Cancer Risk Assessment, Indicators, and Guidelines for Polycyclic Aromatic Hydrocarbons in the Ambient Air

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Polycyclic aromatic hydrocarbons (PAHs) are formed during incomplete combustion. Domestic wood burning and road traffic are the major sources of PAHs in Sweden. In Stockholm, the sum of 14 different PAHs is 100–200 ng/m^3 at the street-level site, the most abundant being phenanthrene. Benzo[*a*]pyrene (B[*a*]P) varies between 1 and 2 ng/m^3. Exposure to PAH-containing substances increases the risk of cancer in humans. The carcinogenicity of PAHs is associated with the complexity of the molecule, i.e., increasing number of benzenoid rings, and with metabolic activation to reactive diol epoxide intermediates and their subsequent covalent binding to critical targets in DNA. B[*a*]P is the main indicator of carcinogenic PAHs. Fluoranthene is an important volatile PAH because it occurs at high concentrations in ambient air and because it is an experimental carcinogen in certain test systems. Thus, fluoranthene is suggested as a complementary indicator to B[*a*]P. The most carcinogenic PAH identified, dibenzo[*a,l*]pyrene, is also suggested as an indicator, although it occurs at very low concentrations. Quantitative cancer risk estimates of PAHs as air pollutants are very uncertain because of the lack of useful, good-quality data. According to the World Health Organization Air Quality Guidelines for Europe, the unit risk is 9 × 10^{-5} per ng/m^3 of B[*a*]P as indicator of the total PAH content, namely, lifetime exposure to 0.1 ng/m^3 would theoretically lead to one extra cancer case in 100,000 exposed individuals. This concentration of 0.1 ng/m^3 of B[*a*]P is suggested as a health-based guideline. Because the carcinogenic potency of fluoranthene has been estimated to be approximately 20 times less than that of B[*a*]P, a tentative guideline value of 2 ng/m^3 is suggested for fluoranthene. Other significant PAHs are phenanthrene, methylated phenanthrenes/anthracenes and pyrene (high air concentrations), and large-molecule PAHs such as dibenz[*a,h*]anthracene, benzo[*b*]fluoranthene, benzo[*k*]fluoranthene, and indeno[1,2,3-*cd*]pyrene (high carcinogenicity). Additional source-specific indicators are benzo[*ghi*]perylene for gasoline vehicles, retene for wood combustion, and dibenzothiophene and benzonaphthothiophene for sulfur-containing fuels. *Key words:* benzo[*a*]pyrene, carcinogenesis, comparative potency, concentrations in air, dose response, fluoranthene, indicator substances, mechanism of action, PAH, risk assessment. *Environ Health Perspect* 110(suppl 3):451–489 (2002).

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The Swedish Governmental Commission on Environment and Health (SOU 1996) and the Governmental Committee on Environmental Objectives (SOU 2000) proposed, among other things, targets for carcinogenic air pollutants in order to fulfill the national objectives for the reduction of harmful emissions to ambient air. However, it was concluded that there was a need for a better scientific basis for the selection of chemical markers in ambient air to meet the national objectives.

Against this background it was decided by the Swedish Environmental Protection Agency to commission The Institute of Environmental Medicine of the Karolinska Institute, to prepare an up-to-date review of the carcinogenicity of polycyclic aromatic hydrocarbons (PAHs), and to recommend suitable indicator substances and guideline values. The purpose was to create a list the most important compounds, suitable for ambient air monitoring, with regard to source specificity, presence in ambient air, and toxicity.

This report has been prepared by an expert group coordinated by Associate Professor Katarina Victorin, The Institute of Environmental Medicine (IMM). Coauthors are Dr. Carl-Elis Boström and Dr. Titus Kyrklund from the Swedish Environmental Protection Agency, Associate Professor Roger Westerholm from the Department of Analytical Chemistry at Stockholm University, and Associate Professor Christer Johansson from the Environment and Health Protection Administration of Stockholm ("Sources, Deposition, and Ambient Concentration" section); Associate Professor Bengt Jernström, Dr. Per Gerde, and Associate Professor Agneta Rannug from IMM, and Associate Professor Margareta Törnqvist from the Department of Environmental Chemistry at Stockholm University ("Mechanistic Aspects of Biologic Activity" section); and Associate Professor

Katarina Victorin and Dr. Annika Hanberg, IMM ("Quantitative Cancer Risk Estimates" section). The document has been reviewed and discussed by Professor Harri Vainio, IMM/International Agency for Research on Cancer; Associate Professor Per Gustavsson, The Karolinska Hospital in Stockholm; and Professor John Christian Larsen, Institute for Food Safety and Toxicology, Søborg, Denmark.

Nomenclature, Structure, and Sources of PAHs

Polycyclic aromatic hydrocarbons constitute a wide class of compounds composed of fused benzenoid rings (alternant PAHs), but they may also be composed of unsaturated four-, five-, and six-membered rings (nonalternant PAHs). Within the group, the compounds range from semivolatile molecules to molecules with high boiling points. The compounds may exist with a great number of structures and, depending on the complexity of the PAHs, in a large number of isomers. The compounds are generally lipophilic, a property that increases with increasing complexity of the compounds (Harvey 1997).

In this context we mainly restrict our discussion to unsubstituted PAHs, although the compounds may exist in substituted form (i.e., alkyl-, nitro-, amino-, or halogen-substituted PAHs). PAHs are generally produced in incomplete combustion processes, and their occurrence and emissions have therefore been substantial during the past centuries because of the abundant use of fuels for industrial applications, heating, transport, and many other purposes. Thus, PAHs are ubiquitous contaminants in both the general environment and in certain working environments (IARC 1983, 1984a,b, 1985). The composition of the PAHs emitted is dependent on a variety of factors, for example, the fuel and its properties, and the combustion technology.

Furthermore, emitted PAHs form or bind to particles and undergo oxidation and degradation in the atmosphere, processes activated by ultraviolet radiation and enhanced by other air contaminants. Because the best-characterized individual source of PAHs is vehicle emissions, this source is more extensively treated in this document than wood burning, which is the other major source.

PAHs and Human Carcinogenesis

The great interest in PAH compounds stems from the observations that some of these compounds may cause tumors in humans (IARC 1983, 1984a,b, 1985). In fact, the key event in this respect was the observation in 1775 by the British surgeon Sir Percival Pott that scrotal cancer in chimney sweeps originates from occupational exposure to soot (Pott 1775). This observation was followed a century later by a report by von Volkman (1875) on elevated incidences of skin cancers in workers in the coal tar industry. In the early 1900s it was widely recognized that soot, coal tar, and pitch are carcinogenic to man (Dipple 1985). More recent animal experiments have shown that the carcinogenic activity of PAHs in vehicle exhaust extracts is associated mainly with the fraction containing compounds composed of four to seven aromatic rings (Grimmer et al. 1983, 1984). The International Agency for Research on Cancer (IARC 1984a,b, 1985, 1987b, 1989a) has evaluated several different PAH-containing materials or mixtures and occupational situations in which exposure to PAHs occurs. The overall evaluations are summarized in Table 1.

Thus, the carcinogenicity of PAHs and PAH-containing materials in humans seems to be beyond dispute. The carcinogenicity of PAHs was demonstrated in 1915 (Phillips 1983), when it was shown that exposure of the ears of rabbits to PAH-containing material caused tumors at the site of application, and a few years later such material proved to be tumorigenic in mice by skin painting. In the late 1920s, dibenz[*a,h*]anthracene was synthesized and as the first pure PAH proved to be carcinogenic in the mouse. In the early 1930s an amount corresponding to a few grams of benzo[*a*]pyrene (B[*a*]P) was isolated from 2 tons of pitch and shown to cause tumors in rodents (Dipple 1985; Phillips 1983). The frequent use of B[*a*]P as a model compound for PAHs stems from this observation. A recent 2-year bioassay with mice demonstrated that coal tar from gasification plant waste sites, mixed in the feed at 0.01–1% induced tumors in the liver, lung, forestomach, and other organs. Parallel treatment with B[*a*]P induced tumors of the forestomach, esophagus, and tongue. A comparison of the results indicated that the lung

and liver tumors appeared to be due to other genotoxic components in coal tar besides B[*a*]P (Culp et al. 1998). Many PAHs have been tested by topical application to the skin of mice or by subcutaneous injection to identify the relationship between structural characteristics of the compounds, their metabolism, and tumorigenic potency. These factors are discussed in detail in a separate section of this document. Many PAHs are considered to be complete carcinogens; thus the compounds are both tumor initiators and promoters/progressors (for a definition, see "Mechanistic Aspects of Biologic Activity"). Although animal experiments indicate that PAHs may also give rise to, for example, immunologic and reproductive effects (ATSDR 1995; WHO/IPCS 1998), carcinogenicity is regarded as the critical effect and is the primary aspect considered in this document.

PAHs in Ambient Air

In Sweden, as well as in other countries, the incidence of lung cancer is generally higher in cities than in rural areas. Some of this cancer is probably due to carcinogenic air pollutants, although a higher rate of smoking in cities and other factors also contribute (Ehrenberg et al. 1985; Hemminki and Pershagen 1994;

Törnqvist and Ehrenberg 1994). For the pollution levels prevailing around 1980, it has been estimated that approximately 100 cases of lung cancer annually in Sweden (out of 2,500) are related to carcinogenic air pollutants that originate mainly from different combustion sources (Swedish Cancer Committee 1984).

The estimated cancer risk from air pollutants is considered to be too high from the national public health point of view. To achieve the objective of reducing the emissions, environmental quality objectives must be defined. The Governmental Commission on Environmental Health (1996) proposed such objectives for indicators of volatile and nonvolatile carcinogens. For PAHs the proposal was that by 2020 the long-term mean level of B[*a*]P should not exceed 0.1 ng/m^3. This level is equivalent to a theoretic excess lifetime cancer risk of 1 in 100,000 (1 × 10^{-5}) for B[*a*]P as an indicator of PAH, based on a risk assessment by the World Health Organization (WHO) (1987). This long-term objective was later adopted by Government Bill 2000/01:130 (Swedish Government 2000).

Although B[*a*]P has been used historically as an indicator of carcinogenic PAHs

Table 1. IARC evaluations of certain complex mixtures and occupational exposures involving exposure to PAH compounds.[a]

| Mixture/exposure | IARC classification | | | |
	Group 1: carcinogenic to humans	Group 2A: probably carcinogenic to humans	Group 2B: possibly carcinogenic to humans	Group 3: not classifiable
Bitumen				X
Bitumen extracts			X	
Carbon black				X
Carbon black extracts			X	
Coal dust				X
Coal tar pitches	X			
Coal tars	X			
Creosotes		X		
Crude oil				X
Diesel fuels				
Light				X
Marine			X	
Fuel oils				
Heavy			X	
Light				X
Gasoline			X	
Jet fuel				X
Mineral oils				
Untreated	X			
Mildly treated	X			
Highly refined				X
Petroleum solvents				X
Shale oils	X			
Soots	X			
Diesel exhausts		X		
Gasoline exhausts			X	
Tobacco smoke	X			
Aluminum production	X			
Coal gasification	X			
Coke production	X			
Petroleum refining		X		

[a]Data from IARC 1984a,b, 1985, 1987a, 1989a,b.

and PAH derivatives, the suitability of B[*a*]P as an indicator has been questioned, mainly because the most-cited quantitative risk assessment is based on an increased risk of lung cancer among coke-oven workers. The PAH profiles of relevant emissions today (traffic exhausts, wood combustion, and other combustion sources) probably differ from those of coke-oven emissions with regard to the relative contribution of B[*a*]P, other PAHs, and PAH derivatives. In ambient air the concentration of B[*a*]P is relatively low compared with other PAHs.

The Goals of This Study

Because there might be other PAH compounds besides B[*a*]P that could be equally or more suitable for risk assessment and as indicator substances, the Swedish Environmental Protection Agency asked the IMM to discuss the suitability of different possible indicators from a scientific point of view and to come up with proposals both for indicator substances and for guideline values.

The authors of this report with representatives from the emission–imission–analytic side and the toxicologic-risk assessment side identified some characteristics for good indicators: *a*) they should ideally be important health risk factors; *b*) it should be possible to quantify the risk contribution from the indicator; *c*) they should include both source-specific indicators and general indicators of ambient air pollution; *d*) both particulate-phase and vapor-phase PAHs should be represented; and *e*) it must be possible to analyze them chemically with high reproducibility.

The authors agreed that possible options for indicator substances should be thoroughly discussed, taking into account the different aspects, and realized that it might be difficult to find a single indicator that would fulfill all these demands.

At an early stage the group also decided that the review should be restricted to unsubstituted PAH compounds. PAH derivatives are also important, especially because the highest mutagenic activity in short-term tests is usually found in the more polar fractions of environmental samples that contain, for example, nitrated, oxygenated, and hydroxylated PAHs. However, much less is known about the chemical identification and toxicologic effects of PAH derivatives than about unsubstituted PAHs.

The intention of the present work has been to highlight certain mechanistic aspects of the carcinogenicity of PAHs and to conduct risk assessment, with the focus on the comparative quantitative potency of different PAHs. The assignment also included a survey on how risk assessment and indicators of PAHs in ambient air have been dealt with in other countries. The authors recommend the recent International Programme on Chemical Safety (IPCS) Environmental Health Criteria document on PAHs as the main reference book (WHO/IPCS 1998).

Sources, Deposition, and Ambient Concentrations

Sources

National data on emissions of PAHs are limited. Data from European countries are presented in Table 2 (Berdowski et al. 1997;

EEA CORINAIR 1997; Pacyna 1999). The emission estimates regarding PAHs are generally more uncertain than for other pollutants such as nitrogen dioxide or sulfur dioxide because of less-developed methodologies for their quantification and less-frequent measurements of PAHs in urban air. In addition, there may be differences in the number of PAHs reported and the sources included in the estimates from various countries. The contribution from different sources such as residential heating, automobile exhaust, industrial power generation, incinerators, and the production of coal tar, coke, and asphalt is difficult to estimate. These estimates may also vary considerably from country to country. In the United States and also in Sweden, residential burning of wood is regarded as the largest source of PAHs. However, in cities, mobile sources including working machinery contribute to the major part of the PAH emissions. The main source sectors in 1994 are given in Table 3. A recent emission inventory for Sweden is presented in Table 4. There was a reduction in the emission of PAHs in Europe from the 1960s to the 1980s, and the concentrations of PAHs in cities also declined during the same period. However, the data are uncertain. Data from Sweden indicate that the emissions of PAHs were reduced by 35% between 1980 and 1987 and by 15% between 1987 and 1995 (Boström 1997; SEPA 1996a).

Road transport. In general, automotive exhaust is an important emission source that contributes substantially to urban air pollution. In all nonideal combustion processes of organic fuels, compounds other than carbon dioxide and water will be formed in different amounts. Emissions of specific PAHs can be associated with particulates; they can be present in the gas phase; or they can be present in mixtures of both forms. Emissions from automobiles comprise regulated and unregulated exhaust emissions. Regulated emissions by law are carbon monoxide, nitrogen oxides, unburned fuel hydrocarbons, and particles. Nonregulated pollutants are defined as compounds not specified by law.

Table 2. Emissions estimates from European countries—anthropogenic emissions of PAHs[a] (tonnes/year) in the EU region.

Country	PAH[b] (1994)	PAH[c] (1990)	B[*a*]P[d] (1995)
Austria	458	243	6.11
Belgium		818	3.35
Denmark	37	76.7	1.44
Finland		104	6.88
France		3,479	26.4
Germany	420	420	26.4
Greece		153	2.89
Ireland		73.7	1.24
Italy		694	13.9
Luxembourg	1.1	6.24	0.24
Netherlands		184	2.29
Norway	181		
Portugal		138	1.64
Spain		521	9.61
Sweden	153	282	6.78
United Kingdom	764	1,437	12.0

[a]PAHs refers to the "Borneff six" (benzo[*a*]pyrene, benzo[*b*]fluoranthene, benzo[*ghi*]perylene, benzo[*k*]fluoranthene, fluoranthene, and indeno[1,2,3-*cd*]perylene). [b]Data from EEA CORINAIR (1997). [c]Data from Berdowski et al. (1997). [d]Data from Pacyna (1999).

Table 3. Main source sectors for PAHs in 1994 (tonnes/year) in six European countries as reported in Table 2 (Sweden excluded).[a]

Sector	PAH	%
Combustion in energy and transformation industries	6.1	0.3
Nonindustrial combustion plants[b]	1,120	60
Combustion in manufacturing industry	63	3.4
Production processes	248	13
Road transport	383	20
Other mobile sources	10	0.5
Waste incineration	30	1.6
Agriculture and forestry	1	<0.1
Natural sources	8	0.4
Total (approximately)	1,900	

[a]Data from EEA CORINAIR (1997). [b]Includes domestic wood burning.

Table 4. Emissions to air of PAHs (tonnes/year) in Sweden.[a]

Sources	1990	1992	1995
Graphite and aluminum works[b]	23	2	2
Domestic heating[c]	108	101	101
Transport and working machinery	50	50	50
Waste incineration	0.9	0.4	0.3
Total	182	153	153

[a]Data from Boström (1997). [b]Graphite production ceased in 1991. [c]Including wood burning and district heating.

However, these may well be included in the group of unburned hydrocarbons. The total number of exhaust constituents is estimated to be more than 20,000 individual chemical compounds (U.S. EPA 1990), and consequently it is not feasible to quantify all of them.

In automotive exhaust several important groups of compounds are emitted that may have a negative impact on health. Among these are aldehydes, some of which have irritant and also carcinogenic effects; alkenes, some of which form highly carcinogenic metabolites; monoaromatic compounds, among which benzene, toluene, cresols, and phenols are of special interest; and the broad group of polycyclic aromatic compounds, several of which are suspected carcinogens. Following the introduction of combustion engines of Otto and diesel types, motor vehicles have become important contributors to air pollution, and they also constitute a health risk with respect to emissions of PAHs, especially in densely populated areas.

The exhaust PAHs emitted from automobiles are present in the gaseous phase as well as associated with particles (Westerholm and Egebäck 1994). As a consequence, PAHs from vehicles are determined in the urban environment as "particle associated" and "semivolatile" (Bidleman 1988; Pankow 1987; Thrane and Mikaelsen 1981), and both PAHs associated with particles and those occurring in the gaseous phase must be considered when marker compounds are chosen. Two extremes are phenanthrene, which is present to approximately 95% in the gaseous phase, and coronene, which is almost completely present in the particle phase. Sampling techniques must be further developed and combined with analytic methodologies to ensure that methods available for monitoring individual PAH emissions are relevant with respect to risk assessment.

Vehicle exhaust is the largest contributor to PAH emissions in central parts of large cities. It is well known that PAH emissions from vehicles depend on several factors such as fuel type (Egebäck and Bertilsson 1983; Lies 1989), fuel parameters (Sjögren et al. 1996a), driving conditions (Rijkeboer and Zwalve 1990), ambient temperatures (Laurikko and Nylund 1993), exhaust after treatment devices (Egebäck and Bertilson 1983), and engine adjustment (Rijkeboer and Zwalve 1990). PAH profiles from different vehicle concepts are presented in Table 5 and Figures 1–3. The total PAH emissions decrease by at least a factor of 5 on changing from the nonenvironmentally classified fuel (MK3) to the environmentally classified diesel fuel (MK1) (Table 5).

MK1s have been available in Sweden since 1991. Fuels of this class emit less PAHs than previous MK3s (Grägg 1994; Westerholm and Egebäck 1991). By using MK1, PAH profiles are shifted toward smaller three-ringed PAHs, significantly reducing the relative contributions of B[a]P or larger PAHs. Emissions from gasoline and diesel passenger cars were compared (Almén et al. 1997; Lenner and Karlsson 1998). In conclusion, the specific emissions of PAHs from modern cars were observed to be 5 times higher from diesel engines than from gasoline cars during transient driving conditions. Older diesel cars and gasoline cars with a catalytic converter of outmoded design have 5–10 times higher PAH emissions than modern cars. In North European cities, cold-start emissions from gasoline vehicles are of considerable importance because they may account for more than 50% of the total PAH emissions from gasoline vehicles (Lenner and Karlsson 1998). Using the emission factors by Lenner and Karlsson (1998) and the 1994 statistics for vehicle use, the emissions of B[a]P can be estimated (Table 6).

In addition to vehicle exhaust, resuspended road dust from wear of tires and asphalt may also contribute to the PAH levels in ambient air (Ahlbom and Duus 1994; WHO/IPCS 1998). Ahlbom and Duus (1994) estimated that the emissions in Sweden of B[a]P from road and tire wear were 45 and 60 kg per year, respectively (Table 6). However, this PAH is probably associated mainly with coarse particles (>10 μm).

Industry and energy production. In Sweden the most important industrial processes suspected of emitting PAHs are aluminum smelters, coke production, the manufacture of asphalt or rubber products, and energy production from oil, coal and various fuels of biomass origin. However, the only industrial sources that have been characterized are emissions from aluminum smelters and the production of graphite electrodes, of which the latter was stopped in 1990 (Table 4). Emissions from asphalt and the rubber industries are not known in detail in Sweden. However, emissions of about 50 tonnes annually of PAH-containing smoke, formed during the vulcanization process of rubber, have been reported (SEPA 1995). These two latter sources may contribute additional emissions of PAHs. Energy conversions by combustion of oil, coal, coke, and different biofuels may also contribute to the emissions of PAHs. However, different industrial sources are not as well characterized with regard to PAH emissions as mobile sources.

Domestic heating. Westerholm and Peterson (1994) presented a comparison of PAH emissions from domestic oil heating with PAH emissions from diesel-fueled vehicles in Sweden. It was concluded that annual PAH emissions from domestic oil heating were approximately 20% of the emissions from diesel vehicles. An important

Table 5. Comparison between examples of different vehicle types with regard to PAH emissions (μg/km) of quantitative importance during transient driving conditions.

Individual PAHs	Light-duty vehicles			Heavy-duty trucks	
	Gasoline[a,b] without catalytic converter	Gasoline[b,c] with three-way catalytic converter	Diesel[b,c] (MK1) with oxidizing catalytic converter	Diesel[b,d] (MK3) without catalytic converter	Diesel[b,d] (MK1) without catalytic converter
2-Methylfluorene	ND	1	2	37	2
Dibenzothiophene[e]	ND	<0.1	1	10	3
Phenanthrene	91	28	38	267	40
Anthracene	28	5	3	28	3
2-Methylphenanthrene	ND	0.3	1	166	8
2-Methylanthracene	ND	2	6	154	10
1-Methylphenanthrene	16	1	6	99	10
Fluoranthene	21	5	33	83	24
Pyrene	22	3	25	212	70
2-Methylpyrene	<0.1	<0.1	0.3	10	1
Benzo[ghi]fluoranthene	4	0.5	1	1	<0.1
Cyclopenta[cd]pyrene	3	1	0.3	0.2	<0.1
Benzo[a]anthracene	4	0.4	0.5	4	<0.1
Chrysene/triphenylene	4	1	1	1	0.2
Benzo[b and k]fluoranthene	5	1	0.4	0.5	<0.1
Benzo[e]pyrene	3	0.2	0.3	<0.1	<0.1
B[a]P	6.6	0.3	0.1	0.2	<0.1
Indeno[1,2,3-cd]fluoranthene	<0.1	<0.1	<0.1	<0.1	<0.1
Indeno[1,2,3-cd]pyrene	2	0.4	0.1	<0.1	<0.1
Dibenzo[a,h]anthracene	ND	<0.1	<0.1	<0.1	<0.1
Benzo[ghi]perylene	6	0.5	0.2	<0.1	<0.1
Coronene	2	0.5	0.1	<0.1	<0.1

ND, not determined. [a]Westerholm et al. (1988). [b]Includes both particle-associated and gas phase–associated PAHs. [c]Almén et al. (1997). [d]Grägg (1995). [e]Contains sulfur, i.e., S-PAH.

contributor to PAH emissions, especially in wintertime in Sweden, is domestic heating by wood burning (Camner et al. 1997). Sweden differs from many other countries regarding the burning of wood. Most frequently, wood is burned in boilers constructed for multiple energy sources (oil, wood, electricity). Today, however, low-emitting boilers have been introduced onto the market. Lately, stoves have come into use increasingly as an additional heating device, often in urban areas. Emissions from wood combustion consist mainly of particulate matter, tar, and volatile compounds. Because the combustion is very often inefficient, large quantities of organic matter are emitted. The emission of particles ranges from 200 to 1,500 mg/MJ in older Swedish investigations on wood-fired boilers under different conditions (Camner et al. 1997). Larsen (1991) reports that, based on the available international literature, 530 mg/MJ is a reasonable average for wood-fired boilers and stoves. The composition of the particles is not known in detail. Tar consists of a great number of condensable organic compounds, among which the PAHs are an important group. The reported specific emissions of PAHs vary considerably (Table 7).

In older Swedish studies, values between 1,400 and 8,300 μg/MJ have been reported (Rudling et al. 1980). The pattern of individual PAHs in wood-fire emissions covers a wide molecular weight range similar to that from mobile sources (Tables 5 and 8). Larsen (1991) looked at a number of investigations from different countries and concluded that 2,900 μg/MJ was a reasonable average for PAH emissions from small-scale wood-heating devices currently in use. Emissions from a low-emission type of boiler are considerably lower (50–150 μg/MJ) than those from the standard types (SEPA 1996b). However, at present less than 10% of the boilers in use are of low-emission type. One important difference when comparing emissions from traffic with those of domestic wood burning is that emission data from wood boilers are not given for the whole emission cycle, including the startup period. This may be important when calculating emissions from modern low-emission boilers if the boiler is not in continuous use.

If the average winter mean concentrations of soot and nitrogen dioxide from an urban and a background site are compared, it can be determined that the concentrations, relative to the background level, are larger for soot than for nitrogen dioxide in areas where residential wood burning is believed to be common, namely, in northern Swedish towns. It can thus be suspected that the contribution to the local environment of soot particles from residential wood heating in
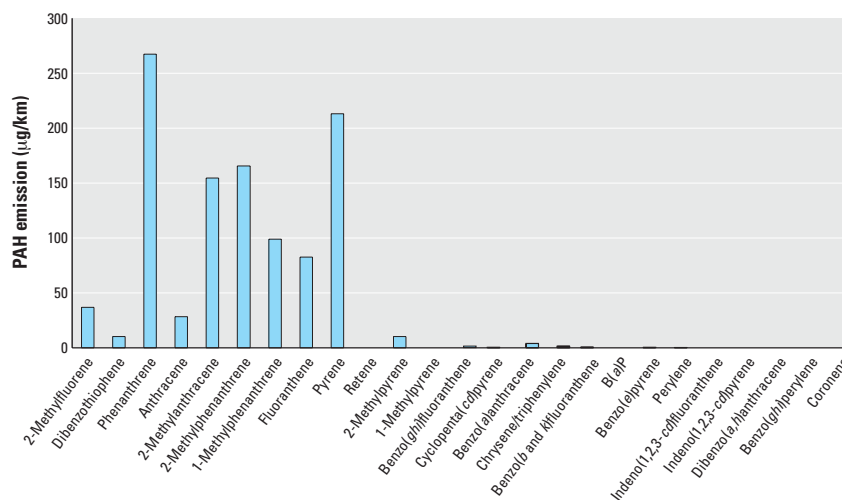

Figure 1. PAH emission profile, diesel-fueled heavy-duty truck, MK3, without oxidizing catalytic converter. Data from Grägg (1995).
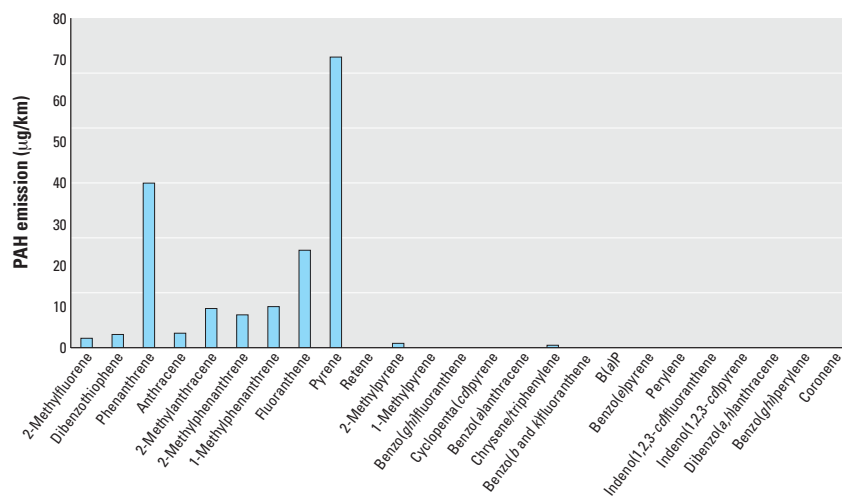

Figure 2. PAH emission profile, diesel-fueled heavy-duty truck, MK1, without oxidizing catalytic converter. Data from Grägg (1995).
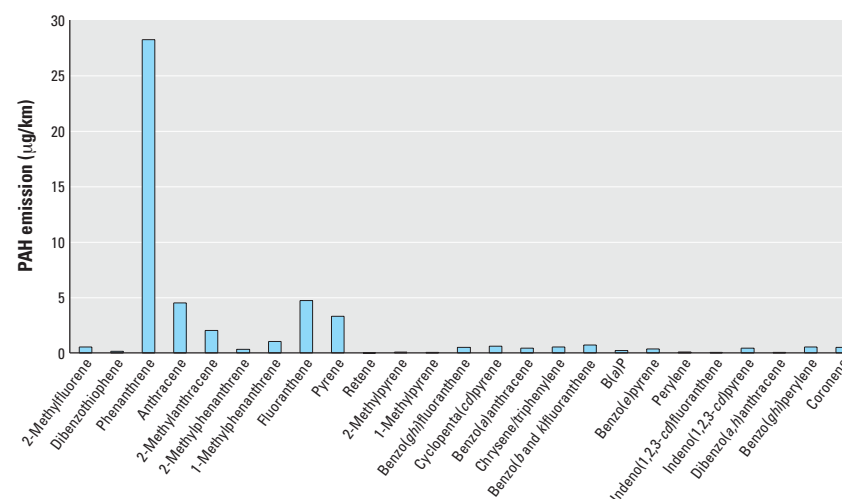

Figure 3. PAH emission profile, gasoline passenger car with three-way catalytic converter. Data from Almén et al. (1997).

Table 6. Estimated emissions to air of PAHs (tonnes) and B[*a*]P (kg) from different sources in Sweden, 1994.

PAH compound	Gasoline vehicles	Diesel vehicles	Wood burning	Residential oil heating	Tire and road wear
B[*a*]P	150[a] (300)[b]	20[a]	430[c]	<1[c]	100
PAH	61[a] (11)[b]	4[a]	60–200[d]	nd	nd

nd, no data. [a]Based on emission factors from Lenner and Karlsson (1998) and total driving distance for different vehicles in Sweden in 1994. Data on total driving distance are as follows: *a*) gasoline vehicles: passenger cars without and with catalytic converter, 27.4 × 10^{-9} km and 28.3 × 10^{-9} km, respectively; *b*) light-duty trucks without and with catalytic converter, 1.79 × 10^{-9} km and 0.55 × 10^{-9} km, respectively; *c*) diesel vehicles: passenger cars, 2.36 × 10^{-9} km; light-duty trucks, 0.44 × 10^{-9} km; heavy-duty trucks, 3.31 × 10^{-9} km; buses, 0.85 × 10^{-9} km (Swedish National Road and Transport Institute 2000). [b]Estimate including cold start. [c]A lower-range estimate based on an example of a well-working boiler, Table 8. [d]Data from Camner et al. (1997).

Table 7. Typical emissions from wood boilers.

Emission	Dry wood[a] (excess air)	Dry wood[a] (restricted air)	Dry wood[b]	Literature[c] average	Low-emission[d] boiler
Particles (mg/MJ)	200	700	1,500	530	nd
Tar (mg/MJ)	130	500	nd	nd	nd
PAH (µg/MJ)	1,400	8,300	5,000	2,900	50–150
B[*a*]P (µg/MJ)	10	200	30	nd	nd

nd, no data. [a]Data from Rudling et al. (1980). [b]Data from Ahlborg et al. (1990). [c]Data from Larsen (1991). [d]Data from SEPA (1996b).

northern Sweden may be substantial, perhaps exceeding that of other sources such as traffic.

Although the number of wood-heated houses is relatively small in urban areas, those houses may account for as much as 25% of the total wood consumption for heating purposes (SEPA 1993). Thus, the problem with emissions from wood combustion for domestic heating may not be restricted only to the small cities in northern Sweden, as is usually believed.

The total use of wood for domestic heating in Sweden was estimated to be between 2.1 and 2.8 megatonnes/year in 1994, which is comparable to a production of 12 TWh energy (SNBITD 1995). The use of oil for domestic heating in 1994 was about 32 TWh (SNBITD 1995). Using the emission factors in Table 7, the emissions of B[*a*]P can be calculated for Sweden for 1994. The yearly emission of B[*a*]P from wood burning is approximately 430 kg and is less than 1 kg from residential oil heating (Table 6). The total emissions for PAHs are estimated to be about 100 tonnes/year from domestic wood burning, with a minor contribution from residential oil heating. According to these estimates, wood combustion dominates the PAH emissions in Sweden. This is consistent with other investigations, but large variations in emission factors, and thus emission estimates for PAHs, are evident (Larsen 1991). This large spread in the data implies a considerable uncertainty in emission factors, but there are also large uncertainties in the estimated amount of wood used for burning.

Concentrations in Ambient Air

Polycyclic aromatic hydrocarbons can be transported over long distances, and measurable atmospheric concentrations can be found throughout the world, even in very-remote areas. A number of studies on marine and lake sediment profiles show a good association between the sediment levels of PAHs and the onset of widespread fossil fuel combustion. The natural background level is influenced by forest fires, for example, but is normally believed to be very low. Data on the sources, fate, and degradation of PAHs are extensively covered in a review by WHO/IPCS (1998).

Gas/particle partitioning of polycyclic aromatic hydrocarbons. A large fraction of the deposition of PAHs in Sweden depends on long-range transport from other parts of Europe. The airborne PAHs are subsequently deposited on the ground, on vegetation, or on other ground surfaces. Of special interest regarding human exposure is the deposition on food crops, which may be an important source of PAH intake in humans. The principal mechanisms for removal of PAHs from the atmosphere are deposition and (photo)chemical transformation. Both dry and wet deposition of gaseous and particulate PAHs may be important. The partitioning of different PAHs between gas and particle phases regulates the efficiency of removal from, and transport to, the atmosphere. Rain scavenging and dry deposition processes are highly dependent on the relative amounts present in the gas and particle phase. In addition, the size distribution of the particles is important for the efficiency of wet and dry deposition.

The partitioning of PAHs between gas and particle phases depends on the ambient temperature, relative humidity, the properties and the concentration of PAHs, and on the chemical composition of the aerosol particles (Goss and Schwarzenbach 1998). Semiempiric partitioning constants have been used to estimate the partitioning (Pankow 1991). As a rule of thumb, Baek et al. (1991) proposed that two- and three-ring PAHs are mainly in the gas phase, four-ringed PAHs are in both gas phase and particle phase, and five- and six-ringed PAHs are mainly attached to particles. An example of this distribution in urban ambient air samples is shown in Figure 4 (Svanberg 1997).

Particulate PAHs are observed predominantly in fractions of fine particles with a diameter ranging between 0.01 and 0.5 µm. Venkataraman and Friedlander (1994) measured a bimodal mass distribution of PAHs

Table 8. Emissions of PAHs[a] from domestic burning of wood and oil (µg/MJ).

PAH compound	Wood[b]	Oil[c]
Phenanthrene	690	1.3
Anthracene	97	0.03
Fluoranthene	148	0.09
Pyrene	114	0.02
1-Methylpyrene	ND	0.05
Benzo[*b*]fluorene	ND	0.1
Benzo[*ghi*]fluoranthene	22	ND
Cyklopenta[*cd*]pyrene	23	ND
Benzo[*a*]anthracene	37	<0.003
Chrysene/triphenylene	ND	<0.003
Benzo[*b* and *k*]fluoranthene	7	<0.003
Benzo[*e*]pyrene	5	ND
Benzo[*a*]pyrene	10	<0.003
Indeno[1,2,3-*cd*]pyrene	3	ND
Dibenzo[*a,h*]anthracene	ND	<0.003
Benzo[*ghi*]perylene	3	ND
Coronene	<1	ND

ND, not determined. [a]Includes both gas-phase and particle-bound PAHs. [b]Data from Rudling et al. (1980). Standard boiler with excess air. [c]Data from Bardh and Ahling (1983). Standard boiler with a clear, nonsmoking flame.

with a second mode between 0.5 and 1 µm in an urban aerosol. Different sources may generate PAHs containing particles of different sizes. Miguel et al. (1998) showed that most of diesel-derived PAHs were present in both an ultrafine size mode (<0.12 µm) and in the accumulation size mode (0.12–2 µm), whereas gasoline engine-derived PAHs were almost entirely in the ultrafine mode.

Chemical transformations of PAHs. Chemical reactions may occur both with gaseous and particulate PAHs. Such reactions may involve either ozone, hydroxyl radical, NO_2, or HNO_3. In general this leads to the formation of more polar and more water-soluble PAH derivatives, for example, compounds substituted with nitro- or hydroxyl- groups. The chemical transformation rate, with half-lives reported in ranges from hours to days, depends on a number of factors. For example, PAHs bound to particles with high organic carbon contents may be much more stable than if the same compound is in the gas phase. The concentrations of ozone and OH are also
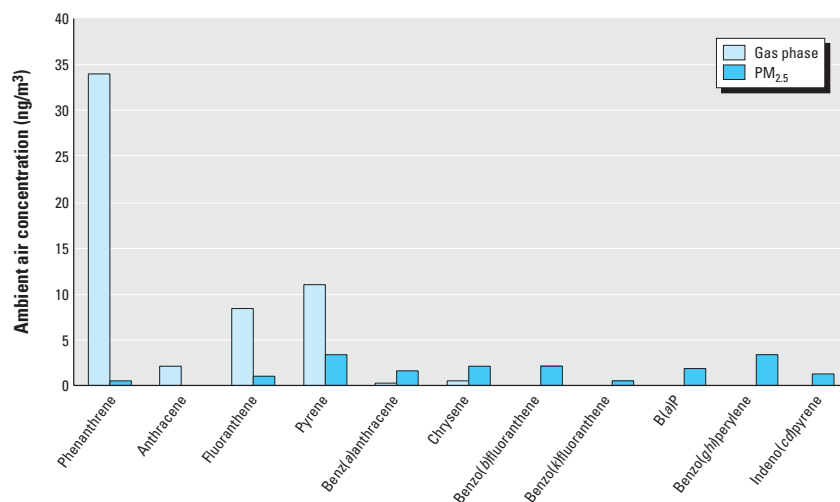
Figure 4. The distribution of individual PAHs to particles (PM$_{2.5}$) and gas phase in a single ambient air sample. Data from Svanberg (1997).

Table 9. Measured deposition and air concentrations of PAHs at two background measurement stations in Sweden and Finland.

Year	Air (ng/m³)		Deposition (µg/m²/year)	
	Sum of 11 PAHs	B[a]P	Sum of 11 PAHs	B[a]P
Rörvik, Sweden				
1994	2.9	0.072	115	4.4
1995	5.5	0.12	96	4.0
1996	4.1	0.095	143	3.9
1997	3.6	0.10	135	6.4
1998	2.2	0.065	84	3.8
Pallas, Finland				
1996	0.87	0.015	17	0.83
1997	0.78	0.021	18	0.67
1998	0.85	0.017	61	2.0

[a]Brorström-Lundén et al. (2000).

important, and they depend on the levels of precursors (NO$_x$ and volatile hydrocarbons) and on a number of meteorologic factors. During winter at high latitudes, with relatively little solar radiation and low temperatures, photochemical oxidation processes will be less important. PAHs may also (re)volatilize from soils and water.

Background air concentrations and deposition of PAHs. Measurements of PAHs in ambient air have been performed since the end of the 1980s at Rörvik, a background measurement station on the west coast of Sweden. In cooperation with Finland, there is also one measurement station at Pallas in the north of Finland (Table 9). At these stations, PAH concentrations in air and deposition rates are measured by the same methods. The PAH determination includes 11 components: phenanthrene, anthracene, fluoranthene, pyrene, benz[a]anthracene, chrysene, benzo[b]fluoranthene, benzo[k]fluoranthene, benzo[a]pyrene, benzo[ghi]perylene, and indeno[cd]pyrene. The background deposition of PAHs at Rörvik shows no trend with time. Furthermore, there is no simple relationship between the deposition and the air concentration. The mean air concentration of PAHs at Rörvik, gas and particle phases combined, was around 4 ng/m³ (range 2.2–5.5) and for B[a]P 0.09 ng/m³ (range 0.06–0.12) for 1995–1998 (Table 9). There is a tendency for the concentrations to decrease. At Pallas in northern Finland, concentrations are lower by a factor of 3–5.

Urban air concentrations of PAHs. About 500 PAHs have been detected in air, but often the measurements include only B[a]P as representative of the whole PAH group. It is difficult to compare different

measurements, as sampling and analysis methods often differ, especially when comparing older data with recent measurements. In the 1960s, the B[a]P levels were sometimes higher than 100 ng/m³ in many European cities, but during the past 30 years, concentrations in urban ambient air have decreased considerably. A survey of international studies has recently been published by WHO/IPCS (1998).

Stockholm. Since 1991, the Environment and Health Protection Administration of Stockholm has carried out measurements at Hornsgatan in the center of Stockholm (Johansson et al. 1999). The measurements are made during the spring (April and May), at 3 m above street level. Figure 5 shows the PAH levels for the sum of 14 PAHs ranging from 100 to 200 ng/m³ (Burman 2001). The B[a]P levels were between 0.4 and 2 ng/m³. The relative abundance of the main PAHs at Hornsgatan during 1996 are shown in Figure 6. These 15 PAHs make up more than 90% of the total amounts of PAHs measured at this site (34 different compounds). The most abundant PAH is phenanthrene, which constitutes 24% of the total amount. The quantitative cancer risk estimates presented in "Quantitative Cancer Risk Estimates" later in this document show that of the PAH measured in urban air, fluoranthene may be an important contributor to cancer risk due to ambient air exposure. The measurements in Stockholm (at Hornsgatan during spring of 1994–2000) have shown ambient air concentrations ranging from 8 to 25 ng/m³. The quotients of fluoranthene to B[a]P have ranged from 7 to 25 with a median value of 13.

The concentrations of PAHs at roof level in central parts of Stockholm are approximately 10–15 ng/m³. It is important to note

that these data also include the volatile PAH fraction and not only the PAH bound to particles (Johansson et al. 1999).

It is difficult to establish any trend in composition or in levels of individual PAHs over time because data have only been available for limited periods of the year. However, the data presented in Figure 5 for central Stockholm indicate that the levels are decreasing. This is qualitatively consistent with lower vehicle exhaust emissions, which are due to increased use of catalytic converters and MK1. Generally the PAH levels are higher during the winter season than during the summer. This is because of higher emissions from combustion sources, more frequent periods with less-efficient atmospheric mixing, and increased residence time in the air due to decreased degradation of PAHs. Data from measurements in Stockholm indicate the presence of more low-molecular PAHs in winter than in summer (EHPA 1984; Östman et al. 1991). This could be because of higher emissions of these PAHs from residential heating during the winter. There are, however, very little data for comparison of the levels between different seasons.

In a series of measurements in Stockholm during 1980–1983, large differences in PAH levels between different streets were observed that could not easily be related to more intense traffic or other differences in PAH emissions (EHPA 1984). These differences could have been due to a number of factors, including different street widths, heights of houses, and street direction compared with wind direction during sampling as well as to different sampling periods.

Gothenburg. In the project "Air Pollution in Urban Areas," investigations concerning particle-bound PAHs were performed from 1984 to 1987 in the Gothenburg area of Sweden (Boström et al. 1994; Brorström-Lundén and Lindskog
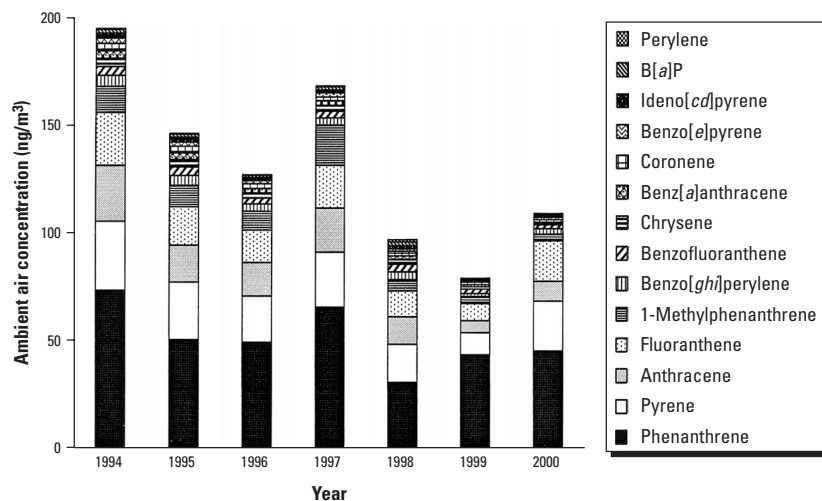
Figure 5. Concentrations of 14 PAHs (sum of gaseous and particle-bound PAH) at Hornsgatan in central Stockholm. Note that the measurements were taken during only 2 months (April and May) each year (Burman 2001).
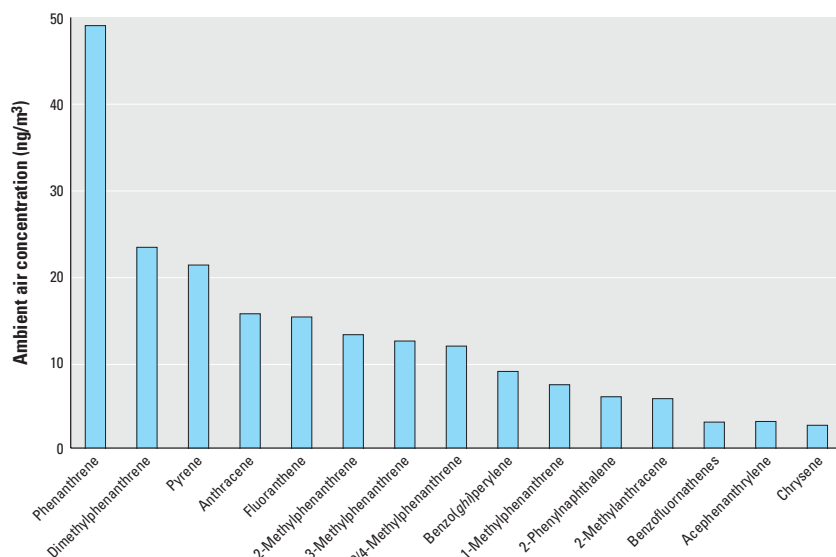

Figure 6. The 15 most abundant PAHs at Hornsgatan (Stockholm city) from April to June 1996. The levels indicated are the sum of particulate and semivolatile PAHs. Data from Johansson et al. (1999).

1985; Löfroth et al. 1990; Steen 1985). However, these invesigations occurred before the introduction of MK1 and catalytic converters in gasoline-driven cars. Thus, the ambient air concentration of PAHs in Gothenburg today is expected to be lower. In this project, samples were taken in the urban background, at street level with high and low traffic, and in suburban areas. Particles were sampled for 2 days with a high-volume sampler at each place, and the measurements were repeated according to a scheme during 18 months at the different sampling places to obtain a representative mean value for the concentration of PAHs in the Gothenburg area. The PAH content of the particles was analyzed for 14 selected individual PAHs. The median level of all measured PAHs (sum of

14) concentrations in the particulate phase was 6.1 ng/m³ (range 0.6–100 ng/m³). The PAHs detected ranged from phenanthrene (mw 178) to coronene (mw 300). At street level the median in a busy street was 12 ng/m³ (range 1–64 ng/m³), and in a street with less traffic, 5.7 ng/m³ (range 0.6–42 ng/m³). At street level the concentration in air of B[a]P was 0.39 ng/m³ (range 0.12–1.6 ng/m³). A seasonal variation by a factor of 3–5 in winter and summer was determined for the PAH concentration of ambient air samples in Gothenburg. In a recent investigation regarding PAHs in both the particle and gaseous phases, the relative distribution of PAHs in urban background air in Gothenburg was similar to that in Stockholm (Svanberg 1997).

Selection of Marker PAHs from Emission and Immission Data

To date, there has been no clear international agreement on which individual PAHs should be reported concerning emission and immission of PAHs. The first attempt to standardize matters was made by the WHO for the analysis of drinking water (Borneff and Kunte 1979; WHO 1971). Six PAHs, namely fluoranthene, B[a]P, benzo[b]-fluoranthene, benzo[k]fluoranthene, indeno-[1,2,3-cd]pyrene, and benzo[ghi]perylene, were suggested for reasons concerning chemical analysis.

The Expert Panel on Heavy Metals and Persistent Organic Pollutants, established within the UNECE (United Nations Economic Commission for Europe) Task Force on Emission Inventories, proposed at a workshop in Regensburg, Germany, in May/June 1994 that the following PAHs be considered in its further work, namely benz[a]anthracene, benzo[b]fluoranthene, dibenz[a,c]anthracene, dibenz[a,h]-anthracene, B[a]P, chrysene, fluoranthene, phenanthrene, naphthalene, anthracene, and coronene. This decision was based on the relative occurrence in the environment of the different PAHs and their general toxicity to the environment.

The following PAHs are common to the two proposals above: fluoranthene, B[a]P, and benzo[b]fluoranthene. These two examples show the difficulties in selecting PAHs for reporting. In the review by WHO/IPCS (1998) PAHs recommended for quantification by various authorities are listed.

To investigate important PAHs representing different mobile sources such as gasoline-fueled and diesel-fueled light-duty vehicles and heavy-duty vehicles, investigators conducted principal component analysis. Emissions data from light and heavy diesel and gasoline vehicles at different starting temperatures (–7°C and 22°C) were analyzed for their similarities and differences (Almén et al. 1997; Grägg 1994).

In summary, PAHs of lower molecular weight were characteristic of heavy diesel vehicles, fluoranthene (mw 202) and pyrene (mw 202) being most important. Characteristic PAH indicators for the light-duty diesel vehicle were 2-methylpyrene, pyrene, 1-methylpyrene, benzo[ghi]fluoranthene, and chrysene/triphenylene. For light-duty gasoline vehicles without catalytic converters, PAHs larger than cyclopenta[cd]-pyrene were characteristic, for example, coronene. For gasoline cars with catalytic converters the total emissions of PAHs were quantitatively much lower, but there was only a small change in the pattern of individual PAHs. Because a covariation exists

among many PAHs, it might be possible to reduce the number of measured PAHs without losing too much information. A suggestion for the selection of PAHs, comparing different vehicles, would be dibenzothiophene, phenanthrene, 2-methyl anthracene, fluoranthene, pyrene, B[*a*]P, benzo[*b*]fluoranthene, benzo[*k*]fluoranthene, indeno[1,2,3-*cd*]pyrene, benzo[*ghi*]-perylene, and coronene.

When the different mobile sources as well as wood burning sources are compared on a quantitative basis, as in Tables 5 and 7, phenanthrene, anthracene, fluoranthene, pyrene, and chrysene are representative for all sources. Specific markers for diesel engines are difficult to specify. To some extent, gasoline cars can be represented by benzo[*ghi*]perylene. Retene (1-methyl 7-isopropyl phenanthrene) has been suggested as a marker PAH for the burning of wood (Ramdal 1983). However, this marker seems applicable only for emissions from the burning of softwood (McDonald et al. 2000).

Ambient air is dominated by smaller PAHs, as for example, phenanthrene, pyrene, and fluoranthene (Figure 6). These PAHs are thus of great importance for human exposure and must therefore be recommended as marker compounds.

In summary, phenanthrene, methylanthracenes/phenanthrenes, fluoranthene, pyrene, B[*a*]P, benzo[*b*]fluoranthene, benzo[*k*]fluoranthene, indeno[1,2,3-*cd*]pyrene, benzo[*ghi*]perylene, and coronene are the most representative PAHs, based on qualitative and quantitative properties of emissions and also with regard to their presence in ambient air (Figure 6). Furthermore, both particles and gas-phase samples should be monitored and analyzed. In addition, dibenzothiophene and benzo[*b*]naphtho[2,1-*d*]thiophene (Alsberg et al. 1989) might be useful indicators of fuels containing sulfur (possibly long-range transport), and retene might be a marker for wood burning in regions where softwood is the dominant fuel.

Conclusions

The emission estimates regarding PAHs are generally more uncertain than those for other pollutants. There might be differences in the number of PAHs reported and the sources included in the estimates from various countries. In the United States and Sweden, residential burning of wood is regarded as the largest source of PAHs. However, in city centers, mobile sources (including working machinery) contribute the major part of the PAH emissions.

The data on total emissions are uncertain because some sources have not been sufficiently well characterized, for example,

wood-fire emissions, many industrial emissions, and diffuse emissions from products containing asphalt and tar components. A substantial decrease has occurred in total PAH emissions in Sweden since 1960. However, such a decrease cannot be observed in the measurements of PAHs in the background air. This discrepancy can be partly explained by large variations in meteorologic conditions and series measurements of insufficient duration.

Today, wood burning is believed to be the major source of PAH emissions to air in Sweden, with about 60% of total emissions; traffic contributes about 30%. Older passenger cars without catalytic converters and older diesel vehicles contribute the greatest part of the traffic-related emissions of PAHs. Cold starting for gasoline-driven vehicles is an important contributing factor for PAH emissions.

PAH emission profiles are not specific to each source but rather reflect efficiency in combustion and fuel quality in general. In general, however, diesel is characterized by PAHs of a lower molecular mass, whereas wood burning and petrol cars without catalytic converters emit a larger fraction of heavy multiringed PAHs. Modern diesel engines using MK1s and modern catalyst-equipped gasoline cars emit minute amounts of heavy PAHs such as B[*a*]P.

Total PAH levels (i.e., the sum of individual PAH concentrations determined) of ambient air from different studies are often difficult to compare, as both the number of PAHs analyzed and individual PAH species may differ. The concentrations of defined PAHs must therefore be presented before a comparison can be made. In Europe, B[*a*]P concentrations are often below 1 ng/m^3 at background stations, whereas at locations close to traffic, concentrations range between 1 and 5 ng/m^3.

In the center of Stockholm (Hornsgatan) the sum of 14 PAHs ranged from 100 to 200 ng/m^3. The B[*a*]P levels were between 1 and 2 ng/m^3, which corresponded to 1% of the total amounts of PAHs measured. The most abundant PAH was phenanthrene, which constituted about one-third of the total amount. In the city of Gothenburg the median level of particle-bound B[*a*]P was 0.39 ng/m^3 (range 0.12–1.6 ng/m^3). The relative distribution of PAHs in urban background air in Gothenburg was similar to that in Stockholm. Because B[*a*]P is such a small fraction of the total PAHs, there is a great need for other health and emission-relevant PAH markers for comparisons and evaluation of trends.

In conclusion, PAH compounds selected for the purposes of monitoring and measuring air pollution were the six so-called

Borneff PAHs (fluoranthene, B[*a*]P, benzo-[*b*]fluoranthene, benzo[*k*]fluoranthene, indeno[1,2,3-*cd*]pyrene, and benzo[*ghi*]-perylene), phenanthrene, methylanthracenes/phenanthrenes, pyrene, and some specialized markers, namely retene, dibenzothiophene (PAH-containing sulfur), and benzo[*b*]naphtho[2,1-*d*]thiophene (PAH-containing sulfur). Both particles and gas-phase samples should be monitored and analyzed.

Mechanistic Aspects of Biological Activity

Mechanisms of Action of PAHs

The concept of carcinogenesis. Carcinogenesis is a multistep, multimechanism process involving genotoxic events (mutations), altered gene expression at the transcriptional, translational, and posttranslational levels (epigenetic events), and altered cell survival (proliferation and apoptosis) (Hanahan and Weinberg 2000). Operationally, the carcinogenic process is often subdivided into three steps: initiation, promotion, and progression (Pitot and Dragan 1996).

Tumor initiation encompasses several distinct requirements, which for chemical carcinogens include the compound (reactive per se or reactive following metabolism) reacting with and thus causing changes in DNA. In many cases these changes consist of adducts. Following DNA replication, the DNA damage caused by these reactive agents may be fixed as a mutation; such compounds are therefore called genotoxic. A mutation in one of a few critical genes in a cell is considered a key event in the cancer process. Such mutations include those in protooncogenes and tumor suppressor genes involved in signal transduction, DNA repair, and cell proliferation and differentiation (Kinzler and Vogelstein 1998). Further development of the mutated or initiated cell to a tumor depends on the interaction of the mutation with inherited and acquired factors that are determinants of growth in the tissue. Available information indicates that genotoxic compounds provoke risk increments that, for low doses, are linearly dependent on the dose of reactive compound or metabolite, namely, without any no-effect threshold dose.

As tumor initiation by definition involves a mutation, this step is in practice an irreversible process unless the mutated cell is removed, for instance, by apoptosis.

The genotoxicity of a particular compound may be potentiated in the presence of cocarcinogens, namely compounds that, for example, increase the dose by increasing the rate of bioactivation and/or decreasing the rate of detoxification of the reactive intermediates.

The promotion phase of carcinogenesis involves the reprogramming of cells toward propensity for proliferation. This phase can be interrupted, if not reversed, when exposure to the promoting condition or agent is stopped. Studies of chemical promoters reveal that, unlike chemical mutagens, these compounds do not require interaction with DNA to exert their action.

Tumor progression is considered irreversible and is characterized by an increased genomic instability and a further developmental evolution toward malignancy and autonomous cell growth.

Certain compounds such as PAHs may exert both mutagenic (genotoxic) and epigenetic (nongenotoxic) actions. PAHs with both initiator and promoter actions are considered complete carcinogens and may act at different stages in the carcinogenic process. The tumor-initiating properties of PAHs have been studied extensively, whereas the epigenetic effects of these compounds have only recently gained interest. Various factors believed to be of importance in this respect are discussed below.

Routes of action. The potent biological activity of PAHs seems to rely on different characteristic properties. One important property of PAHs is their metabolic conversion to reactive electrophilic intermediates that can covalently bind nucleophilic targets in DNA, RNA, and proteins (Sims and Grover 1974; Thakker et al. 1985). Thus, in addition to forming adducts with DNA and inducing mutations and eventually tumors, reactive metabolites may react with other cellular targets and interfere with transcription, DNA replication, and protein synthesis. Furthermore, certain PAHs may, following metabolism, induce inflammatory processes (Casale et al. 1998). A second important property of certain PAHs is their high affinity to the cytosolic aryl hydrocarbon, or Ah receptor, and the subsequent transcriptional upregulation of a battery of genes involved in biotransformation, growth, and differentiation. The stimulation of growth seems to be the main component of promotion in chemical carcinogenesis. The Ah receptor is a ligand-activated transcription factor that acts in concert with the Ah receptor nuclear translocator (ARNT) to alter the expression of target genes such as cytochrome P4501A1, P4501A2, and P4501B1, and other biotransformation enzymes, including glutathione transferases (GSTs) (Nebert et al.1993; Okey et al. 1994). From recent studies it has become clear that the Ah receptor belongs to the bHLH-PAS family of transcriptional regulatory proteins, whose members play key roles in development, circadian rhythmicity, and environmental homeostasis. Another

property of PAHs is their inhibitory effect on gap junctional intercellular communication. It is interesting to note that PAHs containing a bay or a baylike region (see below) are more inhibitory than PAHs lacking this structural feature (Upham et al. 1996; Weiss et al. 1998).

It could be noted that halogen-substituted polycyclic compounds such as dioxins and dioxinlike compounds exert biological activity through nongenotoxic mechanisms, whereas the carcinogenic potency of PAHs seems to rely more on genotoxic mechanisms (Harvey 1991; Jerina et al. 1991; Sims and Grover 1974; Thakker et al. 1985).

Structure–activity relationship. Systematic studies employing different experimental animal species including rats and mice have revealed the structural requirement for PAHs to be mutagenic and carcinogenic. PAHs composed solely of fused benzenoid rings (alternant PAHs)

must be composed of at least four rings and arranged in such a fashion that the molecule contains a bay or a fjord region (see Figure 7 for definition) (Sims and Grover 1974; Thakker et al. 1985). Exceptions exist where the requirements are fulfilled, but the substances lack or demonstrate very low mutagenic and carcinogenic activity (see below). For nonalternant PAHs composed of both benzenoid and five-carbon–membered rings such as fluoranthene and its derivatives, different structural requirements are important for their action.

IARC has evaluated the carcinogenicity of several individual PAHs (IARC 1983, 1987a). As no human data exist for individual PAHs, the evaluations are based on animal experiments. The most common experiments are rodent skin assays, but there are also intraperitoneal, oral, intrapulmonary, and intratracheal exposures. Only B[*a*]P has been tested by inhalation. The
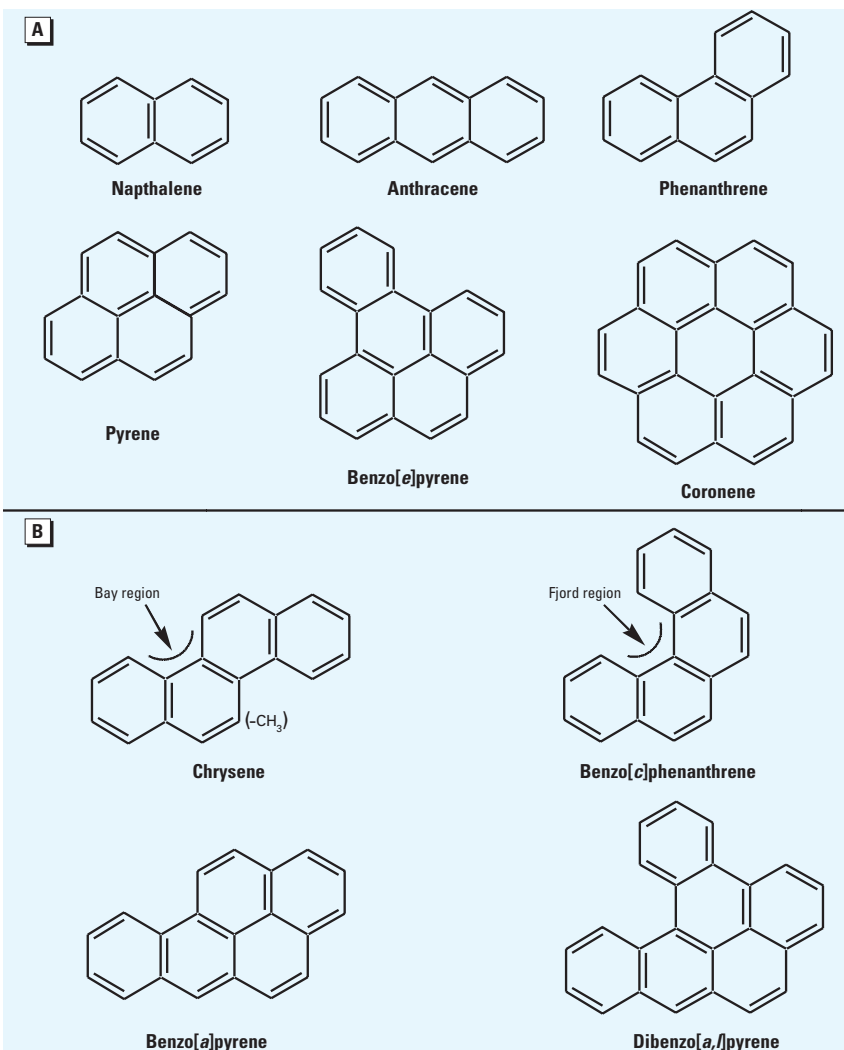

Figure 7. Examples of nontumorigenic (*A*) and documented tumorigenic (*B*) PAHs. The bay and fjord regions are indicated by arrows.

evidence that the compound is carcinogenic to experimental animals is classified by the IARC as either inadequate (I), limited (L) or sufficient (S). These classifications, together with the overall evaluations concerning carcinogenicity to humans, are shown in Tables 10 and 11. In a recent IPCS document (WHO/IPCS 1998), the carcinogenicity of 33 individual PAHs was reevaluated. These results are also shown in Tables 10 and 11. It can be concluded from Tables 1, 10, and 11 that complex mixtures rich in PAHs and an increased molecular mass of the PAHs, and thus an increasing number of benzenoid rings, seem to be associated with an increased risk for tumor development.

Structural requirements for genotoxic action. As previously mentioned, fjord-region compounds are more active as mutagens and carcinogens (Harvey 1991; Jerina et al. 1991). Figure 7 shows examples of PAHs that were either noncarcinogenic or carcinogenic in experimental animals. Although we are dealing mainly with unsubstituted PAHs here, it is interesting to note that substitutions such as methylation at certain positions may increase or decrease the biological potency of a particular PAH. For instance, methylation of the 5-position in chrysene (Figure 7) greatly potentiates the mutagenic and carcinogenic effect, whereas methylation at other positions may have no effect or, rather, reduce the potency (Hecht et al. 1985). The effect of methylation of phenanthrenes offers another interesting example. The parent compound (Figure 7) and all possible monomethyl derivatives lack tumorigenic activity (LaVoie et al. 1981, 1982). However, certain monomethyl-phenanthrenes possess mutagenic activity in human cells *in vitro* (Barfknecht et al. 1982). The lack of tumorigenic activity seems to be related to factors other than metabolic activation to electrophilic intermediates (Chu et al. 1992; Hoepfner et al. 1987; Ng et al. 1991; Nordqvist et al. 1981). However, dimethylation renders phenanthrene tumorigenic (LaVoie et al. 1982). A systematic study of a number of methyl-substituted phenanthrene as tumor initiators in mouse skin has shown that 1,4- and 4,10-dimethylphenanthrene are active, in particular the former (LaVoie et al. 1982). This and other studies indicate that the activity requires inhibition of dihydrodiol formation at the 9,10 position to block detoxification, in addition to a methyl group and a free peri position adjacent to the unsubstituted angular ring. For further information on effects of methylation of various PAHs, consult Hecht et al. (1985).

Structural requirements for promoter action. For a promotive action of PAHs, interaction with the Ah receptor or some similar receptor seems to be one essential mechanism (Poland et al. 1982). This would mean that in this case the promoter action is exerted by the parent hydrocarbons, i.e., species different from the mutagenic diol epoxide (DE) (see "Metabolism"). The Ah receptor is postulated to play a role in normal growth and development based upon patterns of Ah receptor expression during the early development of mouse and human embryos (Abbott et al. 1994; Peters and Wiley 1995). The receptor is widely expressed, but a physiologic ligand has not yet been convincingly shown. Indications that endogenous Ah receptor ligands may be derived from the amino acid tryptophan have repeatedly been reported (Helferich and Denison 1991; Perdew and Babbs 1991; Rannug et al. 1987). Derivatives of tryptophan with an indolo[3,2-*b*]carbazole skeleton have been found to possess very strong affinity for binding to the receptor, suggesting that they are the endogenous ligands (Rannug et al. 1987, 1995).

Inappropriate activation of the Ah receptor by aromatic hydrocarbons induces a variety of biological effects. These include increased proliferation, inhibition of differentiation as well as endocrine disruption, and tumor promotion in experimental animals. The mechanisms for Ah receptor-mediated tumor promotion can involve genes transcribed simultaneously with cytochrome P450 genes (Nebert et al. 1993) or result from the activation of tyrosine kinase activity and subsequent phosphorylation of growth factors and hormones (Enan and Matsumura 1996).

To possess strong Ah receptor binding affinity, the molecules must fit into a rectangle with the approximate size of 6.8 × 13.7 Å (Gillner et al. 1985). Another important structural requirement for Ah receptor binding is the presence of substructures such as the bay region that are also linked to metabolism. This indicates strong similarities between the PAH recognition site of the Ah receptor and the active

Table 10. The degree of evidence for carcinogenicity of alternant PAHs in experimental animals, and overall evaluations of carcinogenicity to humans.[a]

PAH compound	Number of rings	IARC		WHO
		Animals	Humans	
Anthracene	3	I	3	−
Phenanthrene	3	I	3	(+/−)
Benzo[c]phenanthrene	4	I	3	(+/−)
Chrysene	4	L	3	+
Benz[a]anthracene	4	S	2A	+
Pyrene	4	I	3	(+/−)
Triphenylene	4	I	3	(−)
B[a]P	5	S	2A	+
Benzo[e]pyrene	5	I	3	+/−
Dibenz[a,c]anthracene	5	L	3	
Dibenz[a,h]anthracene	5	S	2A	+
Dibenz[a,j]anthracene	5	L	3	
Perylene	5	I	3	(−)
Anthanthrene[b]	6	L	3	+
Benzo[ghi]perylene	6	I	3	−
Coronenea	6	I	3	(+/−)
Dibenzo[a,e]pyrene[b]	6	S	2B	+
Dibenzo[a,h]pyrene[b]	6	S	2B	+
Dibenzo[a,i]pyrene[b]	6	S	2B	+
Dibenzo[a,l]pyrene[b]	6	S	2B	+

Abbreviations: I, inadequate evidence; L, limited evidence; S, sufficient evidence; 2A, probably carcinogenic to humans; 2B, possibly carcinogenic to humans; 3, not classifiable; −, negative; +, positive; +/−: questionable; ( ), limited number of studies. [a]Evaluated by IARC (1983, 1987a) and WHO/IPCS (1998). [b]For nomenclature according to the IUPAC system, see the Appendix.

Table 11. The degree of evidence for carcinogenicity of nonalternant PAHs in experimental animals, and overall evaluations of carcinogenicity to humans.[a]

PAH compound	Number of rings	IARC		WHO
		Animals	Humans	
Fluoranthene	4	I	3	(+)
Benzo[b]fluoranthene[b]	5	S	2B	+
Benzo[j]fluoranthene	5	S	2B	+
Benzo[k]fluoranthene	5	S	2B	+
Benzo[ghi]fluoranthene	5	I	3	(−)
Cyclopenta[cd]pyrene	5	L	3	+
Dibenzo[a,e]fluoranthene	6	L	3	
Indeno[1,2,3-cd]pyrene	6	S	2B	+

Abbreviations: see Table 10. [a]Evaluated by IARC (1983, 1987a) and WHO/IPCS (1998). [b]For nomenclature according to the IUPAC system, see the Appendix.

site of the cytochrome P450 enzymes (Rannug et al. 1991).

The ability of PAHs to act as promoters very strongly increases their carcinogenic potency, as shown at the high doses that are administered in animal cancer tests. It is therefore expected that a multifactorial analysis of a number of bay-region PAHs shows Ah receptor affinity to be a much stronger predictor of carcinogenicity than the mutagenic potency (Sjögren et al. 1996). This general view is also reflected in the carcinogenicity evaluation of the IARC: Those PAHs that are considered carcinogenic have mainly high Ah receptor affinity, and those judged to be noncarcinogenic have no or low affinity to this receptor. It should be emphasized that this conclusion is restricted to the planar bay-region PAHs and may not reflect the very high mutagenic/carcinogenic potency of the fjord-region PAHs. Available information indicates that the latter are strong mutagens and carcinogens (Harvey et al. 1991; Jerina et al. 1991), despite their lower affinity to bind to the Ah receptor (Ionanides and Parke 1990, 1993), and induce their own metabolism to yield DEs through a non-Ah receptor–mediated mechanism (see below). In addition to promoting the carcinogenic process by interacting with the Ah receptor, PAHs may amplify the tumor promotion process via alternative mechanisms such as induction of inflammatory processes and stimulated oxidative stress (Casale et al. 1998).

Metabolism. PAHs are highly lipophilic compounds of low chemical reactivity and have to be metabolically activated to electrophilic intermediates (a species with an absolute positive or a relative positive charge). The metabolism of PAHs has been studied using cells and cell fractions derived from both animal and human tissues, and it is exceedingly complex (Cooper et al. 1983; Gelboin 1980; Sims and Grover 1974; Thakker et al. 1985). In general, biotransformation of xenobiotics involves a number of enzymes, some of which are localized in the endoplasmic reticulum and others in the nuclear envelope, mitochondria, and cytosol. The metabolism of xenobiotics is usually divided into three phases: phase 1 leads to the formation of electrophilic intermediates, phase 2 most often leads to deactivation of reactive electrophiles by various conjugation reactions, and phase 3 is the active transport of polar metabolites from the cell into the surrounding environment. With respect to PAHs, alternative phase 1 activation pathways have been identified. One leads to the formation of various epoxides, and one involves one-electron oxidation to yield radical cation intermediates (Cavalieri and Rogan 1995). The electrophiles formed undergo phase 2 reactions to phenols, diones, dihydrodiols, and more polar and excretable metabolites such as glucuronides and conjugates with sulfate or glutathione (Cooper et al. 1983; Gelboin 1980; Sims and Grover 1974; Thakker et al. 1985).

It has been shown for various PAHs that the radical cations formed by the one-electron oxidation pathway give rise to labile DNA adducts that readily decompose by depurination (Cavalieri and Rogan 1995), whereas the epoxide pathway preferentially leads to the formation of stable adducts (see below).

Extensive studies of mutagenic and carcinogenic PAHs and their metabolites have identified so-called bay- and fjord-region DEs as ultimate reactive species (Harvey 1991; Jerina et al. 1991). The formation of DEs is a three-step process and it will be described for B[a]P. It should be emphasized

that what is described for B[a]P regarding metabolic transformation can be applied to many alternant PAHs. As shown in Figure 8, the first step in the metabolism of B[a]P results in the formation of BP-7,8-epoxide (the isomer preferentially formed is depicted). This step is mainly catalyzed by the cytochrome P450 isoenzyme CYP1A1. The second step is catalyzed by epoxide hydrolase (EH) and yields a *trans*-dihydrodiol (BP-7,8-dihydrodiol). The last step involves a second epoxidation at the 9,10 position, and results in the formation of diol epoxide diastereomers, *syn*-benzo[a]pyrene 7,8-dihydrodiol 9,10 epoxide (*syn*-BPDE) (the hydroxyl groups and the epoxide are localized on the same side of the molecule) and *anti*-BPDE (the hydroxyl groups and the epoxide are localized on opposite side of the molecule), respectively. Each diastereomer may in turn exist as a pair of enantiomers, or mirror images of each other [(+)- and (–)-*syn*-DE in Figure 8, respectively]. This step may be carried out by CYP1A1, peroxidase-catalyzed epoxidation, or through cooxidation by simultaneous exposure to B[a]P and sulfur or nitrogen oxides (Cavalieri and Rogan 1995; Constantin et al. 1994; Petruska et al. 1992; Thakker et al. 1985). In addition to CYP1A1, cytochrome P450 isoenzymes such as CYP1A2, CYP1B1, and CYP3A4 may also participate in the metabolic activation of PAHs (Guengerich 1993; Kim et al. 1998; Nelson et al. 1996). This seems to be of particular importance with respect to the metabolic activation of fjord-region PAHs. With these compounds CYP1B1 seems to be of major importance (Einolf et al. 1997; Luch et al. 1998). It should be emphasized that cells from different human organs contain the enzymes and enzyme systems required for
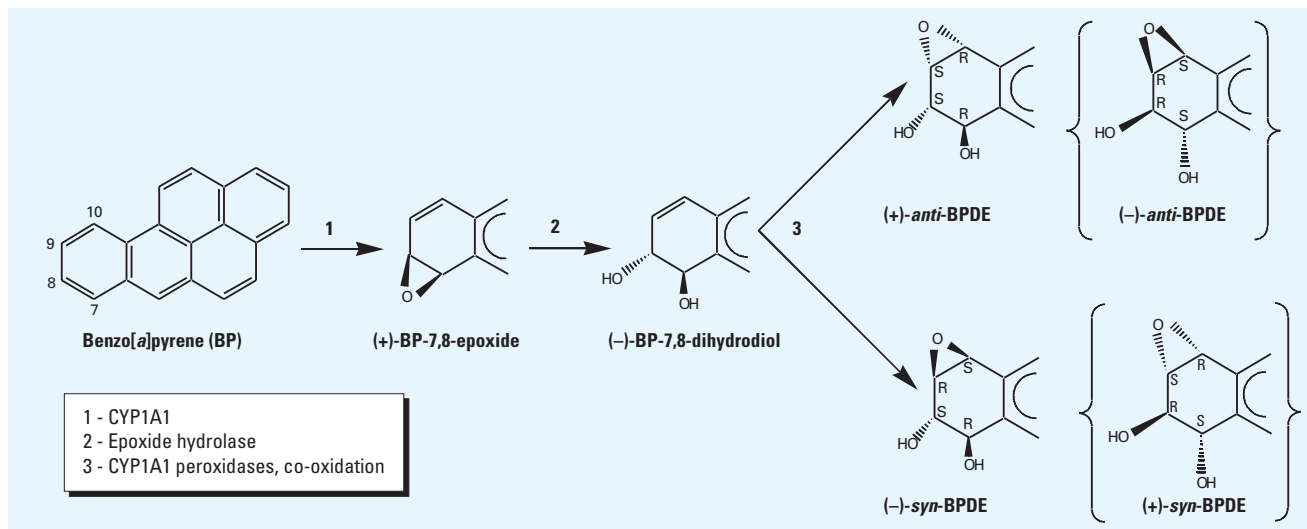

Figure 8. The metabolic activation route of B[a]P to *anti*- and *syn*-DEs. The two possible enantiomers (mirror images) of each diastereomer are shown in brackets.

the formation of mutagenic and carcinogenic DEs (Gonzalez 1992; Raunio et al. 1995).

In humans a substantial variability in biological response to PAHs is to be expected because of interindividual differences in the activity of the enzyme systems required for the formation of reactive intermediates and for their detoxification through conjugation and excretion. The enzymes involved in the metabolism are inducible by different classes of xenobiotics (e.g., drugs, environmental factors), and different forms of metabolizing enzymes (polymorphic variants) are also found in the population that may vary in reactivity toward PAHs (see "Individual susceptibility").

Requirements for diol epoxide-induced genotoxicity. **Diol epoxide structure.** All possible bay-region DEs from a number of PAHs have been investigated in different bacterial and mammalian cell systems and in experimental animals (primarily mice but also rats) with regard to mutagenic and carcinogenic potency. In studies using mice, the compounds are usually administered by skin painting to adult animals but are also administered orally or by subcutaneous injection to newborn animals. Female rats have been used for mammary carcinogenicity studies after injection of PAHs under the nipples. Taken together, the DEs associated with high biological activity in mammalian systems are in general the *anti*-diastereomers and, in particular, the enantiomers with *R*-absolute configuration at the benzylic arene carbon (Glatt et al. 1991; Thakker et al. 1985); in BPDEs, this position corresponds to C-10 (Figure 8). In contrast, bacterial systems respond differently, and experiments with BPDEs suggest that *anti*-enantiomers with *S*-absolute configuration are usually more mutagenic (Figure 8) (Burgess et al. 1985). The reason for the different response in mammalian versus bacterial cells is not known. However, the phenomenon may be related to the different structures of the DNA adducts derived from DE isomers with *R*- or *S*-absolute configuration (see "DNA adducts" below) and how these adducts are recognized and handled by the enzyme systems participating in DNA repair and replication. Certain implications in the risk assessment of PAHs are obvious using bacterial systems, as the results may falsely identify less-relevant derivatives as the most active forms.

With the fjord-region DEs, the situation seems to be more complex with respect to the structure–effect relationship. Although these compounds are in general less chemically reactive than the bay-region DEs, they are in many cases considerably more mutagenic and carcinogenic (Glatt et al. 1991; Wood et al. 1984). In contrast to most bay-region DEs, both the *anti*- and *syn*-diastereomers of the fjord-region derivatives demonstrate high mutagenic and tumorigenic activity (Amin et al. 1995; Higginbotham et al. 1993; Levin et al. 1986; Nesnow et al. 1997).

DNA adducts. Detailed studies have been conducted on the interaction of DEs with DNA both *in vitro* and *in vivo* (Geacintov et al. 1997; Gräslund and Jernström 1989; Jeffrey 1985; Jerina et al. 1991). It has been shown that DEs demonstrate a high preference for the exocyclic amino groups of deoxyguanosine (dG) and deoxyadenosine (dA) (Figure 9). Unless removed by DNA repair processes, the resulting adducts may give rise to mutations following DNA replication. In mammalian cells, exposure to stereochemically different DEs results in mutations that differ in number, type (base substitutions such as transversions and transitions, deletion of one or several bases, etc.), and sequence context distribution (Jernström and Gräslund 1994). The heterogeneous distribution of mutations is the combined result of the initial adduct distribution and adduct removal by DNA repair processes. Recent results have shown that adduct recognition and the rate of adduct removal depend on the bases surrounding the adducted base (Hess et al. 1997; Wei et al. 1993, 1994).

The great majority of DE-induced mutations in cells are localized in the nontranscribed strand of DNA. The main reason for this phenomenon is that the excision repair system responsible for recognition and handling of DNA adducts preferentially eliminates lesions localized in the coding strand (Jernström and Gräslund 1994; Mellon et al. 1987).

Transversion mutations (GC→TA or AT→TA) are most prevalent in mammalian cells after DE exposure. It is interesting to note that the *p53* tumor suppressor gene is frequently mutated in different human cancers and that the types of mutation and base(s) involved differ depending on the causative agent. Thus, tumors believed to be caused by PAHs show critical transversion mutations (GC→TA or AT→TA) in the *p53* gene, whereas alkylators like nitroso amines or amides show transitions derived from alkyl-dG adducts (Harris 1991; Holstein et al. 1991). A recent study has shown that mutational hot spots in the *p53* gene coincide with codons demonstrating a preference for adduct formation with DEs from B[*a*]P (Denissenko et al. 1996; Smith et al. 2000). It can be concluded that different DEs vary in their preference for dG or dA, the preference being dependent on the bases adjacent to the target base and because DEs with higher mutagenic and carcinogenic potency induce a different pattern of mutations than less-active DEs. Studies employing oligonucleotides with known base composition have clearly shown that
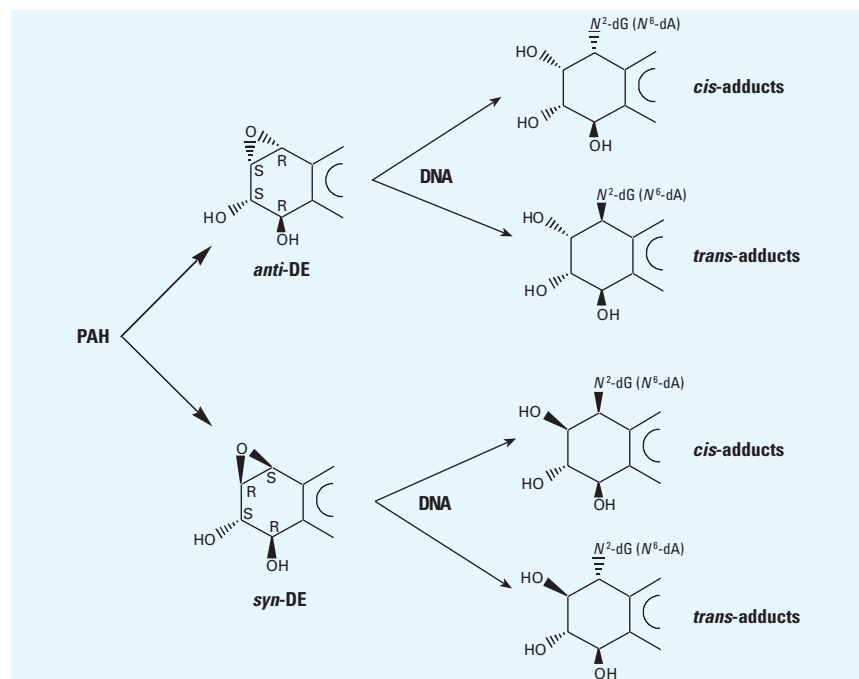

Figure 9. The principal targets in DNA for adduct formation with DEs. Alternative reaction routes exist: *cis*-addition, in which the adducted base is located on the same side of the DE molecule as the adjacent hydroxyl group, and *trans*-addition, in which the same groups are located on the opposite side of the DE molecule. *R* and *S* denote the absolute structure of the DE stereoisomers shown.
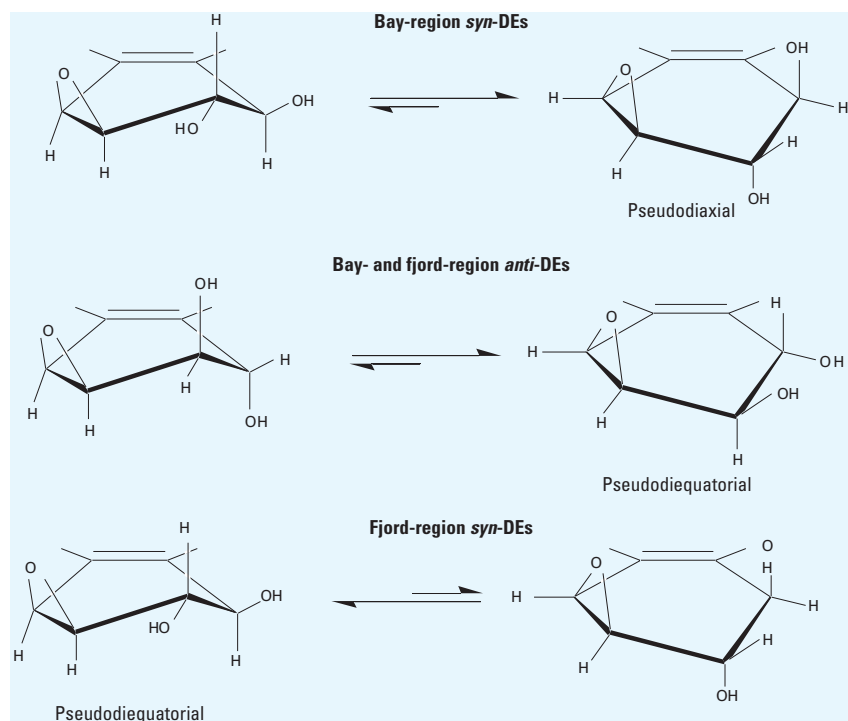
Figure 10. The conformations of DE in solution. The longer arrow indicates the preferred conformation.
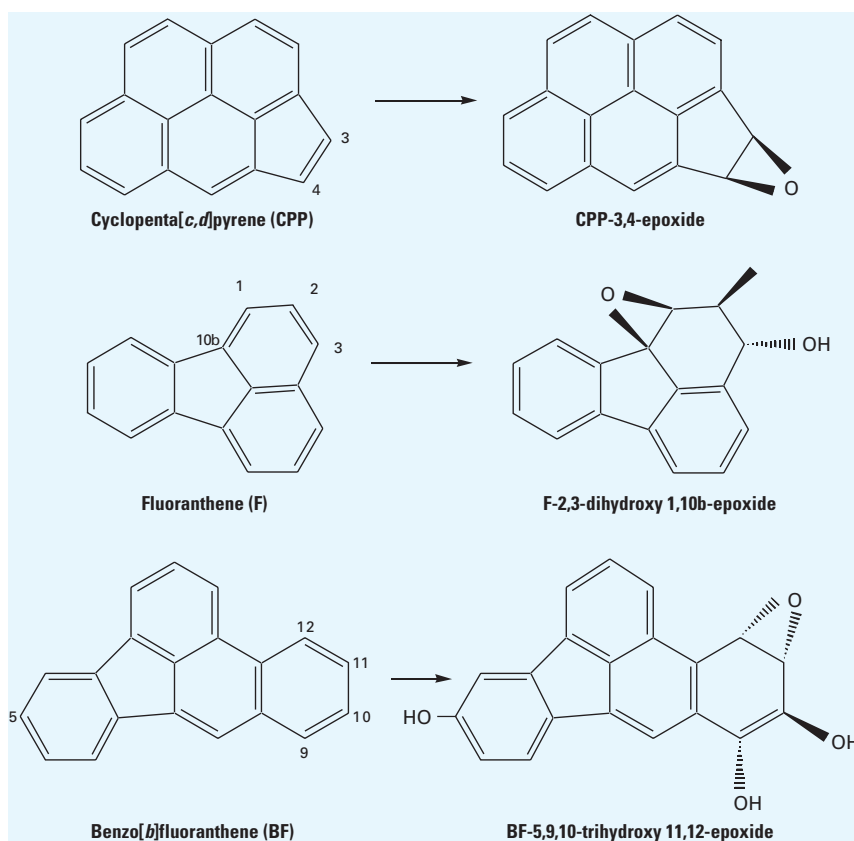

Figure 11. An example of potentially tumorigenic PAHs composed of benzenoid rings and cyclopentane. The corresponding active intermediates are also shown.

whether the covalent binding of DEs involves dG or dA and to what extent this occurs greatly depends on both bases being adjacent to the target base and on stereochemical features of the DEs (Geacintov et al. 1997; Jernström and Gräslund 1994).

Much is known about the structure of the DNA–DE adducts (Geacintov et al. 1997; Gräslund and Jernström 1989; Jerina et al. 1991). The reaction of a DE with the exocyclic amino group of dG or dA can proceed through *trans* or *cis* addition of the nitrogen to the benzylic carbon of the arene oxide. Figure 9 shows the alternative reaction pathways. The *trans* addition pathway dominates. At present only limited information exists on the relationship between adduct structure and the type of mutation induced in mammalian systems. In other words, it is not known whether *trans* adducts are more mutagenic than the corresponding *cis* adducts. These interesting and important problems are presently being intensively studied.

The greater biological activity usually observed with fjord-region DEs relative to the bay-region analogs may be due to the higher preference of the former for reacting with dA. A contribution to the difference may be that the *syn*-diastereomers of fjord-region-DEs are active in contrast to those derived from the bay-region DEs. The reason may be that the hydroxyl groups in the sterically hindered fjord-region DEs remain in a pseudodiequatorial position, which is not the case in the weakly active *syn*-diastereomers of the bay-region DEs (Figure 10). The importance of the spatial orientation of the hydroxyl groups for the biological activity has been shown experimentally (Chang et al. 1987). The crowdedness in the fjord-region renders these compounds nonplanar in contrast to the planar bay-region DEs.

Biologically active PAHs composed of both fused benzenoid and five-member rings such as fluoranthene and its derivatives along with cyclopenta[*c,d*]pyrene (Figure 11), may be activated through alternative pathways. One pathway results in the formation of classical bay- and fjord-region DE intermediates, whereas the other gives rise to a DE in which the final epoxidation involves a carbon in the cyclopentyl residue (Keohavong et al. 1995; Phillips and Grover 1994). The available data indicate that the classical DEs are the most active. To further complicate the picture, activation of certain derivatives of fluoranthene (i.e., benzo[*b*]fluoranthene) requires, in addition to the formation of a DE, aromatic hydroxylation, and thus an intermediate formation of a triol epoxide (Mass et al. 1996).

Dose–response relationships for carcinogenicity. The very high tumor incidences observed in rodent cancer tests of PAHs have

obscured the identification of mechanisms relevant to the cancer risk at the mostly low levels of PAHs in human exposures. It is recognized that several PAHs are complete carcinogens, namely, they are able to cause both initiation (mutation) and promotion (stimulation of clonal expansion and growth). The dose–response relationships of PAH-induced cancer in animal experiments are mostly nonlinear, with an upward rise at high doses (Ehrenberg and Scalia-Tomba 1991). This is in agreement with the idea that promotion is a nonstochastic (deterministic) effect, with an S-shaped dose–response curve above a no-effect threshold. This is in contrast to purely genotoxic carcinogens, which elicit tumors in linear dose–response relationships. These tumors appear at sites where inherited or acquired promotive conditions occur, namely, where tumors occur in the unexposed control (Granath et al. 1999). This gives some support to the suggestion that compared with other mathematic models, a multiplicative model for cancer incidence, P_{can}, is the one best adaptable to experimental data for PAH carcinogenesis.

$$P_{can} = P_{ini} \times P_{pro}$$

In this approach, the probability of initiation, P_{ini}, is modeled by a linear, non-thresholded curve, and the probability (and intensity) of promotion P_{pro} by the S-shaped cumulative probability function (Ehrenberg and Scalia-Tomba 1991). Furthermore, the thresholded, S-shaped dose response for skin tumors induced by B[a]P becomes linearized if an effective nonmutagenic promoter, 12-O-tetradecanoylphorbol-13-acetate) (TPA), is added (Burns et al. 1983) (Figure 12A). This general picture is important to the risk estimation for PAHs at low exposure levels.

The risk (probability) of cancer at low doses of a genotoxic agent at the present level of knowledge has been assumed to be linearly dependent on the dose without a threshold (Ehrenberg 1998; Törnqvist and Ehrenberg 2001). The cancer-initiating ability of a purely genotoxic agent, according to the expression above, could only be expressed in animal tests if a background promotion (P^0_{pro}) is present. If little or no background promotion exists, the cancer-initiating ability will be expressed at high doses only when and if the tested compound, through different mechanisms, can act as a promoter. In this case, a threshold or a no-effect level will be observed. If the tested compound acts as an efficient promoter, the dose–response relationship will deviate from linearity.

According to this model it is assumed that because of the ubiquitous occurrence of background mutations, promoters will lead to a raised cancer risk above some threshold

dose. When the mechanism is epigenetic, the dose–response relationship is expected to be S-shaped with a no-effect threshold. However, if a compound is added to other compounds acting by the same mechanism and already present at levels exceeding the threshold, it will increase the risk in a linear, nonthreshold dose dependence (Crump et al. 1976) (Figure 12B). For PAHs acting by interaction with the Ah receptor, this may happen if there is simultaneous exposure to certain planar PCBs, chlorinated dibenzo-p-dioxins, and dibenzofurans (Ahlborg et al. 1994).

If the cytochromes P450 required for bioactivation of PAHs are already expressed, the initiating (mutagenic) action of the DE will be of major importance to the risk at the lower levels below the threshold for P450 induction (this threshold is probably approximately the same for the concomitant promoter action). Induction of the P450 enzymes responsible for DE formation, at least from certain bay-region PAHs (Luch et al. 1998), is exerted by the interaction of the PAHs with the Ah receptor. The ensuing increase of the rate of DE formation may contribute to the rise of the dose–response curves at higher doses. Because both promotion and increased DE production lead to the same upward bend of the dose–response curves, it is difficult to identify the operating mechanism without measurement of the *in vivo* dose of the DE.

Comments on indicator compounds. A central point in the present discussion of cancer risk at low-exposure levels of PAHs and the selection of indicator compounds is whether we should accept a qualitative paradigm based on animal experiments at high exposure levels that will never occur in the human environment. A mutagenic compound not acting as a promoter may, on the basis of a negative animal cancer test, be

classified as a noncarcinogen. However, such a compound is expected to interact with inherited and acquired promotive conditions, increasing the incidence of the kinds of tumors that already occur at low levels in the unexposed control population (Granath et al. 1999; Törnqvist and Ehrenberg 2001). There are PAHs that are metabolized to effective mutagens but lack strong tumor-promoting activity and could therefore be expected to belong to this group of compounds.

One example of a PAH as possible important risk factor, although it has previously been classified as a noncarcinogen (IARC 1987b), is fluoranthene. This compound is interesting because of its occurrence at relatively high concentrations in vehicle emissions and other types of emissions of PAHs, in ambient air (see "Sources, Deposition, and Ambient Concentrations" and WHO/IPCS 1998), inside vehicles (Fromme et al. 1998), and also because the dietary intake of PAHs comprises relatively large amounts of fluoranthene compared with other measured PAHs (reviewed in WHO/IPCS 1998).

Fluoranthene, like B[a]P, is metabolized to mutagenic DEs and its mutagenic potency is close to that of B[a]P (Vaca et al. 1992). The carcinogenic action of fluoranthene diolepoxide has been demonstrated experimentally (Amin et al. 1995; Hecht et al. 1995). In carcinogenicity tests with high doses, however, B[a]P is considerably more effective than fluoranthene (Busby et al. 1984), evidently because of the promoter action of B[a]P (Vaca et al. 1992). Although fluoranthene is now considered a weak carcinogen (WHO/IPCS 1998), the observed cancer incidence and the numbers of tumors per animal are compatible with linear dose–response relationships (Wang and Busby 1993). Therefore, at low exposure levels, at which induced mutation is a determinant of
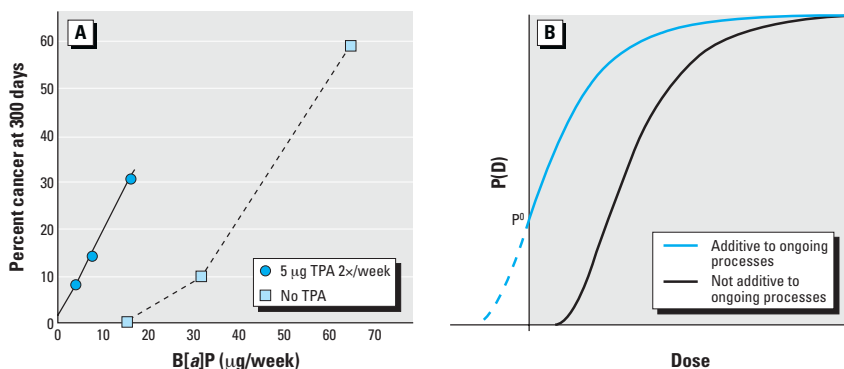

Figure 12. With higher doses of B[a]P, when it acts as both initiator and promotor, skin tumors are induced in mice (thresholded curve). If the B[a]P treatment is combined with a promotor treatment (TPA), B[a]P initiates tumors with a linear dependence on dose (*A*). Hypothetical dose–response curve for the action of a promoter operating in the absence or presence of another promoter that operates by the same mechanism and that has exceeded the no-effect threshold (*B*). P(D) denotes risk for health effects; P0 denotes background frequency.

the cancer risk increment, fluoranthene, because of its abundance in the environment, might be an important contributor to the risk from PAH exposure (Barfknecht et al. 1982; Sjögren et al. 1996).

Whereas the bioactivation of B[*a*]P by CYP1A enzymes is well documented, the metabolism of fluoranthene has not yet been clarified. It has been shown, however, that fluoranthene is metabolized to the corresponding DEs by human liver microsomes (Day et al. 1992).

PAH Exposure in Humans

Routes of exposure. Humans can be exposed to PAHs *a*) through the respiratory tract by inhalation of PAH-containing matter such as cigarette smoke, vehicle exhaust, PAH-contaminated air emitted from certain industries or by the burning of wood for heating, etc., *b*) through the digestive tract following intake of PAH-containing foodstuffs (e.g., fried and charcoal-grilled meat) and PAH-contaminated vegetables and crops grown close to areas with intense traffic, etc., and *c*) through the skin following contact with substances such as petroleum products (e.g., soot, pitch, and tars). Several organs are believed to be susceptible to tumor formation after exposure to PAHs (Doll et al. 1994; IARC 1983, 1987a,b; U.S. PHS 1979). These include the lungs (in particular the bronchi), the skin, the esophagus and colon, the pancreas, the bladder, and the breast in women.

In an earlier study on the cancer risk from urban air pollutants, uptake via food of precipitated particulate material on crops, etc., has been discussed as a possible major source of PAH uptake (Törnqvist and Ehrenberg 1994). Several studies have indeed shown that the intake of PAHs via the diet is large (Beckman Sundh et al. 1998; de Vos et al. 1990) and much higher than the intake via inhalation (Lioy et al. 1988; Lodovici et al. 1995; Vaessen et al. 1988; WHO/IPCS 1998). Data on the origin of PAHs in food are limited; however, it has been suggested that the major part originates from precipitated particulate material (de Vos et al. 1990; Lodovici et al. 1995). In fact, it has been demonstrated that the PAH content is higher in products from crops cultivated near roads and cities (Larsson 1986). The relatively high background levels of PAH adducts to both protein and DNA observed in nonsmokers (see below, "Biomarkers of exposure") indicate that the diet might be quantitatively the most important source of PAHs. Furthermore, it has been shown in mice that oral intake (or by gavage) of B[*a*]P gives approximately the same dose of BPDE in the lung as in other organs (Godschalk et al. 2000; Helleberg et al. 2001). However, the

relative contributions to the total PAH exposure from different sources and, more important, to the internal dose of PAHs, are still very uncertain.

Biomarkers of exposure. Biomonitoring of exposure to PAHs has been extensively reviewed by Angerer et al. (1997). The methods used—DNA adduct and protein adduct measurement and the measurement of urine metabolites—are discussed regarding analytic techniques and usefulness, and studies of exposed populations are discussed with regard to results obtained in relation to exposure measurements. A drawback with the methods used for DNA adduct measurement, according to the authors, is the nonspecificity of the detection, although this could be partly counteracted by the use of the high-performance liquid chromatography (HPLC) methods now being developed for the separation of DNA adducts (Hemminki et al. 1997; Zeisig and Möller 1997; Tuominen et al. 2002). The analysis of protein adducts and urine metabolites is favorable with regard to the specificity of detection when mass spectrometry is used. According to Angerer et al. (1997), analysis of urine metabolites is the procedure for assessment of PH exposure which has so far given the most clear-cut results. A drawback with this method is the difficulty in drawing conclusions about the *in vivo* dose of the reactive metabolites.

DNA adducts. As mentioned previously, the enzymatic activities required for the metabolic transformation of PAHs to DEs exist in human tissues. Experiments with human cells or tissues in culture have clearly demonstrated that DEs formed bind covalently to DNA. Several studies have been performed to identify and quantify the DNA adducts in human tissues following exposure to PAH-containing material in, for example, cigarette smoke, urban air, and contaminated workplaces. Several methods for adduct analysis have been developed, including antibodies against specific PAH adducts (e.g., enzyme-linked immunosorbent assay [ELISA]), fluorescence spectroscopy, mass spectrometry, and ^{32}P-postlabeling of modified nucleotides (Phillips 1996). All the methods have advantages and disadvantages. The first three methods can in principle be used for both identification of specific adducts and quantification, but they often lack the required sensitivity for practical use in molecular epidemiologic studies. However, fluorescence spectroscopy has been successively employed for the detection of DNA adducts derived from B[*a*]P in individuals exposed to PAHs (Rojas et al. 1994, 1998). In human monitoring, peripheral blood cells such as leukocytes and lymphocytes are most frequently used as the source of DNA, but biopsies from target

tissues have also been studied. The ^{32}P-postlabeling technique possesses the required sensitivity (1 adduct per 10^7–10^9 nucleotides) but yields little information on adduct identity. This method, in conjunction with thin-layer chromatography (TLC) of labeled adducts, has been used in a number of studies. It has revealed that the extent of adduct formation in human tissues most often varies by a factor of about 20, although a variation by a factor of more than 70 has been observed (Perera et al. 1992). A recent study indicates that the adduct levels in humans estimated by TLC poorly reflect the true levels. The recovery of labeled adducts with TLC was only a few percent (5%) relative to the recovery with HPLC (Hemminki et al. 1997). Furthermore, the resolution of radioactive material is dramatically increased with HPLC relative to TLC, and at least 50 different DNA adducts in the general Swedish population have been detected (Möller 2001). However, information on their identities is lacking. Because the ^{32}P-postlabeling technique involves chromatography, TLC, or HPLC, the results obtained can be compared with authentic standards to obtain information on adduct identity.

The method with the greatest potential for identifying the structure of a DNA adduct is mass spectroscopy, and a number of adducts have been characterized (Sweetman et al. 1998). However, the wider application of the method in human biomonitoring has been hindered by insufficient amounts of DNA from individuals exposed to environmental contaminants (Phillips et al. 1996). The methodology is developing rapidly and further application is anticipated.

It should also be noted that in most cases the formation of assumed PAH adducts in humans has been studied in blood cells, which reflect the systemic concentration of the parent compound and/or reactive metabolites. In a few studies, however, a positive and exposure-related correlation between biomarkers in the lung or larynx and in peripheral blood cells has been observed (Szyfter et al. 1994; Tang et al. 1995; Wiencke et al. 1995). The results demonstrated by Wiencke et al. (1995) in particular emphasize the potential use of blood cells as surrogates for estimating the burden of DNA adducts in the lung. In these studies, the adducts were measured in lung tissue and blood mononuclear cells from the same individuals, thereby reducing the influence from interindividual differences in susceptibility. High local concentrations of inhaled PAHs retained in the bronchial epithelium may, however, lead to higher DNA adduct levels at that site, which

is not reflected by the adduct levels in circulating blood cells (see "Site of formation of DNA-binding intermediates").

The results obtained thus far on the relationship between the exposure of humans to complex mixtures containing PAHs and the extent of DNA adduct formation indicate a correlation, although weak in most cases (Phillips 1996). This is particularly surprising in individuals such as heavy smokers, in which substantially increased adduct levels were anticipated relative to that in nonsmokers. The apparent lack of, or minor effect of, smoking on adduct formation is probably due to the extensive exposure of individuals to PAHs through other routes (e.g. the digestive tract) and, accordingly, high basal levels of adducts in most tissues, including the lung (Beckman Sundh et al. 1998; WHO/IPCS 1998).

The adducts identified after PAH exposure have been classified as aromatic or lipophilic, and only in a very few cases have the adducts been identified (Phillips 1996; Rojas et al. 1998).

Protein adducts. Protein adducts of PAH DEs have been measured in hemoglobin (Hb) and serum albumin (SA) with different methods in several studies of occupational exposure, e.g., in foundry workers (Ferreira et al. 1994; Sherson et al. 1994; Tas et al. 1994) and in humans with occupational exposure to automobile exhaust (e.g., Hemminki et al. 1994; Pastorelli et al. 1996). Adducts have been detached from the protein by mild hydrolysis and analyzed by HPLC and fluorescence detection, by ELISA, or by gas chromatography/mass spectrometry (GC/MS). Background levels in control persons and significant increases in adduct levels in occupationally exposed persons have been found. Analysis by GC/MS has the highest specificity and also allows structural identification of the adduct. Adducts from B[*a*]P were specifically determined by GC/MS as B[*a*]P tetrahydrotetrols in studies of persons with occupational exposure to traffic exhaust, with a significant increase in exposed nonsmokers (Pastorelli et al. 1996). A hydrolyzable adduct from (+)-*anti*-BPDE binds to carboxyl oxygen in aspartate in human Hb (Skipper et al. 1989).

One drawback with these hydrolyzable adducts to carboxyl oxygen is their sensitivity to hydrolysis (and the ensuing fact that they are not completely stable) *in vivo*, particularly in Hb from rat and mouse (Naylor et al. 1990; Viau et al. 1993). Thus, these adducts are suitable as exposure markers but cannot be used for the calculation of doses *in vivo* of DEs from accumulated adduct levels.

To overcome this problem of *in vivo* instability of adducts, suitable amino or sulfur adducts from DEs in Hb and SA have

been studied. In human SA, histidine and lysine adducts have been found after *in vitro* treatment with several DEs, among others from B[*a*]P and fluoranthene (Brunmark et al. 1997). After *in vitro* treatment of human SA and human Hb with BPDE, a large fraction of the BPDE adducts is bound to histidine (Helleberg and Törnqvist 2000). Recently, a very sensitive method was published based on measurement of BPDE-histidine adducts in human SA and measured with high sensitivity by laser-induced fluorescence as dipeptides after enzymatic digestion (Özbal et al. 2000). With this method a background adduct level of about 150 fmol per g SA histidine adduct was measured in humans. In parallel work a liquid chromatography–mass spectrometry method was developed for measurement of histidine adducts from BPDE after hydrazinolysis of the protein (Helleberg and Törnqvist 2000). Studies in mice after intraperitoneal injections of B[*a*]P have shown that histidine adducts from BPDE are formed much faster in SA than in Hb (Helleberg 2001).

Urinary PAH biomarkers. Pyrene is a regular constituent in mixtures containing B[*a*]P and other carcinogenic PAHs. The highly fluorescent pyrene metabolite 1-hydroxypyrene (1-OHP) can be quantified in urine by HPLC. As a biomarker of PAH exposure, 1-OHP has gained a strong position (Angerer et al. 1997; Jongeneelen 1997; Levin 1995). Particulate pyrene is well correlated with the total PAHs in breathing zone air samples and 1-OHP in urine gives a more accurate assessment of the total PAH exposure from all exposure routes, including dermal absorption, than the PAH levels in air. Urinary 1-OHP may also reflect interindividual variation in PAH metabolism. Pyrene is metabolized by CYP1A1 and possibly by CYP1B1 (Elovaara et al. 1995) to 1-OHP, and is excreted in the urine as the corresponding glucuronide. CYP1B1 may be particularly important in the metabolism of pyrene in the human liver, as the activity has not been found to be inhibited by CYP1A1/2 antibodies (Elovaara et al. 1995).

Most people in Sweden have detectable amounts of 1-OHP in the urine (Levin et al. 1986). Background levels of 1-OHP are normally low, but an influence from environmental PAH contamination and smoking can be detected. Median 1-OHP values of 0.03 and 0.09 µmol/mol creatinine have been reported in Swedish nonsmokers and smokers, respectively (Levin et al. 1986). In occupational settings the 1-OHP content in urine may be increased by a factor of 10–100. Coke ovens, carbon electrode production plants, tar distillation plants, aluminum smelters, and creosote

impregnation plants represent workplaces where high urinary 1-OHP levels are often observed. In a recent biomonitoring study of a Söderberg aluminum reduction plant in Sweden, urine samples from 96 pot-room workers and 5 control subjects were analyzed for 1-OHP (Carstensen et al. 1999). Values observed (median, range) were 4.31 (0.09–17.7) µmol/mol creatinine for workers and 0.13 (0.06–0.75) µmol/mol creatinine for controls. Canadian residents living less than 500 m from a Söderberg aluminum reduction plant had significantly increased excretion of 1-OHP compared with controls living in another industrial town (Gilbert and Viau 1997).

Urinary metabolites of phenanthrene (dihydrodiols and phenols) can also be used for monitoring human exposure to PAHs. However, this system seems to be less suitable for monitoring the extent of exposure and may rather provide information on the cytochromes P450 participating in the metabolism. For instance, smokers and nonsmokers demonstrate different distribution of phenanthrene metabolites (Jacob et al. 1999).

The HPLC-based procedure is relatively simple and has been further developed to analyze phenanthrene metabolites (Jacob et al. 1999; Lintelmann et al. 1994). It is now possible to determine levels of 1-OHP in addition to the metabolites of phenanthrenes down to the nanogram per liter range, which allows estimation of the PAH exposures of the general population (Angerer et al. 1997). In summary, the HPLC procedure is sensitive and can be used to determine the levels of different hydroxylated PAHs in urine.

Individual susceptibility. As evident from the discussion above, the genotoxic activity of a particular PAH requires metabolic activation to the ultimate active form and subsequent binding of these intermediates to critical positions in DNA. It can also be assumed that the extent of DNA binding in conjunction with the qualitative and quantitative distribution of adducts and their structures are intimately associated with mutagenic and carcinogenic potency. Given that the results obtained in experimental systems of animal origin are applicable to the human situation, interindividual differences in the enzyme/enzyme systems participating in the metabolism of PAHs are expected to play an important role in the tumor susceptibility of an individual. Polymorphisms in the enzymes participating in the activation of PAHs to their ultimate mutagens and the subsequent detoxification and elimination of these intermediates have been identified in humans. The balance between the rate of formation of reactive

DNA-binding intermediates on one hand and the rate of their elimination on the other are expected to be directly correlated with the extent of DNA binding. Accordingly, variations in the cytochrome P450s, EHs, peroxidases, NAD(P)H: quinone oxidoreductases, and GSTs seem to be the most important determinants of the individual susceptibility to DNA adduct formation from PAHs.

Cytochrome P450. As mentioned earlier, CYP1A1 is the cytochrome P450 isoenzyme most active in the metabolic activation of PAHs. Cigarette smoke induces both CYP1A1 protein levels and the metabolism of BP to fluorescent phenols. This activity is usually referred to as aryl hydrocarbon hydroxylase activity (AHH) in the lung (Anttila et al. 1991). Furthermore, a positive correlation has been reported between the incidence of lung cancer and the inducibility of AHH in human lymphocytes (Gahmberg 1979; Kellerman et al. 1973; Kiyohara et al. 1998). Certain alleles of the human CYP1A1 gene have been implicated both in lung cancer and in prostate cancer in Japan (Hayashi et al. 1992; Murata et al. 1998; Rojas et al. 2000), but these observations have not been reproduced in studies on Caucasian populations where the indicated alleles appear at much lower frequencies. Two closely linked mutations in particular have been studied extensively in relation to cancer risks; one results in a new restriction site (MspI) in the 3′ untranslated region of the gene, and the other is a mutation in the 7th exon that results in an amino acid exchange (Ile to Val). A growing number of studies link the mutations in the *CYP1A1* gene to increased susceptibility to DNA damage. The allele carrying the Ile to Val mutation was more commonly found in lung parenchyma DNA from lung cancer patients and in white blood cells from PAH-exposed individuals with high levels of DNA adducts derived from *anti*-BPDE (Rojas et al. 1998, 2000). This allele was also associated with increased occurrence of p53 mutations in tumor tissue (Kawajiri et al. 1996; Lazarus et al. 1998; Przygodzki et al. 1998). In some studies, but not all, it has been associated with higher AHH inducibility (Daly et al. 1998; Kiyohara et al. 1998; Wedlund et al. 1994).

Another cytochrome P450 enzyme recently identified in humans, CYP1B1, is also induced by PAHs. There are at least four common mutations resulting in amino acid exchanges in the human *CYP1B1* gene, which may explain some of the variation in human AHH activity (Stoilov et al. 1998). Finally, a recent study shows considerable variation in the human pulmonary CYP3A4 and CYP3A5 expression (Anttila et al. 1997).

Epoxide hydrolase. Microsomal EH catalyzes the hydrolysis and thus, the detoxification of epoxide intermediates of PAHs. The human EH gene was recently isolated and two relatively common amino acid variants were characterized (Hassett et al. 1994). Thus, human EH polymorphism exists and may cause interindividual differences in EH catalytic function.

Myeloperoxidase. A-463 G to A polymorphism in the promoter region of the human myeloperoxidase (MPO) gene, which leads to the loss of an SP1 transcription binding site in an Alu hormone-responsive element, reduces MPO mRNA expression. The *in vivo* formation of BPDE–DNA adducts in human skin treated with coal tar was reduced in the MPO-463AA/AG genotype compared with the GG genotype (Rojas et al. 2001).

NAD(P)H:quinone oxidoreductase. In humans, a C to T base change at position 609 of NAD(P)H:quinone oxidoreductase 1 (NQO1) RNA, which changes proline in the wild-type protein to serine in the mutant protein, has been demonstrated. This mutation results in the loss of NQO1 activity. The NQO1 protein catalyzes the metabolic detoxification of quinones and their derivatives. NQO1 has been reported to specifically prevent the formation of B[*a*]P quinone–DNA adducts generated by CYP1A1 and P450 reductase (Joseph and Jaiswal 1994) and NQO1–/– mice had an increased susceptibility to B[*a*]P-induced skin carcinogenesis (Long et al. 2000).

Glutathione transferases. Glutathione transferase-catalyzed conjugation of DE and the subsequent enzyme-mediated transport of the water-soluble glutathione (GSH) that conjugates out from the cell is probably the most important system of protection. Several classes of cytosolic human GST (Alpha, Mu, Pi, Theta, and Zeta) have been defined, and each class contains a variable number of closely related enzyme variants, or isoenzymes (Board et al. 1997; Mannervik and Widersten 1995). The catalytic efficiency of different GSTs (isoenzymes of Alpha, Mu, and Pi have been tested so far) with respect to a number of DE diastereomers and their corresponding enantiomers varies markedly. In addition, certain isoenzymes, for example, those belonging to class Pi, exhibit an exclusive preference for the DE enantiomers with *R*-absolute configuration at the benzylic arene carbon (of the DE isomers identified as ultimate carcinogens), whereas others (e.g., class Alpha and Mu isoenzymes) are less selective (Sundberg et al. 1997).

Several epidemiologic studies have been performed to establish a correlation between the GST genotype and the incidence of lung cancer due to cigarette smoking and consequent high exposure to various PAHs. A great deal of interest has been focused on class Mu GST, in particular GSTM1-1, as a high and (depending on ethnic group) variable proportion of individuals lack this isoenzyme. Accordingly, because it is suspected that the PAHs in cigarette smoke are involved in lung carcinogenesis, and because GSTM1-1 actively detoxifies DE by conjugation with GSH, individuals with low GST activity may be at a higher risk than individuals expressing high conjugating ability. The association between GSTM1 polymorphism and lung cancer is still controversial. It has been investigated in numerous epidemiologic studies. Two recent meta-analyses of case–control studies, 1 of 21 studies (d'Errico et al. 1999) and 1 of 23 studies (Houlston 1999), reported a positive association between GSTM1 deficiency and lung cancer. The suggested associations are weak and not observed in all studies but are reportedly stronger among Asians and for squamous cell and small cell carcinomas (Vineis et al. 1999). The most obvious explanation for the weak association between GSTM1-1 deficiency and lung cancer risk is that GSTM1-1 is not highly expressed in the respiratory tract.

In biomarker studies, the levels of DNA damage in peripheral lymphocytes from smokers were higher in some instances in donors with the *GSTM1*-null genotype compared with *GSTM1*-positive donors (Scarpato et al. 1997; van Poppel et al. 1992). These findings were substantiated in a recent study (Rojas et al. 1998, 2000) in which convincing evidence was presented for the involvement of GSTM1-1 in protection against the formation of DNA adducts derived from *anti*-BPDE. In a total of 40 individual DNA samples obtained from lung tissue from smokers with lung cancer and white blood cells from PAH-exposed coke-oven workers, no adducts ascribed to *anti*-BPDE were detected in any of the 23 individuals carrying active *GSTM1* genes, whereas all of the subjects with the *GSTM1*-null genotype had measurable levels of DNA adducts.

Studies on a possible protective role of class Pi and Theta GST in human carcinogenesis have also been conducted. The major GST in human lung is GSTPi; this enzyme detoxifies a number of PAH DEs by GSH conjugation. Two polymorphic sites are known, at codon 105 and codon 114 in the human *GSTP1* gene, that may alter the kinetic properties of the enzyme. In fact, replacing isoleucine at position 105 by alanine in GSTP1-1 significantly increases the conjugating activity toward various DE substrates (Sundberg et al. 1998a, b). Interestingly, DNA adducts believed to

originate from PAH exposure in white blood cells in newborns are considerably lower in those expressing GSTP1 ile/ile than those with GSTP1 val/val, thus suggesting a protective role of the latter isoenzyme (Whyatt et al. 2000). With respect to lung cancer in humans and exposure to PAH-containing material, the results from studies on GSTPi and Theta polymorphism are too limited and variable to allow any definite conclusion. However, the importance of GSTPi in tumor susceptibility was recently demonstrated in mice treated with the PAH 7,12-dimethylbenz[*a*]anthracene and the tumor promoter TPA. The tumor incidence in animals in which the *GSTP1* gene cluster had been deleted was more than three times higher than in normal mice (Hendersson et al. 1998). Accordingly, in addition to GSTPi polymorphism in individuals, variation in the phenotypic expression of the enzymes may also be a factor to consider in the context of tumor susceptibility.

Absorption, Disposition, and Metabolism of PAHs in the Respiratory Tract

As discussed previously, PAH-containing matter may enter the human body via the respiratory tract, the digestive tract, and the skin. Because this document deals primarily with airborne PAHs and human exposure via the respiratory tract, we discuss this route in more detail here.

Transport and PAH metabolism in the airway epithelium. Recent experiments on dogs have shown that after a low-level exposure of a highly lipophilic compound (i.e., B[*a*]P or pyrene) via the respiratory tract, a substantial part of the substance is selectively retained in the tracheobronchial epithelium. These observations raise important questions related to the effective dose of PAHs in the airway epithelium of humans: *a*) What is the significance of the fact that most carcinogenic PAHs are to a high extent associated with airborne particles? *b*) How fast are PAHs transported from different regions of the respiratory tract into the circulatory system? and *c*) What is the relative contribution of the seemingly modest metabolic capacity of lung tissues compared with the liver in the overall formation of ultimate DNA-binding intermediates to which target cells are exposed?

Early studies on the influence of particle association of PAHs on carcinogenicity in animals indicated that particles increase the carcinogenicity of PAHs by prolonging the retention of the compounds in the lung, thereby increasing the effective dose (Henry and Port 1975). However, the experiments were conducted by instilling very large amounts of particles and PAHs into rodents,

and most likely the observed effect of the particles was the artefactual consequence of the extreme dosing scenario. This observation is important, as the early results suggested that a certain particle-retained fraction of PAHs would be more carcinogenic in the lung than fractions that are rapidly eluted from the particles. In addition, the findings masked the behavior of PAHs at realistic exposure levels. PAHs that are desorbed from their carrier particles absorb within minutes into the blood from the thin alveolar epithelium (Gerde et al. 1993) but more slowly from the thicker epithelia of the conducting airways.

The prime determinant for the rate of absorption of organic compounds through the tracheobronchial epithelium is their lipophilicity; the more lipophilic the compound, the lower the rate of diffusion through the tracheobronchial epithelium into the circulatory system (Figure 13). For highly lipophilic carcinogens such as B[*a*]P, the delayed absorption in the airway mucosa is entirely the result of slow passage through the tracheobronchial epithelium, giving a very high dose to these target cells (Gerde et al. 1998). When the compound reaches the circulation following diffusion through the epithelium basement membrane and the endothelium, the immense transport capacity of the blood will rapidly dilute it to the low level at which all distal tissues are exposed. The effect of the highly localized dose in the airway epithelium can easily be overlooked, or confused with artefactual

effects of particles with which the compound is associated.

By decreasing the lipophilicity of a toxic compound and thereby enhancing the rate of clearance to capillary blood, metabolism is an integral part of the removal of harmful substances from the conducting airways. Because of the long retention time of lipophilic compounds in the epithelium at the site of entry, the metabolic conversion can be substantial even at low enzyme activities (Bond and Harkema 1988). The ultimate carcinogenic metabolites generated in this process, such as BPDE in the case of B[*a*]P, are still quite lipophilic (Ooi et al. 1994), and they can be expected to be retained in the airway epithelium. Increased local concentrations in airway target cells can thus be anticipated. Therefore, at low inhalation exposure levels, the contribution of reactive PAH intermediates generated locally in the airway epithelium probably dominates over the contribution of corresponding metabolites formed in the liver and subsequently transported to the lungs via the systemic circulation. At higher exposure levels, however, the liver seems to be the dominant contributor of active metabolites in the lungs (Wall and Gao 1991; Wiersma and Roth 1983).

Site of formation of DNA-binding intermediates. Exposure of experimental animals to PAHs results in adduct formation in most tissues. However, the relationship between adduct levels in different tissues and cancer risk is not yet clear. At
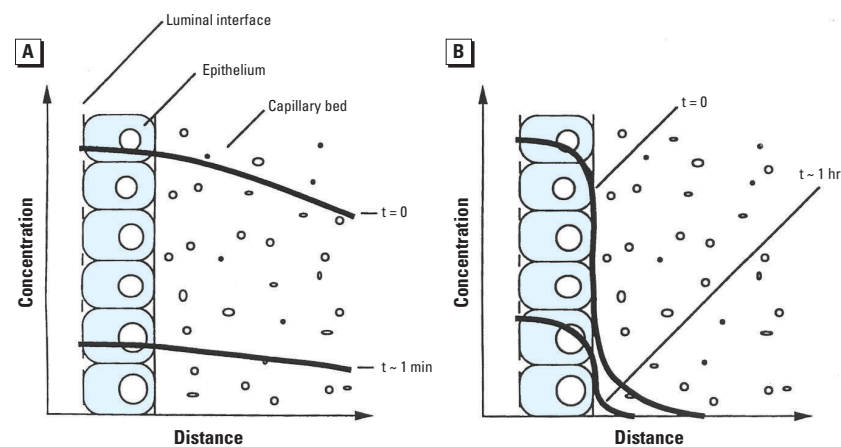

Figure 13. A schematic representation of the two major mechanisms of the absorption of organic carcinogens in the tracheobronchial mucosa. Abbreviation: t, time. Two concentration profiles are indicated in each cross-section, separated by typical time intervals. Water-soluble to moderately lipophilic carcinogens, i.e., the tobacco-specific nitrosamines, are blood-flow limited during absorption in the mucosa. Such substances diffuse rapidly into the capillary bed and are taken up by the blood during time periods on the order of minutes. The exposure at the site of absorption will be brief and not very different from that of distal tissues exposed via the systemic circulation (*A*). Highly lipophilic carcinogens such as PAHs are diffusion limited in their absorption in airway mucosa. PAHs diffuse slowly along steep concentration gradients through the airway epithelium, and they are likely to enter the systemic circulation via the most superficial capillaries of the subepithelium (*B*). Even after a brief exposure, the site-of-entry epithelium will be selectively exposed for hours at considerably higher concentrations than the rest of the organism. Figure modified from Gerde et al. 1993.

higher exposure levels the quantity of adducts per unit weight of total tissue seems to be less dependent on the administration route (Boroujerdi et al. 1981; Bresnick and Eastman 1982; Kleihues et al. 1980). This was recently illustrated in repair-deficient mice after administration of B[a]P by stomach gavage. The level of DNA adducts after 7 weeks of exposure was approximately the same in different organs (Helleberg et al. 2001). These findings imply that the liver, as the major site for biotransformation of xenobiotics, participates in the metabolism of PAHs independently of the route of entry. It is believed that primarily formed metabolites, or the ultimate reactive intermediates, are formed in the liver and subsequently released into the circulation and transported to extrahepatic tissues. It should

be emphasized, however, that these tissues also possess the ability to activate PAHs to reactive intermediates.

In the lung, the highest expression of CYP1A1 has been reported in the terminal bronchiolar epithelium (Mace et al. 1998; Saarikoski et al. 1998). Of interest also is the CYP1A1-dependent metabolic capacity of the endothelial cells (Granberg et al. 2000 and references therein). The vascular endothelium makes up approximately 1% of the body weight of humans, which implies that the metabolically active endothelial cells could serve as an important site for formation of reactive metabolites. Moreover, the above experiments were made at high exposure levels, with the potential for saturation of activation in the site-of-entry epithelium. At realistic exposure levels, the relative

importance of activation in the airway site-of-entry epithelium is likely to be greater.

Dosimetry. In estimating the risk of lung cancer from inhaled PAHs, three aspects of their distinctive site-of-entry dosimetry are of particular importance: *a*) the relationship between biomarkers of exposure in the systemic circulation and the dose of PAHs and relevant metabolites in airway target cells, *b*) the saturation of PAH metabolism and limited solubility of the parent compound and metabolites in the airway mucosa, and *c*) the dose response of the particular PAH inhaled.

During normal exposure to PAH-containing aerosols, a major fraction (probably >80%) of the inhaled PAHs is expected to be deposited on the thin alveolar epithelium. and is rapidly absorbed into the blood. The major part of this fraction is not metabolized during absorption in the lungs (Gerde et al. 2001) but in the liver. A minor fraction (<20%) is absorbed and metabolized in the tracheobronchial epithelium (Figure 14). This leads to great uncertainty when investigators try to estimate the target dose of a compound in the airway epithelium by quantifying the metabolites in the systemic circulation or DNA adducts in blood cells (Gerde et al. 1997, 1998), particularly if the activation of PAHs proceeds differently in the liver relative to the lungs. The second important aspect of the PAH dosimetry is a likely nonlinear dose–response relationship. The lipophilic PAHs that penetrate the mucous lining layer dissolve readily in the bronchial epithelial membranes but are transported slowly into the capillary blood. This process is dependent on the lipophilicity of the PAH; for example, B[a]P comprising five benzenoid rings partitions more readily into the membranes than into cellular water compared with pyrene comprising four rings. As a consequence, B[a]P is released more slowly into the circulatory system (Gerde et al. 1997, 1998). Therefore, the bronchial epithelium attains high PAH concentrations even at low environmental exposure levels. At higher levels, the capacity of the airway epithelium to dissolve and metabolize PAHs is likely to be saturated.

Although unaccounted for in an experimental exposure scenario, these limiting capacities may introduce drastic nonlinearities between exposure and airway target dose. However, because of the large metabolic capacity of the liver, the major fraction of PAHs absorbed into the blood from the thin alveolar epithelium is not likely to saturate hepatic metabolism even at high exposure levels. Accordingly, any saturation of metabolism in the airway epithelium, if measured in the systemic circulation, is likely to be masked by the larger contribution of metabolites formed and released from the
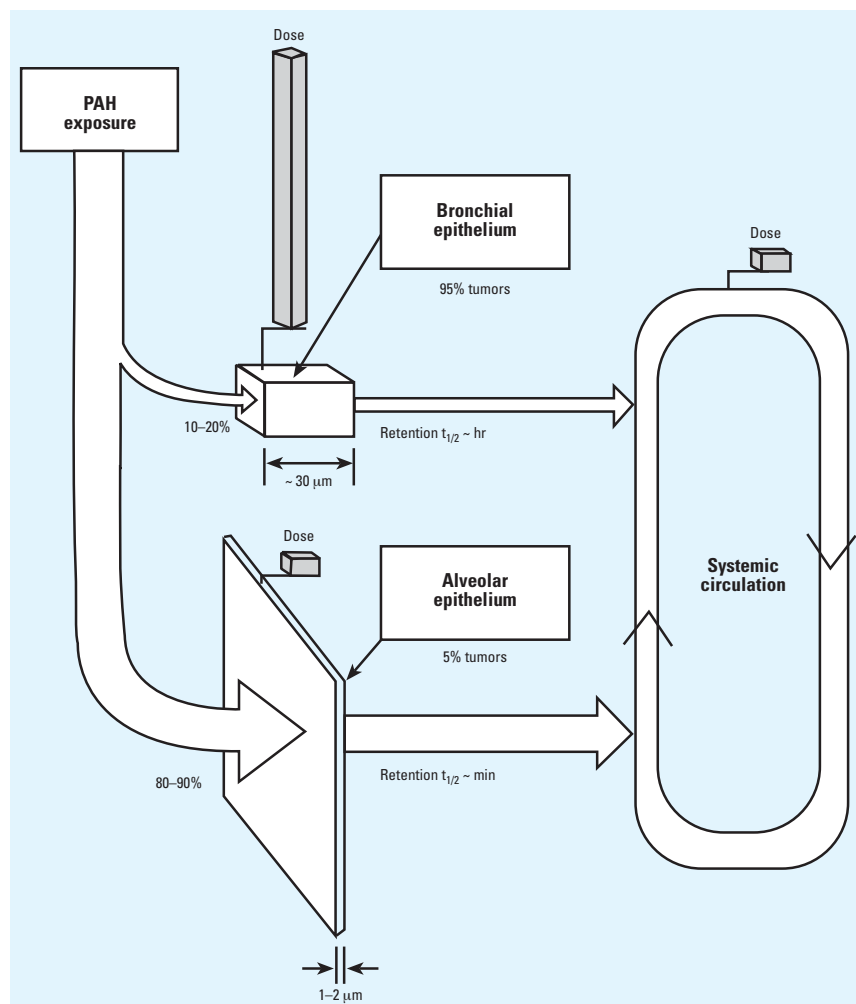

Figure 14. A schematic representation of the two major routes of entry of PAHs via inhalation. A major fraction is deposited on the thin air–blood barrier of the alveolar type I cells, and it is rapidly absorbed and diluted in the systemic circulation. Despite the larger fraction absorbed here (absorbed dose), type I cells will experience a comparatively low tissue dose of inhaled PAHs. A minor fraction is deposited on the thicker bronchial/bronchiolar epithelium and it is rapidly absorbed into epithelial cells, but it is transported slowly into the circulating blood. Very high tissue doses of inhaled PAHs will result in these cells, and carcinogenicity at the site of entry is likely to dominate completely over contributions to carcinogenicity delivered with the systemic circulation.

liver. A likely consequence for highly lipophilic PAHs is that risk assessments based on animal exposures conducted at exposure levels exceeding such a saturation may underestimate cancer risk in humans after decades of environmental exposure (Gerde et al. 1997, 1998). However, a better understanding of the way in which inhaled PAHs are distributed in target and nontarget tissues will improve the feasibility of extrapolating dose–response relationships to the low levels at which humans are exposed and help to improve the interpretation of the results from various biomarkers of exposure.

Conclusions and Recommendations for Indicators for Environmental PAHs

Experiments on animals and in mammalian cells have revealed that several PAHs are mutagenic and carcinogenic, and that these activities are associated with certain properties of the compounds. For both alternant (e.g., B[*a*]P and dibenzo[*a,l*]pyrene) and nonalternant PAHs (e.g., benzo[*b*]fluoranthene and cyclopenta[*c,d*]pyrene), the mutagenic and ensuing carcinogenic activities depend on metabolic activation to reactive intermediates (in particular DEs) and their covalent binding to critical targets in DNA. In addition to the mutagenic potency, many PAHs exhibit a cancer-promoting ability, for instance, via interaction of the parent PAH with a cellular receptor. The promoter activity may lead to very high tumor incidences in animals exposed to high doses. If based on animal experiments, carcinogenic potency may therefore overestimate the risk at the low exposure levels in the general environment, where mutation is expected to play a predominant role. The mutagenic and carcinogenic potency of a PAH is associated with the structural features and the complexity of the molecule; a more complex compound is usually more potent.

A number of epidemiologic studies have demonstrated a close association between exposure to PAH-containing mixtures and an increased risk of tumor formation in humans. This correlation is particularly evident for cigarette smokers and primary cancers in the respiratory tract. Accordingly, reduction and ultimately elimination of PAHs from the environment is expected to reduce the incidence of PAH-induced tumors. Factors likely to influence the susceptibility of an individual toward PAH exposure include polymorphisms in genes encoding enzymes participating in the metabolism of the PAHs (e.g., cytochromes P450 and GSTs).

An important route of exposure to PAHs in ambient air in humans is via inhalation. Because of the lipophilic properties of PAHs, fractions of the compounds are likely to be retained in the lung tissue and attain high local concentrations even at the low levels of exposure to which humans are subjected. The retention is related to the lipophilicity of the compounds; the more lipid soluble the compounds are, the more efficient is the retention. At higher exposure levels the capacity of the airway epithelium to retain the compounds becomes saturated, and nonlinearities between exposure and airway target dose can be expected.

For human monitoring purposes, a number of analytic methods have been applied for determining PAH exposure. DNA adducts and blood–protein adducts of aromatic compounds have been analyzed, particularly in association with cigarette smoking and occupational exposures. There are still problems with regard to the sensitivity and specificity as well as the stability of different adducts; this renders such methods less suitable at present for use in routine biological monitoring. Determination of hydroxylated PAH metabolites in urine can be used to detect specific metabolites. The determination of 1-hydroxyphenanthrene in urine is sensitive enough to quantify exposure at environmental PAH levels. Therefore, risk assessment based on animals exposed to high levels of PAHs may underestimate cancer risks in humans after decades of environmental exposures.

To form a basis for action against PAHs in the environment, frequent monitoring of selected PAH species under various conditions is essential. The choice of compounds should be based on both practical and biochemical/biological considerations. Because of their abundance in the environment, compounds such as phenanthrene and pyrene are suitable indicators for PAH contamination in general and overall human exposure to PAHs. However, substances such as fluoranthene, B[*a*]P, and dibenzo[*a,l*]pyrene are suitable carcinogenic indicators.

Quantitative Cancer Risk Estimates

Cancer risk assessment of individual PAHs and PAH mixtures are based mainly on tests on laboratory animals and occupational epidemiologic studies. For several reasons, risk estimation of PAH exposures is a complex issue.

PAHs in the environment comprise several hundred compounds, most of which occur together with substituted PAHs and with a large number of other carcinogenic pollutants. The composition profile of the PAHs, as well as of other pollutants simultaneously present, varies between environmental compartments, for example, different occupational settings. This renders risk estimates for the whole mixture based on epidemiologic studies, with data on exposure restricted to one or a few components, very uncertain.

Individual PAHs may provoke a cancer risk by more than one mechanism (initiation of tumor formation and effects on the tumor development at later stages), often in interaction with other inherited or acquired factors (cf. "Mechanistic Aspects of Biological Activity"). The mechanisms operate with different dose–response relationships, and it is difficult to clarify which mechanism has been mainly causative in the effect observed in animal cancer tests where very high doses are often applied. This strongly contributes to the difficulties in obtaining reliable cancer risk estimates with relevance for the human situation, usually characterized by low exposure levels.

Nevertheless, at the present stage of knowledge, risk estimation for PAHs at low exposure levels should be based on the assumption of linear dose–response relationships despite the nonlinear responses often seen for high doses in animal tests.

Because the scientific basis for quantitative risk assessment of inhaled PAHs is weak, the basis for recommended guideline values in ambient air is accordingly also weak. It is thus important for the Swedish regulatory agency, the Swedish Environmental Protection Agency, to gain experience in how risk assessment of PAHs has been handled in other countries. A survey is presented in this section.

Epidemiologic Data

As mentioned earlier (Table 1), exposure to soot, coal tar, and other PAH-containing mixtures is carcinogenic to humans. Concerning inhalation exposure, tobacco smoking and certain occupational exposures within the aluminum production, coal gasification, and coke production industries have been classified by IARC as carcinogenic to humans. Diesel exhaust is classified as probably carcinogenic to humans. More recent epidemiologic studies have been reviewed *inter alia* by Mastrangelo et al. (1996) and Boffetta et al. (1997). These studies confirm that heavy occupational exposure to mixtures of PAHs entails a substantial risk of lung, skin, or bladder cancer. Exposure–response relationships have been demonstrated in several studies, although quantitative risk estimates relative to PAH levels are confined mainly to lung cancer in coke-oven workers.

The increased risk for lung cancer among coke-oven workers is used for the quantitative risk assessment of PAHs with

B[*a*]P as the indicator substance by WHO in the Air Quality Guidelines for Europe (WHO 1987, 2000). According to WHO (1987), a strongly increased risk of death from cancer of the respiratory system had been demonstrated among workers at coke ovens in Allegheny County, Pennsylvania, USA, for 1953–1970, especially in top-oven workers (relative risk [RR] = 6.6–15.7 for some 300 topside, full-time workers, divided into different categories according to the years of exposure). WHO (1987) further refers to a risk assessment by the U.S. Environmental Protection Agency (U.S. EPA) in 1984 that applied a linearized multistage mathematic model to the individual exposure estimates, which generated an upper-bound risk estimate expressed in terms of benzene-extractable material. The U.S. EPA estimate was converted in terms of B[*a*]P levels by assuming a 0.71% content of B[*a*]P in the benzene extract, thus estimating the lung cancer risk from a lifetime exposure to PAHs in ambient air at 8.7×10^{-5} per ng/m^3 B[*a*]P (WHO 1987, 2000). The difficulties in dealing with guidelines for PAH mixtures are discussed, as are the advantages and disadvantages of using a single indicator carcinogen to represent the carcinogenic potential of a fraction of PAHs in air. It is stated that no specific guideline can be recommended for individual PAH compounds in air. An evaluation of B[*a*]P alone, for example, is likely to underestimate the carcinogenic potential of airborne PAH mixtures, because other co-occurring substances are carcinogenic as well. A complicating factor is that PAHs in air are adsorbed onto particles, which may also play a role in their carcinogenicity. B[*a*]P was chosen as an indicator of carcinogenic PAHs in ambient air, although the limitations and uncertainties in such an approach were recognized. WHO does not set guideline values for genotoxic carcinogens such as PAHs because no safe level can be recommended, but it specifies a risk estimate as a basis for policy makers.

Using measurement data on PAHs from German coke ovens applied to the same epidemiologic data on coke-oven workers, Pott (1985) calculated a similar risk (5×10^{-5} per ng/m^3 of B[*a*]P).

An update of this cohort and the mortality among other coke-oven workers in Pennsylvania, USA, providing 30 years of follow-up, has been presented (Costantino et al. 1995). The results are consistent with those from earlier assessments, indicating an excess mortality from cancer of the respiratory system.

An earlier quantitative risk estimate based on lung cancer in workers in British gas works (Pike 1983) gave a higher estimate

(43×10^{-5} per ng B[*a*]P/m^3) than the WHO risk estimate.

The exposure to PAHs in an aluminum production plant (Armstrong et al. 1994) gave a quantitative risk estimate of 1×10^{-5} per ng B[*a*]P/m^3 as workplace exposure for 40 years. If converted to lifetime continuous exposure, the corresponding lifetime unit risk for respiratory cancer would be approximately 9×10^{-5} per ng/m^3 (70/40 years × 365/220 days × 24/8 hr). This risk figure is identical to the WHO risk estimate based on coke-oven workers.

For most other occupational studies, quantitative risk estimates cannot be derived because of lack of exposure estimates. For example, an increased risk for lung cancer in Swedish chimney sweeps has been demonstrated (Evanoff et al. 1993).

Several epidemiologic studies have demonstrated an increased risk of lung cancer in persons occupationally exposed to diesel exhausts, for example, American railroad workers (Garshick et al. 1987, 1988) and Swedish dock workers (Emmelin et al. 1993; Gustafsson et al. 1986) and bus garage workers (Gustavsson et al. 1990). These studies have not yet provided quantitative risk estimates relative to PAHs. However, Pott and Heinrich (1990) made a rough comparison of the amount of B[*a*]P inhaled from diesel exhaust and coke-oven emissions that would induce a certain incidence of lung tumors. These authors concluded that a much smaller amount of B[*a*]P was needed in diesel exhaust than in coke-oven emissions.

The lung cancer risk associated with smoking is well characterized, but when the risk is compared with the risk in coke-oven workers on a B[*a*]P basis, the amount of B[*a*]P inhaled has a much lower significance for the carcinogenicity of cigarette smoke than for coke-oven emissions (Pott and Heinrich 1990). Thus, both diesel exhaust and cigarette smoke obviously contain other potent carcinogenic substances besides PAHs. For example, it is known that cigarette smoke contains gas-phase carcinogens and tumor promoters, and diesel exhaust contains nitro-PAH (IARC 1987b, 1989b).

Because the content of unsubstituted PAHs is probably responsible for only part of the carcinogenicity of cigarette smoke and diesel exhaust, these exposures are less well suited for a quantitative risk assessment of PAHs.

The incidence of lung cancer is generally higher in urban areas than in rural areas. This difference can be attributed partly to air pollutants. According to a review of 9 cohort studies and 13 case–control studies worldwide (Pershagen and Simonato 1993), smoking-adjusted relative risks of lung

cancer in urban areas were generally on the order of 1.0–1.5. Exposure data on the levels of PAHs are generally lacking in these studies, and they cannot be used for a quantitative risk estimation of PAH or B[*a*]P.

A high rate of lung cancer has been described for women in Xuan Wei in China as a result of cooking with smoky coal without proper ventilation. According to the RIVM (1989), the average B[*a*]P level was 14.7 μg/m^3. Tuomisto and Jantunen (1987) used these data for a quantitative estimate of the risk of lung cancer, which extrapolated to low levels would give a unit risk value of 6.7×10^{-5} per ng/m^3 B[*a*]P (RIVM 1989). We have not found any other quantitative risk estimate in the literature based on these data.

Some of these risk estimates mentioned were cited in a Dutch criteria document on PAHs (RIVM 1989), and a risk of 10×10^{-5} per ng/m^3 B[*a*]P (as an indicator of carcinogenic PAHs) was considered the most appropriate value.

In a Canadian PAH document by Muller (1997), the risk assessment was based on the data from U.S. coke-oven workers, but the estimate (2.3×10^{-5} per ng/m^3 B[*a*]P) was lower than the WHO estimate because the maximum likelihood estimate was used instead of the upper-bound estimate. Muller (1997) also estimated that the risk for B[*a*]P as such was 1.5×10^{-6} per ng/m^3, assuming that 15% of the carcinogenicity of coke-oven emissions is due to B[*a*]P, which is indicated by the potency ratio between extracts of particulate emissions from a coke-oven and B[*a*]P in a mouse skin initiation study (Nesnow et al. 1982).

Muller (1997) also discussed the two main approaches to risk assessment of PAH mixtures, namely, either to estimate the potency of individual PAHs based on animal data and sum up the risks, or to estimate the potency of the PAH fraction as a whole, based on epidemiologic data and using B[*a*]P as indicator substance. According to these authors, a comparison of the two models suggests that the individual PAH model underestimates the risk based on epidemiology by almost two orders of magnitude. This result is consistent with the predictions, as the individual PAH model takes into account the risk attributable to only a handful of PAH compounds. An uncertainty assessment indicated that the epidemiology approach is associated with a much lower uncertainty than the individual PAH model.

In Great Britain, an Expert Panel on Air Quality Standards has prepared a report on PAHs (Expert Panel 1999). Based on the similarity of the PAH profiles in urban air and in an aluminum smelter workplace (seven measured PAH compounds; see

below, "United Kingdom"), the panel concluded that occupational studies on workers at aluminum smelters form a suitable basis for recommending an environmental standard. The study chosen was the Canadian study on aluminum workers by Armstrong et al. (1994). In this study, a 50% increase in the risk of lung cancer was demonstrated, with a cumulative exposure to B[a]P as indicator substance at levels of 10–100 μg/m^3 × year (equivalent to an exposure to 0.25–2.5 μg/m^3 B[a]P for 40 years). A safety factor approach was then used to derive a recommended ambient air quality standard. Recalculating from a working-life exposure to continuous lifetime exposure (a factor of 10), using a safety factor of 100, leads to a recommended value of 0.25 ng/m^3 B[a]P as an annual average.

The WHO risk estimate was used by the Swedish Governmental Commission on Environmental Health (Commission on Environmental Health 1996) when proposing an action plan for Sweden to reduce environmental health risks. A target was set up for PAHs with B[a]P as the indicator substance at 0.1 ng/m^3 as the long-term average. This level corresponds to a theoretic lifetime cancer risk of 1×10^{-5}, according to the WHO risk assessment.

Data from Animal Experiments

Experiments with benzo[a]pyrene. The best-investigated single PAH compound is B[a]P. Besides dermal exposure, B[a]P is carcinogenic by intraperitoneal injection, intratracheal instillation, inhalation, and when given in the diet. For our discussion, the inhalation route is the most relevant one. However, the inhalation study by Thyssen et al. (1981) is the only one found in Western scientific literature. Groups of 24 male hamsters were each exposed to B[a]P condensed onto sodium chloride particles at concentrations of 2.2, 9.5, and 46.5 mg/m^3 for 4.5 hr/day, 7 days/week for the first 10 weeks, then for 3 hr per day. Exposure was by nose breathing only. There were no tumors in the low-exposure group or in the control group. In the other groups, exposure-related tumors were found in the nasal cavity, larynx, trachea, pharynx, esophagus, and forestomach. However, there were no tumors in the lung. The average survival time was lower in the highest exposure group: 59 weeks compared with 96 weeks for the control group. This study has been used for quantitative risk assessment using the so-called linearized multistage model. The upper bound of the 95% confidence limit of the dose–response curve was used to calculate the risk corresponding to a specific inhalation dose. However, because of the high mortality in the highest dose group,

these data had to be omitted; as there were no tumors in the lowest dose group, the calculation will actually be based on only one dose group. Moreover, there were relatively few animals per dose group, and the study was not reported according to modern standards. Thus, the resulting estimates will be quite uncertain. According to Collins et al. (1991), a linearized multistage model using three different assumptions concerning the inhalation rate in hamsters will give so-called unit risk estimates for humans at 0.37×10^{-6}, 1.1×10^{-6}, and 1.7×10^{-6} per ng/m^3, respectively. These unit risk figures indicate the theoretic increased lifetime risk for respiratory tract tumors resulting from continuous inhalation of 1 ng/m^3 for a lifetime, and they were obtained by converting the inhalation regimen in the animal experiments into continuous exposures and using a species conversion factor from hamster to humans based on inhaled dose per body surface area. The higher estimate, 1.7×10^{-6} per ng/m^3, was used by the U.S. EPA in 1984, but because of the inadequacies of the study by Thyssen et al., the U.S. EPA currently has no official quantitative inhalation risk estimate for B[a]P (IRIS 2001). However, the California EPA uses the middle estimate, 1.1×10^{-6} per ng/m^3 (CARB 1994). In a Dutch criteria document on PAHs (RIVM 1989), the risk was estimated to be 0.28×10^{-6} per ng/m^3. (Note that this risk is smaller than that calculated by Collins above because no upper confidence limit or species conversion factor was applied.)

According to the Dutch criteria document there was a Russian inhalation study with mice (Knizhnikow et al. 1982, cited in RIVM 1989), in which malignant lung tumors were found, which indicates a much higher risk than the study by Thyssen et al. (1981). In this study, female white mice were exposed to 0.2, 6.3, or 78 μg/m^3 B[a]P as a dry aerosol, 6 hr daily, 5 days per week for 3 months. According to the RIVM (1989), linear extrapolation from the highest equivalent lifetime concentration would give a risk of 4×10^{-4} per ng/m^3. However, this study has not been cited in any other criteria document on PAHs that we have reviewed.

The Dutch document (RIVM 1989) also refers to an inhalation study with rats by Laskin et al. in 1970, in which malignant lung tumors were observed after exposure to B[a]P in combination with sulfur dioxide. By means of linear extrapolation, this study would give a risk for rats of 0.59×10^{-6} per ng/m^3.

Two studies using intratracheal instillation have also been used for quantitative risk assessments. Saffiotti et al. (1972) administered a mixture of B[a]P (0.25, 0.5, 1.0, or 2.0 mg) and Fe$_2$O$_3$ (hematite) (2 mg) in a

saline suspension to hamsters once a week for 30 weeks. A dose-related increase in respiratory tract tumors was observed for all groups of animals. In another experiment, Feron et al. (1973) gave groups of 30 male Syrian golden hamsters intratracheal doses of 0.06, 0.12, 0.5, or 1.0 mg B[a]P weekly for 52 weeks. A variety of tumors was produced in a dose-dependent fashion throughout the respiratory tract. Using the linearized multistage model, Collins et al. (1991) estimated the unit risk for humans, based on these studies, to be 4.4×10^{-6} and 4.8×10^{-6} per ng/m^3, respectively.

The cited studies with B[a]P are far from optimal for quantitative cancer risk assessments. However, they are the only ones available concerning respiratory tract exposure. In the Dutch criteria document (RIVM 1989), it was concluded that the uncertainties in the extrapolation from animal experiments with B[a]P are too high to justify a risk assessment for man.

PAHs have been assessed by Environment Canada/Health Canada under the Canadian Environmental Protection Act (Government of Canada 1994; Meek et al. 1994). Because of the possible confusion with concomitant exposure to other substances that may have contributed to the observed effects, available epidemiologic data (see "Epidemiologic Data") were considered inadequate to assess the health risks of PAHs in humans. Instead, the Canadian risk assessment is based on the carcinogenicity of B[a]P and four other PAH compounds classified as probably carcinogenic to humans, namely, benzo[b]fluoranthene, benzo[j]-fluoranthene, benzo[k]fluoranthene, and indeno[1,2,3-cd]pyrene. The carcinogenic potency of B[a]P was obtained by multistage modeling of the study by Thyssen et al. (1981). For these substances the estimated concentrations, expressed as B[a]P equivalents, were calculated for different localities. The priority for "analysis of options to reduce exposure of the general population" was considered "moderate to high."

Experiments with mixtures. An inhalation study performed by Heinrich and co-workers (1994), in which female Wistar rats were exposed to a coal tar/pitch aerosol, has also been used for the calculation of a unit risk. In this case the animals were exposed to a mixture of PAHs, but the cancer risk was related to the B[a]P content. Thus, B[a]P was used as an indicator of carcinogenic PAHs in the mixture, and the approach is equivalent in this respect to the way B[a]P is used as an indicator of PAHs in epidemiologic studies. Groups of 72 rats were exposed to a coal tar/pitch aerosol containing either 20 or 46 μg/m^3 B[a]P for 17 hr/day, 5 days/week for 10 or 20 months, followed

by a clean air period of up to 20 or 10 months, respectively. The cumulative doses of inhaled B[*a*]P of the four exposure groups were 71, 142, 158, and 321 mg B[*a*]P/m^3 × hr, and the corresponding lung tumor rates were 4.2, 33.3, 38.9, and 97.2%. There was no lung tumor in the control group. Using the linearized multistage model, the lifetime unit risk for lung tumors was calculated to be 2×10^{-5} per ng/m^3. In similar experiments in which rats were exposed to coal tar/pitch vapor condensed on the surface of fine carbon black particles, the resulting lung tumor rate was about twice as high.

Heinrich and co-workers have also performed a lifelong inhalation study with rats exposed to diesel exhausts. In this study, tumor rates similar to those in the study with pitch pyrolysis vapors were induced, although the PAH content (measured as B[*a*]P) was 100–1000 times lower (Pott and Heinrich 1990). This result shows that diesel exhaust contains other potent carcinogenic or tumor-promoting compounds besides unsubstituted PAHs. Further, mutagenicity studies have shown that the most mutagenic components of diesel exhaust seem to be substituted PAHs such as nitro-PAH. The particulate fraction of diesel exhaust is known to cause inflammatory reactions that may indirectly lead to tumors if the concentration of particles in the inhaled air is so high that it leads to so-called overloading in the lung. Such particle-induced lung cancer has also been demonstrated in rats from the inhalation of inert particles (for a review, see Camner et al. 1997). The cited quantitative risk estimates are summarized in Table 12.

Comparative Cancer Potency of Individual PAH Compounds Relative to B[*a*]P

The available experimental studies on B[*a*]P are not ideal for a quantitative risk assessment for inhalation lung cancer and those for practically all other individual PAHs are either inadequate or nonexistent. However, many other PAH compounds are classified by the IARC as probable or possible human carcinogens, and several authors have used data from various cancer tests to rank the compounds according to cancer potency relative to B[*a*]P. Although such comparative rankings are not based on inhalation experiments but on other cancer tests, the results may still be used for grouping of individual PAH compounds as more or less potent. A more potent PAH would be preferable over a less potent one when selecting indicator substances for ambient air, based on biological activity. Such cited rankings are presented in Table 13 and are restricted mainly to those PAHs for which more than one author has presented rankings.

Toxic equivalency factors (TEFs) can be used as a practical tool for regulatory purposes for large groups of compounds with a common mechanism of action (e.g., dioxin-like compounds and PAHs) when there are limited data except for one reference compound, 2,3,7,8-tetrachlorodibenzo-*p*-dioxin and B[*a*]P, respectively. The TEF concept is based on the following assumptions:
• There is a reasonably well-characterized reference compound.
• These are qualitatively similar toxic effects for all members of the class.
• TEFs for different toxic end points are similar.
• The toxic effects of different compounds in a mixture are additive.

In the following text we will use the abbreviation TEF to denote the cancer potency of specific PAH compounds relative to the potency of B[*a*]P. The TEF values are not true values but are based on the best available data, which in many cases are scanty. The calculated TEF value can also vary within the dose range; this may be a problem, as animal studies are performed with high doses and humans are exposed at low concentrations. The TEFs 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 (RIVM 1989).

In the following text, TEF values for individual PAHs are discussed mainly with the aim of selecting biologically relevant PAH compounds as indicators of carcinogenic PAHs in ambient air. For this purpose, the TEFs are especially interesting when combined with actual concentrations of the PAH compounds (see "Fluoranthene as an indicator"). The purpose has not been to try to estimate the cancer risk by calculation of added individual risks.

Different toxic equivalency factor schemes. Nisbet and LaGoy (1992) reviewed earlier relative potency estimates in 1992 and provided revised ones (Table 13). The end points of the studies included carcinomas in the lungs of rats exposed via intrapulmonary administration; complete carcinogenesis in mouse skin; papillomas and/or carcinomas on mouse skin in initiation-promotion studies, sarcomas at the site of injection following subcutaneous administration to mice; and PAH–DNA adducts in *in vitro* studies. Relative potency factors (estimates of TEFs) were calculated using the data from each study by applying the same mathematic model of the dose–response relationship to the data for each compound and comparing the results to those obtained for B[*a*]P. According to the authors, the approach adopted by the U.S. EPA in 1984 was to separate the PAHs into carcinogenic and noncarcinogenic PAHs and then to regard all the carcinogenic PAH compounds as potent as B[*a*]P (TEF = 1). All noncarcinogenic PAHs were given a TEF of 0 by the U.S. EPA. The TEF values by Krewski et al. (1989) (Table 13) were based on diverse bioassay and related data, but those original data are not shown in the article. Some other earlier TEFs were considered to be unreasonably precise by Nisbet and LaGoy (1992). The TEF values given by Nisbet and LaGoy (Table 13) were rounded to the order of

Table 12. Summary of unit risk estimates for B[*a*]P and for PAHs with B[*a*]P as the indicator substance (life-time risk per ng/m^3 of B[*a*]P).

Basis for calculation	Unit risk	Reference
Animal experiments		
Inhalation of B[*a*]P in hamsters (Thyssen et al. 1981)	0.28×10^{-6} [a]	RIVM (1989)
Inhalation of B[*a*]P in hamsters (Thyssen et al. 1981)	$0.37–1.7 \times 10^{-6}$ [b]	CARB (1994); Collins et al. (1991); Muller (1997)
Inhalation of B[*a*]P + SO$_2$ in rats (Laskin et al. 1970 cit. RIVM 1989)	0.59×10^{-6} [a]	RIVM (1989)
Inhalation of B[*a*]P in mice (Knizhikow et al. 1982 cit. RIVM 1989)	400×10^{-6} [a]	RIVM (1989)
Intratracheal instillation of B[*a*]P in hamsters		
Saffiotti et al. (1972)	4.4×10^{-6} [b]	CARB (1994); Collins et al. (1991)
Feron et al. (1973)	4.8×10^{-6} [b]	CARB (1994); Collins et al. (1991)
Inhalation of coal tar/pitch aerosol with B[*a*]P as the indicator substance	20×10^{-6} [b]	Heinrich et al. (1994)
Epidemiology (PAH with B[*a*]P as indicator)		
U.S. coke-oven workers	87×10^{-6}	WHO (1987, 2000)
U.S. coke-oven workers	23×10^{-6}	Muller (1997)
U.S. coke-oven workers	50×10^{-6}	Pott (1985)
U.K. gas workers	430×10^{-6}	Pike (1983)
Smoky coal indoors in China	67×10^{-6}	RIVM (1989)
Most appropriate estimate	100×10^{-6}	RIVM (1989)
Aluminum smelters	90×10^{-6}	Armstrong et al. (1994); converted from workplace exposure to continuous lifetime exposure

[a]Linear extrapolation. [b]Linearized multistage model.

Table 13. Relative potency of individual PAHs compared with B[a]P (TEF values), according to different authors.[a]

Compound	Chu and Chen (1984) (cit. Nisbet and LaGoy 1992)	Clement (1986) (cit. Nisbet and LaGoy 1992); Krewski et al. (1989)	Nisbet and LaGoy (1992)	The Netherlands (RIVM 1989)	CARB (1994); Collins et al. (1998)	Health Canada (Meek et al. 1994)	Ontario (Muller 1997)	Larsen and Larsen (1998)
Anthracene			0.01	0				0.0005
Phenanthrene			0.001	0.01			0.00064	0.0005
Benz[a]anthracene	0.013	0.145	0.1	0–0.04	0.1		0.014	0.005
Benzo[c]phenanthrene							0.023	0.023
Chrysene	0.001	0.0044	0.01	0.05–0.89	0.01		0.026	0.03
Fluoranthene			0.001	0–0.06				0.05
Pyrene		0.081	0.001				0	0.001
B[a]P	1	1	1	1	1	1	1	1
Benzo[e]pyrene		0.004					0	0.002
Benzo[b]fluoranthene	0.08	0.14	0.1		0.1	0.06	0.11	0.1
Benzo[j]fluoranthene		0.061			0.1	0.05	0.045	0.05
Benzo[k]fluoranthene	0.04	0.066	0.1	0.03–0.09	0.1	0.04	0.037	0.05
Cyclopenta[cd]pyrene		0.023					0.012	0.02
Dibenzo[a,h]anthracene	0.69	1.11	5				0.89	1.1
Anthanthrene		0.32					0.28	0.3
Benzo[ghi]perylene		0.022	0.01	0.01–0.03			0.012	0.02
Dibenzo[a,e]pyrene					1		1.0[b]	0.2
Dibenzo[a,h]pyrene					10		1.2	1
Dibenzo[a,i]pyrene					10			0.1
Dibenzo[a,l]pyrene					10		100[b]	1
Indeno[1,2,3-cd]pyrene	0.017	0.232	0.1	0–0.08	0.1	0.12	0.067	0.1

[a]See comments in the text. [b]Data from Muller et al. (1995), cited in WHO/IPCS (1998).

magnitude that according to the authors appropriately reflects the actual state of knowledge on the relative potencies.

The TEF value for dibenz[a,h]-anthracene set by Nisbet and LaGoy (1992) is higher than earlier published values. Dibenz[a,h]anthracene has a TEF of 5, which is the ratio with B[a]P in the lower dose range (appropriate for environmental exposures), whereas 1 is the ratio for higher doses. Some "noncarcinogenic PAHs" (fluoranthene, phenanthrene, pyrene) have been assigned TEFs of 0.001 in contrast to the U.S. EPA TEF scheme where they are 0. The authors claim that assigning a TEF of 0.001 to the "noncarcinogenic PAHs" is motivated by their having "some, albeit limited, carcinogenic activity in some studies." However, this factor seems very uncertain, and it should be recognized that even a low factor becomes important in cases with high levels.

The observed tumor incidences from two experimental studies on exposure to mixtures of PAHs were compared by Nisbet and LaGoy (1992) to expected incidences (based on TEFs). The observed and expected incidences were quite similar except for mixtures including noncarcinogenic PAHs, in which the expected incidences were higher than those observed. From these comparisons, the assumption of additivity seems to be correct. However, better-designed studies are needed to confirm this.

In a criteria document on PAHs from the Netherlands (RIVM 1989), 10 individual PAH compounds were selected for evaluation. The carcinogenic potency of the individual selected PAH compounds was evaluated on the basis of oral, inhalatory, intraperitoneal, or dermal animal experiments. The potencies relative to B[a]P are shown in Table 13. As can be seen by the ranges in this table, the potencies may differ strongly depending on the route of administration and the target organ. As can also be seen from Table 13, the TEF values for phenanthrene and fluoranthene are relatively high compared with the TEFs given by the U.S. EPA and Nisbet and LaGoy (0.01 and up to 0.06, respectively, compared with 0 and 0.001). The upper range of the TEF value for chrysene is also relatively high (0.89) and is based on liver tumors after intraperitoneal injection.

In a criteria document issued by the California EPA (CARB 1994), TEF values were developed for PAHs and PAH derivatives known to be carcinogenic in animals (see also Collins et al. 1998). For most of these chemicals, data on mouse skin carcinogenesis were used to compare the cancer activity relative to B[a]P. For some compounds, data were also available from experiments using intrapulmonary administration to rats and tests for lung adenomas in newborn mice. The TEF values (rounded to a factor of 10) are shown in Table 13. In contrast to the other lists of PAHs considered, the California EPA included four dibenzopyrenes. Dibenzo-[a,l]pyrene, dibenzo[a,h]pyrene, and dibenzo[a,i]pyrene were given TEF values of 10, and dibenzo[a,e]pyrene was given a

TEF value of 1 based on skin tumor initiation assays in mice and mammary gland tumors in rats. Dibenzo[a,l]pyrene was the most potent member of the group (Cavalieri et al. 1989, 1991).

In a report from Health Canada (Government of Canada 1994; Meek et al. 1994), five PAHs classified as "probably carcinogenic to humans" were evaluated based on a study by Deutsch-Wenzel et al. (1983). In this study, there were exposure–response relationships in Osborn-Mendel female rats administered B[a]P, benzo[b]fluoranthene, and benzo[j]fluoranthene, and benzo[k]-fluoranthene, and indeno[1,2,3-cd]pyrene by lung implantation. Carcinogenic potencies were estimated on the basis of multi-stage modeling of the tumor incidence to calculate a $TD_{0.05}$ value (the dose associated with a 5% increase in tumors). The potencies relative to B[a]P (TEF values) were 0.06 for benzo[b]fluoranthene, 0.05 for benzo[j]fluoranthene, 0.04 for benzo[k]-fluoranthene, and 0.12 for indeno[1,2,3-cd]pyrene (Table 13). It should be noted, however, that the relative potency values are different in the original article by Deutsch-Wentzel et al. (1983). These authors used a probit analysis of the results and they reported the following relative potency values: 0.19 for anthanthrene; 0.11 for benzo[b]fluoranthene; 0.03 for benzo[j]fluoranthene; 0.03 for benzo[k]fluoranthene; and 0.08 for indeno[1,2,3-cd]pyrene (data not shown in Table 13).

The lung implantation study by Deutsch-Wenzel et al. (1983) was also

used as the main basis for the relative potency values put forward in a recent British report (Expert Panel 1999). PAHs regarded as probably or possibly carcinogenic were assigned the following TEF values relative to B[*a*]P: benz[*a*]anthracene, 0.1; dibenz[*a,h*]anthracene, 1.91; benzo[*b*]fluoranthene, 0.11; benzo[*k*]fluoranthene, 0.03; indeno[1,2,3-*cd*]pyrene, 0.08; and chrysene, 0.03 (data not shown in Table 13).

Nesnow et al. (1996) have examined some PAHs for their lung tumorigenic activities in strain A/J mice. PAHs were administered by intraperitoneal injection, and the mice were sacrificed after 8 months. The dose–response data for each PAH were modeled to obtain potency values relative to B[*a*]P (data not shown in Table 13). The authors also made some comparisons with earlier relative potencies derived from subcutaneous injection studies and dermal application in mice. In those studies, dibenz[*a,h*]anthracene was as active as B[*a*]P, but in the study by Nesnow et al. (1996), dibenz[*a,h*]anthracene was 16.5 times more potent than B[*a*]P in inducing lung adenomas in mice. Cyclopenta-[*cd*]pyrene was as active as B[*a*]P in inducing lung adenomas in mice (TEF 1.2), but in earlier skin application studies in mice, cyclopenta[*cd*]pyrene was less active than B[*a*]P. Benzo[*b*]fluoranthene was less active (TEF 0.56) than B[*a*]P in the strain A/J mouse lung adenoma system.

In a Canadian report, prepared for the Ontario Ministry of Environment and Energy (Muller 1997), TEF values were assigned for 209 individual PAHs. The TEFs are based primarily on tumor initiation in mouse skin. If such data were lacking, data from assays on rat lung or complete carcinogenicity data from mouse skin were used. To be able to use data from different experimental protocols, they were compared at a standardized time of observation. The reported TEF values agree reasonably well with those of Nisbet and LaGoy (1992), except for dibenz-[*a,h*]anthracene, which was assigned a value near 1 (Table 13). Despite the large number of TEF values, many of the most abundant PAHs in air still lack TEF values. The vast majority of the Canadian TEFs are for substituted PAHs not found or analyzed for in ambient air.

In addition to the 209 TEFs set by Muller in 1997, TEFs for dibenzo-[*a,e*]pyrene and dibenzo[*a,l*]pyrene were set to 1 and 100, respectively, by Muller and coworkers in 1995 according to the WHO/IPCS document on PAHs (WHO/IPCS 1998). The TEF value of 100 for dibenzo-[*a,l*]pyrene is the highest TEF set in any of

the TEF schemes. Some of the TEF schemes reported here, as well as some other schemes, are listed in the WHO/IPCS document (WHO/IPCS 1998).

In a recent review of chemical carcinogens in air, Larsen and Larsen (1998) listed estimates of the carcinogenic potencies of various PAHs relative to B[*a*]P (Table 13). This TEF scheme is based on the extensive database on carcinogenicity studies using various routes of administration. The TEF values are quite similar to other schemes, such as those of Nisbet and LaGoy (1992). However, the TEF for fluoranthene is 0.05 compared with 0.001, which makes quite a difference, as fluoranthene occurs at relatively high levels in ambient air. In addition, anthracene and benz[*a*]anthracene are assigned lower TEF values by Larsen and Larsen (0.0005 and 0.005, respectively) than by Nisbet and LaGoy (0.01 and 0.1, respectively).

Fluoranthene as an indicator. Fluoranthene is interesting because of its occurrence at relatively high concentrations in the environment. According to Swedish measurements (see "Sources, Deposition, and Ambient Concentrations"), fluoranthene is present at approximately 10 times higher levels than B[*a*]P in ambient air, in gasoline exhausts (from engines with catalytic converters), and in emissions from wood combustion. In emissions from domestic oil heating, the levels of fluoranthene are approximately 30 times higher than those of B[*a*]P, but they are more than 100 times higher in emissions from modern diesel engines (Tables 5 and 8). In contrast, the emissions from coke-oven plants contain concentrations of fluoranthene around 3 times higher than B[*a*]P (IARC 1984b).

Fluoranthene is mutagenic but not classified as a carcinogen by IARC (based on dermal application studies). However, according to the WHO/IPCS document (WHO/IPCS 1998), a limited number of more recent studies with intraperitoneal administration to newborn mice show that fluoranthene is an experimental carcinogen. Fluoranthene caused lung and liver tumors after 12 months in a study by LaVoie et al. (1994). Because B[*a*]P was also tested in the same study, a TEF value can be calculated. The B[*a*]P dose and the high dose of fluoranthene gave approximately the same tumor frequency and the resulting TEF value would thus be 0.08. As mentioned above, the TEF assigned by Larsen and Larsen (1998) is 0.05 (Table 13).

Because of its abundance in emissions from combustion, fluoranthene might be an important contributor to the risk from PAH exposure.

Combination of Toxic Equivalency Factor Values and Concentrations of PAHs in Air: Examples from Different Countries

In the choice of indicator substances for carcinogenic PAHs, the relative cancer potency as well as the relative concentration of individual compounds found in different emissions and in ambient air are important. In several countries measured concentrations along with assigned TEF values (Table 13), have been used to estimate the relative contribution of individual PAH compounds to the added total carcinogenicity of the measured PAHs in ambient air. Obviously, the results of such calculations depend on several factors such as the number of PAH compounds considered, whether both particulate and volatile PAHs are included, how representative the sampling is, and of course, the assigned TEF values. Additivity is assumed in these calculations; however, whether this assumption is appropriate/correct has yet to be demonstrated. The examples given below illustrate different outcomes depending on the assumptions that were made.

The Netherlands. In the Dutch criteria document from RIVM (1989), a subset consisting of at least two PAHs per ring class was selected. The following 10 compounds were selected for evaluation: naphthalene, anthracene, phenanthrene, fluoranthene, benz[*a*]anthracene, chrysene, benzo[*a*]fluoranthene, B[*a*]P, benzo[*ghi*]perylene, and indeno[1,2,3-*cd*]pyrene. The selection was based on a number of criteria, such as connection with internationally used PAH lists, the analytic selectivity, recovery and fluorescence susceptibility during the determination, the carcinogenicity of the compound, and the relation of the PAH list to emission profiles of sources. The ranges of TEF values discussed are shown in Table 13. The average concentrations of the selected PAH compounds in urban and rural air were multiplied by the upper range of the TEF values to obtain the concentrations expressed as B[*a*]P equivalents. Both particles and volatile PAHs were sampled. In these calculations, phenanthrene, fluoranthene, and chrysene contributed more than B[*a*]P to the sum of B[*a*]P equivalents from the 10 PAHs as a result of their relatively high assigned TEF values in combination with their relatively high concentrations.

Switzerland. In an article by Petry et al. (1996) the concentrations of 14 selected PAHs were measured on two occasions in a Swiss city. Only particle-bound PAHs were analyzed. The individual PAHs were assigned the TEF values proposed by Nisbet and LaGoy (1992), and the relative contribution

to the carcinogenicity of the air mixtures was calculated. According to these calculations, B[a]P contributed 65 and 58% to the sum of the B[a]P equivalents. Benzo[b]fluoranthene, benzo[j]fluoranthene, benzo[k]fluoranthene, indeno[1,2,3-cd]pyrene, and dibenz[a,h]-anthracene contributed about 10% each. Compared with the calculations from the Netherlands, much lower TEF values were used for phenanthrene, fluoranthene, and chrysene. Consequently, these PAHs contributed much less to the total carcinogenicity, which was further accentuated by the fact that only particle-bound PAHs were measured. Phenanthrene and fluoranthene are relatively volatile PAHs. Petry and co-workers (1996) also made similar calculations for some occupational exposures (coke, anode, graphite, silicon carbide, metal-recycling plants, and bitumen paving), but in this case both gaseous and particulate PAHs were measured by personal monitoring. In these occupational settings, B[a]P contributed 27–67% of the total carcinogenicity of the PAHs considered. The authors concluded that B[a]P is a good marker for these different PAH mixtures.

United Kingdom. When the mean concentrations of seven selected carcinogenic PAHs (particulate and vapor phase) in ambient air (London and Middlesborough) and in an aluminum smelter workplace were multiplied by their assigned TEF values, the contributions of B[a]P to the sum of the B[a]P equivalents were 45, 38, and 49% in London, Middlesborough, and the aluminum smelter, respectively. The PAH compounds were the following: B[a]P, benz[a]anthracene, dibenz[a,h]anthracene, benzo[b]fluoranthene, benzo[k]fluoranthene, indeno[1,2,3-cd]pyrene, and chrysene (Expert Panel 1999).

France. Personal exposure to particulate-phase atmospheric PAH was assessed in Grenoble for 48 hr (Zmirou et al. 2000). The measured PAHs were B[a]P, benz[a]anthracene, benzo[b]fluoranthene, benzo[k]fluoranthene, indeno[1,2,3-cd]pyrene, benzo[ghi]perylene, chrysene, fluoranthene, and pyrene. When the TEF values by Nisbet and LaGoy (1992) (Table 13) were applied to the measured concentrations, about two-thirds of the total cancer risk was related to B[a]P, and the second most influential compound was indenopyrene. Although fluoranthene was measured at a concentration 10 times higher than B[a]P, the low TEF value used (0.001) had a small influence on the total carcinogenicity.

Canada. The Canadian risk assessment of PAHs (Government of Canada 1994; Meek et al. 1994) is based on the carcinogenicity of five PAHs classified as "probably carcinogenic to humans," namely, B[a]P,

benzo[b]fluoranthene, benzo[j]fluoranthene, benzo[k]fluoranthene, and indeno[1,2,3-cd]pyrene. The carcinogenic potencies of these PAHs relative to B[a]P are shown in Table 13. The concentrations of these PAHs in different localities in Canada (particles and volatiles) were combined with the corresponding TEF values, and the relative contributions from these PAHs in ambient air (in B[a]P equivalents) show that B[a]P contributes more than the other selected PAHs (70–100% of the carcinogenic activity).

The State of California, USA. The Air Resources Board of the California Environmental Protection Agency has prepared a health risk assessment of B[a]P as a toxic air contaminant (CARB 1994). B[a]P was chosen as representative of PAHs because it is the best-investigated individual PAH compound. The statewide population-weighted exposure to B[a]P in California was estimated to be 0.53 ng/m³ (only particle-associated PAHs). Based on the ambient concentrations and potency equivalency factors (TEFs, see Table 13) for benzo[b]-fluoranthene, benzo[k]fluoranthene, indeno[1,2,3-cd]pyrene, and dibenz[a,h]-anthracene, the combined risk from exposure to these four PAHs was calculated to be approximately one-third that of B[a]P.

In an article by Collins et al. (1998), the California TEF values for those nine PAHs considered to be carcinogenic (Table 13) were applied to measured concentrations of particle-bound PAHs in Riverside, California. In contrast to the data from other countries, dibenzopyrenes were also measured. Because of the high TEF value assigned to dibenzo[a,l]pyrene, this individual PAH compound made the greatest contribution to the carcinogenicity (5 times that

of B[a]P). B[a]P, benzo[b]fluoranthene, benzo[j]fluoranthene, and benzo[k]fluoranthene contributed equally. In this article some nitro-PAHs were also considered (1- and 4-nitropyrene, 2-nitrofluoranthene, 1,6-dinitropyrene, 6-nitrochrysene, and 2-nitrofluorene). However, the total carcinogenic activity of these compounds was insignificant compared with that of B[a]P, benzofluoranthenes, indeno[1,2,3-cd]pyrene, and dibenzo[a,l]pyrene.

Sweden. To be able to discuss which individual PAHs are most important from a Swedish perspective, B[a]P equivalents were calculated for ambient air [in the center of Stockholm and at a background station, Rörvik, situated at the west coast of Sweden (Table 14)], emissions from gasoline and diesel engines (Table 15), and emissions from domestic wood and oil heating (Table 16). The TEF scheme by Larsen and Larsen (1998) was used for two reasons: it takes into account the most recent data, and the TEFs for fluoranthene agree well with the latest reports on the carcinogenic potential of fluoranthene (see "Fluoranthene as an indicator"). It should be noted that the percentage values given in Tables 14–16 are dependent on the number and the individual PAHs analyzed, and they should not be regarded as true values.

In the ambient air, it is obvious that out of the analyzed PAHs that have been assigned TEFs, B[a]P and fluoranthene contribute most to the B[a]P equivalents (Table 14). B[a]P accounts for 58 and 50% of total B[a]P equivalents in Stockholm and Rörvik, respectively, whereas fluoranthene contributes 21 and 26%, respectively. Benzofluoranthenes and indeno[1,2,3-cd]pyrene also contribute more than 5% of the total B[a]P equivalents.

Table 14. PAH concentrations, B[a]P equivalents, and percentage contribution of 11 PAHs to the B[a]P equivalents calculated for ambient air[a] in Stockholm[b] and Rörvik.[c]

| PAH | TEF[d] | Stockholm (1997) | | | Rörvik (1994) | | |
		Conc. (ng/m³)	B[a]P eq. (ng/m³)	B[a]P (%)	Conc. (ng/m³)	B[a]P eq. (ng/m³)	B[a]P eq. (%)
Anthracene	0.0005	12.6	0.0063	0.2	0.044	0.000022	0.02
Benz[a]anthracene	0.005	1.7	0.0085	0.3	0.065	0.00033	0.2
B[a]P	1.0	1.7	1.7	58	0.072	0.072	50
Benzo[b]fluoranthene	0.1	3.6[e]	0.27[e]	9.3[e]	0.17	0.017	12
Benzo[k]fluoranthene	0.05				0.074	0.0037	2.5
Benzo[ghi]perylene	0.02	3.6	0.072	2.5	0.079	0.0016	1.1
Chrysene	0.03	2.1	0.063	2.2	0.15	0.0045	3.1
Fluoranthene	0.05	12	0.6	21	0.76	0.038	26
Indeno[1,2,3-cd]pyrene	0.1	1.6	0.16	5.5	0.075	0.0075	5.2
Phenanthrene	0.0005	30	0.015	0.5	1.2	0.0006	0.4
Pyrene	0.001	18	0.018	0.6	0.21	0.00021	0.1
Total (of 11)			2.9	100		0.15	100
Dibenz[a,h]anthracene	1.1	0.1	0.11	3.8[f]			

[a]Note that the sum is calculated for the given PAH only, although there are other PAHs present in the ambient air that might also contribute to the carcinogenic risk. [b]Data from Burman (2001). [c]Data from Brorström-Lunden et al. (2000). [d]Data from Larsen and Larsen (1998). [e]Reported as benzofluoranthene. A TEF value of 0.075 has been used. [f]This PAH is not included in the total above.

Table 15. The relative contribution of individual PAHs[a] to B[a]P equivalents calculated for emissions from gasoline and diesel engines.[b]

PAH	TEF[c]	Light-duty vehicles			Heavy-duty trucks	
		Gasoline without catalytic converter	Gasoline + three-way catalytic converter	Diesel light (MK1) + oxidizing catalytic converter	Diesel (MK3) without catalytic converter	Diesel (MK1) without catalytic converter
		% of total B[a]P equivalents				
Anthracene	0.0005	0.2	0.4	0.1	0.3	0.1
Benz[a]anthracene	0.005	0.2	0.3	0.1	0.4	d,e
B[a]P	1	77	43	5.3	4.2	7.1[d]
Benzo[b and k]fluoranthene	0.075	4.4	11	1.6	0.8	0.5[d]
Benzo[ghi]perylene	0.02	1.4	1.4	0.2	d,e	0.1[d]
Chrysene/triphenylene	0.03[f]	1.4	4.3	1.6	0.6	0.4
Fluoranthene	0.05	12	36	88	86	85
Indeno[1,2,3-cd]pyrene	0.1	2.3	1.4	0.5	0.2[d]	0.7[d]
Phenanthrene	0.0005	0.5	2.0	1.0	2.8	1.4
Pyrene	0.001	0.3	0.4	1.3	4.4	4.9
Total (µg/km)		8.6	0.7	1.9	4.8	1.4

[a]Note that the sum is calculated for the given individual PAH only, although there are other PAHs present in the emissions that might also contribute to the carcinogenic risk of the emissions. [b]For concentrations of individual PAHs, see Table 5. [c]Data from Larsen and Larsen 1998. [d]Concentration below the detection limit. The detection limit is used for calculations. [e]Below 0.1%. [f]TEF for chrysene.

Table 16. The relative contribution of individual PAHs[a] to B[a]P equivalents calculated for emissions[a] from domestic burning of wood and oil.[b]

PAH	TEF[c]	Wood	Oil
		% the of total B[a]P equivalents	
Anthracene	0.0005	0.3	0.2
Benz[a]anthracene	0.005	1.0	0.2[d]
B[a]P	1	53	35[d]
Benzo[b and k]-fluoranthene	0.075	2.8	2.6[d]
Benzo[ghi]perylene	0.02	0.3	ND
Chrysene/triphenylene	0.03[e]	ND	1.1[d]
Fluoranthene	0.05	39	53
Indeno[1,2,3-cd]pyrene	0.1	1.6	ND
Phenanthrene	0.0005	1.8	7.6
Pyrene	0.001	0.6	0.2
Total (µg/MJ)		19	0.0085

ND, not determined. [a]Note that the sum is calculated for the given individual PAH only, although there are other PAHs present in the emissions that might also contribute to the carcinogenic risk of the emissions. [b]For concentrations of individual PAHs, see Table 8. [c]Data from Larsen and Larsen 1998. [d]Concentration below the detection limit. The detection limit is used for calculations. [e]TEF for chrysene.

For emissions from gasoline and diesel engines, B[a]P and fluoranthene are also the major contributors to total B[a]P equivalents (Table 15). However, it should be noted that fluoranthene alone accounts for the greatest part (85–88%) in diesel emissions, whereas B[a]P contributes more than fluoranthene in gasoline emissions.

B[a]P and fluoranthene are also the major contributors to the B[a]P equivalents of emissions from domestic wood and oil heating, together representing 92 and 88%, respectively (Table 16). In emissions from wood burning, B[a]P contributes slightly more than fluoranthene, and vice versa for emissions from domestic oil heating. In the emissions from domestic oil heating, phenanthrene is also an important contributor.

The results of the calculations of total B[a]P equivalents for ambient air using the TEFs by Larsen and Larsen (1998) agree well with the results obtained with the TEF scheme by Nisbet and LaGoy (1992), although the individual TEF values vary considerably. The TEF scheme by RIVM (1989) leads to B[a]P equivalents that differ most from the other schemes. Generally, the RIVM TEFs result in comparably higher B[a]P equivalents for chrysene and phenanthrene, whereas B[a]P, indeno[1,2,3-cd]pyrene, and benzofluoranthenes get lower B[a]P equivalents (data not shown). A problem with the RIVM TEFs is that the TEFs are given as ranges in most cases. The upper range is used in the calculations, although the scientific validity of this is questionable.

Summary and Conclusions

Epidemiologic data have demonstrated that occupational exposure to soot, coal tar, and other PAH-containing mixtures is carcinogenic to humans. The increased risk for lung cancer in coke-oven workers has been used for quantitative risk estimates with the content of B[a]P as indicator substance. The WHO unit risk estimate for humans is 8.7×10^{-5} per ng/m^{3} B[a]P as indicator. A similar risk estimate can be derived from the increased risk for lung cancer in aluminum smelters.

In an inhalation study with hamsters, B[a]P induced tumors in the nasopharyngeal tract and the trachea but not in the lung. This study has been used for quantitative risk estimates, but because of various deficiencies in the study, the quantitative estimate must be regarded as very uncertain. The lifetime unit risk estimate for humans, based on this study, is reported as $0.3–1.7 \times 10^{-6}$ per ng/m^{3}. Calculations based on

intratracheal administration in hamsters led to a risk of $3.3–4.8 \times 10^{-6}$ per ng/m^{3}. A more recent study with rats inhaling a coal tar/pitch aerosol led to a risk for lung tumors of 20×10^{-6} per ng/m^{3} B[a]P as indicator of the PAH mixture.

In principle, the cancer risk assessment of PAHs in ambient air can be performed in two ways. One approach is to add the risks from selected individual PAH compounds as determined from animal experiments. The other approach is to use B[a]P as an indicator of the mixture of carcinogenic PAHs in air and apply that to the dose–response relationship observed in epidemiologic studies. Both of these approaches have considerable weaknesses. WHO has chosen epidemiologic data on coke-oven workers for risk assessment in the Air Quality Guidelines for Europe (WHO 1987, 2000).

Several authors have calculated the relative potency of different PAHs compared with the potency of B[a]P in bioassays such as the skin application tumor assay in mice, or other cancer tests. The TEF value of B[a]P is set to 1. In almost all of the published rankings, the TEF value for most other PAHs is less than 1, except for dibenz[a,h]anthracene, which was given TEF values higher than 1 by some authors. The dibenzopyrenes were considered in the California EPA document (CARB 1994), as well as by Muller in 1997 and Larsen and Larsen in 1998, and the ah, ai, and al isomers were assigned TEF values of 0.1–100. Phenanthrene, pyrene, anthracene, and fluoranthene, which occur at relatively high concentrations in ambient air but are generally not considered to be carcinogenic, have been assigned low but varying TEF values by some authors but not by others. However, fluoranthene is an experimental carcinogen in a specific test system, and in a recent TEF scheme, fluoranthene was assigned a higher TEF value (0.05) (Larsen and Larsen 1998).

TEF values for a few selected carcinogenic PAHs, together with their estimated concentrations in ambient air, indicated B[a]P as the dominating contributor to the carcinogenicity of these PAHs in England, California, and Canada. In a more recent California article (Collins et al. 1998), dibenzopyrenes were also measured. This study indicated dibenzo[a,l]pyrene as the main contributor to the carcinogenicity. Similar calculations in the Netherlands also included some PAHs not generally considered carcinogenic. Because of their relatively high concentrations in ambient air and assigned TEF values of 0.01, 0.06, and 0.89, respectively, phenanthrene, fluoranthene, and chrysene contributed more than B[a]P to the carcinogenicity in the Dutch calculations. In calculations on Swedish

ambient air and emissions from diesel and gasoline vehicles and domestic wood and oil heating, B[*a*]P together with fluoranthene was the major contributor to the carcinogenicity. B[*a*]P was the most important PAH in ambient air, gasoline exhausts, and emissions from wood burning, whereas fluoranthene was the dominating PAH in diesel exhausts and emissions from oil heating. These calculations support the use of B[*a*]P as an indicator of carcinogenic PAHs in ambient air.

Although B[*a*]P is a good indicator of carcinogenic compounds in coke-oven emissions and other PAH-rich emissions, its adequacy as indicator of carcinogenic ambient air pollutants has been questioned. For example, it has been shown that the potency of cigarette smoke and diesel exhaust that contain large amounts of carcinogenic compounds other than PAHs is much higher at a given level of B[*a*]P than coke-oven emissions, which derive much of their carcinogenicity from unsubstituted four- to seven-ring PAHs. Nevertheless, of a number of selected PAH compounds, B[*a*]P has been estimated to be a dominating contributor to the carcinogenicity both in ambient air and in different occupational settings, and it should still be regarded as a relevant indicator of carcinogenic airborne PAHs. This also lends some credit to the WHO risk estimate, which is based on epidemiology with B[*a*]P as an indicator, although the PAH profile in ambient air is not identical to that in coke-oven emissions.

Considering the TEF values presented in Table 13 together with their calculated relative contribution to the carcinogenicity of ambient air in Sweden (Table 14), the following PAHs can be recommended as indicators: B[*a*]P, benzofluoranthenes, dibenz[*a,h*]anthracene, dibenzo[*a,l*]pyrene, fluoranthene, and indeno[1,2,3-*cd*]pyrene.

However, it should be noted that the relative order of PAH potency might not be the same for the inhalation route as for the different routes of exposure that formed the basis for establishment of the TEF values.

One disadvantage of using B[*a*]P as surrogate for the PAH mixture in ambient air is that substituted PAHs are not well represented by B[*a*]P and they must be considered separately. Nevertheless, when some nitro-PAHs were considered in calculations from California, their relative contribution to the carcinogenicity of ambient air was minor compared with that of dibenzo-[*a,l*]pyrene, B[*a*]P, and benzofluoranthenes.

Summary and Conclusions

Polycyclic aromatic hydrocarbons (PAHs) are important air pollutants. Some of the individual PAHs are known carcinogens,

and the group as a whole is regarded as carcinogenic. Historically, B[*a*]P has been used as an indicator of carcinogenic PAHs, although the relevance for today's air pollution pattern has been questioned in view of a change in emission profiles of modern diesel engines and fuels. The aim of the present study was to discuss the suitability of possible indicators and to devise proposals for both indicator substances and guideline values. The intention has been to highlight certain mechanistic aspects of the carcinogenicity of PAHs and of risk assessment, with the focus on comparative quantitative potency of different PAHs. The relative carcinogenic activity of individual PAHs together with the concentrations found in ambient air have been important selection criteria for the choice of indicator substances. The following summary is based on the preceding sections of this document, and the reader is referred to those for literature references.

Emissions and Concentrations

PAHs constitute a wide class of compounds with fused aromatic rings. PAHs are formed in incomplete combustion processes, and it has been known for a long time that exposure to soot, coal tar, and pitch entails an increased risk for tumor development in humans. IARC has also classified several other PAH-containing complex mixtures as carcinogenic to humans (e.g., occupational exposures in aluminum production, coal gasification, and coke production) or as probably carcinogenic to humans (e.g., creosotes, diesel exhausts). Individual PAH compounds have been tested in skin-painting assays and other animal experiments, and many have demonstrated carcinogenic effects. In this report we restrict the discussion mainly to unsubstituted PAHs, although the compounds may exist in substituted form (i.e., alkyl-, nitro-, amino-, or halogen-substituted PAHs). PAHs also participate in atmospheric chemical reactions, leading to the formation of more polar and more water-soluble PAH derivatives such as hydroxylated, oxygenated, or nitrated PAHs. The atmospheric half-life of PAHs is on the order of a few hours to a few days.

The data on emissions of PAHs are uncertain, but there has been a substantial reduction in emissions since 1960. However, more regular measurements during the last decade at a background station at Rörvik at the west coast of Sweden and at Hornsgatan in the center of Stockholm (see "Concentrations in Ambient Air") have not shown any definite trends in the air concentrations. Today, wood burning is believed to be the major source of PAH emissions to air in Sweden, producing about 60% of the

total emissions, whereas traffic contributes about 30%. Old passenger cars without catalytic converters and diesel vehicles with older combustion technology contribute most of the traffic-related emissions of PAHs. Cold starts of petrol-driven vehicles are an important contributing factor for PAH emissions.

PAH emission profiles are not specific to each source but rather reflect efficiency in combustion and fuel quality in general. Diesel exhaust, however, is characterized by PAHs with a lower molecular mass, whereas wood burning and petrol cars without catalytic converters emit a larger fraction of heavy multiringed PAHs compared with diesel exhaust. Modern diesel engines using environmentally classified diesel fuel and modern catalyst-equipped petrol cars emit only minute amounts of heavy PAHs such as B[*a*]P.

Total PAH levels of ambient air from different measurements are often difficult to compare, as different individual PAHs have been measured. In Europe, B[*a*]P concentrations are often below 1 ng/m^3 at background stations, whereas at locations close to traffic, concentrations range between 1 and 5 ng/m^3. At the street-level site in the center of Stockholm (Hornsgatan), the sum of 14 PAHs ranges from 100 to 200 ng/m^3. The B[*a*]P levels vary between 1 and 2 ng/m^3. The most abundant PAH is phenanthrene, which constitutes about one-third of the total amount.

Carcinogenicity of PAHs

The carcinogenic activity of PAHs is considered to be the critical effect, although animal experiments indicate that such compounds may also give rise, for example, to immunologic and reproductive effects. In this document we focus on the carcinogenicity. Several PAHs are considered complete carcinogens, and thus they may act at different stages in the carcinogenic process at both the genotoxic and nongenotoxic levels. Interaction of the parent PAH compound with the so-called Ah receptor may induce enzymes participating in the metabolism and subsequent increases in genotoxic metabolites. Another effect of Ah receptor binding may be on the level of cell proliferation and differentiation. Ah receptor binding is thus one of the mechanisms contributing to the carcinogenicity of PAHs. Other mechanisms may include the initiation of inflammatory processes and stimulated oxidative stress.

The mutagenic and carcinogenic activity of PAHs requires metabolic activation to reactive intermediates (mainly DEs) and their subsequent covalent binding to critical targets in DNA. The mutagenic and carcinogenic activity of a PAH is associated

with the structural features and the molecular mass of the molecule; a more complex compound is usually more potent. Recognized carcinogenic unsubstituted PAHs belong to the class of four- to seven-ring members. Factors likely to influence an individual's susceptibility toward PAH exposure include polymorphisms in genes encoding enzymes participating in the metabolism of the PAHs (e.g., activating cytochromes P450 and detoxifying GSTs). Metabolism of PAHs occurs mainly in the liver. However, inhalation is the main route of exposure to PAHs in ambient air; consequently, metabolism in lung tissue also has to be considered. Because of the lipophilic properties of PAHs, a fraction of the compounds is likely to be retained in the lung tissue and to attain high local concentrations. Despite the rather modest metabolic capacity of lung tissue, local activation and formation of active metabolites in the airway epithelium may be of importance in specific parts of the lungs, such as the bronchial epithelium.

In human biomonitoring of PAH exposure, blood cells are frequently employed, and protein and/or DNA adducts estimated as a measure of overall exposure. The intake of PAHs is generally higher by food than by inhalation. Determination of DNAs or protein adducts of PAHs has been considered a suitable way of estimating the systemic internal dose to humans. There are still problems with regard to the sensitivity, specificity, and the stability of different adducts that render such methods less suitable at present for use in routine biological monitoring. Determination of hydroxylated metabolites in urine, derived from pyrene and phenanthrene, can be used for monitoring exposure to environmental PAHs.

Quantitative Risk Estimates

Estimates derived from human data. Quantitative cancer risk estimates of PAHs as air pollutants are uncertain because of lack of useful, good-quality data in addition to the complexity of the problem. Although several epidemiologic studies indicate that urban air pollution is a risk factor for lung cancer, these studies do not generally provide a quantitative correlation to estimated PAH levels. Cigarette smoke obviously contains many other strongly carcinogenic compounds besides PAHs, which renders cigarette smoke less suitable as a basis for risk assessment of PAH exposure. Diesel exhaust is an important source of PAHs in ambient air, but the epidemiologic studies on diesel exhausts and lung cancer have not yet provided any quantitative risk estimates in relation to PAHs. Diesel exhaust also contains nitro-PAHs and other carcinogenic

substances besides pure PAH. There are no epidemiologic data concerning wood combustion. Accordingly, it is still necessary to use earlier studies on coke-oven emissions to assess the human risk to PAH exposure, as coke-oven emissions have clearly been associated with an increased risk for lung cancer, also in quantitative terms. One difficulty in comparing different exposures is that the PAH profiles may differ.

At the present stage of knowledge, risk estimation of PAHs at low exposure levels should be based on the assumption of linear dose–response relationships. In the WHO Air Quality Guidelines for Europe, the risk assessment is based on lung cancer in coke-oven workers, with the underlying assumption that any differences in the PAH profiles in coke-oven emissions and ambient air are not too big to prevent such an extrapolation. The WHO unit risk estimate for humans is 9×10^{-5} per ng/m^3 B[a]P as an indicator. This risk thus refers to the total PAH mixture and not only to the content of B[a]P. A risk assessment based on lung cancer in aluminum-production workers would lead to a very similar estimate.

The epidemiologic approach for risk assessment has also been used in national risk assessment for PAH compounds in the Netherlands. In a recent document from Ontario, Canada, the epidemiologically based risk assessment for PAHs is recommended. On the other hand, the available epidemiologic data were considered inadequate for risk assessment by Health Canada. The U.S. EPA formerly used a quantitative risk estimate for B[a]P based on a hamster inhalation study, but because of the inadequacy of this study, the U.S. EPA does not currently have an official inhalation risk estimate for B[a]P (or PAHs) in ambient air.

Estimates derived from studies on rodents. Only one single PAH, B[a]P, has been tested in animal inhalation studies. In the most-cited study, tumors were induced in the nasopharyngeal tract and the trachea of hamsters but not in the lung. This study has been used for quantitative risk estimates, but because of various deficiencies in the study, the quantitative estimate must be regarded as very uncertain. The lifetime unit risk estimate for humans, based on this study, has been reported as $0.3–1.7 \times 10^{-6}$ per ng/m^3, using different assumptions.

An alternative approach to risk assessment of PAHs in ambient air might be to add the risks from selected individual PAH compounds as determined from animal experiments. In this case, the potencies of the individual compounds are expressed relative to the potency of B[a]P as TEF values. However, ambient air contains many more PAH compounds than have been investi-

gated experimentally, and only a limited number of PAHs are usually measured. Thus, important contributors to the overall carcinogenic risk may be overlooked. In addition, because of the high exposure levels in the animal carcinogenicity studies, the results may mainly reflect the PAH promotive effects. In conclusion, quantitative risk assessment of PAHs in ambient air, based on animal experiments, must be regarded with caution because of such shortcomings.

Indicators according to toxic equivalency considerations. In all published rankings of PAHs, B[a]P has been used as the reference substance. Only a few compounds, such as some dibenzopyrenes and dibenz[a,h]-anthracene, are regarded as more potent than B[a]P. Thus, B[a]P should be regarded as an essential indicator of carcinogenic compounds in ambient air. However, other PAHs such as phenanthrene, pyrene, fluoranthene, and various methylated PAHs are found in higher concentrations in ambient air. By multiplying the concentration of individual PAHs with their cancer potency relative to B[a]P (TEF value), the carcinogenic activity can be calculated as B[a]P equivalents. Depending on how many and which compounds are considered, the relative contribution from B[a]P and other selected PAHs to the carcinogenicity of these PAHs in ambient air may vary. For example, TEF values for a few selected carcinogenic PAHs, together with their estimated concentration in air, indicated B[a]P as the dominating contributor to the sum of the B[a]P equivalents from these PAHs in England, France, California, and Canada. In a more recent California study, dibenzopyrenes were also measured. This study indicated dibenzo[a,l]pyrene as the main contributor to the B[a]P equivalents. Similar calculations (not including dibenzopyrenes) in the Netherlands and in Switzerland also included some PAHs, such as phenanthrene, pyrene, fluoranthene, and various methylated PAHs, that are not generally considered carcinogenic. In the Dutch calculations, phenanthrene, fluoranthene, and chrysene were assigned relatively high TEF values; because of their high concentrations in ambient air, these PAHs together contributed more than B[a]P to the B[a]P equivalents. In the Swiss calculations, the corresponding TEF values were less than one-tenth of the Dutch figure, and B[a]P became the dominating contributor, also partly because only particle-bound PAHs were measured.

PAHs as carcinogens in ambient air in Sweden. Of 11 PAHs considered in Swedish ambient air at the center of Stockholm and at a background station (Rörvik), B[a]P and fluoranthene contributed most to the B[a]P

equivalents. B[*a*]P accounted for 50–58% of the total B[*a*]P equivalents, whereas fluoranthene contributed 21–26%. Benzo-fluoranthenes and indeno[1,2,3-*cd*]pyrene also contribute more than 5% of the total B[*a*]P equivalents. B[*a*]P and fluoranthene are the major contributors to the total B[*a*]P equivalents for emissions from petrol and diesel engines also. However, it should be noted that fluoranthene alone accounts for the major part (85–88%) in diesel emissions, whereas B[*a*]P contributes more than fluoranthene in petrol emissions. B[*a*]P and fluoranthene are also the major contributors to the B[*a*]P equivalents of emissions from domestic wood and oil heating. In emissions from wood burning, B[*a*]P contributes slightly more than fluoranthene, although the reverse is true for emissions from domestic oil heating. In the emissions from domestic oil heating, phenanthrene is also an important contributor. In these calculations, fluoranthene was assigned the relatively high TEF value of 0.05, which is based on studies with intraperitoneal exposure in newborn mice. Contrary to earlier studies with dermal exposure, fluoranthene was an experimental carcinogen in these later studies.

It is striking that several of the most abundant PAHs in ambient air (see "Sources, Deposition, and Ambient Concentration" and Table 13) apparently have not been studied experimentally; consequently, they have not been assigned TEF values. Furthermore, some of the most carcinogenic PAHs, such as dibenzopyrenes, are not usually analyzed.

Conclusions concerning quantitative risk estimates. All the cited risk estimates are uncertain because of various deficiencies in the database. We do not recommend the use of experimental animal data on single PAH substances for purposes other than relative potency rankings. The epidemiologic data on lung cancer in coke-oven workers are still the best basis for a quantitative risk estimate, and we accept the unit risk estimate in the WHO Air Quality Guidelines for Europe (9×10^{-5} per ng/m³ B[*a*]P as an indicator of the total PAH mixture). One concern with the validity of this estimate is a possible difference in PAH profiles between coke-oven emissions and ambient air. However, the fact that B[*a*]P is a major contributor to the added carcinogenicity of selected PAH compounds in studies on relative potency rankings, combined with actual measured concentrations in ambient air, supports the WHO approach using B[*a*]P as an indicator.

Recommended Indicators of PAHs in Ambient Air

Air quality considerations. According to the section "Sources, Deposition, and Ambient Concentrations," the following PAHs were considered the most representative, based on qualitative and quantitative properties of emissions and also with regard to their presence in ambient air: phenanthrene, methylanthracenes/phenanthrenes, fluoranthene, pyrene, B[*a*]P, benzo[*b*]fluoranthene, benzo[*k*]fluoranthene, indeno[1,2,3-*cd*]pyrene, and benzo[*ghi*]perylene. In addition, compounds such as dibenzothiophene and benzonaphthothiophene might be useful indicators of fuels containing sulfur, such as exhausts from heavy diesel vehicles, and retene might be useful as a marker for wood burning.

PAHs should be measured in both particulate and gas-phase samples from ambient air. The sampling mode and analytic techniques should be harmonized. From the health point of view, PAHs of all particle sizes are interesting.

Exhausts from modern diesel engines and fuels contain comparatively less of the high-molecular PAHs than older diesel engines, gasoline vehicles, or emissions from space heating. As this trend may be accentuated in the future, the relative importance of volatile PAHs in ambient air may increase. Thus, in a monitoring program it is essential that volatile PAHs such as phenanthrene, fluoranthene, or pyrene are included.

Biological considerations. The choice of indicator substances should be based on both practical and biochemical/biological considerations. B[*a*]P has been used traditionally, and it must still be regarded as the first choice because of its well-documented activity as an experimental carcinogen. When some of the measured PAH compounds in ambient air are assigned TEF values (potency relative to B[*a*]P) and their concentrations are converted into B[*a*]P equivalents, B[*a*]P will, in most cases, be the main contributor to the carcinogenic activity.

The WHO risk estimate, 9×10^{-5} per ng/m³ B[*a*]P, refers to the total PAH mixture where B[*a*]P is used as an indicator. B[*a*]P should be supplemented with another indicator to ensure that the risk does not increase if the composition of the PAH profile is changed. Preferably it should be a representative of more volatile PAHs, as they are more abundant in ambient air. In the first instance, we recommend fluoranthene because it is an experimental mutagen and carcinogen in certain test systems and it occurs at relatively high concentrations in the environment. According to calculations based on Swedish data, in addition to B[*a*]P, fluoranthene can be considered a main contributor to the added carcinogenicity of a number of PAHs in ambient air.

The relative contribution of high-molecular PAHs, such as B[*a*]P, will probably decrease in the future when better diesel technology and qualities have become more common. The highest concentration of individual PAH compounds in air samples from Stockholm is due to phenanthrene. Both phenanthrene and pyrene, another abundant PAH, are generally considered noncarcinogenic, although they have been assigned TEF values higher than zero by some authors. They are metabolized in humans to phenols that can be detected in urine, and they can thus serve as indicators for PAH exposure in humans.

At present, only a few other PAHs have been identified that are equally or more potent than B[*a*]P, for example, dibenz-[*a,h*]anthracene. Dibenzopyrenes, in particular dibenzo[*a,l*]pyrene, are more potent than B[*a*]P (>10-fold). Dibenzo[*a,l*]pyrene is in fact the most potent PAH identified so far. Up to now there are no Swedish measurement data on dibenzopyrenes, but in a recent study from California, dibenzo-[*a,l*]pyrene was the main contributor to the B[*a*]P equivalents. Dibenzo[*a,l*]pyrene and dibenz[*a*]anthrazene are therefore recommended as additional indicator substances. However, reliable analytic techniques for dibenzo[*a,l*]pyrene must be developed for this purpose.

Other PAHs that contribute substantially to the B[*a*]P equivalents in Swedish ambient air are indeno[1,2,3-*cd*]pyrene and benzofluoranthenes.

PAHs constitute only part of the larger group of polycyclic aromatic compounds that also consists of substituted and transformed PAHs. Some nitro-PAHs have been fairly well studied, but otherwise there is a lack of knowledge about the carcinogenicity of these compounds. Nitro-PAHs could be used as an indicator of diesel exhaust, but their instability and difficulties in the measurements may render them less suitable as indicator substances. Because the mutagenic activity of particulate extracts from ambient air mainly resides in the more polar fractions, it may be suspected that transformed PAHs also constitute a carcinogenic risk. However, when some nitro-PAHs were considered in TEF calculations from California, their relative contribution to the carcinogenicity was minor. Furthermore, it should be noted that methylated PAHs constitute a large part of the analyzed PAHs in the air samples from Stockholm. The recommended indicators are summarized in Table 17.

Suggested Guideline Values

The WHO risk estimate, based on lung cancer in coke-oven workers, can be used to

recommend a health-based guideline value for ambient air. However, in the WHO Air Quality Guidelines for Europe, the unit risk is used only to express the concentrations in air that theoretically would lead to lifetime cancer risks of 1×10^{-4}, 1×10^{-5}, and 1×10^{-6}, respectively. The individual countries then have to decide which risk level should be regarded as acceptable. There is very little guidance internationally on how to look upon such low theoretic risks. The EU Commission provides no recommendations. In the WHO guidelines for drinking-water quality (WHO 1996), guideline values for genotoxic carcinogens are set at the concentration in drinking water associated with an estimated upper-bound excess lifetime cancer risk of 1×10^{-5}. Although this risk level (one additional cancer case per 100,000 of the population) is arbitrarily chosen, it has previously been used also at the Institute of Environmental Medicine in Stockholm to propose so-called low-risk levels for some genotoxic carcinogens in the environment. If the risk level of 1×10^{-5} is chosen also in the present context, the WHO risk estimate for PAHs in air would lead to a guideline value of 0.1 ng/m^3 B[a]P as an indicator of the PAH mixture.

As discussed above, B[a]P should be supplemented with an indicator of the more volatile fraction of the PAH mixture to prevent any increased risks in the case of a relative increase of volatile PAHs in the future. As the guideline for B[a]P refers to the total PAH mixture, a guideline for a complementary indicator should be set at a concentration that represents the same risk as B[a]P does at 0.1 ng/m^3. Of the volatile PAHs, fluoranthene could be a suitable indicator substance. Fluoranthene is an experimental carcinogen in newborn mice, but the limited number of studies prevents too far-reaching conclusions regarding its

potential carcinogenicity. There are no epidemiologic studies linking fluoranthene to an increased cancer risk in humans. Nevertheless, it has been assigned a TEF value relative to B[a]P of 0.05, based on the tests in newborn mice. Such a TEF would render fluoranthene the second most important PAH among a selected number of PAHs, according to Swedish measurements of ambient air. Although the scientific basis for fluoranthene as an indicator of carcinogenic PAH is much weaker than that for B[a]P, fluoranthene may serve as a complementary indicator. Thus, assuming that the carcinogenic potency of fluoranthene is approximately 20 times lower than that of B[a]P, a tentative guideline value of 2 ng/m^3 is suggested for fluoranthene (Table 18). It should be stressed that the risks from B[a]P and fluoranthene (or any other carcinogenic PAH) should not be added, as they both represent the total cancer risk of the PAH mixture (1×10^{-5} at 0.1 ng/m^3 B[a]P, or less well based, 2 ng/m^3 fluoranthene).

Research Needs

Any quantitative risk assessment of PAHs in ambient air will be hampered by any serious weaknesses in the basis for the calculations. Specifically designed epidemiologic studies are needed to address the quantitative aspects relating lung cancer risks to B[a]P or PAHs in different environments.

The development of markers for carcinogenic risk among volatile PAHs is of interest. For example, the carcinogenicity of fluoranthene should be studied in relevant test systems, and any relation to human cancer investigated in epidemiologic studies.

Although PAHs have long been recognized as carcinogenic environmental pollutants, only inadequate animal inhalation studies are so far available. Many of the most

common PAHs analyzed in ambient air apparently have not been tested in animal experiments at all.

Methods for cancer risk estimation of PAHs (individual compounds or whole mixture) must be further developed and applied firsthand to the individual PAHs selected as indicator compounds for carcinogenicity.

Specific biological markers of PAH exposure and individual susceptibility are needed for monitoring purposes. Methods to identify and quantify specific PAH adducts to DNA and protein need to be further developed.

Better knowledge of exposure–target dose relationships of PAHs is needed, both concerning realistic exposures to humans, and at the much higher exposure levels at which most in vivo/in vitro biological experiments with PAHs are conducted. In particular, hidden nonlinearities between exposure and target dose of PAHs may greatly hamper both efforts to extrapolate from high-dose animal experiments to realistic human exposures, efforts to interpret biomarkers of exposure to PAHs.

Studies on mechanisms and dose–response relationships for promoter action of PAHs should be performed, including the influence of other promoters—for example, those acting by interaction or additivity.

There is a general lack of knowledge about the large group of substituted and transformed PAHs except for some nitro-PAHs. Effective mutagens and potential carcinogens among substituted (i.e., more polar) PAHs should be identified in emissions and in air pollution.

A selection of PAHs, including those compounds recommended in this report, should be more regularly measured to acquire more information about concentrations and trends. In addition, the distribution of PAHs of different particle sizes is of interest.

Dibenzopyrenes should be analyzed, and the analytic methods should therefore be developed. The analytic techniques for nitro-PAHs should be developed to facilitate their possible use as indicators.

The importance of wood combustion should be validated with measurements in areas/regions where wood is used for heating purposes.

The possible role of the precipitation of airborne particles as a source of PAHs in foodstuffs should be clarified.

Table 17. Summary of PAHs and related substances recommended for inclusion in ambient air monitoring.

Substance	Physical state	Reason for selection
Abundance		
Phenanthrene	Volatile	High concentration
Methylated anthracenes/ phenanthrenes	Volatile	High concentration
Pyrene	Semivolatile	High concentration
Carcinogenicity		
Fluoranthene	Volatile	High concentration, carcinogenic
B[a]P	Particulate bound	Carcinogenic, well studied
Dibenz[a,h]anthracene	Particulate bound	Carcinogenic
Dibenzo[a,l]pyrene	Particulate bound	Strongly carcinogenic
Benzo[b and k]fluoranthene	Particulate bound	Carcinogenic; indicator of petrol exhaust
Indeno[1,2,3-cd]pyrene	Particulate bound	Carcinogenic; indicator of petrol exhaust
Source specificity		
Retene	Semivolatile	Indicator of wood combustion emissions
Dibenzothiophene	Semivolatile	Indicator of sulfur-containing fuel (diesel exhaust)
Benzonaphthothiophene	Semivolatile	Indicator of sulfur-containing fuel (diesel exhaust)
Benzo[ghi]perylene	Particulate bound	Indicator of petrol exhaust

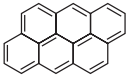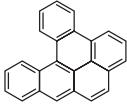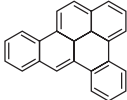**Table 18.** Main suggested indicators and guideline values.
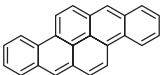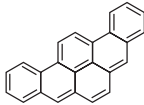
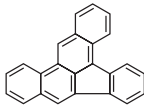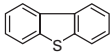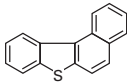| PAH	Guideline value
B[a]P	0.1 ng/m^3
Fluoranthene	2 ng/m^3 (tentative)

Appendix. Selected polycyclic aromatic hydrocarbons and polycyclic aromatic heterocycles containing sulfur.

	Formula	Molecular weight	CAS registry number	Chemical structure	Other names
Polycyclic aromatic hydrocarbons					
Phenanthrene	$C_{14}H_{10}$	178	85-01-8		Phenanthrin
Anthracene	$C_{14}H_{10}$	178	120-12-7		Anthracin; green oil; paranaphthalene
2-Methylanthracene	$C_{15}H_{12}$	192	613-12-7		
1-Methylphenanthrene	$C_{15}H_{12}$	192	832-69-9		
Fluoranthene	$C_{16}H_{10}$	202	206-44-0		Benzo[jk]fluorene; idryl; 1,2-benzacenaphthene; 1,2-(1,8-naphthalenediyl)benzene
Pyrene	$C_{16}H_{10}$	202	129-00-0		Benzo[def]phenanthrene
Chrysene	$C_{18}H_{12}$	228	218-01-9		Benzo[a]phenanthrene; 1,2-benzophenanthrene
Benz[a]anthracene	$C_{18}H_{12}$	228	56-55-3		Benzo[b]phenanthrene; tetraphene; 1,2-benzanthracene; 1,2-benzanthrene; 2,3-benzophenanthrene; naphthanthracene
Retene	$C_{18}H_{18}$	234	483-65-8		1-Methyl-7-isopropylphenanthrene; 7-isopropyl-1-methylphenanthrene; 1-methyl-7-(1-methylethyl)phenanthrene
Benzo[a]pyrene	$C_{20}H_{12}$	252	50-32-8		Benz[a]pyrene; 1,2-benzpyrene; 3,4-benzopyrene; 6,7-benzopyrene; benzo[def]chrysene
Benzo[e]pyrene	$C_{20}H_{12}$	252	192-97-2		4,5-Benzopyrene; 4,5-benzpyrene
Benzo[k]fluoranthene	$C_{20}H_{12}$	252	207-08-9		Dibenzo[b,jk]fluorene; 11,12-benzofluoranthene; 2,3,1′,8′-binaphthylene; 8,9-benzofluoranthene
Benzo[b]fluoranthene	$C_{20}H_{12}$	252	205-99-2		Benz[e]acephenanthrylene; benzo[e]fluoranthene; 2,3-benzofluoranthene; 3,4-benzofluoranthene; 3,4-benz[e]acephenanthrylene
Benzo[ghi]perylene	$C_{22}H_{12}$	276	191-24-2		1,12-Benzoperylene

(Continued)

Appendix. *Continued.*

	Formula	Molecular weight	CAS registry number	Chemical structure	Other names
Dibenzo[*def,mno*]chrysene	C$_{22}$H$_{12}$	276	191-26-4		Anthanthrene; dibenzo[*cd,jk*]pyrene
Coronene	C$_{24}$H$_{12}$	300	191-07-1		Hexabenzobenzene; dibenzo[*ghi,pqr*]perylene
Dibenzo[*a,l*]pyrene	C$_{24}$H$_{14}$	302	191-30-0		1,2:3,4-Dibenzpyrene; dibenzo[*def,p*]chrysene; 4,5,6,7-dibenzopyrene; 2,3:4,5-dibenzopyrene
Naphtho[1,2,3,4-*def*]chrysene	C$_{24}$H$_{14}$	302	192-65-4		1,2:4,5-Dibenzopyrene; dibenzo[*a,e*]pyrene
Dibenzo[*b,def*]chrysene	C$_{24}$H$_{14}$	302	189-64-0		3,4:8,9-Dibenzpyrene; dibenzo[*a,h*]pyrene
Dibenzo[*a,i*]pyrene	C$_{24}$H$_{14}$	302	189-55-9		3,4:9,10-Dibenzopyrene; benzo[*rst*]pentaphene; dibenzo[*b,h*]pyrene; 1,2:7,8-dibenzpyrene
Dibenz[*a,e*]fluoranthene	C$_{24}$H$_{14}$	302	5385-75-1		Dibenz[*a,e*]aceanthrylene
Polycyclic aromatic heterocycles containing sulfur					
Dibenzothiophene	C$_{12}$H$_{8}$S	184	132-65-0		
Benzonaphthothiophene	C$_{16}$H$_{10}$S	234	205-43-6		

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