have produced human skin and scrotal cancers.[106–108] Although PAHs are believed to be the main cause of cancer from these sources, a number of other compounds are present, probably also contributing to the effect. A particularly high rate of lung cancer mortality was found in coke-oven workers. The increases in lung cancer

[101] F. Pott and U. Heinrich, in *Complex Mixtures and Cancer Risk*, ed. H. Vainio *et al.*, IARC Scientific Publications 104, International Agency for Research on Cancer, Lyon, France, 1990, p. 288.

[102] R. O. McClellan, *Annu. Rev. Pharmacol. Toxicol.*, 1987, **27**, 279.

[103] U. Mohr, S. Tanenaka and D. L. Dungworth, *Dev. Toxicol. Environ. Sci.*, 1986, **13**, 459.

[104] U. Heinrich, R. Fusht, S. Rittinghausen, O. Creutzenberg, B. Bellmann, W. Koch and K. Levsen, *Inhal. Toxicol.*, 1995, **7**, 533.

[105] D. B. Warheit, J. F. Hansen, I. S. Yuen, D. P. Kelly, S. I. Snajdr and M. A. Hartsky, *Toxicol. Appl. Pharmacol.*, 1997, **145**, 10.

[106] IARC, *Polynuclear Aromatic Compounds: Part 3, Industrial Exposures to Aluminium Production, Coal Gasification, Coke Production, and Iron Steel Founding*, IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Humans, vol. 34, International Agency for Research on Cancer, Lyon, France, 1984.

[107] IARC, *Polynuclear Aromatic Compounds: Part 4, Bitumens, Coal Tars and Derived Products, Shale-oils and Soots*, IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Humans, vol. 35, International Agency for Research on Cancer, Lyon, France, 1985.

[108] IARC, *Overall Evaluations of Carcinogenicity: An Updating of IARC Monographs Volumes 1 to 42*, IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Human, suppl 7, International Agency for Research on Cancer, Lyon, 1987.

cases correlate closely with the time spent working on top of ovens, where an average BaP concentration of about 30 $\mu g\,m^{-3}$ has been detected.[37,106]

The US EPA has summarized a number of older risk estimates of lung cancer deaths based on epidemiological data and BaP levels in ambient air and in workplace air. The estimated unit risks ranged from 7.7×10^{-5} to 98×10^{-5} per ng BaP per m^3.[109]

Evaluation and Risk Assessment

Assessment of Single PAHs. All epidemiological studies available have involved exposure to complex mixtures of which PAHs are only constituents. Therefore, there are no epidemiological studies that can be used to estimate the risk from exposure to a single PAH. On the basis of animal experiments, risk assessments of BaP and attempts to derive relative potencies of individual PAHs (relative to BaP) have been performed several times with the purpose of summarizing the contributions from selected PAHs into a total BaP equivalent dose, assuming additivity in their carcinogenic effects.[37,110–113] The main problem in absolute risk assessment is the lack of adequate data from long-term studies with purified PAHs. The multidose long-term studies so far available for risk assessment are mostly of an older date and concern only BaP. For BaP, unit lifetime risks calculated from experiments with various routes of administration, and using various modelling, yield comparable results. The range of unit lifetime risks calculated from a number of selected BaP studies included in a meta-analysis was 1.1×10^{-3} to 4.8×10^{-3} (mean: 3×10^{-3}) per $\mu g\,m^{-3}$. A linearized multistage model was used, and the risk estimates were converted to human risk.[114] A new two-year gavage study with BaP in rats has been performed at the RIVM in the Netherlands, but has not yet been finally published. In that study, BaP produced dose-related increases of liver and forestomach tumours. Interestingly, high DNA adduct levels were found in many tissues, including the lungs, but measures of enhanced cell proliferation (due to toxicity) were only increased in the target organs.[115] A preliminary estimate of a unit risk derived from this study would expect it to be in the same order of magnitude as those calculated from the earlier studies.

Based on the extensive database on carcinogenicity studies using various routes of administration, an (entirely subjective) estimate of relative potencies for a number of PAHs is given in Table 1.[41] Such estimates should be used with great caution, as studies on mixtures of individual PAHs have shown that they may interact metabolically in a number of ways, resulting in synergistic, additive

[109] EPA, *Review and Evaluation of the Evidence for Cancer Associated with Air Pollution*, EPA-450/5-83-006R, US Environmental Protection Agency, Arlington, VA, 1984.
[110] I. C. T. Nisbet and K. LaGoy, *Regul. Toxicol. Pharmacol.*, 1992, **16**, 290.
[111] P. J. Rugen, C. D. Stern and S. H. Lamm, *Regul. Toxicol. Pharmacol.*, 1989, **9**, 273.
[112] T. W. Thorslund and D. Farrar, *Development of Relative Potency Estimates for PAHs and Hydrocarbon Combustion Product Fractions Compared to Benzo[a]pyrene and their Use in Carcinogenic Risk Assessment*, EPA/600/R-92/134, Dept. Commerce, NTIS, Springfield, VA, 1990.
[113] D. Krewski, T. Thorslund and J. Withey, *Toxicol. Ind. Health*, 1989, **5**, 851.
[114] J. F. Collins, J. P. Brown, S. V. Dawson and M. A. Marty, *Regul. Toxicol. Pharmacol.*, 1991, **13**, 170.
[115] D. Kroese, personal communication, January 1998.

Table 1 Best estimates of carcinogenic potencies of various PAHs, relative to BaP[a]

Compound	*Relative potency*	*Compound*	*Relative potency*
Anthracene	0.0005	Benzo[*a*]pyrene	1
Fluorene	0.0005	Benzo[*e*]pyrene	0.002
Phenanthrene	0.0005	Dibenz[*a,h*]anthracene	1.1
Benz[*a*]anthracene	0.005	Anthanthrene	0.3
Chrysene	0.03	Benzo[*ghi*]perylene	0.02
Cyclopenteno[*cd*]pyrene	0.02	Dibenzo[*a,e*]pyrene	0.2
Fluoranthene	0.05	Dibenzo[*a,h*]pyrene	1
Pyrene	0.001	Dibenzo[*a,i*]pyrene	0.1
Benzo[*b*]fluoranthene	0.1	Dibenzo[*a,l*]pyrene	1
Benzo[*j*]fluoranthene	0.05	Indeno[1,2,3-*cd*]pyrene	0.1
Benzo[*k*]fluoranthene	0.05	Coronene	0.01
Benzo[*ghi*]fluoranthene	0.01		

[a]Based on the authors' compilation of carcinogenicity studies in experimental animals using oral, pulmonary and skin application of PAH.[41]

or antagonistic effects, and nothing definitive can be concluded on the resulting tumorigenic actions of individual PAHs in complex mixtures.[116]

Assessment of Complex Mixtures of PAHs. A number of PAHs, nitro-PAHs, heterocyclic-PAHs, and their derivatives, have been found to be carcinogenic in animal experiments, and many more, including their reaction products in ambient air, have shown genotoxic effects *in vitro*. Therefore, the combined carcinogenic risk of exposure to the complex mixtures present in ambient air presumably is much higher than can be expected from either BaP alone or the use of BaP equivalent doses of the PAH determined by chemical measurements. If the composition of all emissions were identical and similar to those in ambient air, the concentration of a single PAH would provide a good index of the carcinogenic potential of the total mixture. However, this is not the situation.

The WHO, in its update of the Air Quality Guidelines for Europe, noted that the variations of PAH profiles in workplaces were not so wide and the deviation from the mean was relatively low in ambient air. The WHO therefore, on a provisional basis, used BaP as an index for the carcinogenic potential of general PAH mixtures in ambient air, although the limitations of the approach were recognized.[37]

The WHO based its evaluation on the mouse skin painting studies showing that 5–15% of the total carcinogenic effect from PAH fractions of different exhaust condensates was due to BaP, and adopted the lung cancer unit risk of 6.2×10^{-4} per 1 $\mu g\,m^{-3}$ of benzene-soluble compounds in ambient air, calculated by the US EPA from exposure to coke-oven emissions.[117] Assuming 0.71% BaP

[116] G. K. Montizaan, P. G. N. Kramers, J. A. Janus and R. Posthumus, *Integrated Criteria Document PAHs: Effects of 10 Selected Compounds*, Appendix to RIVM report no. 758474011, National Institute of Public Health and Environmental Protection, RIVM, Bilthoven, The Netherlands, 1989.

[117] EPA, *Carcinogen Assessment of Coke Oven Emissions*, EPA-600/6-82-003F, US Environmental Protection Agency, Office of Health and Environmental Assessment, Washington, DC, 1984.

in benzene-soluble coke-oven emissions, a lifetime risk of respiratory cancer of 8.7×10^{-2} per $\mu g\,m^{-3}$ BaP, or 8.7×10^{-5} per $ng\,m^{-3}$ BaP, was calculated.[37] This risk assessment implies that about 9 per 100 000 exposed individuals may die from cancer of the respiratory tract as a result of spending a lifetime in ambient air containing an average level of 1 ng BaP per m^3.

In a Dutch Integrated Criteria Document on PAHs a unit risk of 6.58×10^{-2} per $\mu g\,m^{-3}$ BaP was estimated from studies of Chinese women in the Xuan Wei province using smoky coal for cooking.[116]

In urban areas, air pollution from motor vehicles, in particular diesel cars, becomes increasingly important. Quantitative estimates of lung cancer risks from exposure to diesel engine particulate emissions have been done using data from the chronic bioassays with rats. Dose was based upon the concentration of carbon particulate matter per unit lung surface area. The unit risk estimates varied from 1.0 to 4.6×10^{-5}, with a geometric mean of 1.7×10^{-5} per $\mu g\,m^{-3}$ of diesel exhaust particulate matter.[118] This approach has been seriously questioned, because the carcinogenic effect seen in the rat studies with diesel particles is mainly due to a mechanism for which there seems to be a threshold.[119] Moreover, it also appears that the rat has a unique sensitivity to the lung effects of poorly soluble, non-fibrous particles, in contrast to the mouse and primates.[120,121] An examination of epidemiological studies of workers highly exposed to airborne carbon black showed no satisfactory evidence for an association with increased lung cancer risk, which was inconsistent with the predictions from the rat bioassay data.[122]

Biological assays have been used for the determination of the potency of various complex mixtures relative to the potency of BaP or potencies calculated on the basis of human data. The database of useful human studies is rather limited, and only a few sources of PAH emissions can be evaluated by this approach, notably cigarette smoke condensates, coke-oven emissions and roofing tar emissions. The *Salmonella* mutagenicity assay, the mouse skin tumour initiation-promotion assay and the rat lung implant assay have been evaluated for use in potency estimations of complex mixtures from combustion sources. Linear correlations have been established between mouse skin initiation potency, bacterial mutagenic potency and potencies calculated from human exposure. These correlations have been used to estimate the human potency of other mixtures from combustion sources for which only mouse skin initiation data or mutagenicity data exist. A particularly good correlation was noted between the mouse skin data and the human data, and good correlations were obtained between mouse skin data and mutagenicity for a series of mixtures from the same source category. When mixtures of emissions from different sources were assayed the correlations decreased, but were still reasonable. Using this *comparative potency approach*, a unit risk of 1.3×10^{-4} per μg organic matter m^{-3} was

[118] W. E. Pepelko and C. Chen, *Regul. Toxicol. Pharmacol.*, 1993, **17**, 52.
[119] P. A. Valberg and A. Y. Watson, *Regul. Toxicol. Pharmacol.*, 1996, **24**, 30.
[120] J. L. Mauderly, D. A. Banas, W. C. Griffith, F. F. Hahn, R. F. Henderson and R. O. McCellan, *Fund. Appl. Toxicol.*, 1996, **30**, 233.
[121] K. J. Nikula, K. J. Avila, W. C. Griffith and J. L. Mauderly, *Fund. Appl. Toxicol.*, 1997, **37**, 37.
[122] P. A. Valberg and A. Y. Watson, *Regul. Toxicol. Pharmacol.*, 1996, **24**, 155.

Table 2 Estimated lifetime cancer risk from air pollution components using different approaches

Exposure indicator	*Average level*[125]	*Unit risk for indicator*	*Estimated lifetime cancer risk*
Diesel particles	$1\ \mathrm{g\,m^{-3}}$	$1.7 \times 10^{-5}\,(\mu\mathrm{g\,m^{-3}})^{-1}$ [c]	1.7×10^{-5}
Extractable organic material from diesel particles[a]	$0.07\,\mu\mathrm{g\,m^{-3}}$	$2.3 \times 10^{-4}\,(\mu\mathrm{g\,m^{-3}})^{-1}$ [d]	1.6×10^{-5}
Extractable organic material from soot[b]	$1\,\mu\mathrm{g\,m^{-3}}$	$1.3 \times 10^{-4}\,(\mu\mathrm{g\,m^{-3}})^{-1}$ [d]	13×10^{-5}
Benzo[*a*]pyrene	$0.7\,\mathrm{ng\,m^{-3}}$	$8.7 \times 10^{-5}\,(\mathrm{ng\,m^{-3}})^{-1}$ [e]	6.1×10^{-5}

[a]Assuming 7% extractable organic material.[125]
[b]Assuming 20% extractable organic material.[41]
[c]Derived from animal bioassays.[128]
[d]Derived by the comparative potency approach.[124]
[e]WHO Air Quality Guidelines for Europe.[37]

obtained for air particle extracts containing 64% contribution from woodsmoke and 36% from mobile source emissions. For automobile diesel (light duty) and automobile gasoline, unit risks of 2.3×10^{-4} and 1.1×10^{-4}, respectively, per μg organic matter $\mathrm{m^{-3}}$ were estimated.[123,124]

Using information on the average levels reported in Sweden[125] of diesel particles ($1\,\mu\mathrm{g\,m^{-3}}$), soot ($5\,\mu\mathrm{g\,m^{-3}}$) and BaP ($0.7\,\mathrm{ng\,m^{-3}}$), several risk estimates can be compared (Table 2). It should be noted that, despite the critique of using rat bioassay data in the risk assessment of diesel exhaust, the use of the comparative potency approach on diesel particles yields a similar risk estimate, probably by coincidence. Somewhat higher risk estimates are obtained when the approach recommended by the WHO[37] is used, and when the comparative potency approach is used on total soot. This is to be expected, since diesel exhaust contributes only a part of the total air pollution with PAHs. It can be added that when epidemiological data from exposures to diesel exhausts are used, an even higher unit risk (30×10^{-5}) has been estimated.[125]

7 Conclusion

The available epidemiological evidence indicates that combustion-related emissions are related to an increased risk of lung cancer from general air pollution. The increased risk appears to be small, compared to the risk from tobacco smoking. This evidence is supported by epidemiological studies from occupational settings and from toxicological studies *in vitro* and in experimental animals with single compounds and complex mixtures related to air pollution. In addition to an increased lung cancer risk from air pollution, compounds that have been found to be carcinogenic in occupational epidemiology and animal experiments are also

[123] J. Lewtas, *Environ. Health Perspect.*, 1993, **100**, 211.
[124] J. Lewtas, *Pharmacol. Toxicol.*, 1993, **72** (suppl. 1), s55.
[125] M. Törnqvist and L. Ehrenberg, *Environ. Health Perspect.*, 1994, **102** (suppl. 4), 173.

present, which may contribute to human cancer at other sites than the lungs, such as leukaemia and cancers of the lymphohaematopoietic system.

The major causal chemical factors that contribute to the cancer risk from air pollution are difficult to identify, because the vast number of chemicals that can be suspected on the basis of their toxicological properties and occupational epidemiology appear in the ambient air in extremely complex mixtures, the composition of which may vary to a large extent from one location to another. In addition to the large number of PAHs and derivatives, benzene, 1,3-butadiene and aldehydes, mentioned in this paper, many other compounds such as styrene, dichloromethane, tri- and tetrachloroethylenes, polychlorinated *p*-dibenzodioxins and dibenzofurans, polychlorinated biphenyls, a number of inorganics and radionuclides may also contribute to the overall cancer risk from air pollution.

The link between the epidemiological evidence for lung cancer risk and the occurrence of PAHs in ambient air is particularly strong, and is supported by data from animal studies, although a definite risk estimate is difficult to obtain. PAHs are locally deposited with particles in the lungs, are slowly released over a long period of time, undergo extensive metabolic activation in the lungs, and in general tend to produce tumours at the site of application, in this case the lungs. Keeping in mind that the carcinogenic process involves both genotoxic and non-genotoxic mechanisms, it is of particular importance for future research to elucidate to what extent the well-known genotoxic properties of PAHs (and other genotoxic agents) act in concert with the irritant and inflammatory properties of other factors in air pollution, such as ozone, aldehydes and particulate matter.