air quality guidelines

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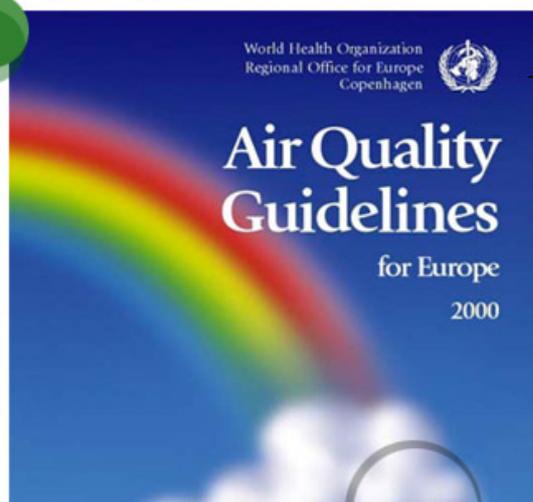Regional Office for Europe
Copenhagen

Air Quality Guidelines

for Europe

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World Health Organization
Regional Office for Europe
8, Scherfigsvej
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Chapter 5.9

Polycyclic aromatic hydrocarbons (PAHs)

General description

Polycyclic aromatic hydrocarbons (PAHs) are a large group of organic compounds with two or more fused aromatic rings. They have a relatively low solubility in water, but are highly lipophilic. Most of the PAHs with low vapour pressure in the air are adsorbed on particles. When dissolved in water or adsorbed on particulate matter, PAHs can undergo photodecomposition when exposed to ultraviolet light from solar radiation. In the atmosphere, PAHs can react with pollutants such as ozone, nitrogen oxides and sulfur dioxide, yielding diones, nitro- and dinitro-PAHs, and sulfonic acids, respectively. PAHs may also be degraded by some microorganisms in the soil (*1,2*).

Sources

PAHs are formed mainly as a result of pyrolytic processes, especially the incomplete combustion of organic materials during industrial and other human activities, such as processing of coal and crude oil, combustion of natural gas, including for heating, combustion of refuse, vehicle traffic, cooking and tobacco smoking, as well as in natural processes such as carbonization. There are several hundred PAHs; the best known is benzo[*a*]pyrene (BaP). In addition a number of heterocyclic aromatic compounds (e.g. carbazole and acridine), as well as nitro-PAHs, can be generated by incomplete combustion (*1*).

The emissions of BaP into the air from several sources in the Federal Republic of Germany in 1981 were estimated to amount to 18 tonnes: about 30% was caused by coke production, 56% by heating with coal, 13% by motor vehicles and less than 0.5% by the combustion of heating oil and coal-fired power generation. Other BaP sources were not taken into consideration (*1*). However, the present contributions from the different important sources, such as residental heating (coal, wood, oil), vehicle exhausts, industrial power generation, incinerators, the production of coal tar, coke and asphalt, and petroleum catalytic cracking, are very difficult to estimate. These figures may also vary considerably from country to country. In the USA, the residental burning of wood is now regarded as the largest source of PAHs (*2*). Stationary sources account for a high percentage of total annual PAH emissions. However, in urban or suburban areas, mobile sources are additional major contributors to PAH releases to the atmosphere (*3*).

Occurrence in air

About 500 PAHs and related compounds have been detected in the air, but most measurements have been made on BaP. Data obtained prior to the mid-1970s may not be comparable with later data because of different sampling and analytical procedures (*1*).

The natural background level of BaP may be nearly zero. In the USA in the 1970s, the annual average value of BaP in urban areas without coke ovens was less than 1 ng/m^3 and in other cities between 1 and 5 ng/m^3. In several European cities in the 1960s, the annual average concentration of BaP was higher than 100 ng/m^3 (*1*). In most developed countries BaP concentrations have decreased substantially in the last 30 years. Thus PAH levels lower by a factor of 5 to 10 than those in 1976 were reported for a traffic tunnel in Baltimore and for ambient air in London in the second half of the 1980s (*3*). The declines were attributed to the increased use of catalytic converters in motor vehicles, a reduction in coal and open burning with a movement to oil and natural gas as energy sources, and improved combustion technology. PAH emissions from open burning, especially coal, have been declining in many developed countries as a result of efforts to control smoke emissions (*3*). In 1990, a German study found BaP concentrations of below 1 ng/m^3 at monitoring stations not affected by emission sources, from 1.77–3.15 ng/m^3 at stations close to traffic, and 2.88–4.19 ng/m^3 at stations with traffic and additional industrial emission sources. The annual (1989-1990) average concentration of BaP close to traffic in the Rhine-Ruhr area was reported to be 3–6 ng/m^3 (*4*). In Copenhagen, the mean BaP concentration (January to March 1992) at a station in a busy street was found to be 4.4 ng/m^3 (*5*).

The relationship between the amount of BaP and some other PAHs is termed the "PAH profile". When routine methods are used to measure PAHs only 6–15 of several hundred existing PAHs are measured quantitatively. Although the PAH profiles from different emissions can differ widely, they appear relatively similar in the ambient air of several cities. The different profiles of emissions appear mixed, producing a relatively uniform PAH profile in the ambient air. Most importantly, these relations seem to be independent of the PAH concentration in the ambient air (*1*). Table 1 shows the PAHs most often included in chemical

analyses of ambient air, together with levels reported in 1992 in a busy street and a city park in Copenhagen (*5*).

Additional contributions from tobacco smoking and the use of unvented heating sources can increase PAH concentrations in indoor air and, in certain cases, PAHs can increase to very high levels indoors (*6,7*). BaP levels of 14.7 µg/m^3 were found in Chinese (Xuan Wei) homes burning smoky coal (*8*). In India, the BaP concentration was reported to average about 4 µg/m^3 during cooking with biomass fuel (*1*).

Very high concentrations of BaP can occur in workplaces. Measurements using stationary samplers or personal samplers over an 8-hour period showed average BaP concentrations of between 22 and 37 µg/m^3 on the topside of older coke oven batteries and between 1 and 5 µg/m^3 at several other worksites in the same plants. High values have also been reported in the retort-houses of coal-gas works in the United Kingdom, ranging from 3 µg/m^3 in mask samples to more than 2 mg/m^3 in peak emissions from the retorts. In the aluminum-smelting industry, concentrations much higher than 10 µg/m^3 were found at some workplaces (*1*).

Routes of Exposure

Air
A study of human exposure to BaP (the Total Human Envirnmental Exposure Study) was conducted in Phillipsburg, New Jersey, a city that contains a metal pipe foundry, suspected as a major source of BaP. The mean outdoor concentration of BaP was 0.9 ng/m^3, and the indoor concentrations ranged from 0.1 to 8.1 ng/m^3. The range of BaP per gram of food (wet weight) was between 0.004 and 1.2 ng/g. In some instances, outdoor air pollution led to a major portion of indoor air BaP exposures. Drinking-water appeared to be a minor pathway of BaP exposures in the study area. Among the study subjects, the range and magnitude of dietary exposures (2–500 ng/day) were much larger than for inhalation (10–50 ng/day) (*9*).

Table 1. Mean PAH concentrations (ng/m^3) in a busy street and a city park in Copenhagen January to March 1992 (*5*)

Compound	Busy street (n = 76)	City park (n = 51)
Anthanthrene	1.6	0.27
Anthracene	0.6	0.18
Benz[*a*]anthracene	4.1	1.0
Benzo[*a*]fluoranthene	1.5	0.4
Benzo[*a*]pyrene	4.4	1.4
Benzo[*b*]naphtho[2,1-*d*]thiophene	0.55	0.18
Benzo[*bjk*]fluoranthene	9.3	2.9
Benzo[*e*]pyrene	4.4	1.3
Benzo[*ghi*]fluoranthene + benzo[*c*] phenanthrene	7.0	1.5
Benzo[*ghi*]perylene	8.0	1.5
Chrysene + triphenylene	7.9	2.3
Coronene	5.8	1.1
Cyclopentena[*cd*]pyrene	6.1	1.5
Dibenzothiophene	0.28	0.07
Fluoranthene	5.6	1.3
Indeno[1,2,3-*cd*]pyrene	4.5	1.1
Methylphenanthrenes	7.0	1.4
Perylene	1.2	0.14
Phenanthrene	2.4	0.9
Picene	0.73	0.26
Pyrene	7.3	1.3

The average total BaP content in the mainstream smoke of 1 cigarette was 35 ng before 1960 and 18 ng in 1978-1979; modern "low tar" cigarettes deliver 10 ng BaP. The concentration of BaP in a room extremely polluted with cigarette smoke was 22 ng/m^3 (*1*).

Drinking-water
Examination of a number of drinking-water supplies for six PAHs (fluoranthene, benzo[*b*]fluoranthene, benzo[*k*]fluoranthene, BaP, benzo[*ghi*]perylene and indeno[1,2,3-*cd*]pyrene) indicated that the collective concentrations generally did not exceed 0.1 μg/litre. The concentrations of these six PAHs were between 0.001 and 0.01 μg/litre in 90% of the samples and higher than 0.11 μg/litre in 1%. Concentrations of BaP in drinking-water have been shown to range from 0.0002 to 0.024 μg/litre (*1,10*).

Food
PAHs are found in substantial quantities in some foods, depending on the mode of cooking, preservation and storage, and are detected in a wide range of meats, fishes, vegetables and fruits. A Dutch "market basket" study of dietary components for 18-year-old males involving determination of 17 different PAHs revealed that all these compounds were detected. The most frequently occurring PAHs were benzo[*b*] fluoranthene, fluoranthene and benzo[*k*]fluoranthene, in 59%, 48% and 46% of the samples, respectively. The highest concentration of a single PAH was found for chrysene, at 36 μg/kg in the commodity group "sugar and sweets". The mean daily intake of the total PAH fraction analysed was between 5 μg/day (low estimate) and 17 μg/day (high estimate). The intake of the carcinogenic PAH fraction was roughly half of these amounts. The largest contribution to the daily PAH intake came from sugar and sweets, cereals, oils, fats and nuts (*11*).

Soil

Carcinogenic PAHs are found in all surface soils. Typical concentrations in forest soil range from 5 µg to 100 µg/kg. Substantial amounts of PAHs are transferred to forest soil from vegetative litter because the compounds are adsorbed from air on organic matter such as leaves and needles. Rural soil contains carcinogenic PAHs at levels of 10–100 µg/kg originating mainly from atmospheric fallout. For both forest and rural soil, values as high as 1000 µg/kg may occasionally be found. Metropolitan areas have higher PAH concentrations than forest and agricultural areas because of the many sources of fossil fuel combustion. The majority of urban soil concentrations fall in the 600–3000 µg/kg range. Higher values near areas of heavy transportation and industrialization are probable. Values in the order of 1000–3000 µg/kg are regarded as being in the upper range. However, levels of 8 000–336 000 µg/kg have been reported for road dust (12).

Relative significance of different routes of exposure
A recent publication has summarized human exposure to the following eight carcinogenic PAHs in the environment: benzo[a]anthracene, chrysene, benzo[b]fluor- anthene, benzo[k]fluoranthene, BaP, indeno [1,2,3-cd]pyrene, dibenzo[ah]anthracene and benzo[ghi]perylene. The exposures calculated were based on US statistics and analysis, and thus related to the situation in North America. Estimates were made for a "reference man" aged between 19 and 50 years and presented on a total body basis. In nonsmokers a mean total intake of 3.12 mg/day was estimated, of which food contributed 96.2%, air 1.6%, water 0.2% and soil 0.4%. Smokers consuming one pack of nonfiltered cigarettes per day had an estimated additional intake of 1–5 µg/day (12).

Toxicokinetics

Absorption
PAHs are highly lipid-soluble and are absorbed from the lung, gut and skin of mammals. Studies on the lung retention of microcrystalline PAHs or PAHs in solution after intratracheal instillation in female rats have indicated that they are rapidly cleared from the respiratory tract. Clearance of the PAHs from the lungs is best described as biphasic. For radiolabelled anthracene, benz[a]anthracene, 1-nitropyrene, BaP, 6-nitrobenzo[a]pyrene and dibenzo[c,g]carbazole, more than 85% of the initial dose was cleared with a half-time of less than 1 hour. The half-times for clearance of the residual radioactivity (1–15% of the dose) ranged from 26–63 hours (13,14).

However, inhaled PAHs are predominantly adsorbed on soot particles. After deposition in the airways, the particles can be eliminated by bronchial clearance. PAHs might be partly removed from the particles during transport on the ciliated mucosa and may penetrate into the bronchial epithelium cells where metabolism takes place (1).

When BaP is adsorbed on particles, the respiratory uptake rate is lower since the particles are retained for a long period of time in the respiratory tract (15). When radiolabelled BaP adsorbed on diesel engine exhaust particles was inhaled by rats, lung clearance of the inhaled particle-associated radioactivity occurred in two phases. The initially rapid clearance had a half-time of less than 1 hour. The second, long-term component had a half-time of 18 days and represented 50% of the radioactivity that had initially been deposited in the lungs (16). Similar results were obtained when BaP was adsorbed on urban air particles (15).

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. The half-time for the decline in ^{14}C levels was 34 weeks for rats exposed to BaP on carbon black and 6 weeks for rats exposed to pure BaP (17).

BaP and other PAHs are readily absorbed from the gastrointestinal tract when present as solutes in various dietary lipids. The absorption is facilitated by the presence of bile salts in the intestinal lumen. In the rat more than 30–50% of low oral doses of BaP or pyrene were readily absorbed and a major part was rapidly metabolized in the liver (first-pass effect) (18,19).

BaP and other PAHs, such as phenanthrene and pyrene, rapidly penetrate the skin of mice and rats. In mice, 80% of BaP was recovered from faeces after 7 days, while a total of 42% was recovered from faeces and urine in rats (20,21). Absorption through human skin has also been demonstrated (22).

Distribution
Irrespective of the route of administration PAHs are rapidly and widely distributed in the organism. The pattern of distribution of BaP was found to be similar after subcutaneous, intraveneous and intratracheal administration to mice and rats. Detectable levels of BaP can be observed in most internal organs from minutes to hours after administration. Highest levels are obtained in the liver (10,18). Mammary and other

fatty tissues are significant storage depots for PAHs (*23*), but owing to the rapid metabolism no significant accumulation seems to take place. The gastrointestinal tract contains relatively high levels of metabolites as the result of hepatobiliary excretion (*24,25*). For pyrene, the distribution to the tissues was highest in the perirenal fat, intermediate in the liver, kidneys and lungs, and lowest in the heart, testes, spleen and brain (*19,26*). BaP can readily cross the placental barrier of rats and mice (*27,28*), consistent with the fetal and developmental toxicity of the substance.

Excretion
Following metabolism, hepatobiliary excretion and elimination through the faeces is the major route by which BaP is removed from the body, independent of the route of administration (*18,29*). Urine is the other major excretory route, although it is quantitatively of minor importance compared to the bile.

Metabolism and activation
The enzyme system primarily responsible for PAH metabolism is the microsomal mixed function oxidase system, which converts the non-polar PAHs into polar hydroxy and epoxy derivatives (*30*). Epoxides are the major intermediates in the oxidative metabolism of aromatic double bonds. The epoxides are reactive and enzymatically metabolized to other compounds such as dihydrodiols and phenols (*31*).

The enzyme systems that metabolize PAHs are widely distributed in the cells and tissues of humans and animals. The highest metabolizing capacity is present in the liver, followed by lung, intestinal mucosa, skin and kidneys, but metabolism may also take place in nasal tissues, mammary gland, spleen, brain, hair follicles, erythrocytes, platelets, leukocytes, placenta and uterus. Animal and human fetal tissues have the capacity to metabolize PAHs, but at a low rate compared to the adult tissues (*32*).

BaP and other PAHs stimulate their own metabolism by inducing microsomal cytochrome P-450 monooxygenases and epoxide hydrolases. The induction of isozymes belonging to the cytochrome P-450IA subfamily (CYPIA1 and CYPIA2) is mediated by binding to a cytosolic receptor protein, the Ah receptor (*33*). Strains of mice (e.g. B6) having high-affinity receptors are readily induced (responsive mice), while other strains (e.g. C3 and D2) having low-affinity receptors are much less prone to induction (non-responsive mice).

BaP is initially oxidized to several arene oxides and phenols. The arene oxides may rearrange spontaneously to phenols (3-OH-, 6-OH-, 7-OH, and 9-OH-BaP), undergo hydration (catalysed by microsomal epoxide hydrolases) to the corresponding *trans*-dihydrodiols (4,5-, 7,8- or 9,10-dihydrodiol), or react covalently with glutathione, either spontaneously or catalysed by cytosolic glutathione-S-transferases. The phenols can be further oxidized to quinones (1,6-, 3,6-, or 6,12-quinone). In addition, secondary epoxides derived from the phenols and the dihydrodiols (resulting in diol epoxides) are formed following further oxidation by the cytochrome P-450 monooxygenase system (*10,34*).

PAHs exert their mutagenic and carcinogenic activity through biotransformation to chemically reactive intermediates which bind covalently to cellular macromolecules (*inter alia* DNA). Extensive and systematic studies on the tumorigenicity of individual PAH metabolites in animals have led to the conclusion that vicinal or so called bay-region diol epoxides are the ultimate mutagenic and carcinogenic species of alternant PAHs, although not necessarily the only ones (*34*). These diol epoxides are easily converted by epoxide ring opening into electrophilic carbonium ions which are alkylating agents that covalently bind to nucleophilic sites in the DNA bases and in proteins.

The principal route of further oxidative metabolism of the BaP-7,8-dihydrodiol is to the bay-region BaP-7,8-dihydrodiol-9,10-epoxide (BPDE). The bay-region diol-epoxides of PAHs may each exist as four optically active isomers. (+)-*anti*-BPDE is the predominant diol-epoxide formed from BaP-7,8-dihydrodiol in almost all tissues examined. It is also the only isomer with high tumorigenic activity, and is the predominant isomer found covalently bound to DNA (*34*).

Nonalternant PAHs, such as benzo[*b*]fluoranthene, benzo[*j*]fluoranthene, benzo[*k*]-fluoranthene, and indeno [1,2,3-*cd*]pyrene may differ in their metabolic activation from the alternant PAHs. These PAHs do not appear to exert their genotoxic effect primarily through the metabolic formation of simple diol-epoxides (*35*).

The mononitro-PAHs may also undergo reductive metabolism at the nitro group to their corresponding *N*-hydroxylamines which yield reactive, DNA-binding species. The metabolites identified as the result of the oxidative metabolism of mononitro-PAHs are similar to the products formed from their parent PAHs. The 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-PAHs predominantly form DNA adducts by binding to C-8 of guanine (*36*).

The implication of covalent binding of PAHs to DNA for carcinogenicity in the lung and other tissues of experimental animals has been intensively studied in cell culture systems and *in vivo* (*10,37*). *In vivo* studies in many animal species have demonstrated that (+)-*anti*-BPDE-DNA adducts are the major adducts formed in liver, lung and skin. In studies using systemic administration in mice and rats, levels of DNA adducts were highest in liver, lung and spleen, with kidney and stomach significantly lower (*38–40*). BaP administration to mice and rats also resulted in the binding to globin (*41,42*).

The *in vitro* formation of reactive, DNA-binding, free radicals of PAHs can be catalysed by a number of peroxidating systems, including microsomal prostaglandin synthetases, present in a variety of different tissues (*43*). However, the significance of this pathway for PAH carcinogenicity in experimental animals and humans is as yet unclear (*33,44,45*).

At the end of a 12-week inhalation exposure to ^{14}C-BaP, DNA adducts in the lungs of rats exposed to pure BaP ranged from 2 to15 adducts per 10^9 bases. In rats exposed to BaP adsorbed on carbon black it ranged from 10 to12 adducts per 10^9 bases (*17*).

Utility of biomarkers
A number of techniques have been developed for the biological monitoring of human exposures to PAHs. BaP has often been used as an indicator for the carcinogenic PAHs present in the environment. The methods most commonly used have been determination of PAHs and their metabolites in blood and urine, measurement of mutagenicity in urine and faeces, chromosome aberrations and sister chromatid exchanges in peripheral blood lymphocytes, and DNA and protein adduct formation in the latter and in other tissues (*46*).

Sensitive immunological methods have been developed to detect BaP and its metabolites in plasma and urine. The antibodies cross-react with a number of BaP metabolites as well as with several other PAHs (and presumably their metabolites). Plasma levels of BaP (and presumably of other PAHs and metabolites) were reported to be significantly higher in humans living in an urban industrial area than in outer suburban subjects. Smokers also had higher levels than nonsmokers (*46*).

Chemical measurements of the urinary excretion of total PAH metabolites showed that while the heavy occupational exposure of workers in an aluminum plant was not reflected to any great extent in the urinary excretion of total PAHs, smokers had significantly higher levels than nonsmokers. Urinary 1-hydroxypyrene, a major metabolite of pyrene, finds increasing use as a marker of exposure to PAHs. Pyrene is normally abundant in complex PAH mixtures, and increased urinary levels of 1-hydroxypyrene have been found in patients treated cutaneously with coal tar, in workers exposed to creosote oil, in coal tar distillery workers, in road-surfacing workers, coke-oven workers, and workers exposed to bitumen fumes. Iin coke-oven workers and city residents, significant correlations were obtained between urinary 1-hydroxypyrene and levels of pyrene and BaP in the ambient air (*46*). A controlled human exposure study showed that a 100- to 250-fold increase in a dietary BaP dose paralleled a 4- to 12-fold increase in urinary 1-hydroxypyrene elimination (*47*).

Measurement of cytogenetic damage, such as chromosomal aberrations in peripheral lymphocytes do not appear to be particularly sensitive as a biomarker of PAH exposure (*48*). However, increased rates of *HPRT* mutations were found in the lymphocytes of workers in an iron foundry with exposure to PAHs with BaP concentrations ranging from < 5 to 60 ng/m^3 and paralleled increases in PAH-DNA adduct levels as measured by immunoassay (*49*).

Adducts of PAHs with proteins such as albumin and haemoglobin seem to be promising biomarkers of exposure to PAHs and potential surrogates for effects (*50*). Foundry workers with high exposure to PAHs were found to have higher levels of covalent PAH serum albumin adducts than non-exposed controls (*51,52*).

Numerous experimental studies have identified DNA adducts derived from reactive metabolites of BaP and other PAHs (*50*). Immunoassays and physicochemical methods, such as synchronous scanning fluorescence spectrometry, have been applied to detect adducts formed through the major intermediate in the activation of BaP, BPDE (*53*).

Polyclonal and monoclonal antibodies against BPDE-DNA adducts have been developed and used in radioimmunoassays or competitive ELISA assays in order to monitor human exposure to BaP. The monoclonal antibodies developed are not specific for BPDE-adducts but also measure adducts formed by other PAHs (*54–56*).

The ^{32}P-postlabelling assay is highly sensitive for detection and quantification of carcinogen-DNA adducts (*50*). Various enhancement procedures have been introduced and new ^{32}P-postlabelling schemes are constantly being developed (*57,58*). ^{32}P-Postlabelling analysis has been used to detect the formation of DNA adducts in skin samples from mice and humans by components of complex mixtures of PAHs in coal-tar, creosote, bitumen, juniper tar, used engine oils and fuel exhaust condensates (*59*).

The principal methods available for the detection of PAH adducts to white blood cell DNA and blood proteins (haemoglobin and albumin) have been reviewed recently and observations made on exposed subjects and populations summarized (*50,60*). Higher levels of PAH-DNA adducts in peripheral blood lymphocytes of occupationally exposed workers (coke oven, foundry, aluminum plant, roofing) and smokers have frequently been found. In several studies significant correlations between the estimated PAH exposure and adduct levels were obtained, while in other studies no such correlations were found. In the general population, large interindividual variations in DNA adduct formation and persistence were found in freshly isolated lymphocytes (*61*). Dietary sources such as charcoal-broiled beef may greatly influence the level of PAH-DNA adducts in white blood cells (*62*).

The effect of environmental pollution on DNA adducts in humans has been analysed 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 two to three times lower. The results showed that the relationship between levels of aromatic adducts in white blood cell DNA and ambient air levels of PAH was not linear and that other sources such as food might be important contributors (*63*). Aromatic adducts on DNA were significantly correlated with chromosomal mutations (*64*). Seasonal variations, with much higher levels of DNA adducts in the winter time, were observed both in residents of the district near the coke-oven area and in individuals from the rural area of Poland (*65,66*).

Health effects

Effects in experimental animals and *in vitro* test systems

Toxicological effects
Adverse haematological effects have been observed in animals following oral exposure to high doses of PAHs. Aplastic anaemia, pancytopenia, severe reduction in peripheral blood leukocytes, and severe bone marrow depression with almost complete destruction of pluripotent haematopoietic stem cells have been seen in non-responsive mice after oral BaP, while extreme resistance to bone marrow toxicity was observed in responsive mice (*67*).

In vitro experiments have demonstrated the cytotoxicity of BaP and various other PAHs to cells from the lungs of experimental animals and humans. Severe, long-lasting hyperplasia and other adverse effects similar to the preneoplastic changes seen *in vivo* following exposure to PAHs have been observed (*68*).

Similar cytokinetic and morphological changes were reported in the lungs of F344 rats exposed by inhalation to a combination of BaP (7 mg/m^3) adsorbed on gallium oxide particles (22 mg/m^3) and sulfur dioxide (5 ppm) or to gallium oxide particles and sulfur dioxide alone for 2 hours/day for 9 days. Cell proliferation in airway and alveolar regions of lungs and small foci of hyperplastic alveolar cells and hypertrophic terminal bronchiolar cells occurred more frequently in the group exposed to BaP (*69*). However, in another experiment no treatment-related lesions were noted in the lungs or nasal cavities of F344 rats exposed to 1-nitropyrene or benzo[*a*]pyrene aerosols (7.5 mg/m^3), and to these same compounds adsorbed on gallium oxide particles (27 mg/m^3) both with and without coexposure to sulfur dioxide (5 ppm) for 2 hours/day, 5 days/week for 4 weeks.

The testes and ovaries contain rapidly proliferating cells and therefore should be considered susceptible to damage by PAHs. However, animal data on reproductive toxicity are scarce and only available on BaP. BaP has affected the reproductive performance of pregnant rats by significantly increasing the number of resorptions and fetal wastage, and by decreasing fetal weight. Decreased uterine weights in these animals as well as in pseudopregnant rats was interpreted as an anti-oestrogenic effect of BaP (70). In female mice single intraperitoneal injections of BaP decreased the number of corpora lutea, indicating a transient adverse effect on follicle growth, ovulation or formation of corpora lutea, with transient infertility as the result (*71*). Intraperitoneal administration of BaP to pregnant mice has produced stillbirths, resorptions and malformations (*72*). *In utero* exposure to BaP has also produced several serious effects in the progeny of mice, such as testicular atrophy and interstitial cell tumours (*73*), immunosuppression and tumour induction (*74*).

A number of PAHs have an immunosuppressive effect in mice. There are data, allthough limited, that suggest that the degree of immunosuppression correlates with their carcinogenic potency (*75*).

On the basis of epidemiological evidence, it has been suggested that several factors associated with an increased risk of cancer are also associated with an increased risk of atherosclerosis. This would indicate that somatic mutation is involved in the formation of the atherosclerotic plaque (*76*). PAHs, including dibenz [*a,h*]anthracene, dibenz[*a,c*]anthracene, 7,12-dimethylbenz[*a*]anthracene and BaP, were shown to act as initiators and/or accelerators in atherosclerotic plaque formation in chickens, pigeons and Ah-responsive mice (*77,78*).

Carcinogenic effects
Many PAHs are capable of producing tumours in experimental animals. BaP has been used for many years as a model compound in a variety of different carcinogenicity bioassays, although no adequate studies that meet modern requirements for toxicological testing have been identified.

When administered by the oral route, BaP and several other PAHs produced tumours in the forestomach, liver, lungs and mammary glands of rodents (*10,79*), while mono- and dinitropyrenes produced pituitary and mammary gland tumours (*80*).

Newborn mice seem to be very susceptible to the carcinogenic action of PAHs. After intraperitoneal or subcutaneous injection of BaP and other PAHs during the first 15 days of life, liver and lung tumours are produced within half a year (*10,79,81–84*). In addition, nitro-PAHs produce leukaemia and tumours of the mammary glands and colon (*85,86*).

Several studies have examined the lung carcinogenicity of single PAHs and nitro-PAHs after administration via the respiratory tract of experimental animals. Inhalation experiments with "pure" BaP have only been performed in the hamster. Other PAHs, including BaP, have been administered by intratracheal instillation (often on a solid carrier, such as ferric oxide particles) to rats and hamsters. In many experiments intrapulmonary injection or implantation in a beeswax/trioctanoin mixture have been used for administration of the test compound. In these experiments BaP and other PAHs have induced lung tumours in rats and hamsters (*10,79,87–93*).

After long-term inhalation of "pure" BaP at a concentration of 10 mg/m^3, cancer of the respiratory tract occurred in 35% of golden hamsters; additionally a substantial number of tumours of the gastrointestinal tract were found (*1,94*). The tumorigenicity of inhaled BaP (10 mg/m^3) in Syrian golden hamsters was enhanced by coexposure to sulfur dioxide (172 ppm) (*95*).

The carcinogenic potencies per unit dose of tested PAHs vary widely although lack of quantitative data permits a firm evaluation. In the rat lung implantation assay using a beeswax/trioctanoin mixture as vehicle, the carcinogenic potencies of phenanthrene, chrysene, dibenz[*a,h*]anthracene and benzo[*b*]naphtho[2,1-*d*] thiophene relative to BaP (1.00) were 0.001, 0.03, 1.91 and 0.02, respectively (*87*). Benz[*a*]anthracene and chrysene are relatively weak carcinogens, while the benzo[*a*]fluoranthenes are moderately carcinogenic.

Risk assessments of BaP and potency assessments of various individual PAHs and complex PAH mixtures have been attempted recently (*96–100*). The main problem in absolute risk assessment is the lack of adequate data from long-term studies with purified PAHs. The only multi-dose long-term feeding studies so far available for risk assessment were published by Rigdon and Neal in 1969 (*101*). 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} µg/m^3. A linearized multistage model was used, and risk estimates were converted to human risk (*102*).

Carcinogenicity of PAH-containing emission condensates
The 4- to 7-ring PAH fraction of condensate from car exhausts (petrol, diesel), domestic coal-stove emissions and tobacco smoke contains nearly all the carcinogenic potential of PAHs. This was found after skin painting, subcutaneous injection and intrapulmonary implantation of fractions (*1,103–111*).

When fractions of condensate from coal-stove and brown-coal emissions and emissions from petrol-driven vehicles were tested on mouse skin, most of the carcinogenicity originated from the fraction containing PAHs with 4–7 rings. This fraction represents only a small proportion by weight of the condensate. The amount of BaP, which varied from 0.414 to 0.702 mg per gram of condensate accounted for 6–15% of the total carcinogenicity (*104,106,107,111*). After implantation of condensate from coal-stove emissions, diesel exhaust and emissions from petrol-driven vehicles into the lungs of rats, the fraction containing PAHs with 3 or more rings accounted for 68–81% of the total carcinogenicity. The amount of BaP in the condensate,

which varied from 0.483 mg/g in the motor vehicle condensate to 1.14 mg/g in the flue-gas condensate accounted for, respectively, 1.4% and 2.4% of the total carcinogenicity (105,108,109).

The most pronounced lung carcinogenic effect of sidestream smoke (100 ng BaP per cigarette) in the lung was caused by the fraction containing PAHs with 4 and more rings (5 carcinomas of the lungs in 35 rats). This fraction represented only 3.5% by weight of the total sidestream smoke condensate. By contrast, the semivolatile material did not provoke any tumours. Only a small contribution to the total carcinogenicity (1 carcinoma of the lungs in 35 rats) was observed for the fraction containing non-aromatic material and 2- and 3-ring PAHs (110).

Epidemiological and experimental studies show that, for the induction of a certain lung tumour incidence, inhaled cigarette smoke contains about 100 times less BaP and inhaled diesel exhaust contains about 1000 times less BaP than the exhaust from coke ovens or heated tar pitch which yield the same result. This indicates that diesel exhaust and cigarette smoke contain – apart from PAHs – highly potent carcinogenic substances and/or substances which are very effective in promoting lung carcinogenesis (112).

Attempts to derive relative potencies of individual PAHs (relative to BaP) have also been published, and the idea of summarizing the contributions from each of the selected PAHs into a total BaP equivalent dose (assuming additivity in their carcinogenic effects) has emerged (96–98,100). However, in studies on exposures to mixtures, the individual PAHs have been shown to interact metabolically in a plethora of ways resulting in synergistic, additive or antagonistic effects, and consequently nothing can be concluded at present on the resulting tumorigenic actions of individual PAHs in complex mixtures (113).

Several new approaches are being explored for the determination of the carcinogenic potency of complex PAH mixtures from emission sources (98,99). The gravimetric determination of the total amount of PAHs with four rings or more (4- to 7-ring PAHs), together with an assumption that this fraction is as potent as BaP, was found to be the best out of eight different calculation methods for the prediction of the tumorigenic potency of a number of emission condensates as determined from bioassays (98).

Carcinogenicity of diesel particulates
An increased incidence of lung tumours, some of which were diagnosed as malignant, was observed in five studies with rats following exposure for 2 or more years to high levels of diesel exhaust. Most of the tumours were observed after 2 years. Similar studies in Syrian hamsters yielded negative results. Studies with mice have given mixed results. The results of some studies with laboratory animals exposed to diesel exhaust and known carcinogens suggest that exposure to diesel exhaust enhances the effect of the known carcinogens (114).

When male and female rats were exposed (for 7 hours/day, 5 days/week) for up to 30 months to diesel engine exhaust at soot concentrations of 0.35, 3.5 or 7.0 mg/m^3, the prevalence of lung tumours was significantly increased (115). DNA-adduct levels accumulated slowly during a 12-week exposure and levels declined rapidly after the termination of exposure. Because adduct levels in lungs were similar at all concentrations examined and were increased in rats at an exposure level that did not significantly increase tumour incidence (soot, 0.35 mg/m^3), it was suggested that factors in addition to lung DNA adduct formation must be involved in diesel-exhaust-induced carcinogenicity (116).

Long-term exposure to unfiltered diesel engine exhaust (4 mg/m^3) caused a 16% lung tumour incidence in male and female rats. A heavy load of particulate matter in the lungs of the rats, caused by an exposure-related impairment of alveolar lung clearance, produced severe inflammatory changes which may have been instrumental in the induction of squamous cell tumours. However, an effect of particle-associated PAHs could not be excluded. Co-carcinogenic effects of diesel exhaust after initial carcinogen treatment were found in the respiratory tract (117). In contrast to the diesel-exhaust-exposed rats, the lungs of rats exposed to coal oven flue gas mixed with pyrolysed pitch had much less severe inflammatory changes, but squamous cell tumour incidence was 17%. It was concluded that diesel exhaust had more promotional effect than PAH-enriched coal-oven flue gas which, in turn, was a more complete carcinogen (118).

Quantitative estimates of lung cancer risk from exposure to diesel engine particulate emissions have recently been developed using data from three chronic bioassays with Fischer 344 rats. Dose was based on the concentration of carbon particulate matter per unit lung surface area. Unit risk estimates were developed using either a time-to-tumour or a linearized multistage model. The unit risk estimates, defined as the 95% upper confidence limit of the cancer risk from continuous lifetime exposure to 1 mg/m^3 of diesel exhaust particulate matter, varied from 1.0 to 4.6 × 10^{-5} with a geometric mean of 1.7 × 10^{-5} (119).

Combined effect of PAHs and particles

The database from rat inhalation bioassays suggests that the rat lung tumour response to diesel soot, under the conditions that the bioassays have been performed, might predominantly be a nonspecific effect unrelated to the mutagenic substances (e.g. PAHs, dinitropyrenes) present in diesel particulates. The cancers presumably result from lung "overloading" and the ensuing inflammatory response (*120*). This view is supported by the fact that a diverse group of solid, poorly soluble, non-fibre particles has been shown to cause lung tumours in rats following chronic inhalation or intratracheal instillation. It was thus shown that fine carbon black particles almost completely free of organic mutagens were able to produce tumours in the rat lung after chronic inhalation exposure with particle mass concentrations in the exposure atmosphere of only 6 mg/m^3 (*121*).

However, the carcinogenic potency of particles, presumably operating through a non-genotoxic mechanisms, at the much lower concentrations present in ambient air is at present not known. In such conditions, the genotoxic action of PAHs and derived mutagenic substances attached to the particles might well be a more significant risk factor. Thus, both genotoxic and non-genotoxic mechanisms have to be considered.

This is apparently supported by results from a recent study in rats exposed by inhalation to coal tar/pitch condensation aerosol (no particles) containing BaP at a concentration of either 20 or 46 µg/m^3 where a clear carcinogenic effect was observed. The lifetime lung tumour risk for rats exposed to 1 µg/m^3 BaP as a constituent of the complex PAH mixture was calculated to be 2% corresponding to 20 per million at a BaP concentration of 1 ng/m^3. In comparison, the estimated unit lung cancer risk for BaP based on epidemiological data from coking plants was 7–9% (*121*). It was suggested that in the evaluation of the lung carcinogenicity of PAHs attached to inhaled, fine particles in environmental samples, the likely enhancing properties of the inflammatory effects of particles on lung tissue should be considered (*121*).

Mutagenic effects
A great number of PAHs and nitro-PAHs as well as a number of emissions containing these compounds have shown genotoxicity and mutagenicity in *in vitro* and *in vivo* assays (*2,10,85*). The Ames test using various strains of *Salmonella typhimurium* has been widely used to monitor the mutagenic activity of PAH and other mutagens present in complex mixtures in ambient air (*5,122*).

Effects on humans

Toxicological effects
On the basis of the experimental results, the most significant health effect to be expected from inhalation exposure to PAHs is an excess risk of lung cancer.

Carcinogenic effects
In the past, chimney sweeps and tar workers were dermally exposed to substantial amounts of PAHs and there is sufficient evidence that skin cancer in many of these workers was caused by PAHs. Epidemiological studies in coke-oven workers, coal-gas workers and employees in aluminum production plants provide sufficient evidence of the role of inhaled PAHs in the induction of lung cancer. An excessively high rate of lung cancer mortality was found in coke-oven workers. The increases in lung cancer cases correlate closely with the time spent working on top of ovens where an average BaP concentration of about 30 mg/m^3 has been detected (*1,123,124*). It should be noted that all these working environments include chemicals, other than PAHs, that may also have contributed to the excesses of lung cancer.

Because several PAHs are carcinogenic, a suitable index for the carcinogenic fraction of PAHs in ambient air has to be found. If all PAH profiles were identical, the concentration of a single PAH would be a good index of the carcinogenic potential of the total fraction. The PAH profiles of different emissions are far from this ideal but, as stated, the variations of PAH profiles in workplaces are not so wide and the deviation from the mean is relatively low in ambient air. Therefore, as 5–15% of the total carcinogenic effect from PAH fractions of different exhaust condensates is due to BaP according to skin-painting studies, BaP may be provisionally regarded as a sufficient index for the carcinogenic potential of the PAH fraction in ambient air. As mentioned, the PAH profiles detected in different emissions and workplaces sometimes differ widely from each other and from PAH profiles in the ambient air. Moreover, it cannot be excluded that the PAH profiles in the ambient air vary under special conditions. More data are necessary in order to develop a precise index for the carcinogenic potential of all PAH profiles that can occur under conditions relevant for lung cancer risk estimates. Furthermore, the carcinogenicity of PAH mixtures may be influenced by the synergistic and antagonistic effects of other components emitted together with PAHs during incomplete combustion (*1*).

The US Environmental Protection Agency calculated the lung cancer risk from exposure to coke-oven emissions based on extensive studies of coke-oven workers in Pennsylvania. Using a linearized multistage model, the most plausible upper-bound individual life time unit risk estimate associated with a continous exposure to 1 $\mu g/m^3$ of benzene-soluble compounds of coke-oven emissions in ambient air was approximately 6.2×10^{-4} (*125*). WHO adopted this risk estimate in the 1987 *Air quality guidelines for Europe*. Using BaP as an index of general PAH mixtures from emissions of coke-ovens and similar combustion processes in urban air, and using a reported value of 0.71% BaP in benzene-soluble coke-oven emissions a lifetime risk of respiratory cancer of 8.7×10^{-5} $(ng/m^3)^{-1}$ was calculated (*1*).

An alternative link with a BaP index was explored. Using measurements of BaP emissions from old German coke-oven plants, and extrapolating according to a linear nonthreshold model a calculated risk of death from respiratory tract cancer of 1% per mg of BaP per m^3 at the workplace after exposure for 25 years and in 5 per 100 000 population exposed to 1 ng of BaP per m^3 for 50 years was obtained (*1*).

Some other risk estimates of respiratory tract cancer related to BaP in the ambient air have been calculated by the US Envirnmental Protection Agency. The estimated risk per year ranged from 0.11×10^{-5} to 1.4×10^{-5} per ng of BaP per m^3 (*126*) corresponding to unit lifetime risks ranging from 7.7×10^{-5} to 98×10^{-5}.

In a Dutch Integrated Criteria Document on PAHs only two additional risk assessments, based on occupational exposure, were considered useful for risk analysis. Using data from a prospective cohort of British gasworkers exposed to carbonization emissions containing BaP at an average of 3 $\mu g/m^3$, a unit risk of 43×10^{-5} per $(ng/m^3)^{-1}$ was calculated. Similarly, from studies of Chinese women in the Xuan Wei province using smoky coal for cooking, a unit risk of 6.58×10^{-5} $(ng/m^3)^{-1}$ was estimated (*113*).

Evaluation of human health risks

Exposure

PAHs are formed during incomplete combustion or pyrolysis of organic material and in connection with the worldwide use of oil, gas, coal and wood in energy production. Additional contributions to ambient air levels arise from tobacco smoking, while the use of unvented heating sources can increase PAH concentrations in indoor air. Because of such widespread sources, PAHs are present almost everywhere. PAHs are complex mixtures of hundreds of chemicals, including derivatives of PAHs, such as nitro-PAHs and oxygenated products, and also heterocyclic PAHs. The biological properties of the majority of these compounds are as yet unknown. Benzo[a]pyrene (BaP) is the PAH most widely studied, and the abundance of information on toxicity and occurrence of PAHs is related to this compound. Current annual mean concentrations of BaP in major European urban areas are in the range 1–10 ng/m^3. In rural areas, the concentrations are < 1 ng/m^3 (*1–5*).

Food is considered to be the major source of human PAH exposure due to PAH formation during cooking or from atmospheric deposition of PAHs on grains, fruits and vegetables. The relative contribution of airborne PAH pollutants to food levels (via fallout) has not been well characterized (*11*).

Health risk evaluation

Data from animal studies indicate that several PAHs may induce a number of adverse effects, such as immunotoxicity, genotoxicity, carcinogenicity, reproductive toxicity (affecting both male and female offspring), and may possibly also influence development of atherosclerosis. However, the critical endpoint for the health risk evaluation is the well-documented carcinogenicity of several PAHs (*10*).

BaP is by far the most intensively studied PAH in experimental animals. It produces tumours of many different tissues, depending on the species tested and the route of application. BaP is the only PAH that has been tested for carcinogenicity following inhalation, and it produced lung tumours in hamsters, the only species tested. Induction of lung tumours in rats and hamsters has also been documented for BaP and several other PAHs following direct application, e.g. intratracheal instillation into the pulmonary tissue. The lung carcinogenicity of BaP can be enhanced by coexposure to other substances such as cigarette smoke, asbestos and probably also airborne particles. Several studies have shown that the benzene soluble fraction, containing 4- to 7-ring PAHs of condensates from car exhausts (petrol, diesel), domestic coal-stove emissions, and tobacco smoke contains nearly all the carcinogenic potential of PAHs from these sources (*112*).

Because several PAHs have been shown to be carcinogenic, and many more have been shown to be genotoxic in *in vitro* assays, a suitable indicator for the carcinogenic fraction of the large number of PAHs in

ambient air is desirable. The most appropriate indicator for the carcinogenic PAHs in air seems to be BaP concentrations, given present knowledge and the existing database. Assessment of risks to health of a given mixture of PAHs using this indicator approach would entail, first, measurement of the concentration of BaP in a given mixture present in a medium such as air. Then, assuming that the given mixture resembles that from coke ovens, the unit risk estimate is applied in tandem with the measured BaP air concentration to obtain the lifetime cancer risk at this exposure level.

The proportions of different PAHs detected in different emissions and workplaces sometimes differ widely from each other and from PAH profiles in ambient air. However, the profiles of PAHs in ambient air do not seem to differ very much from one area to another, although large variations may be seen under special conditions. Furthermore, the carcinogenicity of PAH mixtures may be influenced by synergistic and antagonistic effects of other compounds emitted together with PAHs during incomplete combustion. It should also be recognized that in ambient air the carcinogenic 4- to 7-7 ring PAHs (representing the majority of PAHs) are preferentially attached to particles, and only a minor fraction, depending on the temperature, exists as volatiles. A few studies indicate that the toxicokinetic properties of inhaled BaP attached to particles are different from those of pure BaP alone. Virtually nothing is known about other PAHs in this respect.

Risk assessments and potency assessments of various individual PAHs and complex mixtures of PAHs have been attempted. BaP is the only PAH for which a database is available, allowing a quantitative risk assessment. Risk assessment of BaP is, however, hampered by the poor quality of the data sets available (102).

Attempts to derive relative potencies of individual PAHs (relative to BaP) have also been published, and the idea of summarizing the contributions from each of the selected PAHs into a total BaP equivalent dose (assuming their carcinogenic effects to be additive) has emerged (96,97). There are doubts, however, about the scientific justification for these procedures.

Risk estimates considered in the USA for coke-oven emissions were used in the 1987 *Air quality guidelines for Europe*. Using a linearized multistage model, the most plausible upper-bound individual lifetime unit risk estimate associated with a continuous exposure to 1 µg/m^3 of benzene-soluble compounds of coke-oven emissions in ambient air was approximately 6.2×10^{-4}. Using BaP as an indicator of general PAH mixtures from emissions of coke ovens and similar combustion processes in urban air, and a reported value of 0.71% BaP in the benzene-soluble fraction of coke oven emissions, a lifetime risk of respiratory cancer of 8.7×10^{-5} (ng/m^3)$^{-1}$ was calculated (1).

From the lung tumour rates obtained in a recent rat inhalation study with coal tar/pitch condensation aerosols, containing two different levels of BaP, a lifetime tumour risk of 2×10^{-5} (ng/m^3)$^{-1}$ for BaP as a constituent of a complex mixture was calculated using a linearized multistage model (121).

Guidelines
No specific guideline value can be recommended for PAHs as such in air. These compounds are typically constituents of complex mixtures. Some PAHs are also potent carcinogens, which may interact with a number of other compounds. In addition, PAHs in air are attached to particles, which may also play a role in their carcinogenicity. Although food is thought to be the major source of human exposure to PAHs, part of this contamination may arise from air pollution with PAHs. The levels of PAHs in air should therefore be kept as low as possible.

In view of the difficulties in dealing with guidelines for PAH mixtures, the advantages and disadvantages of using a single indicator carcinogen to represent the carcinogenic potential of a fraction of PAH in air were considered. Evaluation of, for example, BaP alone will probably underestimate the carcinogenic potential of airborne PAH mixtures, since co-occurring substances are also carcinogenic. Nevertheless, the well-studied common constituent of PAH mixtures, BaP, was chosen as an indicator, although the limitations and uncertainties in such an approach were recognized

To set priorities with respect to control, an excess lifetime cancer risk, expressed in terms of the BaP concentration and based on observations in coke oven workers exposed to mixtures of PAHs, is presented here. It must be emphasized that the composition of PAHs to which coke-oven workers are exposed may not be similar to that in ambient air, although it was noted that similar risks have been derived from studies of individuals exposed to other mixtures containing PAHs. Having also taken into consideration some recent animal data from which a unit risk of the same order of magnitude can be derived, it was concluded that the occupational epidemiology data should serve as the basis for the risk estimate.

Based upon epidemiological data from studies in coke-oven workers, a unit risk for BaP as an indicator in air constituent is estimated to be 8.7×10^{-5} $(ng/m^3)^{-1}$ which is the same as that established by WHO in 1987. The corresponding concentrations of BaP producing excess lifetime cancer risks of 1/10 000, 1/100 000 and 1/1 000 000 are 1.2, 0.12 and 0.012 ng/m^3 respectively.

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